A Case-Based Approach to Acid-Base Disorders

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Disclosures

None
Objectives

At the completion of this activity, pharmacists will be able to:

1. Describe acid-base physiology and disease states that lead to acid-base disorders.
3. Analyze contemporary literature regarding the use of sodium bicarbonate in metabolic acidosis.

At the completion of this activity, pharmacy technicians will be able to:

1. Explain the importance of acid-base balance.
2. List the acid-base disorders seen in clinical practice.
3. Identify potential therapies used to treat acid-base disorders.
A 51 year old man with history of erosive esophagitis, diabetes mellitus, chronic pancreatitis, and bipolar disorder is admitted with several days of severe nausea, vomiting, and abdominal pain.

**What additional data should be obtained?**

**What acid base disturbance(s) is/are present?**

<table>
<thead>
<tr>
<th>135</th>
<th>87</th>
<th>31</th>
<th>861</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6</td>
<td>20</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

pH 7.46 / pCO₂ 29 / pO₂ 81
BE -3.8 / HCO₃ - 18 / SaO₂ 96
Introduction

• Acid base status is tightly regulated to maintain normal biochemical reactions and organ function

• Body uses multiple mechanisms to maintain homeostasis

• Abnormalities are extremely common in hospitalized patients with a higher incidence in critically ill with more complex pictures

• A standard approach to analysis can help guide diagnosis and treatment
## Important acid-base determinants

Blood gas generally includes at least:

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Description</th>
<th>Normal range (arterial blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>-log [H⁺]</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>pCO₂</td>
<td>partial pressure of dissolved CO₂</td>
<td>35-45 mmHg</td>
</tr>
<tr>
<td>pO₂</td>
<td>partial pressure of dissolved O₂</td>
<td>80-100 mmHg</td>
</tr>
<tr>
<td>Base excess</td>
<td>calculated measure of metabolic acid/base deviation from normal</td>
<td>-3 to +3</td>
</tr>
<tr>
<td>SO₂</td>
<td>calculated measure of Hgb O₂ saturation based on pO₂</td>
<td>95-100%</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>calculated measure based on relationship of pH and pCO₂</td>
<td>22-26 mEq/L</td>
</tr>
</tbody>
</table>

Haber RJ. West J Med 1991;155:146-51
## Definitions

<table>
<thead>
<tr>
<th>Acidemia</th>
<th>Alkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>A state of low blood pH (&lt; 7.35)</td>
<td>A state of high blood pH (&gt; 7.45)</td>
</tr>
</tbody>
</table>

Haber RJ. West J Med 1991;155:146-51
## Definitions

<table>
<thead>
<tr>
<th>Acidosis</th>
<th>Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A process tending to acidify body fluids</td>
<td>A process tending to alkalinate body fluids</td>
</tr>
</tbody>
</table>

Haber RJ. West J Med 1991;155:146-51
Definitions

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relating to gain/loss of acid or bicarbonate (HCO$_3^-$)</td>
<td>Relating to gain/loss of carbon dioxide (CO$_2$)</td>
</tr>
</tbody>
</table>

Haber RJ. West J Med 1991;155:146-51
Definitions

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurring over minutes to hours</td>
<td>Occurring over days</td>
</tr>
</tbody>
</table>

Haber RJ. West J Med 1991;155:146-51
<table>
<thead>
<tr>
<th>Consequences of acidemia</th>
<th>Consequences of alkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>• Increased pulmonary vascular resistance</td>
<td>• Arteriolar constriction</td>
</tr>
<tr>
<td>• Reduced cardiac output, blood pressure</td>
<td>• Reduction in coronary blood flow</td>
</tr>
<tr>
<td>• Reduced responsiveness to catecholamines</td>
<td>• Arrhythmias</td>
</tr>
<tr>
<td>• Arrhythmias</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>• Hyperventilation</td>
<td>• Hypoventilation</td>
</tr>
<tr>
<td>• Respiratory muscle fatigue</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>• Increased metabolic demand</td>
<td>• Stimulation of anaerobic glycolysis</td>
</tr>
<tr>
<td>• Insulin resistance</td>
<td>• Hypokalemia, hypomagnesemia, hypophosphatemia</td>
</tr>
<tr>
<td>• Inhibition of anaerobic glycolysis</td>
<td>• Ionized hypocalcemia</td>
</tr>
<tr>
<td>• Hyperkalemia</td>
<td></td>
</tr>
<tr>
<td><strong>Cerebral</strong></td>
<td></td>
</tr>
<tr>
<td>• Altered mental status, coma</td>
<td>• Reduction in cerebral blood flow</td>
</tr>
<tr>
<td></td>
<td>• Tetany, seizures</td>
</tr>
</tbody>
</table>

Henderson-Hasselbalch equation

\[
\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^- \\
\]

\[
\text{pH} = \text{P}k + \log_{10}\left(\frac{\text{HCO}_3^-}{0.03 \text{ (PaCO}_2)}\right)
\]

• Used by blood gas analyzers to calculate HCO₃⁻
• May be used to check the internal consistency of a blood gas

pH – log of hydrogen ion concentration [H⁺]
Pk – acid dissociation constant
PaCO₂ – partial pressure of arterial carbon dioxide
0.03 – solubility of CO₂ in blood

### Ionic components of plasma

<table>
<thead>
<tr>
<th>Cations</th>
<th>mEq/L</th>
<th>Anions</th>
<th>mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>140</td>
<td>Cl⁻</td>
<td>100</td>
</tr>
<tr>
<td>K⁺</td>
<td>4</td>
<td>CO₂</td>
<td>25</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>2</td>
<td>Protein</td>
<td>15</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>2</td>
<td>Phosphate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organic acids</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total cations</strong></td>
<td>~148</td>
<td><strong>Total anions</strong></td>
<td>~148</td>
</tr>
</tbody>
</table>

CO₂ on a metabolic panel represents *total* CO₂ (tCO₂), including HCO₃⁻, pCO₂, and other organic compounds. Generally tCO₂ ≈ HCO₃⁻ but may be slightly higher with severe hypercapnia. More than 95% of tCO₂ and HCO₃⁻ results are within 3 points of each other.

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Morris CG. Anaesthesia 2008;63:294-301
Kumar V. Clin Chem 2008;54:1586-7
## Endogenous acids

<table>
<thead>
<tr>
<th>Type</th>
<th>Substances</th>
<th>Approximate Quantity</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volatile</strong></td>
<td>CO$_2$</td>
<td>15,000 mmol H$^+$ equivalents per day</td>
<td>Lungs</td>
</tr>
<tr>
<td><strong>Organic acids</strong></td>
<td>Primarily ketones and lactate</td>
<td>Several thousand mmol per day</td>
<td>Primarily liver</td>
</tr>
<tr>
<td><strong>Inorganic acids</strong></td>
<td>Primarily sulfate and phosphate</td>
<td>1.5 mmol/kg per day</td>
<td>Primarily renal</td>
</tr>
</tbody>
</table>

Morris CG. Anaesthesia 2008;63:294-301
Maintenance of homeostasis

• Plasma buffer system (HCO$_3^-$, Hgb, phosphate)
• Respiratory system – increase/decrease pCO$_2$
  • Fast – seconds to minutes
• Renal system – increase/decrease HCO$_3^-$
  • Slow – hours to days
Metabolic acidosis

• Gain of anion
  • Hyperchloremic
  • Anion gap acidosis
  • Hyperphosphatemic

• Loss of cation (Na\(^+\), K\(^+\))
  • Renal – renal tubular acidosis, natriuretic agents, hypoaldosteronism, excretion of sodium with non-chloride/nonbicarbonate anions (lactate, hippurate, ketones)
  • Gastrointestinal – diarrhea, vomiting pancreatic secretions

Anion gap

• Estimation of unmeasured anions (esp. phosphate, sulfate, organic anions, plasma proteins)

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

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

• Other measured ions (K^+, Mg^{2+}, Ca^{2+}, PO_4^{3-}) are assumed to be unmeasured

• Normal value < 12 ± 4 mEq/L
Anion gap metabolic acidosis (AGMA) mnemonics

**MUDPILES**
- Methanol
- Uremia
- Diabetic ketoacidosis
- Paraldehyde
- Isoniazid, iron
- Lactate
- Ethylene glycol
- Salicylates

**KUSMALE**
- Ketoacidosis
- Uremia
- Salicylate
- Methanol
- Aldehyde
- Lactate
- Ethylene glycol

**GOLDMARK**
- Glycols (ethylene, propylene)
- Oxoproline (pyroglutamic acid)
- L-lactate
- D-lactate
- Methanol
- Aspirin
- Renal failure
- Ketoacidosis

**Critique**
- Some intoxications outdated e.g. paraldehyde
- Some drugs listed cause AGMA via lactate (other lactate-inducing drugs/conditions missing)
- Ketoacidosis is not exclusively diabetic
- Glycols other than ethylene glycol
- Oxoproline missing (chronic acetaminophen use/glutathione depletion)
- Reminder of different forms of lactic acidosis

Mehta AN. Lancet 2008;372:892
**Anion gap metabolic acidosis**

- Addition of unmeasured anions ($X\text{A}^-$)
- $X\text{A}^-$ increases and $\text{HCO}_3^-$ decreases

**Example:** Lactic acidosis

$X\text{A}^-$ = unmeasured anions

Morris CG. Anaesthesia 2008;63:294-301
Non-anion gap metabolic acidosis (NAGMA) mnemonics

<table>
<thead>
<tr>
<th>HARDUP</th>
<th>ACCRUED</th>
<th>PANDA RUSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperchloremia</td>
<td>Ammonium chloride / acetazolamide</td>
<td>Pancreatic secretion loss</td>
</tr>
<tr>
<td>Acetazolamide, Addison’s</td>
<td>Chloride intake</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td>Cholestryamine</td>
<td>Normal saline intoxication</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Renal tubular acidosis</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Ureteroenterostomy</td>
<td>Urine diverted into intestine</td>
<td>Aldosterone antagonists</td>
</tr>
<tr>
<td>Pancreatoenterostomy</td>
<td>Endocrine disorders (e.g. Addison’s)</td>
<td>Renal tubular acidosis</td>
</tr>
</tbody>
</table>

All involve gain of chloride or loss of bicarbonate (i.e. measured ions)

Yartsev A. http://www.derangedphysiology.com
Non-anion gap metabolic acidosis

• *Measured ions* are relevant here
• Addition of chloride, direct loss of HCO$_3^-$
• No change in XA$^-$

Example: NaCl 0.9% administration

Morris CG. Anaesthesia 2008;63:294-301
Metabolic alkalosis

• Loss of anion
  • Gastrointestinal – vomiting, villous adenoma, chloride secretory diarrheas
  • Renal – chloruretic agents (loop or thiazide diuretics), chloride channelopathies, hypokalemia
  • Sweat – cystic fibrosis
  • Hypoalbuminemic state, malnutrition

• Gain of cation
  • Sodium bicarbonate/lactate/acetate/citrate
  • Hypernatremia (hyperaldosteronism)
  • Hypercalcemia (milk alkali syndrome, calcium carbonate)
Metabolic alkalosis

• Addition of $\text{HCO}_3^-$, direct loss of chloride, (loss of $\text{XA}^-$)

Example: Chloride loss from loop diuretic

$\text{XA}^-$ = unmeasured anions

Morris CG. Anaesthesia 2008;63:294-301
## Respiratory acidosis

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS depression</td>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>Neuromuscular disorders</td>
<td>Chronic neuromuscular disorders</td>
</tr>
<tr>
<td>Acute airway obstruction</td>
<td>Chronic respiratory center depression</td>
</tr>
<tr>
<td>Severe pneumonia or pulmonary edema</td>
<td></td>
</tr>
<tr>
<td>Impaired lung motion (e.g. pneumothorax)</td>
<td></td>
</tr>
<tr>
<td>Flail chest</td>
<td></td>
</tr>
<tr>
<td>Ventilator dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

## Respiratory alkalosis

### Etiologies

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Lung diseases (e.g. asthma,</td>
<td>Sepsis</td>
</tr>
<tr>
<td>pneumonia, PE)</td>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td>CNS diseases</td>
<td></td>
</tr>
<tr>
<td>Drugs – salicylates, catecholamines, progesterone</td>
<td>Mechanical ventilation</td>
</tr>
</tbody>
</table>
Acid-base analysis methods

• Bicarbonate-pH-pCO$_2$ aka physiological method
  "Boston method"
• Base excess method
  "Copenhagen method"
• Physicochemical method
  "Stewart/strong ion difference method"
Important caveats and principles

• Results tend to be more qualitative than quantitative
• The body does not overcompensate
• At most there can be 3 acid-base processes
  • Respiratory acidosis OR alkalosis
  • Anion gap metabolic acidosis
  • Non-anion gap metabolic acidosis OR metabolic alkalosis
• Assigning diagnoses becomes challenging in the setting of mechanical ventilation, ECMO
Case

• AL is a 44-year-old man with a history of HIV, nonadherent to medications, and smoking (30 pack year history) admitted to the ED with a two-day history of severe diarrhea.

<table>
<thead>
<tr>
<th>134</th>
<th>108</th>
<th>31</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.9</td>
<td>16</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

pH 7.19 / pCO₂ 43 / pO₂ 77 / BE -9
HCO₃⁻ 15 / SaO₂ 94% / Lactate 2.2

Albumin 4.1 g/dL
Acid-base interpretation steps

1. Acidemia or alkalemia

Assess pH

Acidemia
pH<7.35

Alkalemia
pH>7.45

Haber RJ. West J Med 1991;155:146-51

<table>
<thead>
<tr>
<th>pH 7.19</th>
<th>pCO₂ 43</th>
<th>pO₂ 77</th>
<th>BE -9</th>
</tr>
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<tbody>
<tr>
<td>HCO₃⁻ 15</td>
<td>SaO₂ 94%</td>
<td>Lactate 2.2</td>
<td>Albumin 4.1 g/dL</td>
</tr>
</tbody>
</table>
Acid-base interpretation steps

1. Acidemia or alkalemia
2. Primary disturbance

Assess pH

- **Acidemia**
  - pH < 7.35
  - pCO₂ (acid) high
  - HCO₃⁻ (base) low
  - Respiratory acidosis
  - Metabolic acidosis

- **Alkalemia**
  - pH > 7.45
  - pCO₂ (acid) low
  - HCO₃⁻ (base) high
  - Respiratory alkalosis
  - Metabolic alkalosis

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<table>
<thead>
<tr>
<th>pCO₂</th>
<th>pO₂</th>
<th>BE</th>
<th>HCO₃⁻</th>
<th>SaO₂</th>
<th>Lactate</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>77</td>
<td>-9</td>
<td>15</td>
<td>94%</td>
<td>2.2</td>
<td>4.1 g/dL</td>
</tr>
</tbody>
</table>
Acid-base interpretation steps

1. Acidemia or alkalemia
2. Primary disturbance
3. Assess compensation

**Metabolic acidosis**: Winter’s formula

\[
\text{Expected } pCO_2 = 1.5 \times HCO_3^- + 8 \pm 2
\]

Expected \( pCO_2 \) = 1.5 \times 16 + 8 \pm 2

= 28-34

**Inadequate compensation**

\( \uparrow \) \( pCO_2 \) = respiratory acidosis

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Acid-base interpretation steps

1. Acidemia or alkalemia
2. Primary disturbance
3. Assess compensation

Respiratory acidosis:
Assess acute (not compensated) vs chronic (compensated)

Acute: pH ↓ 0.08 for every 10 mmHg ↑ pCO2 from 40 mmHg
HCO₃⁻ increases 1 for every 10

Chronic: pH ↓ 0.03 for every 10 mmHg ↑ pCO2 from 40 mmHg
HCO₃⁻ increases 4 for every 10

If acute, (70-40)/10 x 0.08 = 0.24 ↓ in pH = pH 7.16
HCO₃⁻ should ↑ 3

If chronic, (70-40)/10 x 0.03 = 0.09 ↓ in pH = pH 7.31
HCO₃⁻ should ↑ 12

pH 7.32 ≈ expected 7.31; appears chronic

Haber RJ. West J Med 1991;155:146-51

<table>
<thead>
<tr>
<th>144</th>
<th>96</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.6</td>
<td>35</td>
<td>1.2</td>
</tr>
<tr>
<td>pH 7.32 / pCO₂ 70 / pO₂ 165 / BE 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCO₃⁻ 38 / SaO₂ 99% / Lactate 1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin 3.5 g/dL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acid-base interpretation steps

1. Acidemia or alkalemia
2. Primary disturbance
3. Assess compensation

Compensation formulas exist for:

- Acute and chronic respiratory acidosis: effect on pH and $\text{HCO}_3^-$
- Acute and chronic respiratory alkalosis: effect on pH and $\text{HCO}_3^-$
- Metabolic acidosis: expected $\text{pCO}_2$
- Metabolic alkalosis: expected $\text{pCO}_2$

Haber RJ. West J Med 1991;155:146-51
Acid-base interpretation steps

1. Acidemia or alkalemia
2. Primary disturbance
3. Assess compensation
4. Calculate anion gap

Haber RJ. West J Med 1991;155:146-51
Anion gap

• Estimation of unmeasured anions (esp. phosphate, sulfate, organic anions, plasma proteins)

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

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

• Other measured ions (K^+, Mg^{2+}, Ca^{2+}, PO_4^{3-}) are assumed to be unmeasured

• Normal value < 12 ± 4 mEq/L

AG correction for albumin

• Albumin is a major component of AG
• Hypoalbuminemia will lower the AG, potentially masking accumulation of other unmeasured anions

\[
AG_{corr} = AG_{measured} + 2.5 (4 - \text{albumin})
\]

2.5 = estimated net negative charge of 1 g/dL albumin
Has been measured to be 2.3-2.5 mEq/L

Normal albumin assumed to be 4-4.4 g/dL

Causes of low or negative AG

- Lab error
- Hypoalbuminemia
- Sodium measurement error (e.g. severe hyperNa)
- Gammopathy (e.g. MGUS); multiple myeloma
- Intoxications – bromide, iodide, lithium
- Hypercalcemia or hypermagnesemia

Albumin’s effects on pH and bicarbonate

<table>
<thead>
<tr>
<th>Pco₂, torr</th>
<th>35</th>
<th>35</th>
<th>36</th>
<th>36</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALBUMIN</td>
<td>9.3</td>
<td>6.6</td>
<td>4.7</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>T.P., g/dl</td>
<td>11.3</td>
<td>8.9</td>
<td>7.4</td>
<td>4.3</td>
<td>3.1</td>
</tr>
<tr>
<td>pH</td>
<td>7.19</td>
<td>7.36</td>
<td>7.42</td>
<td>7.53</td>
<td>7.57</td>
</tr>
</tbody>
</table>

In vitro manipulation of human blood

Acid-base interpretation steps

1. Acidemia or alkalemia
2. Primary disturbance
3. Assess compensation
4. Calculate anion gap
5. Delta gap
Delta gap / “Delta Delta”

- AGMA may overlap with NAGMA or metabolic alkalosis
- $[\text{HCO}_3^-]$ decreases ~ 1 point for every point increase in AG
- Various methods exist to assess the additional metabolic component
  - Corrected bicarbonate
  - Expected bicarbonate
  - $\Delta\text{AG} - \Delta\text{HCO}_3^-$ (difference)
  - $\Delta\text{AG} / \Delta\text{HCO}_3^-$ (ratio)
  - Sodium-chloride effect
- No need to conduct if AG normal (Na-Cl effect could still be used)
Delta gap (corrected HCO$_3^-$ method)

• Estimates what [HCO$_3^-$] would be if anion gap process was removed

\[
\Delta AG = AG_{corr} - 12
\]

\[
[HCO_3^-] + \Delta AG = \text{“corrected” } [HCO_3^-]
\]

• “Corrected” [HCO$_3^-$] elevated i.e. > 28-30: metabolic alkalosis
• “Corrected” [HCO$_3^-$] reduced i.e. < 20: NAGMA

Haber RJ. West J Med 1991;155:146-51
Corrected $\text{HCO}_3^-$

This is not a real number but estimates what the bicarbonate would be if there was no anion gap process.
Delta gap (Na-Cl effect method)

• Sodium-chloride effect is a derivation of $\Delta \text{gap} = \Delta \text{AG} - \Delta \text{HCO}_3^-$

\[
\Delta \text{Gap} = \Delta \text{AG} - \Delta \text{HCO}_3^-
\]

\[
\Delta \text{Gap} = ([\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]) - 12 - (24 - \text{HCO}_3^-)
\]

\[
\Delta \text{Gap} = [\text{Na}^+] - [\text{Cl}^-] - 36
\]

< -6 suggests NAGMA

> +6 suggests metabolic alkalosis

Urinary charge gap / urinary anion gap

\[
\text{Urine gap} = [\text{U}_{\text{Na}^+}] + [\text{U}_{\text{K}^+}] - [\text{U}_{\text{Cl}^-}]
\]

- **Negative urine gap**
  - Increased excretion of unmeasured cation ammonium
  - Alkalizing effect via chloride excretion
  - Suggests etiology of NAGMA not intrinsic to kidneys (e.g. GI, diuretics, saline)

- **Positive urine gap**
  - Increased excretion of unmeasured anions (bicarbonate, lactate, hippurate, ketones)
  - Acidifying effect via chloride retention
  - Suggests renal etiology of NAGMA (e.g. RTA)

### Urine chloride in metabolic alkalosis

<table>
<thead>
<tr>
<th>Urine chloride low (&lt; 10-25 mEq/L) (“chloride-responsive alkalosis”)</th>
<th>Urine chloride high (&gt; 20-40 mEq/L) (“chloride-nonresponsive alkalosis”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting, nasogastric suctioning</td>
<td>Excess mineralocorticoid activity</td>
</tr>
<tr>
<td>Diuretic use in the past</td>
<td>Ongoing diuretic use</td>
</tr>
<tr>
<td>Posthypercapnia</td>
<td>Excess alkali administration</td>
</tr>
<tr>
<td>Contraction alkalosis</td>
<td>Refeeding alkalosis</td>
</tr>
</tbody>
</table>

Kellum JA. Crit Care 2000;4:6-14
## Buffer therapy

<table>
<thead>
<tr>
<th>Buffer</th>
<th>Dosage forms</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium bicarbonate</td>
<td>IV, PO</td>
<td>Most common</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>IV</td>
<td>Mostly used for TPN</td>
</tr>
<tr>
<td></td>
<td>Contained in Plasmalyte, Normosol</td>
<td>Risk of cardiovascular toxicity with rapid administration</td>
</tr>
<tr>
<td>Sodium or potassium citrate</td>
<td>PO</td>
<td>Treatment of chronic metabolic acidosis</td>
</tr>
<tr>
<td>Sodium lactate</td>
<td>Contained in Lactated Ringer’s</td>
<td>Potential increase in lactate if unable to metabolize</td>
</tr>
<tr>
<td>Tromethamine (THAM, tris-hydroxymethyl aminomethane)</td>
<td>IV</td>
<td>Not CO₂-based</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No longer manufactured</td>
</tr>
<tr>
<td>Carbicarb</td>
<td>IV</td>
<td>Equimolar mixture of Na₂CO₃ and NaHCO₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not available in US</td>
</tr>
</tbody>
</table>
Bicarbonate deficit

\[
Bicarbonate\ Deficit = 0.5 \times Wt \times (\text{desired } \Delta HCO_3^-), \text{ or}
\]

\[
Bicarbonate\ Deficit = \left( 0.4 + \frac{2.6}{HCO_3^-} \right) \times Wt \times (\text{desired } \Delta HCO_3^-)
\]

For example, to increase $HCO_3^-$ from 8 to 15 mEq/L for a 70 kg person
= $0.5 \times 70\text{kg} \times (15-8) = 245 \text{ mEq}$
Alternatively, $[0.4 + (2.6/8)] \times 70\text{kg} \times (18-5) = 355 \text{ mEq}$

- May be used to guide bicarbonate replacement
- Caution with overshooting if buffering a process that is clearing (e.g. lactate, ketoacidosis, renal failure) \(\rightarrow\) typically safest to only administer until pH is out of a dangerous range (e.g. pH > 7.2, $HCO_3^- > 10-12$ mEq/L)
Potential harms with bicarbonate

- Increasing pCO\(_2\)
  - Especially if unable to ventilate extra load (obstructive lung disease, paralyzed, low tidal volume ventilation, cardiac arrest)
  - Intracellular/CSF acidosis – largely based on animal data
  - Severity may relate to rate of infusion
- Stimulation of lactate / impaired clearance
- Fluid/sodium load
- Hypokalemia, hypocalcemia

Forsythe SM. Chest 2000;117:260-7
BICAR-ICU Trial

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Randomized, controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>26 French ICUs</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>389 adult patients with severe acidemia (pH ≤ 7.2; PaCO2 ≤ 45 mm Hg) and SOFA score ≥ 4 or lactate ≥ 2 mmol/L</td>
</tr>
</tbody>
</table>
| **Intervention**   | Sodium bicarbonate vs no sodium bicarbonate  
• Administered 4.2% NaHCO₃ in 62.5-125 mEq doses over 30 minutes  
• ABG checked 1-4 hours after bicarbonate, repeated if pH < 7.3  
• Max 500 mEq per 24 hours  
• Central line recommended (1000 mOsm/L)  
• Goal pH ≥ 7.30 |
| **Primary outcome**| • Composite of 28-day mortality and ≥ 1 organ failure at 7 days  
• Standardized indications for mechanical ventilation and RRT |
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n=194)</th>
<th>Bicarbonate (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>65 (55-75)</td>
<td>66 (55-75)</td>
</tr>
<tr>
<td><strong>SAPS II</strong></td>
<td>60 (48-73)</td>
<td>59 (49-73)</td>
</tr>
<tr>
<td><strong>SOFA</strong></td>
<td>10 (7-13)</td>
<td>10 (7-13)</td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td>115 (59)</td>
<td>123 (63)</td>
</tr>
<tr>
<td><strong>AKIN 0-1</strong></td>
<td>104 (54)</td>
<td>103 (53)</td>
</tr>
<tr>
<td><strong>AKIN 2-3</strong></td>
<td>90 (46)</td>
<td>92 (47)</td>
</tr>
<tr>
<td><strong>Cause of acidemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cardiac arrest</td>
<td>18 (9)</td>
<td>18 (9)</td>
</tr>
<tr>
<td>- Septic shock</td>
<td>98 (51)</td>
<td>107 (55)</td>
</tr>
<tr>
<td>- Hemorrhagic shock</td>
<td>40 (21)</td>
<td>45 (23)</td>
</tr>
<tr>
<td>- Others</td>
<td>38 (20)</td>
<td>25 (13)</td>
</tr>
<tr>
<td><strong>Mechanical ventilation</strong></td>
<td>160 (82)</td>
<td>164 (84)</td>
</tr>
<tr>
<td><strong>Vasopressors</strong></td>
<td>156 (80)</td>
<td>154 (79)</td>
</tr>
</tbody>
</table>

Data represented as n (%) or median (IQR)

SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; AKIN, Acute Kidney Injury Network
Baseline acid/base characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n=194)</th>
<th>Bicarbonate (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH</td>
<td>7.15 (7.11-7.18)</td>
<td>7.15 (7.09-7.18)</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ratio</td>
<td>229 (142-355)</td>
<td>264 (114-403)</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>37 (32-42)</td>
<td>38 (33-42)</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L</td>
<td>13 (10-15)</td>
<td>13 (10-15)</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>5.3 (3.4-9)</td>
<td>6.3 (3.6-9.7)</td>
</tr>
<tr>
<td>Lactate ≥ 2 mmol/L</td>
<td>152 (78)</td>
<td>168 (86)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.8 (1.2-2.5)</td>
<td>1.7 (1.1-2.3)</td>
</tr>
</tbody>
</table>

Data represented as n (%) or median (IQR)

26% vs 60% achieved pH > 7.3 and maintained for at least 36 hours

Jaber S. Lancet 2018;392:31-40
### Results

<table>
<thead>
<tr>
<th></th>
<th>Control (n=194)</th>
<th>Bicarbonate (n=195)</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary: composite of mortality and ≥ 1 organ failure at day 7</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28 mortality</td>
<td>104 (54)</td>
<td>87 (45)</td>
<td>-9 (-19.4 to 1.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥ 1 organ failure</td>
<td>134 (69)</td>
<td>121 (62)</td>
<td>-2.8 (-15.4 to 9.8)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>AKIN 2-3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite outcome</td>
<td>74/90 (82)</td>
<td>64/92 (70)</td>
<td>-12.3 (-26 to -0.1)</td>
<td>0.046</td>
</tr>
<tr>
<td>Mortality</td>
<td>57/90 (63)</td>
<td>42/92 (46)</td>
<td>-17.7 (-33 to -2.3)</td>
<td>0.027</td>
</tr>
<tr>
<td>≥ 1 organ failure</td>
<td>74/90 (82)</td>
<td>61/92 (66)</td>
<td>-15.9 (-28.4 to -3.4)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Renal replacement therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>100 (52)</td>
<td>68 (35)</td>
<td>-16.7 (-26.4 to -7)</td>
<td>0.001</td>
</tr>
<tr>
<td>AKIN 2-3</td>
<td>66/90 (73)</td>
<td>47/92 (51)</td>
<td>-22.2 (-36 to -8.5)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Dialysis dependent at ICU discharge</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>11/32 (34)</td>
<td>7/32 (22)</td>
<td>-12.5 (-34.3 to 9.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>AKIN 2-3</td>
<td>10/21 (48)</td>
<td>5/25 (20)</td>
<td>-27.6 (-54.1 to -1.1)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

- No difference in any mechanical ventilation, vasopressor, length of stay, or infectious outcomes
- Heterogeneous effects between AKIN 0-1 and 2-3 (p=0.007) and presence of sepsis (p=0.008)
Safety

- Alkalemia (pH > 7.45): 16% (bicarbonate) vs 9% (control)
  - Severe alkalemia (pH > 7.5): 9% vs 2%
- Hyperkalemia (K > 5 mmol/L): 32% vs 49%
- Hypernatremia (Na > 145 mmol/L): 49% vs 29%
- Hypocalcemia (iCa < 0.9 mmol/L): 24% vs 15%
- No difference in hypokalemia

Jaber S. Lancet 2018;392:31-40
BICAR-ICU discussion

• No overt outcome benefits in overall population (though effects potentially diluted from ~25% crossover)

• Reduced need for RRT – indications seemed reasonable

• Patients with AKIN scores 2-3 may have improvements in mortality, dialysis dependence
  • What is the mechanism for improved mortality?

• No obvious signs of significant harm (i.e. bicarbonate for lactic acidosis) but patients with very high lactate levels not explored
Case

A 51 year old man with history of erosive esophagitis, diabetes mellitus, chronic pancreatitis, and bipolar disorder is admitted with nausea, vomiting, abdominal pain, and shortness of breath.

- What additional data should be obtained?
- What acid base disturbance(s) is/are present?

<table>
<thead>
<tr>
<th>pH 7.46</th>
<th>pCO₂ 29</th>
<th>pO₂ 81</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE -3.8</td>
<td>HCO₃⁻ 18</td>
<td>SaO₂ 96</td>
</tr>
</tbody>
</table>
Case

1. Acidemia or alkalemia
2. Primary disturbance
3. Assess compensation
4. Calculate anion gap
5. Delta gap

Table:

<table>
<thead>
<tr>
<th>135</th>
<th>87</th>
<th>31</th>
<th>861</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6</td>
<td>20</td>
<td>0.9</td>
<td></td>
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pH 7.46 / pCO\(_2\) 29 / pO\(_2\) 81
BE -3.8 / HCO\(_3\) 18 / SaO\(_2\) 96
Case

1. Acidemia or alkalemia
2. Primary disturbance
3. Assess compensation
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pH 7.46 / pCO₂ 29 / pO₂ 81
BE -3.8 / HCO₃⁻ 18 / SaO₂ 96
Case

1. Acidemia or alkalemia
2. Primary disturbance – respiratory alkalosis (?)
3. Assess compensation
4. Calculate anion gap
5. Delta gap

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<th>135</th>
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</table>

pH 7.46 / pCO₂ 29 / pO₂ 81
BE -3.8 / HCO₃⁻ 18 / SaO₂ 96
1. Acidemia or alkalemia
2. Primary disturbance – respiratory alkalosis (?)
3. Assess compensation – acute-on-chronic respiratory alkalosis (?)
4. Calculate anion gap
5. Delta gap
Case

1. Acidemia or alkalemia
2. Primary disturbance – respiratory alkalosis (?)
3. Assess compensation – acute-on-chronic respiratory alkalosis
4. Calculate anion gap – 135-87-20 = 28 (high = AGMA)
5. Delta gap
Case

1. Acidemia or alkalemia
2. Primary disturbance – respiratory alkalosis (?)
3. Assess compensation – acute-on-chronic respiratory alkalosis
4. Calculate anion gap – 135-87-20 = 28 (high = AGMA)
5. Delta gap – (28-12) + 20 = 36 (high = metabolic alkalosis)
Case

**Diagnoses:**
Respiratory alkalosis, anion gap metabolic acidosis, metabolic alkalosis

**Next steps:**
Evaluate causes of AGMA – low level ketosis; lactate 9.5
Evaluate causes of metabolic alkalosis – likely from recent vomiting (chloride 87)

Problem can also be assessed using metabolic acidosis as the primary problem which will give you the same diagnoses and is more pertinent to the patient rather than focusing on the mild respiratory alkalosis
Summary

• Acid base problems can be assessed in a systematic way to identify simple or mixed disorders

• Sodium bicarbonate therapy remains controversial but can be considered in critically ill patients with severe acidosis – especially those with renal dysfunction

• Acid base analyses need to be interpreted in the context of the clinical picture of the patient. Not every disorder requires treatment.
A Case-Based Approach to Acid-Base Disorders

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