Acid-Base Disorders

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General Acid-Base Relationships

Henderson-Hasselbach equation:

\[ \text{pH} = \text{pK} + \log \frac{\text{HCO}_3^-}{\text{pCO}_2} \]

\[ \text{H}^+ = 24 \times \frac{\text{pCO}_2}{\text{HCO}_3^-} \]

\[ \Delta \; 0.1 \text{ pH unit} = \Delta \; 10 \text{ nm/L H}^+ \]
Approach to Acid-Base Disorders

1. Consider the clinical setting!
2. Is the patient acidemic or alkalemic?
3. Is the primary process metabolic or respiratory?
4. If metabolic acidosis, gap or non-gap?
5. Is compensation appropriate?
6. Is more than one disorder present?
## Simple Acid-Base Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>pH</th>
<th>Primary Disorder</th>
<th>Compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>↓pH</td>
<td>↓ HCO3</td>
<td>↓ pCO2</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>↑pH</td>
<td>↑ HCO3</td>
<td>↑ pCO2</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>↓pH</td>
<td>↑ pCO2</td>
<td>↑ HCO3</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>↑pH</td>
<td>↓ pCO2</td>
<td>↓ HCO3</td>
</tr>
</tbody>
</table>
Metabolic Acidosis

- **Etiology:** Inability of the kidney to excrete the dietary $H^+$ load, or increase in the generation of $H^+$ (due to addition of H+ or loss of $HCO_3^-$)
Metabolic Acidosis: Elevated Anion Gap

\[ AG = Na^+ - (Cl^- + HCO_3^-) = 12 \pm 2 \]

[Note: Diagnostic utility is best when AG > 25]
Causes of AG Metabolic Acidosis [Classic]

CAT MUDPIILERS
C – cyanide, carbon monoxide, CPK (rhabdo)
A – alcoholic ketoacidosis
T – toluene
M – methanol
U – uremia
D – DKA/alcoholic KA
P – paraldehyde, phenformin
I – INH, iron
L – lactic acidosis
E – ethylene glycol
R – rhabdo, renal failure
S – salicylates
Causes of AG Metabolic Acidosis [Updated]

**GOLDMARK**

G – glycols (ethylene, propylene, diethylene)
O – oxoproline
L – L-lactate
D – D-lactate
M – methanol
A – aspirin
R – renal failure
K – ketoacidosis
Intoxications Causing High AG Acidosis

- Aspirin - [high salicylate level; also primary respiratory alkalosis]
- Methanol - [optic papillitis]
- Ethylene Glycol - [calcium oxalate crystals]
- Paraldehyde
Anion Gap in Hypoalbuminemia

- The true anion gap is underestimated in hypoalbuminemia (= fall in unmeasured anions); AG must be adjusted
- Formulas for adjusted AG:
  - For every 1.0 fall in albumin, ↑ AG by 2.5
  - Consider the patient’s “normal” AG to be (2 x alb) + (0.5 x phosphate)
  - Adjusted AG = Observed AG + (2.5 x [normal alb - adjusted alb])
The Delta/Delta: $\Delta$ AG/ $\Delta$ HC0$_3$

**Rationale:**
For each unit **INCREASE** in AG (above normal), HC0$_3$ should **DECREASE** one unit (below normal)

“Normal” values: AG = 12, HC0$_3$ = 24
Use of the Delta/Delta:  Examples

<table>
<thead>
<tr>
<th>AG</th>
<th>HCO₃</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 (↑6)</td>
<td>18 (↓6)</td>
<td>Appropriate; pure AG acidosis</td>
</tr>
<tr>
<td>18 (↑6)</td>
<td>22 (↓2)</td>
<td>HCO₃ has ↓ less than predicted, so HCO₃ is too high; mixed AG acidosis AND met alk</td>
</tr>
<tr>
<td>18 (↑6)</td>
<td>12 (↓12)</td>
<td>HCO₃ has ↓ more than predicted, so HCO₃ is too low; mixed AG AND non-AG acidosis</td>
</tr>
</tbody>
</table>
Causes of Low Anion Gap

**Etiology:** Fall in unmeasured anions or rise in unmeasured cations

- Hyperkalemia
- Lithium intoxication
- Hypercalcemia
- Multiple myeloma
- Hypermagnesemia
- Bromide (dextromethorphan, ipratropium, pyridostigmine)
Osmolar Gap

**Measured serum osmolality >**

**calculated serum osmolality by > 10 mOsm**

Calc Sosm = (2 x Na) + BUN/2.8 + Glu/18
Causes of High Osmolar Gap

- Isotonic hyponatremia
- Hyperlipidemia
- Hyperproteinemia
- Mannitol
- Glycine infusion
- Chronic kidney disease
- Ingestions
  - Ethanol, isopropyl alcohol, ethylene glycol, diethylene glycol; mannitol infusion
- Contrast Media
# Relationship between AG and Osmolar Gap

<table>
<thead>
<tr>
<th></th>
<th>AG</th>
<th>Osm gap</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene glycol</td>
<td>+</td>
<td>+</td>
<td>* Double gap</td>
</tr>
<tr>
<td>Methanol</td>
<td>+</td>
<td>+</td>
<td>* Double gap</td>
</tr>
<tr>
<td>Renal failure</td>
<td>+</td>
<td>+</td>
<td>* Double gap</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lipids, proteins</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Causes of Normal AG (Hyperchloremic) Metabolic Acidosis

<table>
<thead>
<tr>
<th>High K⁺</th>
<th>Low K⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>RTA</td>
</tr>
<tr>
<td>NH₄Cl, Arg HCl</td>
<td>Ureteral diversion</td>
</tr>
</tbody>
</table>
Causes of Normal AG (Hyperchloremic) Metabolic Acidosis

HARDUPS

Hyperalimentation
Acetazolamide, amphotericin
RTA
Diarrhea; overcorrected or early DKA
Ureteral diversion
Pancreatic fistula, posthypocapnia
Spironolactone/saline resuscitation
Use of the Urine Anion Gap (UAG) in Normal AG Acidosis
Batlle et al. NEJM 318:594, 1988

Urine AG = (Na + K) - Cl

Negative UAG = Normal, or GI loss of HCO₃

Positive UAG = altered distal renal acidification

Caveats: Less accurate in patients with volume depletion (low urinary Na); and in patients with increased excretion of unmeasured anions (e.g. ketoacidosis), where there is increased excretion of Na and K to maintain electroneutrality)
Use of the Urinary AG in Normal Gap Acidosis
Batlle et al. NEJM 318:594, 1988

<table>
<thead>
<tr>
<th>Plasma K</th>
<th>UAG</th>
<th>U pH</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-</td>
<td>&lt; 5.5</td>
<td>Normal</td>
</tr>
<tr>
<td>Elevated</td>
<td>+</td>
<td>&lt; 5.5</td>
<td>Aldo deficiency</td>
</tr>
<tr>
<td>Elevated</td>
<td>+</td>
<td>&gt; 5.5</td>
<td>Distal RTA</td>
</tr>
<tr>
<td>Normal-low</td>
<td>+</td>
<td>&gt; 5.5</td>
<td>Classic RTA</td>
</tr>
<tr>
<td>Normal-low</td>
<td>-</td>
<td>&gt; 5.5</td>
<td>GI HCO₃ loss</td>
</tr>
</tbody>
</table>
Use of the Urine Osmolal Gap

• When UAG is positive, and it is unclear if increased cation excretion is responsible, urine NH₄ concentration can be estimated from urine osmolal gap
• Calc Uosm = (2 x [Na+K]) + urea nitrogen/2.8 + glu/18
• The gap between the calculated and measured Uosm = mostly ammonium
• In patients with metabolic acidosis, urine ammonium should be > 20 mEq/L. Lower value = impaired acidification
# Renal Tubular Acidosis

<table>
<thead>
<tr>
<th></th>
<th>Type 1 (distal)</th>
<th>Type 2 (proximal)</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defect</td>
<td>↓ distal acid.</td>
<td>↓ prox HCO₃ reab</td>
<td>↓ aldo</td>
</tr>
<tr>
<td>HCO₃</td>
<td>May be &lt; 10</td>
<td>12-20</td>
<td>&gt; 17</td>
</tr>
<tr>
<td>Urine pH</td>
<td>&gt; 5.3</td>
<td>Variable</td>
<td>&lt; 5.3</td>
</tr>
<tr>
<td>Plasma K</td>
<td>Usually low</td>
<td>Usually low</td>
<td>High</td>
</tr>
<tr>
<td>Response to HCO₃ Rx</td>
<td>Good</td>
<td>Poor</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Calculation of Bicarbonate Deficit

- The bicarbonate “space” differs according to the clinical setting – look it up!
- If metabolic acidosis warrants Rx, bicarb deficit may be hundreds of mEq; need continuous infusion, not random amps
- **In metabolic acidosis**

  Bicarb deficit = $\text{HCO}_3^-$ space x $\text{HCO}_3^-$ deficit/liter

  $\text{HCO}_3^-$ space = 0.4 x lean body wt (kg)

  $\text{HCO}_3^-$ deficit/liter = [desired $\text{HCO}_3^-$] - [measured $\text{HCO}_3^-$]
Approach to Metabolic Acidosis

Osmolar Gap

- Normal
  - Uremia
  - Lactate
  - Ketoacids
  - Salicylate

- Increased
  - Ethylene glycol
  - Methanol

Anion Gap

- Normal
  - GI Fluid Loss?
    - Yes
      - Diarrhea
      - Ileostomy
      - Enteric fistula
    - No
      - Urine pH
        - > 5.5
          - Distal RTA (Type 1)
        - < 5.5
          - Serum K
            - Low
              - Proximal RTA (Type 2)
            - High
              - Type 4 RTA
Metabolic Alkalosis

**Etiology:** Requires both generation of metabolic alkalosis (loss of $\text{H}^+$ through GI tract or kidneys) and maintenance of alkalosis (impairment in renal $\text{HCO}_3^-$ excretion)

**Causes of metabolic alkalosis**
- Loss of hydrogen
- Retention of bicarbonate
- Contraction alkalosis

**Maintenance factors:** Decrease in GFR, increase in $\text{HCO}_3^-$ reabsorption
Metabolic Alkalosis

**CLEVER PD**

- Contraction
- Licorice
- Endo: Conn’s, Cushing’s, Bartter’s
- Vomiting
- Excess Alkali
- Refeeding alkalosis
- Post-hypercapnia
- Diuretics
## Use of Urine Cl⁻ in Metabolic Alkalosis

<table>
<thead>
<tr>
<th>Chloride –responsive</th>
<th>Chloride-resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>(U Cl &lt; 15 mEq/L)</td>
<td>U Cl &gt; 20 mEq/L)</td>
</tr>
</tbody>
</table>

- GI loss
- Renal loss
- Low Cl intake
- Exogenous alkali

- With urine K < 15
  - Laxative abuse, K depletion
- With urine K > 20
  - Hypotensive: Bartter’s
  - Hypertensive: hyperaldo,
  - Cushing’s, Liddles, other
Use of Spot Urine Cl and K

**Urine Chloride**

- Very Low (< 10 mEq/L)
  - Vomiting, NG suction
  - Postdiuretic, posthypercapneic
  - Villous adenoma, congenital chloridorrhea, post- alkali

- > 20 mEq/L

**Urine Potassium**

- Low (< 20 mEq/L)
  - Laxative abuse
  - Other profound K depletion

- > 30 mEq/L

**Diuretic phase of diuretic Rx,**
**Bartter’s, Gitelman’s, primary aldo,**
**Cushings, Liddle’s, secondary aldosteronism**
Treatment of Metabolic Alkalosis

1. Remove offending culprits.
2. Chloride (saline) responsive alkalosis: Replete volume with NaCl.
3. Chloride non-responsive (saline resistant) alkalosis:
   - Acetazolamide (CA inhibitor)
   - Hydrochloric acid infusion
   - Correct hypokalemia if present
Respiratory Disorders

- Result from abnormal hypoventilation (acidosis) or hyperventilation (alkalosis)
- Can be due to either CNS, pulmonary, or thoraco-abdominal disorders
Respiratory Acidosis

Causes of Respiratory Acidosis

- Inhibition of medullary respiratory center (e.g. drugs)
- Disorders of respiratory muscles and chest wall
- Upper airway obstruction
- Disorders affecting gas exchange across pulmonary capillaries
- Mechanical ventilation

Treatment of Respiratory Acidosis

- Rx the primary disorder; mechanical ventilation
Respiratory Alkalosis

Causes of Respiratory Alkalosis
- Hypoxemia
- Pulmonary disease
- Stimulation of medullary respiratory center
- Mechanical ventilation

CHAMPS
- CNS Disease
- Anxiety
- Progesterone
- Hypoxia
- Mech vent
- Salicylates/sepsis

Treatment of Respiratory Alkalosis
- Rx the primary disorder; mechanical ventilation; paper bag
Mixed Acid-Base Disorders: Clues

- Degree of compensation for primary disorder is inappropriate
- Delta AG/delta $\text{HCO}_3^-$ = too high or too low
- Clinical history
## Common Clinical States and Associated Acid-Base Disturbances

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Acid-Base Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Embolus</td>
<td>Respiratory Alkalosis</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Metabolic Acidosis</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Metabolic Alkalosis</td>
</tr>
<tr>
<td>Severe Diarrhea</td>
<td>Metabolic Acidosis</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Respiratory Alkalosis</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>Metabolic Acidosis</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Respiratory Alkalosis/Metabolic Acidosis</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Respiratory Alkalosis</td>
</tr>
<tr>
<td>Diuretic Use</td>
<td>Metabolic Alkalosis</td>
</tr>
<tr>
<td>COPD</td>
<td>Respiratory Acidosis</td>
</tr>
</tbody>
</table>
## Acid-Base Disorders in GI Disease


<table>
<thead>
<tr>
<th>GI Disorder</th>
<th>Acid-Base Disorder</th>
<th>Potassium</th>
<th>ECFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting, NG suction</td>
<td>Metabolic alkalosis</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Diarrheal states</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholera, infections</td>
<td>Metabolic acidosis</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>None</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Congenital achloridorrhea</td>
<td>Metabolic acidosis</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Villous adenoma</td>
<td>Variable</td>
<td>Normal-low</td>
<td>Normal-low</td>
</tr>
<tr>
<td>Laxative abuse</td>
<td>None unless severe</td>
<td>Low</td>
<td>Normal-low</td>
</tr>
<tr>
<td>Panc/biliary drainage</td>
<td>Metabolic acidosis</td>
<td>Normal-high</td>
<td>Low</td>
</tr>
<tr>
<td>Ileostomy drainage</td>
<td>Metabolic acidosis, metabolic alkalosis</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Short bowel</td>
<td>Metabolic acidosis (D-lactic acidosis)</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
# Acid-Base Disorders with Antibiotic Therapy


<table>
<thead>
<tr>
<th>Drug</th>
<th>Acid-Base Disorder</th>
<th>Mechanism</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Anion gap acidosis</td>
<td>Pyroglutamate</td>
<td>Rare</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Anion gap acidosis</td>
<td>Mitochondrial toxicity</td>
<td>Rare</td>
</tr>
<tr>
<td>Most antibiotics</td>
<td>Anion gap acidosis (D-lactic acidosis)</td>
<td>Bacterial overgrowth</td>
<td>Rare</td>
</tr>
<tr>
<td>Tetracyclines, aminoglycosides</td>
<td>Non-gap acidosis</td>
<td>Fanconi syndrome</td>
<td>Rare</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Non-gap acidosis</td>
<td>Blocks eNAC</td>
<td>Frequent</td>
</tr>
<tr>
<td>Ampotericin B</td>
<td>Non-gap acidosis</td>
<td>Proton leak</td>
<td>Frequent</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Metabolic alkalosis</td>
<td>Bartter-like</td>
<td>Rare</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Metabolic alkalosis</td>
<td>Bartter-like</td>
<td>Rare</td>
</tr>
</tbody>
</table>
# Acid-Base Disorders in Liver Disease

<table>
<thead>
<tr>
<th>Acid-Base Disorder</th>
<th>Mechanisms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anion gap metabolic acidosis</td>
<td>Type B lactic (compensated), Type A lactic (not compensated)</td>
<td>10-20% 30-40%</td>
</tr>
<tr>
<td>Non-gap metabolic acidosis</td>
<td>Diarrhea (lactulose); distal RTA; Wilson’s disease; PBC</td>
<td>Variable</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>Hypoxemia; progesterone</td>
<td>Most common</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>Volume contraction from diuretics</td>
<td>Variable</td>
</tr>
</tbody>
</table>
References


4. Fenves AZ, et al. Increased anion gap metabolic acidosis as a result of oxoproline (proglutamic acid): a role for acetaminophen. CJASN 1:441, 2006
References, cont.


