Acid-Base Disturbances - A plACIDly BASE-ic Approach for Clinical Pharmacists

Objectives
- Understand acid-base chemistry & physiology
- Systematic approach to acid-base interpretation
- Understand etiology of acid-base disturbances
- Identify drug-related acid-base disturbances
- Understand the principles of treatment

Workshop Outline
- Anatomy of an arterial blood gas (ABG)
- Acid-base chemistry & physiology
- Consequences of acid-base disturbances
- Stepwise approach → "Rules of Five"
- Acid-base disorders and their causes
- Acid-base disorders and their treatment
- Cases

Anatomy of an ABG
- Laboratory method
- Co-oximetry
- Major components
  - pH
  - PCO2
  - PaO2
  - HCO3
  - SaO2

Acid-Base Terminology
- Acid
- Base
- pH
- Buffer
- Henderson-Hasselbalch equation
- Acidemia
- Alkalemia
- Acidosis
- Alkalosis
- Anion gap
- Normal anion gap

Anatomy of an ABG

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"Normal" Arterial Blood Gas (ABG)
- pH - 7.35 - 7.45
- \( P_{CO_2} \) - 40 mmHg
- \( PaO_2 \) - > 80 mmHg
- HCO\textsubscript{3} - 24 mEq/L
- SaO\textsubscript{2} - ≥ 0.94

Consequences of Altered pH

**Severe Acidemia** (pH < 7.20)
- Obtundation/coma
- Impaired ♥ contractility
- Arteriolar dilatation
- Venoconstriction
- ↓ BP
- Arrhythmias
- Hyperventilation
- Resp. muscle fatigue
- Insulin resistance
- ↑ K+

**Severe Alkalemia** (pH > 7.60)
- ↓ Cerebral blood flow
- Tetany/seizures/delirium
- Arteriolar constriction
- ↓ ♥ blood flow
- ↓ Anginal threshold
- Arrhythmias
- Hypoventilation
- ↓ Ionized calcium
- ↓ Magnesium/phosphate
- ↓ K+

Acid-Base Chemistry

**Acid**
- Donates protons (H\(^+\))
- HCl (Acid) → H\(^+\) + Cl\(^-\)

**Base**
- Accepts protons (H\(^+\))
- \( NH_3 \) (Base) + H\(^+\) → NH\(_4^+\)

Clinically Significant Acid-Base Pairs

**Acid**
- Carbonic acid (H\(_2\)CO\(_3\))
- Monobasic PO\(_4\) (H\(_2\)PO\(_4\))
- Ammonium (NH\(_4^+\))
- Lactic acid (H\(_5\)C\(_3\)O\(_2\))

**Base**
- Bicarbonate (HCO\(_3^-\))
- Dibasic PO\(_4\) (HPO\(_4^−\))
- Ammonia (NH\(_3\))
- Lactate (H\(_2\)C\(_3\)O\(_2\))

"Potential of Hydrogen" (pH)
- pH devised to facilitate working with small [H\(^+\)]
- pH = -log [H\(^+\)]
- Lower the pH → more acidic
- Higher the pH → more alkaline

Henderson-Hasselbalch Equation

\[ \text{pH} = \text{pK}_a + \log([\text{base}]/[\text{acid}]) \]
- Henderson derived equation in 1908
- Hasselbalch later re-expressed Henderson’s formula in logarithmic terms
Buffering

"Ability of weak acid and its corresponding base to resist change in pH of a solution upon adding a strong acid or base"

- $\text{H}_2\text{CO}_3/\text{HCO}_3^-$ is principal extracellular buffer

What are the sources of an acid-load?
What occurs when acid-load is introduced?

Acid Production/Elimination in Humans

- Volatile acid (CO$_2$)
  - Majority of acid produced
  - Produced from CHO/lipid/protein metabolism
  - Average daily CO$_2$ production = 15,000 mmol
  - Eliminated via normal ventilation

- Fixed (non-volatile) acids
- Digestion of dietary substances/tissue metabolism
- Amino acids (cysteine & methionine)
- Ingested sulfur
- Protein/phospholipid metabolism $\rightarrow$ phosphates
- Incomplete metabolism of neutral substances
  - Glucose $\rightarrow$ lactic acid & pyruvic acid
  - Fatty acids $\rightarrow$ acetoacetic acid & ß-hydroxybutyric acid
- Eliminated by kidneys (0.8 mEq/kg/day)

Buffering Applied

$$\text{pH} = \text{pKa} + \log\left(\frac{[\text{base}]}{[\text{acid}]}\right)$$

$$\text{pH} = 6.1 + \log\left(\frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]}\right)$$

$$\text{pH} = 6.1 + \log\left(\frac{[\text{HCO}_3^-]}{(\text{P}_{\text{CO}_2} \times 0.03)}\right)$$

Buffering Applied

Example: in response to acid load, serum bicarbonate fell to 10 mEq/L, then predicted pH would be:

$$[\text{HCO}_3^-] = 10 \text{ mEq/L}$$
$$\text{P}_{\text{CO}_2} = 40 \text{ mmHg}$$
$$\text{pH} = 6.1 + \log\left(\frac{10}{0.03 \times 40}\right)$$
$$\text{pH} = 6.1 + 0.92$$
$$\text{pH} = 7.02$$

But, humans are so much more complex than that . . . . .

The 3 Mechanisms of Acid-Base Homeostasis

1. Extracellular buffering
   - Immediately acts
   - The “first-responder”
2. Ventilatory regulation of CO$_2$ elimination
   - Fast onset (minutes)
   - Alveolar ventilation responds to P$_{\text{CO}_2}$
3. Renal regulation of H$^+$/HCO$_3^-$ excretion
   - Slower onset (≥ 48 hr)
   - Kidney excretes excess [H$^+$]
Acid-Base Homeostasis Applied

Example: in response to an acid load, serum bicarbonate fell to 10 mEq/L, however, normal respiratory response to an acid load is hyperventilation (↓ PCO₂)

\[
[HCO₃^-] = 10 \text{ mEq/L} \\
PCO₂ = 26 \text{ mmHg} \\
pH = 6.1 + \log\left(\frac{10}{0.03 \times 26}\right) \\
pH = 6.1 + 1.1 \\
pH = 7.2
\]

Being Human is a Beautiful Thing!
Case Revisited

Buffering

\[
[HCO₃^-] = 10 \text{ mEq/L} \\
PCO₂ = 40 \text{ mmHg} \\
pH = 6.1 + \log\left(\frac{10}{0.03 \times 40}\right) \\
pH = 6.1 + 0.92 \\
pH = 7.02
\]

Buffering + Physiology

\[
[HCO₃^-] = 10 \text{ mEq/L} \\
PCO₂ = 26 \text{ mmHg} \\
pH = 6.1 + \log\left(\frac{10}{0.03 \times 26}\right) \\
pH = 6.1 + 1.1 \\
pH = 7.2
\]

Approach to Acid-Base Disturbances

- History
- Prescription medications
- OTC medications
- Naturopathic products
- Illicit drugs
- Diagnostic agents
- Order ABG and serum chemistry/albumin

Demystifying "Bicarbonate" Terminology

- Arterial blood gas (ABG)
  - Determined by co-oximetry (hemoximetry)
  - HCO₃⁻ (calculated using H-H equation)
- Serum electrolytes
  - Total CO₂ (measured sum of HCO₃⁻, H₂CO₃, PCO₂)
  - HCO₃⁻ should be 1-2 mEq/L less than total CO₂

Normal “ABG-Related” Values

- pH: 7.35-7.45
- PCO₂: 40 mmHg
- Na⁺ (cation): 135-145 mmol/L
- HCO₃⁻ (anion): 24 mmol/L
- Cl⁻ (anion): 95-107 mmol/L
- Anion gap: 7 ± 4 mmol/L
- Albumin: 40 g/L

Don’t Break the Rules!
Approach to ABG Interpretation

"Rules of Five"

Rule 1. Determine pH status
Rule 2. Determine primary process
Rule 3. Calculate serum anion gap
Rule 4. Check degree of compensation
Rule 5. Determine the delta anion gap
**Case Example**

ID: 68 y/o male; wt: 75 kg; ethanol abuse

HPI: Found unresponsive on Downtown Eastside Vancouver; empty bottle of windshield washer antifreeze nearby; maintaining airway; unknown medical history

ABG: 7.20 / 26 / 98 / 10 / 0.96

Na: 139 mmol/L; Cl-: 106 mmol/L; CO2: 10 mmol/L;

Albumin: 20 g/L

Ethanol: Undetectable

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**Rule 1 - Determine pH Status “-emia”**

"emia" - alterations in blood pH

- pH < 7.35 → acidemia
- pH > 7.45 → alkalemia

**Rule 1 - Determine pH Status “-emia” Case Revisited**

ID: 68 y/o male; wt: 75 kg; ethanol abuse

ABG: 7.20 / 26 / 98 / 10 / 0.96

pH < 7.35, therefore it is an ACIDEMIA

---

**Rule 2 - Determine Primary Process “-osis”**

"osis" - pathologic process that results in alterations in blood pH

- Primary process (es)
  - Metabolic Acidosis: HCO3- < 24 mmol/L
  - Respiratory Acidosis: PCO2 > 40 mmHg
  - Metabolic Alkalosis: HCO3- > 24 mmol/L
  - Respiratory Alkalosis: PCO2 < 40 mmHg

**Rule 2 - Determine Primary Process “-osis” Case Revisited**

ID: 68 y/o male; wt: 75 kg; ethanol abuse

ABG: 7.20 (26) 98 (10) 0.96

Rule 1. pH < 7.35, therefore it is an ACIDEMIA

Rule 2. PCO2 is NOT > 40, therefore primary process is NOT respiratory

HCO3- < 24, therefore primary process is metabolic
Rule 2 - Determine Primary Process
"osis" Case Revisited

Reminder

PCO₂ is an ACID that is regulated by the respiratory system; HCO₃⁻ is a BASE that is regulated by the kidneys!

SKG 2007

Rule 2 - Determine Primary Process
"-osis"

Clinical Pearl

BOTH METABOLIC AND RESPIRATORY PROCESSES MAY SIMULTANEOUSLY BE THE PRIMARY ACID-BASE DISTURBANCE!

SKG 2007

Rule 3 - Calculate Serum Anion Gap

Law of electrical neutrality
- There are no sparks in our blood!
- +VE = -VE
- Serum cations
  - Measured: Na⁺
  - "Un-measured": Ca²⁺, K⁺, Mg²⁺
- Serum anions
  - Measured: Cl⁻, HCO₃⁻
  - "Un-measured": phosphates, sulfates, organic anions, proteins (albumin)

MIND THE GAP


Rule 3 - Serum Anion Gap

Sources of unmeasured anions (+ve SAG)
- Consumption of HCO₃⁻ by organic acids (lactic acid, acetoacetic acid, 8-hydroxybutyric acid)
- Ingestion of toxins (methanol, ethylene glycol)
- Accumulation of organic anions, phosphates, sulfates in renal failure

Rule 3 - Serum Anion Gap

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

Normal SAG = 7 ± 4 mmol/L

\[\text{SAG} > 11 \text{ mmol/L can indicate metabolic acidosis}\]

\[\text{SAG} > 20 \text{ mmol/L always indicates metabolic acidosis}\]

SKG 2007
**Rule 3 - Serum Anion Gap**

- Corrected SAG
  - Albumin is negatively charged
  - For every 10 g/L below 40 g/L, ↑ SAG by 2.5
- Normal anion gap (hyperchloremic) metabolic acidosis
  - H⁺ is accompanied by Cl⁻ therefore no ↑ SAG

**Rule 3 - Calculate Serum Anion Gap**

**Case Revisited**

ID: 68 y/o male; wt: 75 kg; ethanol abuse
ABG: 7.20 / 26 / 98 / 10 / 0.96
Na: 139 mmol/L; Cl⁻: 106 mmol/L; CO₂: 10 mmol/L; Albumin: 20 g/L

Rule 1. pH < 7.35, therefore it is an ACIDEMIA
Rule 2. Primary process is metabolic
Rule 3. Anion Gap: 139 - 106 - 10 = 23 mmol/L
Albumin correction: 2.5 x 2 = 5 mmol/L
Corrected Anion Gap: 23 + 5 = 28 mmol/L
This is an Anion Gap Metabolic Acidosis

**Rule 3 - Calculate Serum Anion Gap**

**Clinical Pearls**

**ALWAYS CALCULATE SAG!**

ANION GAP > 11 mmol/L CAN INDICATE METABOLIC ACIDOSIS

ANION GAP > 20 mmol/L ALWAYS INDICATES A METABOLIC ACIDOSIS

FOR EVERY 10 G/L ALBUMIN IS LESS THAN 40 G/L, ADD 2.5 TO THE CALCULATED SAG

**Rule 4 - Check Degree of Compensation for Primary Disturbance**

1. Extracellular buffering (see previous slide)
   - Immediately acts
   - The "first-responder"
2. Ventilatory regulation of CO₂ elimination
   - Fast onset
   - Alveolar ventilation responds to PCO₂
3. Renal regulation of H⁺/HCO₃⁻ excretion
   - Slower onset
   - Kidney excretes excess hydrogen ion

**Rule 4 - Acid-Base Compensation**

<table>
<thead>
<tr>
<th>Primary Disturbance</th>
<th>ABG Value Disturbed</th>
<th>Physiologic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Acidosis</td>
<td>↓ HCO₃⁻</td>
<td>Hyperventilation ↑ PCO₂</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>↑ HCO₃⁻</td>
<td>Hypoventilation ↑ PCO₂</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td>↑ PCO₂</td>
<td>Buffering↑ HCO₃⁻ resorption↑ H⁺ secretion ↑ HCO₃⁻</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td>↓ PCO₂</td>
<td>Buffering↓ HCO₃⁻ resorption↓ H⁺ secretion ↓ HCO₃⁻</td>
</tr>
</tbody>
</table>

**Primary Disturbance** | **ABG Value Disturbed** | **Expected Compensation** |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Metabolic Acidosis</td>
<td>↓ HCO₃⁻ 1 mmol/L</td>
<td>↓ PCO₂ 1 mmol/L</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>↑ HCO₃⁻ 1 mmol/L</td>
<td>↑ PCO₂ 0.6 mmol/L</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td>↑ PCO₂ 10 mmHg</td>
<td>↑ HCO₃⁻ 1 mmol/L (A)</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td>↓ PCO₂ 10 mmHg</td>
<td>↑ HCO₃⁻ 4 mmol/L (C)</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td>↓ PCO₂ 10 mmHg</td>
<td>↓ HCO₃⁻ 2 mmol/L (A)</td>
</tr>
<tr>
<td></td>
<td>↓ PCO₂ 10 mmHg</td>
<td>↓ HCO₃⁻ 5 mmol/L (C)</td>
</tr>
</tbody>
</table>
ID: 68 y/o male; wt: 75 kg; ethanol abuse
ABG: 7.20 (26) 98 (10) 0.96
Na: 139 mmol/L; Cl: 106 mmol/L; CO2: 10 mmol/L; Alb: 20 g/L

Rule 1. pH < 7.35, therefore it is an ACIDEMIA
Rule 2. Primary process is metabolic
Rule 3. Anion Gap: Positive
Rule 4. Compensation for a metabolic acidosis → 1:1
   HCO3- is ↓ by 14, therefore PCO2 should ↓ by 14
   PCO2 should be 40-14 = 26 mmHg

PCO2 is 33 mmHg (higher than predicted)
Respiratory acidosis is secondary disturbance

Rule 5 - Determine Delta Anion Gap

Only required if:
- Metabolic alkalemia or alkalosis not yet diagnosed
- Relies on law of electroneutrality
  - If an anion gap ↑, HCO3- must ↓ by same number
  - If HCO3- has dropped less than delta gap → metabolic alkalosis
  - If HCO3- has dropped more than delta gap → normal anion gap metabolic acidosis
Rule 5 - Determine Delta Anion Gap

Clinical Pearl
THE DELTA ANION GAP IS MOST RELIABLE IN THE SETTING OF A POSITIVE ANION GAP METABOLIC ACIDOSIS

THE DELTA ANION GAP ALLOWS DIAGNOSIS OF METABOLIC ALKALOSIS EVEN IF THERE IS A POSITIVE ANION GAP METABOLIC ACIDOSIS

"Rules of Five" at Work
ID: 68 y/o male; wt: 75 kg; ethanol abuse
HPI: Found unresponsive on Downtown Eastside Vancouver; empty bottle of windshield washer antifreeze nearby; maintaining airway; unknown medical history
ABG: 7.20/26/98/10/0.96
Na: 139 mmol/L; Cl-: 106 mmol/L; CO2: 10 mmol/L;
Albumin: 20 g/L
Ethanol: Undetectable
Acid-base disturbance: Primary anion gap metabolic acidosis with a secondary metabolic alkalosis

Applying the “Rules of Five”

Clinical Pearl
COMMENTING ON AN ISOLATED SET OF ABGs WITHOUT BENEFIT OF ANY PERTINENT HISTORY CAN LEAD TO SERIOUS ERROR!

Specific Acid-Base Disturbances
- Metabolic acidosis
  - Anion gap
  - Normal anion gap
- Metabolic alkalosis
  - NaCl-responsive
  - NaCl-resistant
- Respiratory acidosis
- Respiratory alkalosis

Anion Gap Metabolic Acidosis - Pathophysiology
- ↓ pH due to primary ↓ HCO3-
- Causes of ↓ HCO3-
  - Endogenous acids
    - Buffering (consumes HCO3-) endogenous organic acids (lactic acid/ketoacids)
    - Progressive accumulation of endogenous acids (phosphates/sulfates) due to renal dysfunction
  - Exogenous acids
    - Buffering (consumes HCO3-) toxins (toxic alcohols)
Anion Gap Metabolic Acidosis –

Endogenous Acids

- Lactic acidosis (↑ acid production)
  - ↓ tissue oxygenation (shock/anemia/CHF/asphyxia)
  - Deranged oxidative metabolism (DM/liver failure/seizures/genetic)

- Ketoacidosis (↑ acid production)
  - Diabetic
  - Alcoholic
  - Starvation

- Renal failure (acid accumulation)
  - Phosphates/sulfates/organic anions

Exogenous Acids

- Drugs

Anion Gap Metabolic Acidosis –

Medications at Therapeutic Doses

- Atypical antipsychotics (DKA)
- β2-agonists (LA)
- Epinephrine (LA)
- HMG CoA reductase inhibitors (LA)
- Linezolid (LA)
- Metformin (LA)
- NRTIs (LA)
  - Stavudine, lamivudine, zidovudine, didanosine
- Sodium Nitroprusside (LA)
- Propofol (LA)
- Propylene glycol (LA)
  - Diazepam
  - Etomidate

Anion Gap Metabolic Acidosis –

Medications at Toxic Doses

- Acetaminophen (LA)
- Isoniazid (LA)
- Iron (LA)
- Paraldehyde (Metabolites/LA)
- Phosphate salts (Metabolites)
- Salicylates (Metabolites)
Anion Gap Metabolic Acidosis - Toxins

- Carbon monoxide (LA)
- Cocaine (LA)
- Cyanide (LA)
- Ethanol (LA)
- Ethylene glycol (Mets)
- Formaldehyde (Mets)
- Hydrogen sulfide (LA)
- Methanol (Mets)
- Toluene (Hippuric Acid)

Toxin Ingestion Suspected - Mind the Osmole Gap!

- Determine if:
  - +ve SAG metabolic acidosis AND
  - Suspected toxic alcohol ingestion

Calculate plasma osmolality:

\[ \text{Measured Osmolality} - \left(2 \times [\text{Na}^+] + [\text{Glucose}] + [\text{Urea}] + [\text{Ethanol}]\right) \]

Measure plasma osmolality

Osmole gap (OG):

\[ \text{OG} = \text{Measured Osmolality} - \text{Calculated Osmolality} \]

- Normal OG \(\rightarrow 10\) - 20 mOsm/kg/H\(_2\)O

Determine Osmole Gap
Case Revisited

ID: 68 y/o male; wt: 75 kg; ethanol abuse; antifreeze

ABG: 7.20 / 26 / 98 / 10 / 0.96

Na: 139 mmol/L; Gluc: 10 mmol/L; Urea: 7 mmol/L; \(\varnothing\) EtOH

Measured osmolality: 320 mOsm/kg/H\(_2\)O

Primary anion gap metabolic acidosis with secondary metabolic alkalosis

Calculated osmolality: \(2 \times 139\) + 10 + 7 = 295 mOsm/kg/H\(_2\)O

Osmole gap: 320 - 295 = 25 mOsm/kg/ H\(_2\)O

Anion gap metabolic acidosis is likely due to toxic alcohol in antifreeze

Normal Anion Gap Metabolic Acidosis - Pathophysiology

- ↓ pH due to primary ↓ HCO\(_3^\)⁻
- Causes of ↓ HCO\(_3^\)⁻:
  - GI tract wastes HCO\(_3^\)⁻
  - Renal losses of HCO\(_3^\)⁻
  - Impaired renal acid excretion
  - Exogenous acid gain
  - Normal saline-induced (Cl\(^{-}\) induces acidosis)
- SAG remains normal because:
  - HCO\(_3^\)⁻ losses are replaced by Cl\(^{-}\)

Normal Anion Gap Metabolic Acidosis - Causes

- GI loss of HCO\(_3^\)⁻:
  - Diarrhea (30 - 50 mEq/L)
  - Biliary drainage
  - Pancreatic fistula
  - Ureteral diversion into sigmoid colon
  - Isolated ileal loop

Anion Gap Metabolic Acidosis - Acronyms

Outdated Acronym

- Methanol
- Uremia
- DKA
- Paraldehyde
- INH/Iron
- Lactic acidosis
- Ethylene glycol
- Salicylates/Starvation

Modern Acronym

- Metformin/Methanol
- Uremia
- DKA
- Propofol
- INH/Iron
- Lactic acidosis/Linezolid
- Ethylene glycol
- Ingestions (cocaine/MDMA)
- NRTIs/Neuroleptics
- Glycol (Propylene)
- Salicylates/Starvation
Normal Anion Gap Metabolic Acidosis - Causes

- Renal loss of HCO₃⁻
  - Proximal renal tubular acidosis (pRTA)
- Impaired renal acid excretion
  - Distal renal tubular acidosis (dRTA)

Normal Anion Gap Metabolic Acidosis - RTA

- Type 1 (distal RTA)
  - ↓ net secretion of H⁺ in collecting tubules
- Type 2 (proximal RTA)
  - Diminished HCO₃⁻ reabsorption
- Type 4 ("distal-like" RTA)
  - Aldosterone resistance or deficiency
  - Often associated with hyperkalemia

Type 1 (distal) RTA

**Signs**
- Hypokalemia, hyperchloremic metabolic acidosis, inability to lower urine pH < 5.5

**Drug-Related Causes**
- Amphotericin B
- Foscarnet
- Lithium
- Methicillin
- Toluene
- Vitamin D intoxication

Type 2 (proximal) RTA

**Signs**
- Hyperchloremic metabolic acidosis

**Drug-Related Causes**
- Acetazolamide
- Adefovir
- Aminoglycosides
- Cidofovir
- Didanosine
- Lamivudine
- Stavudine
- Tetracycline (outdated)
- Topiramate
- Valproic acid

Type 4 ("distal-like") RTA

**Signs**
- Hyperkalemia, hyperchloremic metabolic acidosis

**Drug-Related Causes**
- ACE-inhibitors
- ARBs
- Heparin
- Spironolactone
- Trimethoprim/sulfamethoxazole

Normal Anion Gap Metabolic Acidosis - Rule Out RTA

**Urinary Anion Gap (UAG)**
- Normal circumstances → urine is free of HCO₃⁻
- NH₄⁺ is predominant UC in urine
- NH₄⁺ is accompanied by Cl⁻
- Measure spot urine electrolytes
- UAG = Na⁺ + K⁺ - Cl⁻
- Normal UAG = -20 - 0 mEq/L
- If non-renal source (diarrhea), normal response is dramatic ↑ NH₄⁺ excretion in urine (UAG -20 → -50)
- If RTA, UAG is positive (EXCEPTION: Type 2 RTA)
Normal Anion Gap Metabolic Acidosis - Acronym

- Hyperalimentation
- Acetazolamide
- RTA
- Diarrhea
- Uretosigmoidostomy
- Pancreatic fistula

Metabolic Acidosis - Clinical Presentation

- pH 7.20 - 7.35
  - Usually asymptomatic
- pH < 7.20
  - CNS: obtundation/coma
  - CVS: flushing/tachycardia/wide pulse pressure/reduced BP
  - RESP: Dyspnea/hyperventilation
  - GI: nausea/vomiting/loss of appetite
  - MET: insulin resistance/increased demands

Metabolic Acidosis - Treatment

- Identify and remove cause(s)
- Effective treatment of underlying disease
  - Fosters conversion of organic acids to HCO₃⁻
  - Consider alkali therapy if pH < 7.20

Goals of Alkali Therapy

- Prevent/reverse consequences of severe acidemia
- Return pH to ≥ 7.20 (↑ HCO₃⁻ to 8-10 mmol/L)

Pharmacotherapeutic Options

- IV Sodium bicarbonate

Dosing Sodium Bicarbonate

- Determine desired change in HCO₃⁻ (mmol/L)
- Determine sodium bicarbonate Vd (0.5 L/kg x Wt)
- Dose (mmol)= Desired change (mmol/L) x Vd (L)
  - Ideally infuse over minutes - hours (avoid bolus)

Metabolic Alkalosis - Pathophysiology

- ↑ pH due to primary ↑ HCO₃⁻
- Accounts for 50% of acid-base disorders

Metabolic Alkalosis

pH > 7.45

Excessive H⁺ Losses  Gain HCO₃⁻ Rich Fluids
Metabolic Alkalosis - Pathophysiology

- Gain HCO₃⁻
  - Infusion of acetate, lactate, citrate
  - Milk-alkali syndrome (uncommon)
- Excessive H⁺ losses
  - GI loss of H⁺ via NG suctioning/vomiting
  - Renal loss of H⁺ due to ↑ Na⁺ delivery to CCD (loop/thiazide diuretics)
  - Renal loss of H⁺ due to ↑ Na⁺ delivery to CCD (intravascular volume contraction)

Metabolic Alkalosis – Causes

- NaCl-responsive (urinary Cl⁻ < 20 mEq/L)
  - Vomiting or nasogastric suctioning
  - Chloride-rich diarrhea
  - Cystic fibrosis
  - Diuretic therapy (loop or thiazide diuretics)
  - Excessive bicarbonate therapy for acidosis
- NaCl-resistant (urinary Cl⁻ > 20 mEq/L)
  - Excess mineralocorticoid activity
  - Tubular abnormalities (Bartter/Gitleman/Liddle Syndrome)
  - Recent loop/thiazide diuretic use

Metabolic Alkalosis - Clinical Presentation

- pH 7.45 - 7.60
  - Usually asymptomatic
- pH > 7.60
  - CNS: ↓ cerebral blood flow/tetany/seizures/lethargy/delirium/stupor
  - CVS: arteriolar constriction/↓ coronary blood flow/↓ anginal threshold/PSVTs/VTs
  - RESP: Hypoventilation/hypoxemia
  - MET: stimulation organic acid production/hypokalemia/hypomagnesemia/hypophosphatemia/↓ ionized calcium

Metabolic Alkalosis - Treatment

- Identify and remove cause(s)
  - Vomiting treated with antiemetics
  - H₂-receptor antagonists/proton pump inhibitors
  - Reduce dose of loop/thiazide diuretics
  - Potentially add K⁺-sparing diuretics (↓ distal acidification)
  - Discontinue lactate/citrate/acetate solutions
  - Reassess/discontinue mineralocorticoids
- Effective treatment of underlying disease

Respiratory Acidosis - Pathophysiology

- ↓ pH due to primary ↑ PCO₂
  - ↑ RR ± Tidal Volume
- Acute respiratory acidosis
- Chronic respiratory acidosis
**Respiratory Acidosis - Causes**

- **CNS**: drugs (opioids, BZDs, TCAs), trauma, stroke, infection
- **SPINE**: trauma
- **NERVE**: trauma, MS, neuropathies
- **NMJ**: MG, paralytics, toxins (red tide/botulism)
- **MUSCLE**: CHO depletion, electrolyte depletion
- **OBSTRUCTIVE**: choking, asthma, COPD
- **RESTRICTIVE**: hemo/pneumothorax/empyema
- **OTHER**: TPN

**Respiratory Acidosis – Clinical Presentation**

- **CNS**: abnormal behavior/seizures/stupor/coma
- **CVS**: refractory hypotension
- **RESP**: hypoventilation

**Respiratory Acidosis – Treatment**

**Goals of Therapy**

- Provide adequate oxygenation
- Establish/maintain patent airway

**Therapeutic Options**

- Treatment depends on cause/chronicity
- Treat underlying cause (ie. bronchodilators → bronchospasm)

**Respiratory Alkalosis – Causes**

- Central stimulation of respiration
  - Anxiety/pain/fever/CNS lesions/
    TBI/pregnancy/progesterone/salicylates
- Peripheral stimulation of respiration
  - PE/CHF/altitude/asthma/pulmonary
    shunts/hypotension/pneumonia/sepsis/cirrhosis
- Voluntary hyperventilation

**Respiratory Alkalosis – Pathophysiology**

- ↑ pH due to primary ↓ PCO₂
- CO₂ excretion exceeds metabolic production
- Hyperventilation - ↑ RR ± Tidal Volume
- Most common acid-base disorder

**Respiratory Alkalosis – Clinical Presentation**

- **CNS**: syncope/seizures
- **CVS**: cardiac arrhythmias
- **RESP**: hyperventilation
Respiratory Alkalosis – Treatment

Goals of Therapy

- Provide adequate oxygenation
- Establish/maintain patent airway

Therapeutic Options

- pH 7.45 - 7.50 → asymptomatic
- Identify/correct underlying cause
- Re-breathing devices

Acid-Base Disorders – Role of the Pharmacist

- Identify patients at risk for acid-base disorders
- Thorough medication history
- Identify acid-base disorders
- “Rules of Five”
- Prevent acid-base disorders
- Eliminate unnecessary potential culprits
- Educate on proper use of potential culprits
- Treatment strategies for acid-base disorders
CASE 2.

A 53-year-old male was 2 days post-op from a coronary angioplasty.
His medi-limb was bridged to the left coronary artery via a stent. The surgery was uneventful with no complications.

CASE 3.

A 60-year-old female was referred for evaluation of shortness of breath.
Her past medical history included hypertension and diabetes.

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CASE 4.

A 60-year-old female was referred for evaluation of shortness of breath.
Her past medical history included hypertension and diabetes.

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CASE 5.

A 53-year-old male was referred for evaluation of shortness of breath.
His past medical history included hypertension and diabetes.

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CASE 6.

A 60-year-old female was referred for evaluation of shortness of breath.
Her past medical history included hypertension and diabetes.

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1. Using the Rules of Five, please determine this patient's acid-base disturbance.

Rule 1: pH < 7.35, acidosis
Rule 2: HCO₃⁻ > 24 mEq/L, therefore metabolic alkalosis
Rule 3: Anion Gap = 140 - 112.7 = 27 (positive), no need to correct for albumin because albumin is normal.

Rule 4: Compensation for primary disturbance: rate of increase in bicarbonate is 2 mmol/L per hour. Therefore, HCO₃⁻ should be increased by 5 mmol/L.

Rule 5: Delta anion gap = 27 - 11 = 16. Therefore, HCO₃⁻ should be decreased by at least 16 mmol/L from 24 mmol/L, which would be 8 mEq/L. Current HCO₃⁻ is 27 mEq/L, therefore this is a metabolic acidosis.

Acid-Base Disturbance: This is a primary metabolic acidosis with a secondary respiratory alkalosis.

2. What are the potential causes of this patient's acid-base disturbance?

With regards to the positive ion gap metabolic acidosis, this is a classic case of diabetic ketoacidosis. Traces are positive for glucose and ketones (normals). Severe, high anion gap is very high (80 mmol/L). This is the predominant form of acidosis. Also, low history and blood gas is suggestive of DKA. The respiratory alkalosis is a consequence of severe muscle fatigue that would be expected if an effective injury was severe trying to compensate for the metabolic acidosis via increasing respiratory rate and tidal volume per breath over a period of time.

3. Very briefly describe a treatment plan for this patient's acid-base disturbance. Start insulin treatment at 0.5 mg/kg IV, then start insulin infusion at 0.1 mg/kg/hr and titrate according to blood sugars. Also, this patient will be administered calcium amount of 2% NaCl. She may also require bicarbonate therapy. Sodium bicarbonate therapy is recommended to control acidosis and currently reserved only for the most refractory-life-threatening acidemics associated with DKA.

CASE 5

1. Using the Rules of Five, please determine this patient's acid-base disturbance.

Rule 1: pH < 7.35, acidosis
Rule 2: PO₂ > 40 mmHg, therefore respiratory alkalosis
Rule 3: Anion Gap = 140 - 112.7 = 27 (positive), no need to correct for albumin because albumin is normal.

Rule 4: Compensation for primary disturbance: rate of increase in bicarbonate is 2 mmol/L per hour. Therefore, HCO₃⁻ should be increased by 5 mmol/L.

Rule 5: Delta anion gap = 27 - 11 = 16. Therefore, HCO₃⁻ should be decreased by at least 16 mmol/L from 24 mmol/L, which would be 8 mEq/L. However, current HCO₃⁻ is 27 mEq/L, therefore this is a respiratory acidosis.

Acid-Base Disturbance: This is a primary respiratory acidosis. It could also be stated as: A simple respiratory acidosis.

2. What are the potential causes of this patient's acid-base disturbance?

The most likely cause of the respiratory acidosis is opioid toxicity. Opiates depress the respiratory center in the brain, which is incapable of regulating CO₂ concentration adequately. Upon further history, the RN realized that a dosage error occurred with the hydromorphone.

3. Are there any pharmacotherapeutic options?

Naloxone is the antidote of choice for presumed or confirmed opioid toxicity.
1. Using the Rule of Two, please determine this patient’s acid-base disturbance.

Rule 1: Acidemia
Rule 2: Metabolic acidosis
Rule 3: Anion gap = 146-205=41 (POSITIVE)
Rule 4: Compensation: 1.1-1.3 x PaCO₂ should be above 10 (24 mmHg) ; therefore no secondary alkalemia
Rule 5: Positive Anion Gap = 17-11=6 ; therefore HCO₃ should be down at least 10 from normal (24) ;

This is a primary positive anion gap metabolic alkalosis.

2. What are the possible causes of this patient’s acid-base disturbance?

Potential Causes: Metabolic acidosis secondary to gastric ulcer, lactic acidosis, prolonged vomiting, or diuretics.

3. Devise a short-term treatment plan for this patient’s acid-base disturbance.

Treat the underlying cause (eg, gastric ulcer, secondary to sepsis or infection):

ACTIONS:

- Fluids
- Corrective 
- Corrective
- Corrective
- Corrective
- Corrective
- Corrective
- Corrective
- Corrective
- Corrective
- Corrective
- Corrective