Acid-Base Disorders

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Background

- Primary alterations in pH may be metabolic or respiratory in origin
  - Metabolic: result from processes that alter pH by changing the plasma [HCO₃⁻]
  - Respiratory: result from primary changes in the arterial carbon dioxide tension (PaCO₂)
  - Degree of acidity is expressed as pH
    - pH is the negative log of the [H⁺]
    - pH & [H⁺] are inversely related
    - Acids donate H⁺; bases accept H⁺
Pathophysiology

• Endogenous metabolism of carbohydrates and fat results in the production of 15000 mmol of CO\textsubscript{2} per day
• CO\textsubscript{2} is not an acid, it combines with H\textsubscript{2}O as it is added to the bloodstream to form carbonic acid

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

• Most of the excess H\textsuperscript{+} combines with intracellular buffers
• The HCO\textsubscript{3} generated by the rxn leaves the cell and enters the ECF
• Therefore, generated CO\textsubscript{2} is primarily carried in the bloodstream as HCO\textsubscript{3} with little change in extracellular pH
  – Able to measure serum HCO\textsubscript{3}
Pathophysiology

- The reverse occurs in the alveoli (lungs)
- When hemoglobin (RBC) is oxygenated, H\(^+\) is released
- H\(^+\) combines with HCO\(_3\) to form carbonic acid, and then CO\(_2\) which is then exhaled
  \[ H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O \]

- Carbonic acid concentration is directly proportional to PCO\(_2\)
  - Able to measure PCO\(_2\) on ABG
  - Ref: BD Rose Clinical Physiology of Acid-Base and Electrolyte Disorders
Acid-Base Balance

• 3 mechanisms maintain acid-base balance:
  – Extracellular buffering
    • 1st & fastest defense against an increase in [H⁺]
  – Ventilatory regulation of CO₂ elimination
  – Renal regulation of H⁺ & HCO₃⁻ excretion

• Buffering system (3 components):
  – Bicarbonate (most important)/carbonic acid
  – Phosphates
  – Proteins
Buffering

• Principal acid-base pair: carbonic acid/bicarbonate
  – Carbonic acid: respiratory component of the buffer pair because its concentration is directly proportional to PCO₂, determined by ventilation
  – Bicarbonate: metabolic component because the kidney may alter [HCO₃⁻] by reabsorption, elimination, or generation of new HCO₃⁻
Buffering

• Phosphate buffering system consists of:
  – Serum inorganic phosphate
  – Intracellular organic phosphate
    • Intracellular >> extracellular so phosphate is primarily intracellular buffer
  – Calcium & phosphate in bone
    • Prolonged metabolic acidosis will cause buffering from bone
Buffering

• Intra- & extracellular proteins
  – Charged side chains of amino acids provide buffering action
  – Intracellular >> extracellular, therefore proteins are mainly intracellular buffers
Respiratory Regulation

• Medullary chemoreceptors sense changes in PCO$_2$ or pH & alter ventilation (rate & depth)
Renal Regulation

• Final & slowest mechanism by which the body maintains acid-base balance
  – Renal excretion of acid
  – Reabsorption of filtered HCO$_3^-$
    • 4000 mEq of HCO$_3^-$ filtered daily
    • Almost all reabsorbed in proximal tubule
  – Generation of new HCO$_3^-$
Proximal Tubule

- Tubular lumen:
- Secreted $H^+$ ions combine with filtered $HCO_3^-$ to form carbonic acid
- $H_2CO_3$ dissociates into $CO_2 + H_2O$
  - Facilitated by luminal CA
  - $CO_2 + H_2O$ passively reabsorbed
Proximal Tubule

- Intracellular H$_2$O breaks down into H$^+$ and OH$^-$
- OH$^-$ combines with CO$_2$ to form HCO$_3^-$
  - Catalyzed by CA
- HCO$_3^-$ is returned to the circulation via Na$^+$-3HCO$_3^-$ cotransporter
Regulation of Acid

- H\(^+\) can combine with:
  - Bicarb to form carbonic acid
  - Phosphate to form titratable acid
  - Ammonia to form ammonium
    - Excreted in urine

\[ \text{Tubular Lumen} \]
\[ \begin{align*}
  \text{Tubular Cell} & : \\
  \text{HCO}_3^- & \quad \text{HPO}_4^{4-} & \quad \text{NH}_3 \\
  \text{H}_2\text{CO}_3 & \quad \text{H}_2\text{PO}_4^- & \quad \text{NH}_4^+ \\
\end{align*} \]
Clinical Assessment of Acid-Base Status

- Arterial blood gases (ABG)
- Serum electrolytes
- Physical exam
- Medical hx
- Medication hx
- Clinical condition of pt
ABG

• Blood gases are measured to determine the patient’s oxygenation & acid-base status
  – Arterial, designated PaO$_2$, PaCO$_2$
    • Arterial blood provides added information about how well the lungs are oxygenating blood
  – Mixed venous, designated PvO$_2$, PvCO$_2$
    • Used when arterial blood cannot be obtained
    • Venous blood from an extremity can be misleading
      – Metabolism in the extremity (thus affecting PvO$_2$, PvCO$_2$) can be altered by hypoperfusion, exercise, infection.
## Blood Gases

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>PCO(_2) mmHg</th>
<th>[HCO(_3)] mEq/L</th>
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</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>7.37 – 7.43</td>
<td>36 – 44</td>
<td>22 – 26</td>
</tr>
<tr>
<td>Venous</td>
<td>7.32 – 7.38</td>
<td>42 – 50</td>
<td>23 – 27</td>
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</table>
## Metabolic or Respiratory Acidosis or Alkalosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>pH</th>
<th>H⁺</th>
<th>Primary Disturbance</th>
<th>Compensatory Response</th>
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<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>Dec</td>
<td>Inc</td>
<td>Dec [HCO₃⁻]</td>
<td>Dec PaCO₂</td>
</tr>
<tr>
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<td>Inc</td>
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<tr>
<td>Respiratory acidosis</td>
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<td>Inc [HCO₃⁻]</td>
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<td>Dec PaCO₂</td>
<td>Dec [HCO₃⁻]</td>
</tr>
</tbody>
</table>
Respiratory Acid-Base Disorders
Pathophysiology

• The reverse occurs in the alveoli (lungs)
• When hemoglobin (RBC) is oxygenated, $H^+$ is released
• $H^+$ combines with $HCO_3^-$ to form carbonic acid, and then $CO_2$ which is then exhaled

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

• Carbonic acid concentration is directly proportional to $PCO_2$
  - Able to measure $PCO_2$ on ABG
  - Ref: BD Rose Clinical Physiology of Acid-Base and Electrolyte Disorders
Respiratory Acid-Base Disorders

- Generated by a primary alteration in CO₂ elimination which changes the concentration of CO₂ and therefore the carbonic acid concentration in the blood
  - A primary reduction in PaCO₂ causes a rise in pH (respiratory alkalosis)
  - A primary increase in PaCO₂ causes a fall in pH (respiratory acidosis)

\[
H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O
\]
Respiratory Acidosis

- Primary retention of CO$_2$ that lowers pH
- Failure of lungs to eliminate CO$_2$
  - Ventilation-perfusion abnormality/inequality
    - Cardiopulmonary
    - Disorder that restricts ventilation
      - Airway obstruction
  - Neuromuscular
    - Disorders of peripheral nerves or skeletal muscle required for ventilation
Causes

- Perfusion abnormalities
  - Cardiac arrest
  - Massive PE
- Airway & perfusion
  - Severe pulmonary edema
  - Severe pneumonia
  - Severe bronchospasm
  - ARDS
  - Obstruction (foreign body, laryngeal edema)
- Neuromuscular
  - Trauma, stroke
  - Narcotic or sedative OD
  - Brainstem or cervical cord injury
  - Guillain-Barre syndrome
  - Myasthenia gravis
- Ventilator malfxn (rare)
- TPN
  - Carbohydrates -> increased CO₂ production
Clinical Sx

• Neurologic
  – MS changes
  – Sz
  – Stupor
  – Coma

• Cardiac contractility & HR
  – Depends on severity of acidosis
Compensation

- Acute respiratory acidosis
  - Nonbicarbonate buffers (proteins, phosphate, hemoglobin) take up the H⁺ from the carbonic acid formed as a result of the increase in PaCO₂
    - Allows [HCO₃⁻] to increase
      - The [HCO₃⁻] will increase by 1 mEq/L above 24 mEq/L for each 10 mmHg increase in PaCO₂

\[
H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O
\]
Compensation

• Chronic respiratory acidosis (beyond 12 - 24 h)
  – In addition to nonbicarbonate buffers, renal excretion of $\text{H}^+$ and generation of new $\text{HCO}_3^-$ increases raising pH towards normal
  – Renal compensation results in the plasma $[\text{HCO}_3^-]$ increasing by 3.5 - 4 mEq/L above 24 mEq/L for each 10 mmHg increase in PaCO$_2$ above 40 mmHg.
Management of Acute Respiratory Acidosis

• Establish a patent airway to reverse life-threatening hypoxia (PaO₂ < 40 mmHg) & to prevent brain damage

• If condition is severe, pt should be intubated & mechanically ventilated. Criteria:
  – Inability to maintain a normal PaCO₂ or a PaO₂ of at least 60 mmHg while receiving 60% inhaled O₂ (FiO₂ = 0.60)
  – Excessive work of breathing or flail chest
  – Metabolic acidemia for which breathing cannot compensate
Bicarb

- Careful in administering bicarb!
  - May aggravate acidosis
  - Bicarb increases venous CO\textsubscript{2} production 2\textdegree to conversion of HCO\textsubscript{3} to CO\textsubscript{2}; CO\textsubscript{2} cannot be effectively removed/exchanged by the lungs
  - In acute respiratory acidosis the drive to breath is hypercarbia (increased PaCO\textsubscript{2})
    - Rapid correction with bicarb may decrease respiratory drive
  - Large doses of bicarb can precipitate a metabolic alkalosis
Chronic Respiratory Acidosis

• Increase in $\text{PaCO}_2$ & hypoxemia but to a lesser degree than acute
  – No noticeable neurologic defects

• Causes
  – Neuromuscular abnormalities: brainstem infarct, MS, obesity-hypoventilation
  – Pulmonary abnormalities: COPD, interstitial pulmonary disease
Oxygen

- Maintain patent airway & adequate oxygenation
- Careful with oxygen!
  - Because of compensation, these pts can tolerate an elevated $\text{PaCO}_2$ & a low $\text{PaO}_2$
  - Drive to breathe is dependent on hypoxemia
  - Administration of $\text{O}_2$ therapy can eliminate the drive to breathe & result in carbon dioxide narcosis
Oxygen

• If $\text{PaCO}_2 \geq 50 \text{ mmHg}$, no $\text{O}_2$ therapy needed

• If $\text{PaCO}_2 < 50 \text{ mmHg}$, $\text{O}_2$ therapy should be initiated cautiously
  – If $\text{PaCO}_2$ increases on $\text{O}_2$ therapy, may be a sign of impending $\text{CO}_2$ narcosis. D/C $\text{O}_2$
Bicarb

• Use when:
  – pH < 7.2 & PaCO₂ remains elevated +/- pt has sx of acidosis (neurologic, cardiac)
  – Amount of bicarb should increase the pH to no more than 7.25
    • Risk of arrhythmia when pH < 7.2
    • Recall, bicarb can worsen acidosis: bicarb increases venous CO₂ production 2° to conversion of HCO₃⁻ to CO₂; CO₂ cannot be effectively removed/exchanged by the lungs
Respiratory Alkalosis

• The PaCO2 falls if the elimination of CO2 by the lungs exceeds the production of CO2
  – CO₂ is generated by diet and tissue metabolism
• Ventilation >>CO₂ production
Causes

• Central stimulation of respiration
  – Pregnancy
  – Salicylates; catecholamines; theophylline; nicotine; progesterone
  – Anxiety
  – Pain
  – Fever
  – CVA; brain tumors; head trauma
Causes

• Peripheral stimulation of respiration
  – CHF
  – PE
  – *Altitude*
  – Asthma
  – Pneumonia
  – Hypotxn

• Mechanical or voluntary hyperventilation
Compensation

• Acute respiratory alkalosis
  – H⁺ are released from body’s buffers (intracellular proteins, phosphates, hemoglobin) to titrate bicarb
  – The \([\text{HCO}_3^-]\) is decreased by a maximum of no more than 3.0 mEq/L for each 10 mmHg decrease in \(\text{PaCO}_2\)
  – Other guidelines say 2 mEq/L decrease in \([\text{HCO}_3^-]\)
Compensation

• Chronic respiratory alkalosis (> 6 hours)
  – Kidneys increase bicarb excretion
    • Decrease in reabsorption of filtered bicarb
    • +/- reduction in the generation of new bicarb
  – The $[\text{HCO}_3^-]$ is reduced by 4 mEq/L below 24 mEq/L for each 10 mmHg drop in $\text{PaCO}_2$
Management

• Acute respiratory alkalosis
  – ID & correct underlying cause
  – Pts with severe hypoxemia – O₂ therapy
  – Life-threatening alkalosis (pH > 7.6) → mechanical ventilation

• Chronic respiratory alkalosis
  – Pts usually asymptomatic; txmt not often required
  – Rebreathing device (paper bag – for pts with anxiety)
Metabolic Acid-Base Disorders
Metabolic Acidosis - Pathophysiology

• Bicarb is lost
  – From buffering of an organic acid that is added to the ECF
    • Lactic acid (septic shock), ketoacids (DKA, EtOH)
  – Loss of bicarb-rich fluids
    • Diarrhea

• Nonvolatile acid is gained
  – Progressive accumulation of endogenous acids 2° to renal impairment
    • Phosphates, sulfates
  – Presence of anions
Metabolic Acidosis

• Anion gap

• Non anion gap
Anion Gap Derivation

- The anions in the blood include:
  - \( \text{HCO}_3^-, \text{Cl}, \text{PO}_4^-, \text{SO}_4^-, \text{albumin}, \text{organic acids} \)
- The cations in the blood include:
  - \( \text{Na}, \text{K}, \text{Ca}, \& \text{Mg} \)
- Because plasma remains neutral, the true \textit{AG is zero} or
  \[
  (\text{Na} + \text{K} + \text{Ca} + \text{Mg}) - (\text{HCO}_3^- + \text{Cl} + \text{PO}_4^- + \text{SO}_4^- + \text{albumin} + \text{organic acids}) = 0
  \]
Anion Gap Derivation

- The AG accounts for anions (SO$_4$, organic acids) that are always present, but not always measured in routine labs:
- Which labs are on the Chem 7?
Anion Gap Derivation

- \( AG = (\text{serum Na} + \text{serum K}) - (\text{serum Cl} + \text{serum HCO}_3) \)
- Since K is relatively low, the formula can be abbreviated to:
- \( AG = \text{serum Na} - \text{serum Cl} - \text{serum HCO}_3 \)
Which values should we use?

• In the past,
  – Normal AG was $12 \pm 4$ mEq/L

• Changes in the lab technique for measuring Cl have lowered the AG to $10 \pm 4$ mEq/L
  • Semin Nephrol 1998;18(1):83-97

• What does an elevated AG mean?
M-U-D-P-I-L-E-S

- M: methanol: formic acid, lactic acid; massive rhabdomyolysis
- U: uremia
- D: DKA: B-hydroxybutyrate
- P: paraldehyde: organic acids; phosphate
- I: ingestions (many plus toluene: hippurate; formaldehyde: formic); iron
- L: lactic acidosis: lactate, D-lactate
- E: ethylene glycol: glycolate, oxalate; EtOH
- S: salicylate: ketones, lactate, salicylate; sulfate; starvation; strychnine
Osmolality

CalculatedOsm = 2 × Na + \frac{\text{glucose (mg/dl)}}{18} + \frac{\text{urea (mg/dl)}}{2.8}
Osmolality

• Solutes other than Na, glucose, & urea can contribute to serum osmolality under abnormal conditions

• Examples:
  – ethanol, mannitol, glycerol, contrast dye, ethylene glycol, and methanol
  – all are effective osmoles
Osmolal Gap

• Equals measured osmolality minus calculated osmolality
• Difference > 10 mOsm/L considered abnormal; suggests presence of exogenous substance or osmole
• Na, glucose, urea do not increase osmolar gap because these affect both measured & calculated osmolality
## Relationship between AG & Osm Gap

<table>
<thead>
<tr>
<th></th>
<th>AG</th>
<th>Osm Gap</th>
<th>Double Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene Glycol</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>Methanol</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>Isopropyl Alcohol</td>
<td>-</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>Ethanol</td>
<td>-</td>
<td>+</td>
<td>No</td>
</tr>
</tbody>
</table>
Effect of Serum Albumin on AG Calculation

• Albumin is an unmeasured anion
• In hypoalbuminemia, you have decreased number/amount of unmeasured anions, thereby “falsely” lowering the AG.
• There is an approximate 2.5 mEq/L fall in the AG for every 1 g/dl reduction in serum albumin concentration.

• Add 2.5 mEq/L onto the AG per 1 g/dl fall in serum albumin
Example

• Na 136, K 3.5, Cl 106, HCO$_3$ 20
• What is the AG?

• The pt has a serum albumin of 2.8 g/dl
  – Normal: 3.8-5.2 g/dl

• Does the pt have an AG?
Please enter your answer

- Na 136, K 3.5, Cl 106, HCO₃ 20
- Calculate AG.
- AG = (Na + K) – (Cl + HCO₃)
- AG = ???.?
Please enter your answer

• The pt has a serum albumin of 2.8 g/dl
  – Normal serum albumin: 3.8 – 5.2 g/dl

• **Recall, add 2.5 mEq/L onto the AG per 1 g/dl fall in serum albumin** Calculate AG.

• \( AG = (Na + K) - (Cl + HCO_3) + 2.5 \)

• \( AG = ???.? \)
Yes or No

- Does the patient have an AG metabolic acidosis?
M-U-D-P-I-L-E-S

- **M**: methanol: formic acid, lactic acid; massive rhabdomyolysis
- **U**: uremia
- **D**: DKA: B-hydroxybutyrate
- **P**: paraldehyde: organic acids; phosphate
- **I**: ingestions (many plus toluene: hippurate; formaldehyde: formate); iron
- **L**: lactic acidosis: lactate, D-lactate
- **E**: ethylene glycol: glycolate, oxalate; EtOH
- **S**: salicylate: ketones, lactate, salicylate; sulfate; starvation; strychnine
Lactic Acidosis

- Lactate is the end product of anaerobic metabolism of glucose (glycolysis)
- $[\text{Lactate}] \geq 4.0-5.0$ mEq/L with a simultaneous decrease in $\text{HCO}_3$ & arterial pH are highly suggestive of lactic acidosis
  - Each 1 mEq/L increase in plasma [lactate] will cause an equivalent decrease in serum $\text{HCO}_3$. 
Lactate Metabolism

- Lactic acid, derived from pyruvate, enters the circulation in small amounts & removed by liver
- In liver, lactate is reoxidized to pyruvate* (requires NAD) which is then metabolized to CO$_2$ & H$_2$O
L/P Ratio

• Normally, blood [lactate] is 10x [pyruvate]
  – If pyruvate is elevated (by increased glucose intake) lactate increases and L/P ratio is unchanged
  – If anaerobic glycolysis increases (tissue hypoxia) and sufficient NAD is NOT available to reconvert lactate to pyruvate, then lactate will increase >> pyruvate and L/P ratio will increase
  – Lactate:pyruvate > 10:1 indicates hypoxic lactic acidosis
Causes

• Tissue hypoxia
  – Shock (cardiovascular, septic, hypovolemic)
  – Severe anemia
  – CHF
  – Asphyxia
  – Carbon monoxide poisoning
Causes

• Deranged oxidative metabolism
  – DM
  – Liver failure
  – Medications (ASA, Fe, INH, metformin)
  – Methanol, EtOH, ethylene glycol
Management

• ID & tx underlying cause
  – In most pts, cause of lactic acidosis is cardiac arrest, shock, or sepsis where impaired O$_2$ delivery to tissues is the primary cause of lactic acid accumulation.
  – Bicarb does not affect underlying tissue hypoxia
Bicarb

• Use of bicarb is controversial
  – Administration of bicarb also increases venous [CO2]. CO2 permeates by passive diffusion into cells and decreases intracellular pH of many tissues: myocardium, liver, CNS (intracellular acidosis). “Paradoxical acidosis”
    • Hepatic cells -> decreased lactic utilization
    • Cardiac myocytes -> decreased contractility
Bicarb

• Risks of bicarb: hypernatremia, volume overload, overshoot to metabolic alkalosis

• Bicarb is used for severe metabolic acidosis
Alternatives to Bicarb

- Tromethamine (THAM)
- Dichloroacetate (investigational)
Tromethamine

- Synthetic alkali that increases the formation of $\text{HCO}_3^-$ from carbonic acid to prevent or correct acidosis
- Does not contain Na
- Given IV, but highly alkaline
  - If it infiltrates:
    - Tissue damage (necrosis, sloughing, pain, phlebitis, thrombosis); severe inflammation; vascular spasm
- ADRs: hyperkalemia, hypoglycemia, hypocalcemia; impaired coagulation, respiratory depression
- Do not use in severe renal or liver failure
Dichloroacetate

- Investigational; but mentioned in textbook
- Stimulates oxidation of lactate to acetyl CoA and CO₂
- Has not been found to increase survival in pts with lactic acidosis
- ADRs: metabolized to oxalate -> can crystallize and cause end organ damage (most likely kidneys); neurotoxicity: may deplete thiamine stores, co-administer w/thiamine
Non AG Metabolic Acidosis

- Sometimes referred to as hyperchloremic metabolic acidosis. Causes:
  - GI loss of HCO3
    - Diarrhea
  - Renal loss of HCO3
    - Type 2 RTA
  - Renal dysfxn
    - Type I or type IV RTA;
    - Renal failure
  - Ingestions
    - Ammonium chloride
How to Distinguish Renal Causes from GI Causes

- Urine anion gap. Normal is zero
  - Urine anion gap = ([Na]_u + [K]_u) − [Cl]_u

- GI cause (diarrhea)
  - In response to acidemia, kidneys rev up by increasing urinary acid excretion, mainly as ammonium
  - Urine [Cl] is high because Cl maintains neutrality with ammonium
How to Distinguish Renal Causes from GI Causes

- Urine anion gap = ([Na]_u + [K]_u) – [Cl]_u

- When [ammonium] is high, [Cl] is high and the urine AG will be (-)

- Renal causes (RTA)
  - Impaired to low levels of ammonium, thus low levels of chloride and the urine AG will be (+)

- Get your clicker ready
If the urine AG is

A) a negative value, then the likely cause of the non AG metabolic acidosis is gastrointestinal, such as diarrhea

B) a positive value, then the likely cause of the non AG metabolic acidosis is renal, such as renal failure or a renal tubular acidosis

C) All of the above
Renal Tubular Acidoses (RTA)

- Falls into the category of non AG metabolic acidosis
- 3 types:
  - *Proximal*, type II RTA
  - *Distal*, type I RTA
  - *Hyperkalemia, hypoaldosterone or aldosterone resistant*, type IV
Acid-Base Balance in Kidneys

- Proximal reclamation of bicarb
- Synthesis of ammonia
- Distal secretion of $H^+$
Type II Proximal RTA

• Defect: decreased proximal $\text{HCO}_3^-$ reabsorption

• Proximal tubule is responsible for reclamation of $\text{HCO}_3^-$

• Self-limiting disorder:
  – The threshold for $\text{HCO}_3^-$ reabsorption is lowered to around 15 – 17 mEq/L
  • Normal serum $\text{HCO}_3^-$ is 23-29 mEq/L
Type II Proximal RTA

• When serum $[\text{HCO}_3^-]$ falls $< 15-17$ mEq/L,
  – $\text{HCO}_3^-$ is reabsorbed/reclaimed
  – $\text{HCO}_3^-$ excretion decreases
  – Urinary pH decreases

• Serum $[\text{HCO}_3^-]$ is usually 14-20 mEq/L in these pts
Type II Proximal RTA

- *Conversely*, above the threshold, HCO₃ is excreted in the urine
- In normal pts, HCO₃ is not excreted in the urine until serum HCO₃ is > 26 mEq/L
- Shifted to a lower level in pts with type II RTA

15 mEq/L  HCO₃  17 mEq/L

**Reabsorption**  **Excretion**
Type II Proximal RTA

• A new steady-state \([\text{HCO}_3^-]\) is achieved
• Results in a mild metabolic acidosis
• Drugs & toxins that cause type II RTA:
  – acetazolamide (CA inhibitor)
  – ifosfamide
  – streptozotocin
  – outdated TCN
  – lead, cadmium, mercury
Proximal Tubule

- Intracellular H$_2$O breaks down into H$^+$ and OH$^-$
- OH$^-$ combines with CO$_2$ to form HCO$_3^-$
  - Catalyzed by CA
- HCO$_3^-$ is returned to the circulation via Na$^+$-3HCO$_3^-$ cotransporter
Acetazolamide

- Carbonic anhydrase (CA) inhibitor
- Tubular cell:
  - Inhibits CA
  - Prevents the production of $\text{HCO}_3^-$ & $\text{H}^+$ from $\text{CO}_2$ & $\text{H}_2\text{O}$
  - Therefore, less $\text{H}^+$ is available for Na/H exchange
  - Less $\text{HCO}_3^-$ is available for exit across basolateral membrane
Distal Tubule

• Responsible for the excretion of a daily fixed load

• Daily metabolism produces acid as $\text{H}^+$ as:
  – non volatile sulphuric acid
  – aminoacid catabolism
  – non-metabolized organic acids
  – remainder: phosphoric & other acids
**Distal Tubule**

- Distal tubule lacks luminal CA; but CA is in tubule cell
- Secreted H⁺ can generate a H⁺ gradient of 1000:1 (lumen:cell)
- For each secreted H⁺, a new HCO₃⁻ is transferred to the circulation
Regulation of Acid

- $\text{H}^+$ can combine with:
  - Bicarb to form carbonic acid
  - Phosphate to form titratable acid
  - Ammonia to form ammonium
    - Excreted in urine

![Diagram showing the regulation of acid with bicarbonate (HCO$_3^-$), phosphate (HPO$_4^{2-}$), ammonia (NH$_3$), carbonic acid (H$_2$CO$_3$), phosphate (H$_2$PO$_4^-$), and ammonium (NH$_4^+$).]
Type I Distal RTA

• A defect at any point may result in a defect in distal urinary acidification:
  – carbonic anhydrase inhibitor (acetazolamide)
  – need adequate pumps (H⁺-ATPase pump) to secrete H⁺
  – cell membrane must prevent H⁺ backleak
Type I Distal RTA

- Unfavorable electrical gradient for H⁺ secretion (voltage defect)
  - Na is reabsorbed at a faster rate than Cl
    - negative intraluminal potential
    - favors secretion of H⁺ and K
  - Amiloride or triamterene (and other drugs)-> inhibit Na reabsorption -> causes a voltage-dependent RTA (->inhibition of H⁺secretion)
Type I Distal RTA

- Decrease in H\(^+\) secretion
- Ability to lower urine pH (make more acidic) is impaired
- Pts cannot lower their urine pH below 5.5, even in the presence of severe metabolic acidosis
  - urine pH can normally be lowered to 4.5-5.0
Type I Distal RTA

• Defect in acidification diminishes ammonium & titratable acid excretion
  – prevents excretion of the dietary acid load

• Continued $H^+$ retention
  – leads to a reduction in plasma HCO3 which may fall to $< 10$ mEq/L
Causes - Drugs & Toxins

• Amphotericin B
  – selective increase in membrane permeability
  – back diffusion of $\text{H}^+$ into tubular cells

• Amiloride, triamterene, lithium, CSA
  – curtails Na reabsorption
    • diminishes or abolishes the electrical potential leading to decrease $\text{H}^+$ & K excretion
    • linked to hyperkalemia

• Ifosfamide - direct tubular toxin
Type IV RTA

• Metabolic acidosis resulting from aldosterone deficiency or resistance
• Associated with diabetic nephropathy & interstitial nephritis
• Possible drug-induced causes:
  – spironolactone
  – ACE inhibitors
Distal Tubule

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<tr>
<th>Tubular Cell</th>
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<tr>
<td>2 K</td>
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<td>Na-K ATPase</td>
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<td>3 Na</td>
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\text{H}_2\text{O} + \text{CO}_2 \rightarrow \text{H}_2\text{CO}_3 \\
\text{H}_2\text{CO}_3 \rightarrow \text{HCO}_3^- + \text{H}^+ \\
\text{Glutamine} \rightarrow \text{Glutamate} \\
\text{Aldo} \rightarrow \text{NH}_3 \\
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Type IV RTA

• Hyperkalemia plays a role in the metabolic acidosis by impairing ammonia production & excretion
  – Rate of ammonia production is increased by K depletion,
  – So hyperkalemia decreases rate of ammonia production
Dose of $\text{HCO}_3^-$ to Normalize Plasma [$\text{HCO}_3^-$]

- **Type I (distal)**
  - 1-2 mEq/kg/day
- **Type II (proximal)**
  - 10-15 mEq/kg/day
    - Reversal of acidemia is difficult because $\text{HCO}_3^-$ is rapidly excreted in the urine
    - 10-15 mEq/kg/day is needed to stay ahead of urinary excretion
Dose of \( \text{HCO}_3 \) to Normalize Plasma [\( \text{HCO}_3 \)]

- Type IV
  - 1-3 mEq/kg/day
  - May require no \( \text{HCO}_3 \) if hyperkalemia is corrected
Compensation of Metabolic Acidosis (all causes)

- Increasing respiratory rate to increase CO₂ elimination
- Decreased cerebral [HCO₃⁻] and pH -> stimulation of respiratory center
- For every 1 mEq/L decrease in [HCO₃⁻] below the average 24 mEq/L, the PaCO₂ decreases by about 1.0 - 1.5 mmHg from the normal value of 40 mmHg.
Na Bicarbonate

- Factors to consider:
  - An increase in arterial blood pH shifts the oxyhemoglobin saturation curve to the left and O2 becomes more tightly bound to hemoglobin (Bohr effect). O2 becomes LESS available - tissue hypoxia
  - Administration of large amounts of bicarb -> severe hypernatremia, fluid overload, hyperosmolality
Na Bicarbonate

• Paradoxical acidosis
  – production of CO$_2$ that freely diffuses into myocardial & cerebral cells
• Decreased iCa with resultant decreased myocardial contractility
Severe Metabolic Acidosis

- Arterial pH < 7.1; HCO$_3^-$ < 5 mEq/L
  - Can result in life-threatening myocardial depression
  - Pt should receive bicarb
How to Determine an Initial Dose of Bicarb

• Initial goal is to raise the pH to approximately 7.2 -> level at which arrhythmias are less likely

• 1st step: Determine $[\text{HCO}_3^-]_{\text{desired}}$

• $[\text{HCO}_3^-]_{\text{desired}} = 24/\text{[H]} \times \text{PaCO}_2$

• $[\text{HCO}_3^-]_{\text{desired}} = 24/63 \times \text{PaCO}_2$

  – note: $\text{pH} = 7.2$ -> $[\text{H}] = 63$
How to Determine an Initial Dose of Bicarb

• 2nd step: calculate the HCO₃ deficit:

\[
\text{HCO}_3 \text{ deficit} = 0.7 \times \text{TBW} \times ([\text{HCO}_3]_{\text{desired}} - [\text{HCO}_3]_{\text{actual}})
\]
Bicarb

• Goals
  – restore hemodynamic stability
  – do not normalize pH
  – arterial pH can be increased over 3-6 hours, but should not be increased to > 7.25 due to changes in serum K & tissue oxygen delivery
Metabolic Alkalosis

- Etiology requires both:
  - generation of metabolic alkalosis
    - loss of H\(^+\) thru GI tract or kidneys
  - maintenance of alkalosis
    - impairment of renal HCO\(_3\) excretion
- Causes:
  - Saline responsive; urine Cl < 10 mEq/L
  - Saline unresponsive; urine Cl > 20 mEq/L
Etiologies of Metabolic Alkalosis

• Chloride depletion results in “chloride-or saline responsive” metabolic alkalosis
  – Chloride may be lost from the gut, kidney or skin
  – Gastric fluid contains 60-140 mM HCL
  – Loss of gastric fluid results in alkalosis because $\text{HCO}_3^-$ generated during gastric acid production returns to the circulation
Chloride Depletion

- Gastric losses
  - Vomiting, NG suction, bulimia
  - Use H-2 blockers during NG suction
- Diuretics
- Cystic fibrosis
  - High sweat chloride
  - Sweat losses

- Low chloride intake
  - Chloride-deficient infant formulas
  - Chloride-deficient IV fluids
Saline-Responsive

• Aka “chloride-responsive”
• When adequate chloride is provided, kidney excretes surplus $\text{HCO}_3^-$
• Restores acid-base balance over a few days
Cortical Collecting Tubule

- $\text{H}_2\text{O}$ dissociates to $\text{H}^+$ & hydroxyl ions
- $\text{H}^+$ secreted into peri-tubular capillary by H-ATPase pump
- Hydroxyl ion combines w/CO$_2$ to from HCO$_3^-$ via CA
- HCO$_3^-$ is secreted via CL- HCO$_3^-$ exchanger
Management

• Saline-responsive: NS or 1/2 NS can lower plasma $[\text{HCO}_3^-]$ in 3 ways:
  – by removing the stimulus to renal Na retention, thereby permitting NaHCO$_3$ excretion in the urine
  – reversing the volume contraction component
  – increasing distal Cl delivery -> promote HCO$_3^-$ secretion in the cortical collecting tubule

• Do not use LR -> converted to HCO$_3^-$; may worsen alkalosis
Saline-Resistant

- aka Saline-Unresponsive
- Rare
- Edematous states
- Mineralocorticoid excess
  - act on distal tubule to increase Na reabsorption and enhance K and H⁺ secretion
  - H⁺ secretion causes generation of new HCO₃ or reclamation of filtered HCO₃
- Severe hypokalemia (increases ammonia production)
- Renal failure
Management

• Acetazolamide
  – increases NaHCO$_3$ excretion
  – decreases HCO$_3$ generation

• Correct hypokalemia
**Acetazolamide**

- Carbonic anhydrase (CA) inhibitor
- Tubular cell:
  - Inhibits CA
  - Prevents the production of $\text{HCO}_3^-$ & $\text{H}^+$ from $\text{CO}_2$ & $\text{H}_2\text{O}$
  - Therefore, less $\text{H}^+$ is available for Na/H exchange
  - Less $\text{HCO}_3^-$ is available for exit across basolateral membrane
Cortical Collecting Tubule

- Nonreabsorbable anions
- Na with a nonreabsorbable anion (e.g., ticarcillin, piperacillin Na) enhances H and K secretion
- With NaCl, Na will be reabsorbed with little effect on H & K secretion
Nonreabsorbable Anions

• The following antibiotics all contain Na:
  – Amoxicillin 2.6 mEq/g
  – Ampicillin 3.0 mEq/g
  – Azlocillin 2.7 mEq/g
  – Piperacillin 1.9 mEq/g
  – Ticarcillin 5.2 mEq/g

• Q: What is the acid-base disturbance seen with high-doses of these antibiotics? Get your clicker ready
What is the acid-base disturbance seen with high-doses of these antibiotics?

A) Metabolic alkalosis
B) Hypokalemic, metabolic alkalosis
C) Hyperkalemic, metabolic alkalosis
D) No clue
Compensation

• Immediate response:
  – movement of $H^+$ from cells to ECF in exchange for K and Na

• Respiratory compensation
  – hypoventilation
  – central & peripheral chemoreceptors sense an increase in pH
Cortical Collecting Tubule

- H₂O dissociates to H⁺ & hydroxyl ions
- H⁺ secreted into peri-tubular capillary by H-ATPase pump
- Hydroxy combines w/CO₂ to form HCO₃ via CA
- HCO₃ is secreted via CL- HCO₃ exchanger
Severe or Prolonged Cases of Metabolic Alkalosis

- pH > 7.55 - 7.6
- Acidifying agents:
  - arginine HCl
  - ammonium Cl
  - HCl
Arginine

- Undergoes liver metabolism to produce $\text{H}^+$
- Arginine combines with free ammonia to make urea -> may increase serum urea and K
- Linked to the development of renal failure
Arginine

- Dangerous hyperkalemia can occur from displacement of intracellular K by the arginine cation
- Serum K should always be monitored during and after arginine
Ammonium Cl

• Combines with CO2 and releases HCl following hepatic conversion to urea
  – caution in renal dz; may worsen uremia

• ADRs: CNS toxicity (confusion, irritability, seizures, coma)

• Caution: pts with hepatic dz cannot metabolize this drug -> hyperammonemia -> significant CNS depression
Hydrochloric Acid

• Indicated in pts:
  • with life-threatening alkalosis that has resulted in respiratory failure or tetany
  • in whom ammonium Cl (hepatic dz) or arginine HCl (development of renal failure) is considered dangerous
  • with life-threatening alkalosis that has not responded to NS
Hydrochloric Acid

- Administration is very dangerous
  - severe extravasations has occurred
  - HCL must be given through a catheter placed in the vena cava or a large tributary vein
  - Catheter placement should be confirmed radiographically
- Very large volumes of fluid needed to make these dilute solns
  - ICU pts w/cardiovascular or renal impairment may be unable to tolerate fluids
- To limit potential ADRs, only 50% of the calculated base excess is corrected in 1st 8h
Base Excess

• Used for all chloride-donating agents
• Base excess = Cl mEq needed =
• ([HCO3]observed - 25) x 50% TBW