Metabolic Alkalosis

Metabolic Alkalosis: Classical Definition

Metabolic alkalosis – a common primary acid-base disturbance with elevated arterial pH, increased bicarbonate, and PaCO₂.
- Frequently accompanied by hypochloremia and hypokalemia
[HCO₃⁻] may be NORMAL or LOW
- Depends on ECFV and content of HCO₃
- AND presence or absence of Mixed Disturbance

Differential Diagnosis of elevated serum HCO₃⁻ and low Cl⁻
- **Metabolic alkalosis**
- **Respiratory acidosis**
  - Therefore, diagnosis requires a concomitant arterial pH.

Respiratory Compensation for Metabolic Alkalosis

- Compensation less effective than for metabolic acidosis; limited by hypoxemia, PCO₂ rarely > 55
- PₐCO₂ will increase 6 mmHg for each 10 mEq/L increase in [HCO₃⁻]
- PₐCO₂ will increase 0.75 mmHg per mEq/L increase in [HCO₃⁻]
- PₐCO₂ = [HCO₃⁻] + 15
  - when HCO₃⁻ in the range of 10-40 mEq/L

Clinical Spectrum of Metabolic Alkalosis
- **Simple**
- **Mixed**
  - Often mixed with respiratory disturbance
  - Very common in critically ill patient
  - Mixed metabolic/respiratory alkalosis in ICU associated with poor prognosis
  - Correlates with severity of alkalemia
- Mixed with metabolic acidosis
  - High anion gap acidosis, not HCMA
  - Look for mismatch of ΔAG and ΔHCO₃⁻

Case 1

A 64 year old woman with a history of severe congestive heart failure, underwent cholecystectomy 3 days previously; on continuous NG suction, fixed rate ventilatory support, and I.V. Ringer’s lactate containing KCl 15 mEq/l.
Laboratory Studies (Case 1)

<table>
<thead>
<tr>
<th>Plasma electrolytes</th>
<th>Urine electrolytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ 133</td>
<td>Na⁺ 35</td>
</tr>
<tr>
<td>K⁺ 3.9</td>
<td>K⁺ 44</td>
</tr>
<tr>
<td>Cl⁻ 80</td>
<td>Cl⁻ 4</td>
</tr>
<tr>
<td>HCO₃⁻ 44</td>
<td></td>
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<tr>
<td>BUN 24</td>
<td></td>
</tr>
<tr>
<td>Creatinine 1.8</td>
<td>CVP = 20 mmHg</td>
</tr>
<tr>
<td>pH 7.67</td>
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</tr>
<tr>
<td>P₂O₅ 98</td>
<td></td>
</tr>
<tr>
<td>P₂CO₂ 38</td>
<td></td>
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<tr>
<td>mmHg</td>
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Question (Case 1): Select the most appropriate therapeutic intervention for the treatment of the acid-base and electrolyte disorder in this case:

A. 0.1N HCl IV
B. 5% dextrose IV
C. 0.9 % NaCl IV
D. Furosemide 80 mg. IV
D. Acetazolamide 250-500 mg IV

Causes of Alkalemia in the ICU

• NaHCO₃
• Citrate (whole blood); or in CRRT
• Acetate; TPN
• NG suction or vomiting
• Diuretics
• Over-ventilation
• Sepsis
• Steroids

Pathophysiology: Phases of Metabolic Alkalosis

1. Generative Stage
   - Loss of acid (vomiting), Cl, K, etc.
   - Gain of HCO₃⁻ (Kidney or exogenous)
   - Primary aldosteronism (enhances renal acid and potassium excretion)

2. Maintenance Stage (kidney loses ability to excrete bicarbonate efficiently and paradoxically, bicarbonate is absorbed)
   - Volume contraction, low GFR, Cl⁻ or K⁺ depletion, high PCO₂, secondary hyperaldosteronism

Gastric and Pancreatic H⁺ and HCO₃⁻ Secretion: Generation of Metabolic Alkalosis from Vomiting or NG Suction

Maintenance of Metabolic Alkalosis

1. Increased RHCO₃⁻
2. Increased NAE
Three Cell Types in CCT

**Association of Hypokalemia with Metabolic Alkalosis**

- **Common Etiologies**
  - Volume contraction, chloride depletion, secondary hyperaldosteronism (diuretics)
  - Selective effects of hypokalemia
    - Increase in renal ammonium production; increased NH4+ transport and NAE; providing new bicarbonate
    - Increase in H+,K+-ATPase activity and abundance in CT
    - Increase in proximal tubule bicarbonate absorption, EBF receptor mediated

- **Two Clinical Presentations: Separate Pathophysiological Mechanisms**
  - **ECF volume contraction, hypotension, CI deficiency, K+ deficiency, decrease in GFR**
    - A-II and ET-1 enhance proximal bicarbonate absorption (NHE-3)
    - Secondary hyperaldosteronism (diuretics)
    - Hypokalemia up-regulates H+,K+-ATPase in OMCT
    - Hypokalemia enhances ammonium excretion (NAE)
    - Repair with i.v. saline and potassium administration
  - **Volume expansion and hypertension associated with aldosterone excess and K+ deficiency (renin low or high)**
    - Aldosterone stimulates H+,K+-ATPase in CCT
    - Hypokalemia stimulates H+,K+-ATPase in OMCT
    - Hypokalemia enhances ammonium excretion
    - Repair by surgical or pharmacologic-specific means not saline

- **Specific Causes of Metabolic Alkalosis**
  - **Volume Contraction (GI, Renal, or Extrarenal)**
    - Low Urine Chloride
      - Vomiting, Nasogastric suction, gastrocytoplasty, chronic laxative abuse and chronic diarrheal states, cystic fibrosis, CI deficiency infant formula
      - Renal loss: remote use of diuretics, drug anions, magnesium deficiency
    - High Urine Chloride
      - Current diuretic administration
      - Bartter or Gitelman Syndrome
      - CaSR stimulation or Bartter variant (pseudo-Bartter)
  - **Volume Expansion, hypertension, potassium deficiency driven by aldosterone excess**
    - High renin (renal artery stenosis, severe hypertension, tumor)
    - low renin (renal adenoma or BAH, AME, licorice (chewing tobacco, London Drop licorice candy), Liddle syndrome)

- **Exogenous Alkali Loads**
  - Acute alkaline administration
    - Reduction in GFR plus source of HCO3
      - NaHCO3, citrate (with blood transfusion and CRRT), antacids plus sodium exchanges; chewing tobacco
  - Chronic alkaline administration
    - Milk alkalosis syndrome
      - Nephrocalcinosis, renal insufficiency and metabolic alkalosis
    - Vitamin D excess and hypercalcemia
    - Ingestion of milk and bicarbonate (Sippy Diet)
    - NaHCO3, pic in CKD, ESRD, CHF, preeclampsia
    - Calcium carbonate in osteoporosis, and in CKD as phosphate binder

- **Homespun remedy, homespun toxicity:** Baking soda ingestion for dyspepsia

A 68-year-old man presented to the Emergency Department with a severe metabolic alkalosis after ingesting large quantities of baking soda to treat his dyspepsia. His underlying pulmonary disease and a progressively worsening mental status necessitated intubation for respiratory failure. Laboratory studies revealed a hynopenemic, hypochloremic, hypokalemic metabolic alkalosis. The patient was successfully treated after cessation of the oral bicarbonate, initiation of intravenous hydration, and correction of electrolyte abnormalities.

Metabolic alkalosis in skilled nursing home patients


Renal failure is common among the long-term care (LTC) elderly. LTC elderly patients, in stable clinical condition, on naso-gastric tube (NGT) feeding, or orally fed (OF), were recruited. As controls, we studied a group of independent, ambulatory patients admitted to the acute geriatric departments of the hospital for different causes which were not related to their acid-base status. Renal function was similar in the two main study groups. The LTC elderly patients had significantly higher venous pH values, with no differences in pCO2 or HCO3. An alkalotic state (pH > 7.45) was found in 13.6% (18% in the NGT and 6.5% in the OF) while none of the independent elderly had such values (p < 0.05). Similarly, HCO3 > 34 was found in 12% of the LTC elderly versus none in the independents (p = 0.06). Values of pO2 and O2 saturation were significantly higher in the nursing elderly and mainly those fed by NGT. Hemoglobin levels had a significantly negative correlation with the pH (r = -0.3, p < 0.002). Daily excretion of sodium and chloride were 50% lower in the NGT fed patients (p < 0.001).

In conclusion, unexpected metabolic alkalosis was found in a group of skilled nursing home patients, more prominent in those fed by NGT. This finding warrants the inclusion of routine pH determination in patients whenever pharmacokinetic considerations are essential.

Genetic and Molecular Basis of Renal Solute Wasting Syndromes with Metabolic Alkalosis

Recent Advances, Recognition and Treatment

Bartter and Gitelman Renal Solute Wasting Syndromes

- **Bartter Syndrome**
  - Autosomal recessive
  - Cl- resistant metabolic alkalosis, hypokalemia, hypovolemia, hyperreninemic-hyperaldosteronism, enhanced distal Na+ delivery, renal K+ wasting, JG hyperplasia.
  - Differential Diagnosis: Must rule out chronic vomiting or diuretic abuse.
    - Five classical forms: mutations of either NKCC2, KCNJ1, ClCNKb genes encoding transport channels in TALH apical membrane.
    - Antenatal Bartter with deafness, polyhydramnious, renal failure: BSND (Barttin, co localizes with ClC-Kb channel)
    - CaSR in TALH - acquired form: aminoglycosides upregulate CaSR to inhibit NKCC2
    - All forms same phenotype: defect in TALH salt absorption, salt wasting.

- **Gitelman Syndrome**
  - Above manifestations plus hypocalciuria, renal Mg2+ wasting, Mg2+ deficiency and salt craving
  - Defect of SLC12A3 or ClCNKB gene = loss of function mutation in NCCT in DCT; mimics thiazides.

Management is a challenge in Gitelman Syndrome

- Salt craving is distinct feature and it drives K wasting.
- Amiloride works better than spironolactone, but underused (or incorrectly used).
- Always give KCl
- Low doses of ACE-Is may not cause BP decline in some (remember that they are borderline hypotensives)

Pendrin Syndrome

- Autosomal recessive mutation of SLC26A4 gene
- Encodes pendrin (anion exchanger in inner ear, thyroid and Type B IC of CCT)
- Common cause of hereditary deafness
- Typically no acid-base abnormality
- Two recent cases of severe metabolic alkalosis and hypokalemia
  - Protracted vomiting
  - Thiazide diuretic
Hypertension, Volume Expansion, K⁺ deficiency, and mineralocorticoid excess

**High Renin**
- Renal artery stenosis
- Renin-secreting tumor
- Estrogen therapy
- Accelerated hypertension

**Low Renin**
- Primary aldosteronism (adenoma, carcinoma, hyperplasia)
- Adrenal enzyme defects (11β or 17α hydroxylase deficiency)
- Cushing syndrome (pituitary, adrenal adenoma, ectopic)
- Syndrome of apparent mineralocorticoid excess (AME), chronic ingestion of licorice or licorice-like compounds (carbenoxolone) mimics primary aldosteronism (11βHSD).
- Liddle syndrome

**Liddle Syndrome**

- **Clinical Features**
  - Early & severe form of inherited hypertension, renal K⁺ wasting, chloride resistant metabolic alkalosis, but low renin and aldosterone (pseudo-hyperaldosteronism):
    - Responds to amiloride and dietary salt restriction
  - Autosomal dominant form of monogenic hypertension; gain of function in ENaC in CCT
    - Increase Na⁺ absorption (volume expansion, HBP)
    - Increase in K⁺ and H⁺ secretion

- **Biology**
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Treatment of Metabolic Alkalosis: Treat associated problems first

- **Low Urine [Cl⁻]** (<10-15 mEq/L)
  - NG suction, or diuretics
  - Give NaCl, PPIs, stop diuretics
  - Stop alkali precursors
    - Lactate, acetate, citrate, calcium carbonate, Kayexalate, glucocorticoids
  - Repair electrolyte deficits (K⁺, Cl⁻, Mg²⁺)
  - Increase excretion of bicarbonate
    - iv. NaCl, acetazolamide (250 - 500 mg. X 1 or 2)
    - 0.1 N HCl ([HCO₃⁻] > 50)
    \[ H^+ \text{ deficit (mEq)} = 0.5 \times \text{BW (kg)} \times (\text{actual } \text{HCO}_3^- - \text{desired } \text{HCO}_3^-) \]

- **High Urine [Cl⁻]** (>15-20 mEq/L)
  - Cause specific (surgery, angioplasty, specific drug therapy)

Specific Treatment of Inherited Metabolic Alkalosis Syndromes

- **Bartter Syndrome**
  - Repair hypokalemia, inhibit renin-angiotensin
  - Spironolactone, propranolol, NSAIDs, KCl, ACE-I or ARB?

- **Gitelman Syndrome**
  - Difficult to manage: Salt restriction, KCl, amiloride, Mg²⁺, ACE-I or ARB?

- **Liddle syndrome**
  - Amiloride, dietary salt restriction