Metabolic alkalosis

September 21, 2019 by Josh Farkas

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diagnosis

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Metabolic alkalosis may be diagnosed in two situations (red arrows above):

1. If the serum bicarbonate is elevated (>28 mM), this alone reveals a metabolic alkalosis.
2. If the anion gap is elevated but the reduction in bicarbonate is considerably less than would be expected for an isolated anion-gap metabolic acidosis, this indicates the presence of a combination of an anion-gap metabolic acidosis plus metabolic alkalosis.

**potential symptoms**

- Seizures, delirium.
- Arrhythmia
- Hypocalcemia due to alkalosis (elevated pH shifts calcium ions onto albumin, thereby reducing ionized calcium levels).
  - Paresthesias, carpopedal spasm.
- Hypoventilation (due to respiratory compensation for the metabolic alkalosis).
  - Generally not a significant issue.
  - For patients with a tenuous respiratory drive (e.g. obesity hypoventilation syndrome or COPD), severe metabolic alkalosis may promote hypoventilation.

**relationship of labs to symptoms?**

- Unclear.
- Bicarbonate levels <40 mM are typically asymptomatic. The likelihood of seizure may increase at levels >50 mM (24766943 [https://www.ncbi.nlm.nih.gov/pubmed/24766943]).

https://emcrit.org/ibcc/metabolic-alkalosis/
compensatory for a severe, chronic respiratory acidosis

- Physiologic response to chronic hypercapnic respiratory failure of any cause, most commonly:
  - Severe COPD
  - Obesity hypoventilation
  - Chronic respiratory muscle weakness

chloride-depletion metabolic alkalosis, a.k.a. “saline-responsive” (urine chloride <10-30 mM, usually patient is hypovolemic)

- Vomiting or nasogastric suction
- Chloride-wasting diarrhea (villous adenoma, laxative abuse)
- Remote diuresis
- High-dose penicillin therapy
- Renal hypoperfusion (due to hypovolemia, heart failure, or cirrhosis) PLUS exogenous alkali
  - TPN with excess acetate
  - Citrate (massive transfusion, plasmapheresis)
  - Bicarbonate administration (e.g. milk-alkali syndrome, calcium carbonate intake)

non-chloride-depletion metabolic alkalosis, a.k.a. “saline-unresponsive” (urine chloride >10-30 mM)

- Active diuresis
- Hypomagnesemia or severe hypokalemia
- Hyper-aldosteronism of any etiology (may be supported by presence of hypertension)
  - Primary aldosteronism: Aldosterone-secreting adenoma, bilateral adrenal hyperplasia, carcinoma
  - Secondary aldosteronism: Renin-secreting tumor, malignant hypertension, renal artery stenosis, renal infarction
  - Cushing's syndrome, exogenous mineralocorticoid
- Renal insufficiency PLUS exogenous alkali
  - TPN with excess acetate
  - Citrate (massive transfusion, plasmapheresis)
  - Bicarbonate administration (e.g. milk-alkali syndrome, calcium carbonate intake)
(a) history, physical, and review of archival data

- Review of available information will usually reveal the cause of the metabolic alkalosis.
- Hypovolemia (e.g. on bedside echocardiography) suggests chloride deficiency.
- Hypertension may suggest a state of aldosterone excess.
- Chronicity may be helpful (e.g. a chronic metabolic alkalosis may suggest chronic compensation for COPD or obesity hypoventilation).

(b) if the cause remains unclear: basic lab evaluation

- Complete electrolytes (including Ca/Mg/Phos).
- VBG or ABG
- Urine potassium and chloride levels:
  - Urine potassium <20-30 mM suggests that hypokalemia may be contributory.
  - Urine chloride concentration is the most important:
    - Chloride < 10-30 mM suggests saline responsive.
    - Chloride > 10-30 mM suggests saline unresponsive.
    - Chloride between 10-30 mM lies in a grey area and doesn't provide reliable diagnostic information (24766943).

(c) evaluation of the renin-angiotensin-aldosterone system (RAAS)

- Generally, this isn't useful in critical care.
- Consider this evaluation if:
  1. Basic evaluation (a-b above) doesn't reveal a cause of alkalosis.
  2. Patient has persistent alkalosis with urine chloride >10-30 mM, and/or is refractory to normal saline infusion.
  3. Other clinical features suggest excessive activity of the renin-angiotensin-aldosterone system (e.g. hypertension, hypokalemia)
- Investigation of the RAAS involves measurement of renin & aldosterone levels.
- These may be interpreted as follows (30369299):
  - Low renin & high aldosterone ==> Primary hyper-aldosteronism (Aldosterone-secreting adenoma, bilateral adrenal hyperplasia, adrenal carcinoma).
  - High renin & high aldosterone ==> Secondary hyper-aldosteronism (Renin-secreting tumor, renal artery stenosis, malignant hypertension).
  - Low renin & low aldosterone ==> State of apparent mineralocorticoid excess (Cushing's syndrome, exogenous mineralocorticoid, licorice ingestion).

when to treat?

compensatory metabolic alkalosis (due to chronic respiratory failure) should usually be left alone

- Patients with chronic hypercapnec respiratory failure will develop a chronic compensatory metabolic alkalosis.
- This is a compensatory mechanism which is generally beneficial. The metabolic alkalosis allows them to have a fairly normal pH, despite hypoventilation.
  - Without metabolic compensation, these patients would be acidemic and have an increased respiratory drive. This could cause dyspnea, respiratory exhaustion, and eventually full-on respiratory failure.
- One exception is that if a chronic compensatory alkalosis is exacerbated (e.g. by diuresis), then it may be reasonable to attempt to return the patient to their chronic baseline bicarbonate level.

ideal treatment is to resolve the cause

- Most cases of metabolic alkalosis don't require specific therapy directed at immediately reducing the bicarbonate. Instead, resolving the underlying cause is generally sufficient. For example, a patient with hypovolemia may be treated with volume resuscitation.
However, specific treatment of the alkalosis may be indicated in the following situations:

- Alkalosis is moderate to severe (either causing or threatening to cause symptoms).
- The process causing the alkalosis can't be easily reversed (e.g. patient develops contraction alkalosis from diuretics, but you need to continue diuretic therapy to achieve volume control).

If a decision is made to treat the alkalosis, potential treatments are listed below. Depending on the severity of the alkalosis and the clinical scenario, either one or several simultaneous therapies may be utilized.

1) **aggressive electrolyte repletion if hypokalemic and/or hypomagnesemic**

- Hypokalemia often serves to maintain alkalosis.
  - Potassium chloride should be supplemented aggressively to **target a potassium > 4.5 mM** (unless the patient has renal failure, which places them at increased risk of hyperkalemia). There is a direct relationship between serum potassium levels and ability to excrete bicarbonate.
  - Don't use other types of potassium salts (e.g. potassium citrate or potassium acetate), as the citrate or acetate anions may contribute to alkalosis.
  - Hypomagnesemia may contribute to alkalosis and make it difficult to successfully treat the hypokalemia. Therefore, hypomagnesemia should also be corrected (see: [hypomagnesemia chapter](https://emcrit.org/ibcc/hypomagnesemia/)).

2) **if hypovolemic, give normal saline**

- Resuscitation with normal saline may be helpful among patients with hypovolemia (“saline-responsive alkalosis”).
- Urine chloride <10-30 mM predicts improvement following normal saline.
- This is one situation where normal saline is superior to Lactated Ringers or Plasmalyte (because you're looking for an acidotic uid).

3) **if hypervolemic, give diuretics which promote bicarbonate excretion**

- **Acetazolamide**
  - Most commonly used diuretic for metabolic alkalosis and perhaps the most effective.
  - Dosing regimens vary. The following regimen is a bit aggressive, yet proven to be safe among ICU patients in the [DIABOLO study](https://www.ncbi.nlm.nih.gov/pubmed/26836730):
    - Metabolic alkalosis in patients receiving simultaneous loop diuretics: 1,000 mg IV acetazolamide q12hr.
    - Metabolic alkalosis in patients not receiving simultaneous loop diuretics: 500 mg IV acetazolamide q12hr.
  - Make sure to monitor potassium levels carefully (acetazolamide may induce hypokalemia, which will aggravate treatment of the metabolic alkalosis).
- **Spironolactone**
  - Increased mineralocorticoid activity is often a primary or secondary cause of metabolic alkalosis.
  - Spironolactone may be useful for patients with volume overload (e.g. congestive heart failure) or hyperaldosteronism.
  - Main drawback of spironolactone is that it works via stimulation of genetic transcription, so it takes ~24-48 hours to work.
- **Amiloride or triamterene**
  - Not commonly used for metabolic alkalosis, but they might help a bit.
  - Additional benefits include: counter-balancing potassium loss induced by acetazolamide, and promotion of overall diuretic efficacy.

4) **hold or decrease the dose of alkalosis-inducing diuretics (e.g. furosemide)**

- If the patient is close to euclidean, then simply discontinuing alkalosis-inducing diuretics makes sense.
- In patients with mild alkalosis plus severe volume overload, it may be possible to continue diuresis using a combination of low-dose furosemide plus diuretics which promote bicarbonate loss (#3 above).
  - This should be done along with other measures in this section to promote resolution of the alkalosis.

5) **proton pump inhibitor in patient with ongoing vomiting or nasogastric suction**
• Loss of acidic gastric contents will cause a metabolic alkalosis.
• Administration of a proton pump inhibitor (PPI) neutralizes the pH of gastric secretions, preventing loss of acid via the stomach.

6) for intubated patients, adjust ventilator to target mildly alkalemic pH
• Hypoventilation leading to a normal or acidemic pH could impair renal bicarbonate excretion.
• To facilitate renal bicarbonate excretion, consider targeting a mildly elevated pH (e.g. 7.45-7.50).

7) reformulate total parenteral nutrition (TPN)
• For patients on TPN, adjust the formulation to remove any sodium acetate.

8) dialysis
• This is a potential treatment of metabolic alkalosis among patients with renal failure.
• Alkalosis alone is an exceedingly uncommon indication for dialysis. However, dialysis could be reasonable in a patient with other indications as well.
  • In a patient with numerous profound electrolyte abnormalities (electrolytic disarray), dialysis will fix all problems simultaneously. This is an artless, yet effective, approach.

9) intravenous hydrochloric acid
• May be used if the above therapies fail or aren't working fast enough (see below).

**hydrochloric acid**

usual indications for IV hydrochloric acid
• Severe metabolic alkalosis (pH over ~7.55 or bicarbonate over ~38 mM), plus one of the following:
  • (a) Failure of more conservative modalities.
  • (b) Alkalosis is so profound that immediate control is needed (insufficient time to use more conservative treatments). Clinical manifestations such as delirium, seizure, or arrhythmia may support a need for immediate therapy.
  • (c) Patient remains volume overloaded, requiring ongoing therapy with diuretics. In this context, HCl may allow for ongoing diuresis with simultaneous management of acid-base status (29359573). Hydrochloric acid is effective and safe (if monitored and dosed properly). However, it's generally avoided due to unfamiliarity with this therapy.
• This must be given via central line, ideally via the distal port of the line (if line gets pulled back a bit, the distal port will remain intravascular).
  • Central line position should be confirmed with chest X-ray and should lie in the superior vena cava or right atrium.

**estimate dosage of acid required**
• Shoot for a desired bicarbonate above normal (e.g., ~35 mEq/L).
  • This is a safe bicarbonate level, but if you overshoot the patient won't be rendered acidemic.
  • The goal isn't to normalize the bicarbonate, but rather merely to remove the patient from immediate danger due to alkalemia.
• Calculate bicarbonate excess:
  • Formula for bicarb excess = \((0.5)(\text{lean body weight})(\text{plasma bicarb} – \text{desired bicarbonate})\)
  • If we're shooting for a bicarbonate level of ~35 mEq/L, then...
    • Bicarb excess = \((0.5)(\text{lean body weight})(\text{plasma bicarbonate} – 35 \text{ mEq/L})\)
• These formulas are very rough estimates, and aren't supported well by evidence (29359573). In a recent published series, the mean amount of HCl infused was 300 mEq.
• This represents a starting point only. It doesn't negate the need to monitor electrolytes & pH during infusion.

**administration**
• Hydrochloric acid is supplied as 0.1-0.2 Normal solution of HCl (0.1-0.2 mEq/ml). Ideally this should be formulated in sterile water, to avoid volume overload.

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- 0.1 Normal = 100 mEq/L
- 0.2 Normal = 200 mEq/L
- The maximum safe infusion rate is 0.2 mEq/kg/hr.
  - For 0.1 Normal, this is equal to 2 ml/kg/hr (i.e. ~150 ml/hr).
  - For 0.2 Normal, this is equal to 1 ml/kg/hr (i.e. ~75 ml/hr).
- In practice, the average infusion rate is ~10 mEq/hour (29359573)
  - For 0.1 Normal, this is equal to 100 ml/hour.
  - For 0.2 Normal, this is equal to 50 ml/hour.
- Monitor electrolytes (including Ca/Mg/Phos) and ABG/VBG (e.g. after every ~75 mEq administered).

**risks**

- (1) If central line is displaced, it may necrose tissue.
- (2) Volume overload (if you are using 0.1 Normal solution, this will take a large volume of fluid).
- Electrolyte abnormalities.

**continue conventional therapy for metabolic alkalosis!**

- In addition to hydrochloric acid, also simultaneously pursue additional treatments to decrease the patient's bicarbonate level (see #1-#9 above).
- The goal of hydrochloric acid is to accelerate treatment, to more rapidly move the patient out of danger from severe alkalemia. However, this isn't really intended as the definitive (or sole) treatment.

**protocol**

- The approach below isn't necessarily optimal for every patient (it might be too conservative in some situations, or a bit aggressive for very small patients). However, it's simple and represents a good place to start in most cases.

**Simple protocol for HCl infusion**

- **Access**
  - Must only be infused via central line.
  - Confirm line placement in vena cava (SVC or IVC) or right atrium.
  - Use the distal port of the line.
- **Infuse HCl at a rate of 10 mEq per hour**
  - With 0.1 Normal HCl, this is equal to 100 ml/hour.
  - With 0.2 Normal HCl, this is equal to 50 ml/hour.
- **Monitor electrolytes every 6 hours**
  - Monitor electrolytes (including Ca/Mg/Phos) and pH (either VBG or ABG).
  - Stop HCl infusion when a safe acid-base status is reached (the goal isn't complete normalization).

- The Internet Book of Critical Care, by @PalmCrit

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**podcast**


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[https://emcrit.org/ibcc/metabolic-alkalosis/](https://emcrit.org/ibcc/metabolic-alkalosis/)
Metabolic alkalosis commonly occurs during diuresis. This isn't a contraindication to further diuresis. Ongoing diuresis may be performed if needed, but this must be done with simultaneous treatment of the metabolic alkalosis (e.g. using acetazolamide, spironolactone, and potassium chloride supplementation).

For severe metabolic alkalosis, don’t rely on a single treatment (e.g. normal saline). Instead, a multimodal strategy may be most effective, with attention to all factors which may be perpetuating the metabolic alkalosis.

Going further:

- **John Hinds lecture on the EMCrit podcast** – Discussion of HCl for metabolic alkalosis 30 minutes into the podcast.


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.