Approach to Metabolic Alkalosis

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INTRODUCTION

Metabolic alkalosis is defined as increased arterial pH greater than 7.42 or an increase in serum bicarbonate to greater than 30 mmol/L. It is the result of an increase in bicarbonate production, a decrease in bicarbonate excretion, or a loss of hydrogen ions. In a person with normal renal function, the regulatory response of the kidney leads to a decrease in bicarbonate by excreting the excess alkali. Metabolic alkalosis can be sustained only when renal regulation is disrupted.1,2

Metabolic alkalosis is common, accounting for half of all acid-base disorders in hospitalized patients.3 Although most of the patients can tolerate mild metabolic alkalosis, severe alkalosis can have significant adverse effects on cellular function and can lead to increased mortality.4 Patients with mild to moderate metabolic alkalosis, with serum bicarbonate levels less than 40 mmol/L, are typically asymptomatic. However, mortality approaches 45% when patients develop arterial pH of 7.55% and 80% when the pH is greater than 7.65.5

CLINICAL PRESENTATION

The workup of any patient in the emergency department should always begin by obtaining a history. Any history of excessive vomiting or diarrhea, recently added or
increased dosages of diuretics, recent history of surgery that required nasogastric tube insertion, or a history of family members with excessive thirst and urination as children or fatigue and muscle wasting as adults may lead the clinician to a diagnosis of metabolic alkalosis.

Patients with mild to moderate metabolic alkalosis, with serum bicarbonate levels less than 40 mmol/L, are typically asymptomatic. When symptoms do occur, they are usually a consequence of an electrolyte abnormality rather than the alkalosis itself. For instance, in patients with ischemic heart disease, hypokalemia increases the risks of developing cardiac arrhythmias. Other symptoms include paresthesias, muscular cramping, and tetany, which are again likely caused by electrolyte abnormalities associated with the alkalosis. As bicarbonate levels increase to 45 mmol/L, the physiologic compensation is to correct the alkalosis by hypoventilation, leading to hypoxemia, especially in patients with chronic obstructive pulmonary disease. Once bicarbonate levels increase higher than 50 mmol/L, patients may develop seizures, altered mental status, and coma. Therefore, identifying the cause of this acid-base disorder and initiating specific treatment is important.

**DIAGNOSIS**

The diagnosis of metabolic alkalosis is sometimes a clinical one, but it is often found incidentally of laboratory work. On a routine serum chemistry panel, a bicarbonate level higher than 30 mmol/L in association with hypokalemia is pathognomonic for metabolic alkalosis. Once the diagnosis of metabolic alkalosis has been established, it is important to fully characterize the disorder by obtaining an arterial or venous blood gas to obtain a pH and PaCO₂ measurement (partial pressure of carbon dioxide, arterial), especially if the alkalosis is severe with bicarbonate levels greater than 40 mmol/L. As the serum bicarbonate level increases, there is an increase in PaCO₂ which is caused by compensatory hypoventilation.

Another useful tool in the diagnosis of metabolic alkalosis is the measurement of the urine chloride concentration. Urine chloride concentration of less than 10 mmol/L is usually observed in chloride-responsive metabolic alkalosis, whereas a concentration greater than 30 mmol/L is usually seen in non–chloride-responsive metabolic disorders such as mineralocorticoid excess or apparent excess syndromes. Patients with metabolic alkalosis associated with severe hypokalemia, volume depletion caused by diuretic use, Bartter and Gitelman syndromes, or alkali ingestion can have a urine chloride concentration in an indeterminate range between 10 and 30 mmol/L. There is little usefulness of urine chloride concentration alone as a diagnostic tool if the result is in this range.1,6

**CAUSE AND MANAGEMENT**

There are several possible causes of metabolic alkalosis in patients. The most common causes are listed in Box 1. The major decision point in making the diagnosis is based on volume status and blood pressure. An algorithmic approach to the workup and management of metabolic alkalosis is detailed in Fig. 1. Patients with evidence of volume depletion who are either normotensive or hypotensive are more likely to have metabolic alkalosis caused by chloride depletion. If the cause is clear, such as a history of vomiting, nasogastric suction, or diuretic use, the appropriate management is to treat the underlying disorder. If the cause is unclear, a trial of chloride repletion often helps elucidate the cause. Metabolic alkalosis that is easily corrected is usually caused by a simple chloride depletion disorder. If it is not easily corrected, then a hereditary chloride wasting disorder such as Gitelman syndrome or Bartter syndrome...
should be considered. In the hypertensive patient with metabolic alkalosis, mineralocorticoid excess or apparent excess syndromes should be considered, which can be examined by measuring serum aldosterone and renin levels.\textsuperscript{7,8}

The causes of metabolic alkalosis can be divided into the following groups based on pathophysiology: chloride depletion syndromes, mineralocorticoid excess syndromes, apparent mineralocorticoid excess syndromes, alkali administration, and other causes.

**Chloride Depletion Alkalosis**

Chloride depletion is the most common cause of metabolic alkalosis. Traditionally, metabolic alkalosis has been described in the literature as either contraction alkalosis or noncontraction alkalosis, but it has become clear that it is truly chloride depletion or

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Studies have shown that chloride repletion in the absence of volume administration can correct alkalosis. In contrast, volume expansion in the absence of chloride administration does not. On its own, potassium depletion causes a small increase in serum bicarbonate concentration. However, when this increase occurs in conjunction with chloride depletion, the resultant alkalosis is 4 times as great. Chloride depletion alkalosis is associated with hyponatremia and hypokalemia as a result of gastrointestinal or renal losses.

**Gastrointestinal losses**

Chloride absorption takes place throughout the gastrointestinal tract. Approximately 7 to 8 L of fluids and electrolytes are excreted and absorbed daily. Chloride is secreted as hydrochloric acid in the stomach. Hydrochloric acid activates pepsinogen into pepsin, which functions in numerous antibacterial and nutrient absorption roles. Hydrochloric acid also removes iron from food and aids in its conversion to the ferrous form. Chloride is secreted into the intestine through 3 channels, which depend on osmotic gradients.

**Vomiting or nasogastric suction** Gastric fluid is a chloride ion-rich solution, which is balanced by sodium, potassium, and hydrogen ions. Vomiting or nasogastric suction causes major chloride losses, which are coupled with losses of hydrogen ions as well. This loss of hydrogen ions leads to an increase in serum bicarbonate at levels often several times greater than 45 mmol/L. Subsequently, this leads to a decrease in serum potassium as potassium ions enter the cell to replace the hydrogen ions. Thus, suctioning leads to a metabolic alkalosis, which is associated with hypochloremia and hypokalemia. This alkalosis persists until both chloride and potassium are repleted.

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**Fig. 1.** An algorithmic approach to the workup and management of metabolic alkalosis. BP, blood pressure; NG, nasogastric.
Congenital chloridorrhea  Congenital chloridorrhea is a disorder caused by a genetic mutation, which leads to an absence of intestinal bicarbonate/chloride exchange in the intestine. Consequently, chloride is not absorbed and bicarbonate is not excreted, resulting in large-volume watery diarrhea, which contains mostly sodium, chloride, and potassium. Management of fluid and electrolyte losses in these patients is difficult, such that they have sustained metabolic alkalosis throughout their lives and are chronically hypovolemic.11

Villous adenoma of the colon  Most patients with villous adenoma are asymptomatic. However, patients with villous adenoma with McKittrick-Wheelock syndrome can present with severe dehydration and hypovolemic shock as a result of chronic diarrhea, with daily fluid losses up to 4 L. Large amounts of sodium and chloride ions are lost as a result of copious diarrhea caused by these rare tumors.12 Although little is known about the mechanism of the tumor, the secretory complication is a known cause of metabolic alkalosis.12

High-output ileostomy drainage  Patients with ileostomy are susceptible to electrolyte disturbances as a result of obligatory large volume and electrolyte loss. When the drainage increases unexpectedly, patients can develop severe metabolic acidosis or alkalosis. Although most patients develop metabolic acidosis as a result of highly concentrated HCO₃⁻ ileostomy fluids, few patients develop metabolic alkalosis. The mechanism is not clear, but these patients produce abnormally high concentrated chloride ion in ileostomy fluids, which leads to severe metabolic alkalosis.13 Because these patients are extremely sensitive to electrolyte and acid-base balance, it is important to treat the underlying cause for increased ileostomy output and replenish extracellular fluids and electrolytes.

Renal losses  Excretion of chloride primarily occurs in the kidney. Fig. 2 shows where the chloride transporters are. The proximal convoluted tubule is the site for most of the sodium, chloride, and bicarbonate reabsorption. The site of aldosterone action for the reabsorption of sodium and chloride and secretion of potassium and hydrogen ions occurs in the distal tubule. The collecting duct plays an important role in acid-base transport via hydrogen ion–adenosine triphosphatase (ATPase) and chloride/bicarbonate exchangers. Chloride is also secreted into the lumen and absorbed into the interstitium of the kidney through the sodium-potassium-chloride and chloride-bicarbonate cotransporters. Net loss of chloride causes a net gain of bicarbonate through the cotransporters, adding to the alkalosis.14

Diuretic administration  Diuretics that inhibit chloride transport proteins in the kidney are the most common cause of metabolic alkalosis. Loop diuretics inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb of the loop of Henle. Thiazide diuretics inhibit the sodium-potassium cotransporter in the distal convoluted tubule. Inhibition of these cotransporter proteins impairs chloride reabsorption, resulting in chloride excretion. It also leads to potassium excretion by increasing sodium delivery to the collecting duct. The alkalosis is typically mild ([HCO₃⁻] <36 mmol/L).1

Impairment of chloride-linked sodium transport  Bartter and Gitelman syndromes are characterized by hypochloremic metabolic alkalosis, hypokalemia, and normal to low blood pressure. Bartter syndrome is caused by one of several mutations that inactivate or impair the function of the sodium-potassium-chloride transporter in the thick ascending limb of the loop of Henle. The pathophysiologic process of metabolic alkalosis is the same as that induced by loop diuretics. In the classic presentation...
of Bartter syndrome, the symptoms of polyuria, polydipsia, dehydration, vomiting, and growth retardation begin in the first 2 years of life.

Gitelman syndrome is a mild, but not asymptomatic, syndrome. Gitelman syndrome is caused by a mutation in the sodium-chloride cotransporter in the distal tubule. The pathophysiologic process of metabolic alkalosis is the same as that induced by thiazide diuretics. Routine laboratory tests show hypochloremic, hypokalemic metabolic alkalosis combined with hypocalciuria. Patients can present as adults with the following symptoms: muscle weakness, muscle cramps, polyuria, polydipsia, hypotension, dizziness, salt craving, and joint pain. Approximately 40% of patients with Gitelman syndrome have QT interval prolongation on electrocardiography.

Treatment The first step in treating patients with chloride depletion metabolic alkalosis is to diagnose and correct the underlying cause. Replacing the chloride losses results in a correction of the alkalosis. In patients with nasogastric suction or vomiting, hypovolemia poses an additional challenge to chloride loss. Administration of intravenous normal saline replaces the chloride and provides volume repletion. If nasogastric suctioning cannot be terminated, hydrogen and chloride losses can be minimized by administration of an H₂ blocker or a proton pump inhibitor.

On the other hand, if a patient develops metabolic alkalosis while in a volume-overloaded state (cirrhosis or congestive heart failure), to replenishing chloride with potassium chloride must be considered. Hypokalemia plays an integral role in development and maintenance of metabolic alkalosis and should be replaced appropriately with potassium chloride either orally or intravenously.
The carbonic anhydrase inhibitors (acetazolamide) can be used to enhance bicarbonate excretion and subsequently lower serum bicarbonate levels. The carbonic anhydrase inhibitors can be particularly useful when hyperkalemia coexists with the need to diurese in the setting of metabolic alkalosis. They can decrease the serum level of bicarbonate within 12 to 24 hours, but careful monitoring of potassium is indicated.

Rarely, rapid reversal with hydrochloric acid infusion is indicated in severe metabolic alkalosis with pH greater than 7.55 or in patients who have altered mental status or cardiac arrhythmia. Hydrochloric acid infusion is indicated in a patient who cannot tolerate intravenous saline or potassium chloride administration because of volume overload status or renal failure. The infusion must be given in a central line, because it can lead to sloughing of perivascular tissue. Close monitoring of potassium and other electrolytes is necessary, because shifts can occur. Dialysis can also be used for severe metabolic alkalosis but should be reserved for patients who have advanced renal failure and are unable to tolerate other traditional therapy.

Mineralocorticoid Excess Syndromes

Metabolic alkalosis in the setting of excess or apparent excess of mineralocorticoids occurs as a result of stimulation of the collecting duct transport. Aldosterone stimulates sodium reabsorption in the collecting duct of the kidney by activating the mineralocorticoid receptor of sodium-potassium-ATPase pumps and hydrogen ion secretion through activating the mineralocorticoid receptor of hydrogen ion-ATPase pumps. It also stimulates extracellular reuptake of potassium, resulting in significant hypokalemia (<3 mmol/L) and mild alkalosis. Aldosterone secretion is increased in states of hypochloremia caused by concomitant volume depletion. The excess sodium reabsorption also leads to increased potassium losses, renal ammonium excretion, and serum bicarbonate levels.

Primary hyperaldosteronism results from either unilateral or bilateral aldosterone-secreting adrenal adenomas or from hyperplasia of the zona glomerulosa, the aldosterone-forming area of the adrenal glands. The characteristics of the disorder include early-onset hypertension that is refractory to multiple medications. Half of these patients also have hypokalemia and metabolic alkalosis.

Glucocorticoid-remediable aldosteronism is an autosomal-dominant mutation in which aldosterone secretion is stimulated by adrenocorticotropic hormone (ACTH) rather than angiotensin. This situation causes sustained increased aldosterone levels. Patients present with features of primary hyperaldosteronism, including hypertension and hypokalemia. Affected individuals have early-onset hypertension, which is usually refractory to treatment. There is also a high incidence of hemorrhagic stroke at a young age (<40 years), often caused by ruptured intracranial aneurysms.

Secondary hyperaldosteronism, also known as high renin syndrome, is another cause of metabolic alkalosis. Renin is secreted in response to a decrease in blood volume or a reduction in sodium to increase plasma volume and increase blood pressure. Conditions such as renal artery stenosis can trigger release of rennin, which results in increased levels of aldosterone. The result of this condition is retention of sodium and extracellular water.

The causes for secondary hyperaldosteronism can be divided into 2 categories: hypertensive state secondary to a renin-producing tumor or increased renin production as a result of poor renal perfusion. Constant edematous states such as cirrhosis and nephrotic syndrome result in a deficit in effective extracellular fluid and blood volume, resulting in activation of renin-angiotensin-aldosterone cascade. This situation increases absorption of sodium ions and excretion of hydrogen ions via the apical
proton pump. Aldosterone also activates the chloride-bicarbonate exchanger, which adds bicarbonate into the systemic circulation.

**Treatment**
The treatment of primary hyperaldosteronism includes either laparoscopic adrenalectomy or administering mineralocorticoid receptor antagonists (spironolactone and eplerenone), depending if the patient is a surgical candidate or has bilateral aldosterone secretion. Glucocorticoid-remediable aldosteronism is treated with glucocorticoid administration to suppress the secretion of ACTH, thereby decreasing the secretion of aldosterone. The treatment of secondary hyperaldosteronism begins with identifying and addressing the underlying cause. Surgical interventions are indicated in rennin-producing tumors.

**Apparent Mineralocorticoid Excess Syndromes**
Clinically, apparent mineralocorticoid excess syndromes cause metabolic alkalosis, which is impossible to differentiate from hyperaldosteronism. Liddle syndrome, also known as pseudohyperaldosteronism, is an autosomal-dominant genetic mutation that prevents downregulation of the sodium ion channel. This situation causes continuous sodium reabsorption, hypertension, and hypokalemic alkalosis. However, renin and aldosterone levels in these patients are very low. Typical presentation is that of a child or adolescent with hypertension, and at times, with renal failure, who may have siblings with the same symptoms.

11β-Hydroxysteroid dehydrogenase is an enzyme that is adjacent to the mineralocorticoid receptor in the collecting duct, which rapidly converts cortisol to cortisone, decreasing the binding of cortisol to the receptor. 11β-Hydroxysteroid dehydrogenase deficiencies, caused by a mutation of this enzyme, increase the binding of cortisol to the receptor and thus stimulate sodium reabsorption and potassium secretion independent of aldosterone. This situation produces a chloride-resistant metabolic alkalosis and hypertension in the setting of low aldosterone levels. Glycyrrhizic acid, a component of natural licorice, inhibits the activity of 11β-hydroxysteroid dehydrogenase and can cause the same clinic picture.

**Treatment**
Metabolic alkalosis caused by apparent mineralocorticoid excess syndromes is treated by restricting a patient’s sodium intake and adding potassium supplementation. Liddle syndrome and 11β-hydroxysteroid dehydrogenase deficiencies also respond to amiloride.

**OTHER CAUSES**

**Alkali Ingestion or Administration**
Under normal circumstances, the kidney responds quickly to excess alkali by increasing bicarbonate excretion, and thus, metabolic alkalosis exists only transiently. However, in patients with renal failure, ingested or administered alkali cannot be excreted as efficiently, which causes a sustained increase in serum bicarbonate levels. In addition, patients with preexisting hypochloremia or hypokalemia or patients placed on a diet with little chloride who are given alkali supplementation also experience a sustained metabolic alkalosis.

**Alkali ingestion**
Pronounced metabolic alkalosis can occur with consumption of a large amount of bicarbonate or its precursors, such as citrate or acetate. Several cases have been reported in which patients presented with severe metabolic alkalosis after ingestion...
of large amounts of bicarbonate to treat various ailments as a home remedy for the treatment of peptic ulcer disease and wound care or the treatment of common cold.\textsuperscript{6,27} In addition, the administration of citrate to be used as anticoagulants in renal patients has been linked to the development of metabolic alkalosis.\textsuperscript{28,29}

Recently, there has been an increase in the practice of ingesting of bicarbonate to improve sports performance.\textsuperscript{30,31} It has been suggested that bicarbonate improves performance by promoting the efflux of hydrogen ions from working cells and tissues.\textsuperscript{32} The efficacy is not clear-cut based on recent literature. However, patients may present to the emergency department after ingestion of a large amount of sodium bicarbonate before the planned event with gastrointestinal symptoms, including abdominal cramps, vomiting, and stomach bloating.\textsuperscript{33} Routine workup of these patients may show alkalosis. Most patients recover without any sequelae with supportive therapy.

\textit{Milk alkali syndrome}
This syndrome was described in the early 20th century, when ingestion of milk and large amounts of alkali (sodium bicarbonate, magnesium bicarbonate, and bismuth subcarbonate) was used to treat peptic ulcer disease. It consists of hypercalcemia, renal failure, and metabolic alkalosis.\textsuperscript{34} However, with the introduction of other H\textsubscript{2} blockers and proton pump inhibitors as the treatment modality of peptic ulcer disease, the occurrence of milk alkali syndrome has reduced significantly. Recently, a similar condition called the calcium alkali syndrome has emerged, with ingestion of a large amount of calcium carbonate to increase calcium uptake to prevent osteoporosis and over-the-counter treatment of dyspepsia. Similar to the traditional milk alkali syndrome, patients present with hypercalcemia, acute renal failure, and metabolic alkalosis. However, serum phosphorus levels can be normal to low in calcium alkali syndrome in contrast to the traditional milk alkali syndrome, in which phosphorus is high because of the large load from milk and cream.\textsuperscript{35}

The initial treatment consists of fluid resuscitation with normal saline to improve calcium and bicarbonate excretion. It is also important to educate patients on appropriate dosing of the calcium containing medications.

\textit{Profound hypokalemia}
Hypokalemia is often found in patients with metabolic alkalosis. In patients deficient in potassium, as the serum potassium decreases, potassium ions are transported from the intracellular space out to extracellular space in exchange with a hydrogen ion to maintain electric equilibrium. The movements of hydrogen ion contribute to the development of alkalosis. Hypokalemia also activates aldosterone to stimulate potassium/hydrogen ion exchange enzymes to further enhance hydrogen ion secretion.\textsuperscript{4} Because potassium is closely linked to the development and maintenance of metabolic alkalosis, it is crucial to monitor the potassium status of these patients.

\textit{Posthypercapnic alkalosis}
The kidney compensates for chronic respiratory acidosis by increasing bicarbonate reabsorption and accelerating excretion of chloride. When hypercapnia is corrected rapidly by means of mechanical ventilation, increased plasma bicarbonate levels persist in the setting of hypochloremia.\textsuperscript{17} Presence of posthypercapnic alkalosis in the intensive care unit setting may be associated with ventilator dependence and increase stay in the intensive care unit.\textsuperscript{36} The treatment consists of correcting the chloride deficit and expanding the volume.
SUMMARY

Metabolic alkalosis is a common disorder amongst patients presenting to the emergency department. Patients often present without any symptoms but can develop neurologic and respiratory symptoms as their alkalosis worsens. The cause of metabolic alkalosis can be divided into 4 main groups: chloride depletion syndromes, which include gastrointestinal and renal losses; mineralocorticoid excess syndromes; apparent mineralocorticoid syndromes; and excess alkali administration. The cause of this acid-base disturbance is identified by obtaining a history from the patient, then assessing the blood pressure and volume status. The mainstay of treatment is supportive care; however, once a specific cause is identified, it should be addressed to correct the alkalosis and any electrolyte abnormalities.

REFERENCES