INTRODUCTION — Metabolic alkalosis is a relatively common clinical problem that is most often induced by diuretic therapy or the loss of gastric secretions due to vomiting (which may be surreptitious) or nasogastric suction. The elevation in the plasma bicarbonate concentration in this disorder may result from hydrogen loss, hydrogen movement into the cells, alkali administration, or volume contraction around a relatively constant amount of extracellular bicarbonate (called a contraction alkalosis) (see table 1) [1-4].

In addition, some factor (most often volume and/or potassium depletion) must be present to increase net bicarbonate reabsorption. This change in renal function is required to prevent the excess bicarbonate from being rapidly excreted in the urine.

The causes of metabolic alkalosis will be reviewed here. The pathogenesis and treatment of this disorder are discussed separately. (See "Pathogenesis of metabolic alkalosis" and see "Treatment of metabolic alkalosis").

GASTROINTESTINAL HYDROGEN LOSS — Hydrogen loss can occur from the gastrointestinal tract or in the urine. Each meq of hydrogen lost generates one meq of bicarbonate: the hydrogen ion is derived from water, while the associated hydroxyl ion combines with carbon dioxide to form bicarbonate.

Removal of gastric secretions — Gastric contents have high concentrations of HCl and a lesser amount of KCl. In normal subjects, gastric hydrogen secretion does not lead to metabolic alkalosis, since it is matched to pancreatic bicarbonate secretion that is stimulated as the acid enters the duodenum. There is, however, no stimulus to bicarbonate secretion when vomiting or tube drainage prevents the acid from reaching the duodenum [5-7]. In some cases, the vomiting is self-induced and denied by the patient [8]. In this setting, measurement of the urine chloride concentration may be
Causes of metabolic alkalosis

helpful. (See "Urine electrolytes in diagnosis of metabolic alkalosis").

In comparison, the administration of nonreabsorbable antacids does not usually lead to metabolic alkalosis. Although the hydroxide or carbonate component of the antacid buffers gastric hydrogen, this is balanced by the combination of most of the cation component of the antacid (magnesium, aluminum, or calcium) with pancreatic bicarbonate [9].

An exception occurs in patients with renal failure being treated with both an antacid and a cation-exchange resin for hyperkalemia. In this setting, some of the cation binds to the resin, leaving more bicarbonate in a soluble reabsorbable form in the intestinal lumen [10]. The renal failure plays an important role in perpetuating the alkalosis by preventing excretion of the excess bicarbonate. (See "Electrolyte complications of antacid therapy").

**Loss of intestinal secretions** — Intestinal secretions typically contain a relative high bicarbonate concentration. As a result, loss of these secretions (as in diarrhea) typically leads to metabolic acidosis. However, some patients with a villous adenoma or factitious diarrhea due to laxative abuse develop metabolic alkalosis [6]. How this occurs is not well understood. (See "Factitious diarrhea").

**RENAL HYDROGEN LOSS** — An inappropriate increase in renal acid loss requires enhanced distal hydrogen secretion. This occurs in those settings in which there is both adequate distal sodium and water delivery and increased secretion of aldosterone. The mineralocorticoid acts both by directly stimulating the secretory H-ATPase pump and, via the stimulation of sodium reabsorption, by making the lumen more electronegative, thereby minimizing the back-diffusion of hydrogen out of the lumen [11,12]. Distal potassium secretion is also enhanced in this setting, resulting in concurrent hypokalemia.

**Primary mineralocorticoid excess** — Any of the causes of primary hypersecretion of mineralocorticoids can lead to metabolic alkalosis. This is generally accompanied by hypertension. (See "Approach to the patient with hypertension and hypokalemia" for a review of these disorders). In comparison, untreated patients with secondary hyperaldosteronism due to congestive heart failure or cirrhosis usually do not present with metabolic alkalosis or hypokalemia. In these disorders, the stimulatory effect of aldosterone is counteracted by decreased distal sodium delivery (in the absence of diuretic therapy).

**Loop or thiazide diuretics** — Both adequate distal delivery and increased secretion of aldosterone are typically present in patients treated with a loop or thiazide-type diuretic. The ensuing increase in urinary hydrogen secretion plus volume contraction (if there has been a large diuresis) can then contribute to the common development of metabolic alkalosis [13-15].

Metabolic alkalosis and hypokalemia also occur in Bartter's and Gitelman's syndromes. These disorders produce similar electrolyte abnormalities to diuretic therapy because they
Causes of metabolic alkalosis

are associated with genetic defects in the transporters in the loop of Henle and distal tubule, respectively, that are the same as those inhibited by the loop and thiazide diuretics. (See "Bartter's and Gitelman's syndromes").

Posthypercapnic alkalosis — Chronic respiratory acidosis leads to an appropriate increase in hydrogen secretion, and the ensuing rise in the plasma bicarbonate concentration will raise the pH toward normal [16]. However, rapid lowering of a chronically elevated PCO2, usually by mechanical ventilation, causes metabolic alkalosis from the sustained increase in the plasma bicarbonate concentration. Furthermore, the fall in PCO2 will acutely raise the cerebral intracellular pH, a change that can induce serious neurologic abnormalities and death [17]. Thus, the PCO2 should be reduced gradually in patients with chronic hypercapnia.

The initial hypercapnia-induced elevation in the plasma bicarbonate concentration is associated with some chloride loss [18]. Thus, a posthypercapnic alkalosis may persist until sodium chloride is given to replete the chloride deficit and allow the excess bicarbonate to be excreted [18].

Hypercalcemia and the milk-alkali syndrome — Hypercalcemia, via an unknown mechanism, increases renal bicarbonate reabsorption [19]. A significant metabolic alkalosis, however, is primarily seen in patients with the milk-alkali syndrome, in whom an increased alkaline load (due to the ingestion of calcium carbonate) and hypercalcemia-induced renal failure both enhance bicarbonate accumulation and diminish bicarbonate excretion [20,21]. (See "The milk-alkali syndrome").

INTRACELLULAR SHIFT OF HYDROGEN — In addition to hydrogen loss, metabolic alkalosis can also be induced by the shift of hydrogen ions into the cells.

Hypokalemia — Hypokalemia is a frequent finding in patients with metabolic alkalosis. Several factors contribute to this association [1]. First, the major causes of metabolic alkalosis (vomiting, diuretics, mineralocorticoid excess), directly induce potassium as well as hydrogen loss. Second, hypokalemia induces a transcellular shift in which potassium leaves the cells (to replete the extracellular stores) and, to maintain electroneutrality, hydrogen enters the cells [1]. The movement of hydrogen into the cells increases the plasma bicarbonate concentration and lowers the intracellular pH. The intracellular acidosis in renal tubular cells promotes hydrogen secretion and therefore bicarbonate reabsorption [22]. (See "Pathogenesis of metabolic alkalosis").

ALKALI ADMINISTRATION — The administration of as much as 1000 meq of sodium bicarbonate per day does not induce metabolic alkalosis in normals, due to rapid urinary excretion [23]. However, metabolic alkalosis can occur if very large quantities of bicarbonate (or any organic anion — such as lactate or acetate — which is metabolized to bicarbonate) are given acutely or if the ability to excrete bicarbonate is impaired.

As an example, a post-correction metabolic alkalosis can be induced by the administration
of sodium bicarbonate to treat lactic acidosis or ketoacidosis. In these settings, the administered bicarbonate represents "excess" alkali, since reversal of the underlying disorder will regenerate bicarbonate from the metabolism of lactate or β-hydroxybutyrate [24]. (See "Bicarbonate therapy in lactic acidosis" and see "Treatment of diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults").

Metabolic alkalosis also can be induced after sodium bicarbonate ingestion or the administration of large quantities of citrate, as with the infusion of more than eight units of bank blood (anticoagulated with acid-citrate-dextran), the use of citrate rather than heparin as an anticoagulant in hemodialysis patients or in continuous renal replacement therapy, after extensive use of crack cocaine (which contains significant amounts of an alkali) in dialysis patients, or the administration of fresh frozen plasma as a replacement fluid during plasmapheresis [1,25-29].

The intentional induction of metabolic alkalosis in athletes is being studied as an approach to improve exercise performance [30,31]. The mechanism of action may include enhanced hydrogen ion efflux out of muscle and decreased interstitial potassium accumulation in muscle, resulting in improved ATP resynthesis and anaerobic glycolysis.

CONTRACTION ALKALOSIS — A contraction alkalosis occurs when there is loss of relatively large volumes of bicarbonate-free fluid [14,15]. The plasma bicarbonate concentration rises in this setting because there is contraction of the extracellular volume around a relatively constant quantity of extracellular bicarbonate. The degree to which this occurs is in part minimized by intracellular buffering, as the release of hydrogen ions from cell buffers lowers the plasma bicarbonate concentration toward the baseline value [15].

Administration of intravenous loop diuretics to induce rapid fluid removal in a markedly edematous patient is the most common cause of a contraction alkalosis [14,32], although increased urinary hydrogen loss also contributes [15]. Contraction alkalosis may also occur in other disorders in which a high-chloride, low-bicarbonate solution is lost. These include sweat losses in cystic fibrosis, possibly loss of gastric secretions in patients with achlorhydria, and congenital chloridorrhea [6,33-36].

Congenital chloridorrhea — Congenital chloridorrhea is a rare congenital secretory diarrhea that is induced by mutations in the Down-regulated adenoma gene, which is presumably an intestinal anion transporter or a regulator of such a transporter [35]. Treatment generally consists of a high chloride intake to prevent volume depletion. However, such an approach also increases the severity of the diarrhea because of the chloride malabsorption. In one report, decreasing gastric chloride secretion with the proton pump inhibitor omeprazole (20 mg twice daily) reduced the stool volume (2.21 to 1.73 L/day) and the fecal excretion of sodium (199 to 138 meq/day) and chloride (308 to 264 meq/day) [36].
REFERENCES

Causes of metabolic alkalosis


Causes of metabolic alkalosis


### GRAPHICS

**Major causes of metabolic alkalosis**

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<tr>
<th>Gastrointestinal hydrogen loss</th>
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<tbody>
<tr>
<td>Vomiting or nasogastric suction</td>
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<td>Antacids in advanced renal failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal hydrogen loss</th>
</tr>
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<tbody>
<tr>
<td>Primary mineralocorticoid excess</td>
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<tr>
<td>Loop or thiazide diuretics</td>
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<tr>
<td>Posthypercapnic alkalosis</td>
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<td>Hypercalcemia and the milk-alkali syndrome</td>
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<th>Intracellular shift of hydrogen</th>
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<td>Hypokalemia</td>
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<th>Alkali administration</th>
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<tr>
<th>Contraction alkalosis</th>
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<tbody>
<tr>
<td>Massive diuresis</td>
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<tr>
<td>vomiting or nasogastric suction in achlorhydria</td>
</tr>
<tr>
<td>Sweat losses in cystic fibrosis</td>
</tr>
<tr>
<td>Villous adenoma or factitious diarrhea</td>
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