Treatment of metabolic alkalosis

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INTRODUCTION

Metabolic alkalosis is characterized by a primary rise in the plasma bicarbonate concentration, which leads to an increase in arterial pH. Two factors are required for the genesis and then maintenance of metabolic alkalosis: a process that raises the plasma bicarbonate concentration and a process that prevents excretion of the excess bicarbonate in the urine [1,2]. Treatment of metabolic alkalosis should be aimed at reversing these two factors.

This topic will provide a brief overview of the pathogenesis of metabolic alkalosis followed by a discussion of how to treat affected patients. The pathogenesis of metabolic alkalosis is reviewed in more detail elsewhere. (See "Pathogenesis of metabolic alkalosis".)

The etiology and evaluation of patients with metabolic alkalosis are discussed separately:

- (See "Causes of metabolic alkalosis".)
- (See "Clinical manifestations and evaluation of metabolic alkalosis".)

OVERVIEW OF THE PATHOGENESIS

The genesis and the maintenance of metabolic alkalosis are distinct processes. Initially, a process that raises the plasma bicarbonate concentration occurs, and then another process prevents excretion of the excess bicarbonate in the urine [1,2].

Factors that increase plasma bicarbonate — Several mechanisms can increase the plasma bicarbonate concentration. They include (table 1) (see "Causes of metabolic alkalosis"):

- Hydrogen loss from the body due to removal of gastric secretions (as with vomiting or tube drainage), loss in the stool when gastrointestinal bicarbonate and chloride transport is abnormal (chloride wasting diarrhea), or excessive urinary acid secretion (due, for example, to loop or thiazide diuretics or primary mineralocorticoid excess).
- Shift of hydrogen ions from the extracellular fluid (ECF) into the cells. This is most often due to hypokalemia.
- Exogenous administration of sodium bicarbonate or other sodium salts that are metabolized to form sodium bicarbonate.

A less common cause is contraction alkalosis due to the loss of relatively large volumes of bicarbonate-free fluid. This, in part, contributes to the rise in serum bicarbonate when loop diuretics are used to treat patients with marked edema.

Factors that impair bicarbonate excretion — The normal kidney filters more than 4000 mEq of bicarbonate per day. This number increases if the serum HCO3 concentration is elevated. Thus, a high serum bicarbonate concentration could be readily corrected by excretion of the excess bicarbonate into the urine. However, such correction will not occur if kidney filtration is markedly reduced or the renal tubules avidly reabsorb the filtered bicarbonate. The importance of reduced bicarbonate excretion for maintenance of metabolic alkalosis was illustrated in a study of adults who had a gastric or duodenal ulcer and were treated with sodium bicarbonate at a dose ranging from 8 to 24 mEq/kg per day (approximately 500 to 1500 mEq per day) for two to three weeks. These large doses of sodium bicarbonate produced only small elevations in the plasma bicarbonate concentration of approximately 3 to 4 mEq/L because nearly all of the ingested bicarbonate was excreted in the urine [3]. A major rise in serum bicarbonate requires a major reduction in renal bicarbonate excretion.

The most common cause of impaired bicarbonate excretion in patients with metabolic alkalosis is a reduction in arterial blood volume or in the effective arterial blood volume (EABV). EABV is a difficult-to-measure entity that refers to the arterial volume that perfuses the tissues [1]. A reduction in EABV stimulates the kidney to retain sodium salts and, because bicarbonate must be excreted with sodium or potassium to maintain electroneutrality, this sodium avidity limits the excretion of bicarbonate. In addition, reduced EABV increases chloride reabsorption proximally and severely reduces the distal delivery of chloride; this limits bicarbonate secretion (in exchange for luminal chloride) by type B intercalated cells in the distal tubule and collecting ducts [4]. The net effect is that renal bicarbonate excretion is largely eliminated by the presence

of a reduced EABV. Under these circumstances, patients may excrete a "paradoxically" acid urine (paradoxical aciduria) despite the presence of metabolic alkalosis [2,5].

The most common causes of a true volume depletion associated with metabolic alkalosis are vomiting or diuretic therapy. The most common causes of reduced EABV are heart failure and cirrhosis.

Hypokalemia can also reduce renal bicarbonate excretion, in part because it stimulates renal ammoniagenesis and ammonium excretion (ammonium excreted with chloride represents renal tubule bicarbonate generation, while ammonium excreted with bicarbonate has no net acid-base impact).

In addition, acute and chronic kidney disease reduces the capacity to excrete bicarbonate. Thus, bicarbonate administration or generation in such patients can generate a persistent metabolic alkalosis. However, metabolic acidosis is much more common in patients with reduced kidney function as a result of an inability to excrete the daily dietary acid load generated by typical Western meat-containing diets.

Virtually all clinical situations associated with true arterial volume contraction, or a reduced EABV, generate avid renal chloride reabsorption. Reduced chloride delivery to the distal tubules markedly impairs the kidney's capacity to excrete bicarbonate and thereby impairs the kidney's capacity to prevent the development, or correct the presence, of metabolic alkalosis. The mechanisms by which these changes occur are discussed elsewhere:

- (See "Pathogenesis of metabolic alkalosis", section on 'Hypokalemia'.)
- (See "Pathogenesis of metabolic alkalosis", section on 'Chloride depletion'.)
- (See "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease".)

TREATMENT

Treatment of metabolic alkalosis should be aimed at two targets:

- The source of bicarbonate generation (or administration)

  and

- Reversing the factors that prevent the kidneys from excreting the excess bicarbonate

In order to accomplish this, two questions must be answered:

- Is the increase in plasma bicarbonate concentration due to gastrointestinal or renal hydrogen ion loss (eg, vomiting, diuretic therapy), contraction of the extracellular fluid (ECF) volume, an intracellular shift of hydrogen ions, an exogenous load of alkali or alkali precursors, or a combination of these factors (table 1)?

- Why is the excess bicarbonate not being excreted in the urine? As discussed above, the major causes of reduced renal bicarbonate excretion are reduced arterial blood volume or effective arterial blood volume (EABV; associated with chloride depletion or inadequate distal tubule chloride delivery), hypokalemia, and acute or chronic kidney disease. (See 'Factors that impair bicarbonate excretion' above.)

Treat the underlying cause — The underlying etiology of the alkalosis should be addressed (eg, treat the cause of vomiting, stop or reduce the removal of gastric secretions, reduce the acid content of the gastrointestinal secretions, and, if possible, stop loop or thiazide diuretics). (See "Causes of metabolic alkalosis", section on 'Gastrointestinal hydrogen loss'.)

Patients who develop metabolic alkalosis as a result of persistent vomiting or gastric suction can be effectively treated with drugs that reduce gastric hydrochloric acid (HCl) secretion. Both H2 blockers and proton pump inhibitors have been utilized [6,7].

All exogenous sources of alkali should be discontinued to the extent possible. This includes sodium or potassium bicarbonate and sodium or potassium salts of any organic anion that is metabolized and thereby generates bicarbonate, such as citrate or lactate. Bicarbonate administered to patients with reversible organic metabolic acidosis (usually lactic or ketoacidosis) can also be considered "excess" bicarbonate (to the extent that the organic anion has been retained in body fluids) and can result in a "rebound" or postcorrection metabolic alkalosis. This occurs because, after correction of the hypotension or insulin deficiency, metabolism of the lactate or beta-hydroxybutyrate regenerates bicarbonate. Thus, the exogenously administered sodium bicarbonate will then represent "excess" bicarbonate. (See "Bicarbonate therapy in lactic acidosis" and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment", section on 'Bicarbonate and metabolic acidosis'.)

Hypokalemia commonly occurs in these patients and, if present, should be reversed. (See "Causes of metabolic alkalosis", section on 'Hypokalemia'.)

Increase renal bicarbonate excretion — The maintenance of metabolic alkalosis requires a reduction in the renal excretion of the excess bicarbonate. Reversing the factors that impair renal bicarbonate excretion will correct the alkalosis. (See "Pathogenesis of metabolic alkalosis", section on 'Pathogenesis'.)

The most important factors that impair renal bicarbonate excretion include (see 'Factors that impair bicarbonate excretion' above):

- A reduced arterial blood volume or EABV
- Chloride depletion, hypochloremia, and reduced distal tubule chloride delivery (almost always associated with reduced arterial or EABV)
- Potassium depletion and hypokalemia
- Reduced kidney function

Reduced arterial or effective arterial blood volume and chloride depletion — Reduced arterial blood volume or EABV is almost invariably associated with chloride depletion, and a high serum bicarbonate concentration is almost invariably associated with hypochloremia. If the arterial volume depletion can be treated and reversed with isotonic saline (sodium chloride), this will simultaneously restore arterial volume, correct the chloride deficit, and increase renal sodium bicarbonate excretion.

All forms of reduced arterial blood volume and EABV promote persistence of metabolic alkalosis since the kidney is stimulated to retain sodium, and this limits the ability to excrete bicarbonate. Causes of true volume depletion include vomiting, nasogastric suction, diuretic therapy, marked sweat loss (especially with a high sweat salt concentration as in cystic fibrosis), blood loss, loss of fluid into the "third" space, and, rarely, villous adenoma (table 1). Causes of EABV depletion include heart failure and cirrhosis. These causes of low EABV do not respond to saline volume expansion, and such treatment can result in clinical deterioration. (See 'Factors that impair bicarbonate excretion' above.)

True volume depletion — In patients with true arterial volume depletion, but not in heart failure and cirrhosis, the metabolic alkalosis should be corrected by expanding volume. Usually, this is accomplished with isotonic saline, which expands the ECF and intravascular compartment. A reasonable regimen in patients with mild-to-moderate hypovolemia is to administer isotonic saline at a rate that is approximately 100 mL/hour greater than the sum of urine output plus other fluid losses that may be present (eg, gastrointestinal losses). More aggressive therapy is required in patients with severe hypovolemia. (See "Maintenance and replacement fluid therapy in adults", section on 'Rate of replacement' and "Treatment of severe hypovolemia or hypovolemic shock in adults", section on 'Initial rate of fluid repletion'.)

Appropriate repletion of the extracellular and intravascular volume has the following beneficial acid/base effects in patients with metabolic alkalosis:

- A reduction in proximal and distal sodium bicarbonate reabsorption, which will increase urinary bicarbonate excretion.

- A reduction in proximal chloride reabsorption, resulting in increased chloride delivery to the distal nephron.

- The increase in distal tubule fluid volume and chloride delivery will reduce acid secretion and promote connecting segment and collecting tubule bicarbonate secretion via the chloride-bicarbonate anion exchanger (pendrin) located on the luminal surface of type B intercalated cells (figure 1) [5,8-11].

The resulting increase in bicarbonate excretion should be reflected by an alkaline urine pH, which will exceed 7 when significant bicarbonaturia exists.

Edematous states — Patients with edematous states such as heart failure, cirrhosis, nephrotic syndrome, and cor pulmonale can develop metabolic alkalosis. This is often due to diuretic therapy. Treatment with isotonic saline is generally **contraindicated** in edematous patients for two reasons: It will increase edema, ascites, and/or effusions, and it will **not** correct the metabolic alkalosis since the underlying renal sodium avidity will persist, limiting urinary excretion of the excess bicarbonate. These patients may be hypokalemic and potassium depleted. In such patients, the metabolic alkalosis is often improved or even corrected by administering potassium chloride. The addition of potassium-sparing diuretics such as amiloride may also be helpful. (See 'Potassium depletion' below and "General principles of the treatment of edema in adults", section on 'Use of diuretics'.)

With respect to potassium-sparing diuretics, patients with heart failure or cirrhosis are often treated with a mineralocorticoid receptor antagonist (spironolactone or eplerenone). However, their use must be carefully monitored to avoid development of potentially life-threatening hyperkalemia. (See "Ascites in adults with cirrhosis: Initial therapy", section on 'Diuretic regimen' and "Ascites in adults with cirrhosis: Initial therapy", section on 'Diuretic therapy' and "Primary pharmacologic therapy for heart failure with reduced ejection fraction", section on 'Mineralocorticoid receptor antagonist'.)

If additional diuresis is required, the carbonic anhydrase inhibitor, acetazolamide, can be administered (250 to 500 mg, once or twice a day) [1]. Acetazolamide is a carbonic anhydrase inhibitor that primarily inhibits proximal sodium bicarbonate reabsorption, thereby increasing urinary bicarbonate excretion. (See "Mechanism of action of diuretics", section on 'Carbonic anhydrase inhibitors (acetazolamide)'.)

In patients treated with acetazolamide, the increase in sodium bicarbonate delivery to the potassium-secretory site in the collecting tubules will generate kaliuresis and can cause or worsen hypokalemia. Potassium chloride replacement may be necessary. Contraindications to

acetazolamide therapy include hypersensitivity to sulfonamides, severe liver disease, hypokalemia (as noted), some forms of chronic lung disease, and severe kidney disease [12].

Chloride depletion — As mentioned above, when sodium and potassium are administered, they should be given with chloride to correct metabolic alkalosis [8,13]. Volume expansion with chloride salts reduces proximal tubule bicarbonate reabsorption and increases the distal tubule delivery of sodium and chloride where the chloride is reabsorbed in exchange for bicarbonate in the connecting segment and collecting tubules by a luminal chloride/bicarbonate exchanger called pendrin (figure 1).

Whether resolution of hypovolemia or repletion of the chloride deficit is the key factor responsible for correcting metabolic alkalosis in response to saline infusion is the subject of ongoing debate [8]. Some experimental models support the principal role of chloride depletion. As an example, administration of chloride with a nonsodium cation (such as choline) can correct some experimental forms of metabolic alkalosis [14] but administration of sodium with a nonchloride anion (such as sulfate or nitrate) does not [2,15]. However, anions such as sulfate and nitrate are freely filtered and delivered to the distal renal tubules, where they cannot be readily reabsorbed. Under those conditions, reabsorption of sodium without an accompanying anion causes the anion to be excreted with ammonium (NH4), titratable acid (H2PO4), and/or potassium, preventing correction of the metabolic alkalosis and further depleting potassium stores [1,16]. In addition, virtually all clinical forms of ECF volume contraction are associated with chloride depletion, and volume expansion requires sodium chloride salts.

Potassium depletion — The administration of potassium chloride is an important component of the treatment of most forms of metabolic alkalosis [1,16].

Potassium depletion with hypokalemia enhances proximal tubule bicarbonate reabsorption and also activates a collecting tubule H-K-ATPase that reabsorbs potassium in exchange for secreted hydrogen. This will increase bicarbonate reabsorption and bicarbonate generation, which act together to maintain the alkalosis [17]. Correction of hypokalemia will decrease the activity of this cation exchanger, allowing bicarbonate to be excreted in the urine.

In addition, potassium chloride replacement restores the large intracellular potassium deficit that accompanies hypokalemia in most forms of metabolic alkalosis. The movement of administered potassium into cells occurs, in part, in exchange for intracellular hydrogen ions to maintain electroneutrality [16]. The movement of hydrogen ions out of cells and the repletion of intracellular potassium have several important effects, each of which will lower the plasma bicarbonate concentration:

- The hydrogen ions entering the ECF reduce the extracellular bicarbonate concentration.

- Raising the renal tubular cell pH reduces hydrogen ion secretion (and therefore bicarbonate reabsorption) and also reduces renal ammonium excretion [18].

The use of potassium salts to correct hypokalemia is discussed in detail elsewhere. When potassium salts are administered to patients with metabolic alkalosis, potassium chloride **is the preferred preparation**. Potassium salts of organic anions, such as citrate or acetate, should be **avoided**, if possible, since metabolism of these anions generates bicarbonate, which will slow the rate of correction of the metabolic alkalosis. (See "Clinical manifestations and treatment of hypokalemia in adults", section on 'Potassium preparations'.)

The usual dose of potassium is 10 to 20 mEq given two to four times per day (20 to 80 mEq per day), depending upon the severity of the hypokalemia. Potassium chloride can be given intravenously in patients who are unable to take oral medications or as an adjunct to oral therapy in patients who have severe or symptomatic hypokalemia. These issues are discussed in detail elsewhere. (See "Clinical manifestations and treatment of hypokalemia in adults", section on 'Mild to moderate hypokalemia' and "Clinical manifestations and treatment of hypokalemia in adults", section on 'Severe or symptomatic hypokalemia'.)

Treatment of posthypercapnic metabolic alkalosis — Chronic respiratory acidosis, which is most often due to chronic obstructive pulmonary disease, is initially associated with increased renal acid excretion and later with increased bicarbonate reabsorption. This results in a compensatory increase in the serum bicarbonate concentration that mitigates the fall in arterial pH (figure 2). (See "Simple and mixed acid-base disorders", section on 'Response to respiratory acidosis'.)

If the partial pressure of carbon dioxide (PCO2) is reduced rapidly as a result of mechanical ventilation and/or medical intervention and the serum bicarbonate concentration remains elevated, this represents a posthypercapnic metabolic alkalosis (the PCO2 is reduced toward normal, but the bicarbonate concentration remains "inappropriately" elevated). Such patients often cannot spontaneously excrete the excess bicarbonate because of a combination of chloride depletion, a reduction in the EABV (due, for example, to diuretic therapy or cor pulmonale), and/or a reduction in glomerular filtration rate. Posthypercapnic metabolic alkalosis can worsen ventilation, exacerbate respiratory acidosis, retard weaning from artificial ventilation, and prolong the intensive care unit (ICU) stay [19,20]. (See "Causes of metabolic alkalosis", section on 'Posthypercapnic alkalosis'.)

When posthypercapnic metabolic alkalosis is due to volume depletion, it can usually be corrected with an isotonic saline infusion [13]. (See "Causes of metabolic alkalosis", section on 'Posthypercapnic alkalosis' and 'Chloride depletion' above.)

However, if the patient requires additional diuresis, then posthypercapnic metabolic alkalosis can be treated with acetazolamide, a diuretic that increases urinary sodium bicarbonate (and potassium) excretion. Several reports suggested that acetazolamide improved the respiratory acidosis, as manifested by a fall in arterial PCO2 [19-21]. By contrast, one randomized study found that acetazolamide failed to shorten the duration on artificial ventilation compared with placebo, despite a "biochemical" improvement in arterial PCO2 [22]. However, the severity of treated metabolic alkalosis in this trial was mild, limiting the conclusions that can be drawn [22].

Red blood cell carbonic anhydrase plays a role in the transport of CO2 from red blood cells to the alveolar space. Thus, inhibition of this enzyme with acetazolamide can cause a small and transient rise in the arterial PCO2 [12,19,23]. This effect is not clinically significant in most patients.

Other forms of metabolic alkalosis can also complicate chronic respiratory acidosis (gastric aspiration, glucocorticoid treatment, aggressive diuresis, etc), and correction of this superimposed derangement can improve respiratory status, as reflected in lower PCO2 levels and improved oxygen exchange in critically ill patients [24].

Treatment of metabolic alkalosis with acute or chronic kidney disease — Metabolic alkalosis can develop in patients with acute or chronic kidney disease in whom therapies aimed at increasing urinary bicarbonate excretion are less likely to be effective (unless their kidney dysfunction is largely due to reversible ECF volume depletion). In some cases, dialysis will be indicated. Dialysis with a low-bicarbonate bath concentration will rapidly improve the alkalosis. However, it may be difficult to markedly reduce bicarbonate bath concentrations. Because the patient's bicarbonate in such cases is much higher than a standard dialysis bicarbonate bath concentration, routine dialysis will improve the metabolic alkalosis, albeit less effectively than dialysis with a low-bicarbonate bath [25,26].

Continuous kidney replacement therapy (CKRT) can be used to correct metabolic alkalosis in patients requiring kidney replacement therapy. When high rates of ultrafiltration are used, the composition of the replacement fluid can markedly alter the electrolyte and acid-base status of the patient. If the replacement fluid contains relatively high concentrations of sodium bicarbonate, or precursors of sodium bicarbonate such as sodium lactate or sodium citrate (potential bicarbonate), then the bicarbonate concentration of the patient can increase. Conversely, adjusting the replacement fluid to reduce the concentration of sodium bicarbonate, and potential bicarbonate salts, can reduce the patient's bicarbonate concentration [27,28]. (See "Continuous kidney replacement therapy in acute kidney injury".)

Hydrochloric acid in selected patients — Patients with severe metabolic alkalosis (for example, bicarbonate greater than 50 mEq/L and/or pH greater than 7.55) who have kidney function impairment and cannot, or should not, be dialyzed can be treated with an intravenous infusion of HCl or an HCl precursor such as ammonium chloride, which is metabolized to urea and HCl.

HCl for infusion can be prepared by passing 100 mL of 1 normal (1 N) HCl through a 22 microm filter into 900 mL of isotonic saline, or sterile water, to produce a 0.1 N (100 mEq/L) solution of HCl [29]. This solution must then be infused through a carefully placed, free-flowing central venous catheter into the superior vena cava over 8 to 24 hours [29-31]. Because HCl may react with plastic, use of glass containers is recommended, and intravenous tubing should be changed every 12 hours [29]. Caution is required because infiltration of this solution will necrose tissues, and this complication can be fatal [32].

In one report, HCl was mixed with an amino acid and fat emulsion solution, which raises the pH sufficiently so that it can safely be infused into a peripheral vein [33].

Ammonium chloride (NH_4Cl) is available in 20 mL vials that contain 100 mEq of NH_4Cl. One or two vials are added to 1000 mL of isotonic saline [34,35]. However, the ammonium is metabolized to urea, and the urea concentration can increase sharply in patients with kidney function impairment. Also, high ammonia levels may develop, especially in patients with liver disease, and can produce central nervous system manifestations. (See "Hepatic encephalopathy: Pathogenesis", section on 'Ammonia'.)

Arginine hydrochloride, which is approved for use in the United States as a diagnostic infusion to test pituitary function, has been used to treat metabolic alkalosis. However, it is not approved in the United States for this indication, and we do not recommend that it be used to treat metabolic alkalosis, because it can cause potassium to shift from cells into the extracellular space, resulting in life-threatening hyperkalemia [36].

A rough estimate of the amount of acid or acid precursor (in mEq) that will be required to reduce the plasma bicarbonate can be determined by multiplying the desired change in plasma bicarbonate concentration by the space of distribution of bicarbonate, which is roughly equal to the total body water (approximately 60 and 50 percent of lean body weight [LBW] in males and females, respectively).

Thus, in males:

$$\text{HCO3 excess (in mEq)} = 0.6 \times \text{LBW} \times (\text{desired plasma HCO3 reduction})$$

In females:

$$\text{HCO3 excess (in mEq)} = 0.5 \times \text{LBW} \times \text{(desired plasma HCO3 reduction)}$$

However, this formula is a very **rough initial estimate**. It does **not** take into account continuing acid losses (as with nasogastric suction), changes in volume status, changes in bicarbonate distribution space related to the bicarbonate concentration, potassium balance, or kidney function. If acid infusion is prescribed, the goal should be partial correction of the alkalosis with intermittent reassessment. Thus, in these rare instances in which acid therapy is used, we recommend that only one liter of solution (containing 100 mEq of HCl or NH4Cl) be infused. Then, serum chemistries should be remeasured, and the clinical status should be reassessed to determine whether or not additional acid therapy is required.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Fluid and electrolyte disorders in adults".)

SUMMARY AND RECOMMENDATIONS

- Two factors are required for the genesis and then maintenance of metabolic alkalosis: a process that raises the plasma bicarbonate concentration (table 1) and a process that prevents excretion of the excess bicarbonate in the urine. (See 'Overview of the pathogenesis' above.)
- The most common causes of impaired renal bicarbonate excretion in patients with metabolic alkalosis are a reduction in the effective arterial blood volume (EABV; also called effective circulating volume), chloride depletion, hypokalemia, and acute and chronic kidney disease. (See 'Factors that impair bicarbonate excretion' above.)
- Treatment of metabolic alkalosis should be aimed at reversing the etiology of bicarbonate generation and reversing the factors that prevent the excretion of the excess bicarbonate. In order to accomplish this, two questions must be answered (see 'Treatment' above):
  - Is the increase in plasma bicarbonate concentration due to an exogenous alkali load, gastrointestinal or renal hydrogen ion loss (eg, vomiting, diuretic therapy) with or

without contraction alkalosis, an intracellular shift of hydrogen ions, or a combination of these disorders (table 1)?

  - Why is the excess bicarbonate not being excreted in the urine?

- The underlying etiology of the alkalosis should be reversed (eg, treating the cause of vomiting, stopping or slowing the removal of gastric secretions and reducing the acidity of these secretions, and stopping loop or thiazide diuretics). Any exogenous sources of alkali should be discontinued. Hypokalemia, which is often present, should be corrected. (See 'Treat the underlying cause' above.)

- Maintenance of metabolic alkalosis is due to a reduction in the renal excretion of the excess bicarbonate. The reversal of metabolic alkalosis requires the renal excretion of bicarbonate whenever possible. (See 'Increase renal bicarbonate excretion' above.)

- Reduced EABV and chloride depletion usually occur together, and the treatment of EABV depletion with isotonic saline (sodium chloride) simultaneously corrects the volume and chloride deficits. This generally increases renal bicarbonate excretion in patients with true volume depletion. However, isotonic saline is not indicated when the EABV depletion is caused by conditions such as heart failure or cirrhosis. (See 'Reduced arterial or effective arterial blood volume and chloride depletion' above and 'True volume depletion' above.)

- When metabolic alkalosis develops in patients with reduced EABV due to conditions such as heart failure or cirrhosis, treatment includes the administration of potassium chloride and/or a potassium-sparing diuretic or, uncommonly, acetazolamide if further diuresis is required. (See 'Edematous states' above.)

- Hypokalemia in patients with metabolic alkalosis represents a large intracellular potassium deficit. The administration of potassium chloride corrects both the potassium deficit and helps reverse the metabolic alkalosis. (See 'Potassium depletion' above.)

- Chronic respiratory acidosis, which is most often due to chronic obstructive pulmonary disease, is initially associated with increased renal acid excretion and, later, with increased bicarbonate reabsorption. This produces a compensatory increase in the serum bicarbonate concentration that mitigates the fall in arterial pH (figure 2). If the chronic respiratory acidosis improves as a result of mechanical ventilation and/or medical intervention, a posthypercapnic metabolic alkalosis may develop. Many patients with posthypercapnic metabolic alkalosis can be effectively treated with isotonic saline infusion, which corrects EABV and chloride deficits. Another option for the treatment of

posthypercapnic metabolic alkalosis is acetazolamide, which increases urinary bicarbonate excretion. (See 'Treatment of posthypercapnic metabolic alkalosis' above.)

- Uncommonly, patients with metabolic alkalosis do not adequately respond to, or are not candidates for, conventional therapies (volume expansion, chloride repletion, and potassium repletion) or therapy with acetazolamide. One example is metabolic alkalosis developing in patients with advanced acute or chronic kidney disease. Such patients can often be treated with dialysis. (See 'Treatment of metabolic alkalosis with acute or chronic kidney disease' above.)

- Continuous kidney replacement therapy (CKRT) can generate metabolic alkalosis (due to the infusion of sodium bicarbonate and potential bicarbonate such as lactate or citrate) but can also be utilized to correct metabolic alkalosis. (See 'Treatment of metabolic alkalosis with acute or chronic kidney disease' above.)

- Rarely, patients with severe metabolic alkalosis (eg, HCO3 greater than 50 mEq/L and/or pH greater than 7.55) fail or are not candidates for conventional therapies and cannot, or should not, be dialyzed. Such patients can be treated with an intravenous infusion of hydrochloric acid (HCl) or an HCl precursor such as ammonium chloride, which is metabolized to urea and HCl. (See 'Treatment of metabolic alkalosis with acute or chronic kidney disease' above.)

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Topic 2345 Version 21.0

GRAPHICS

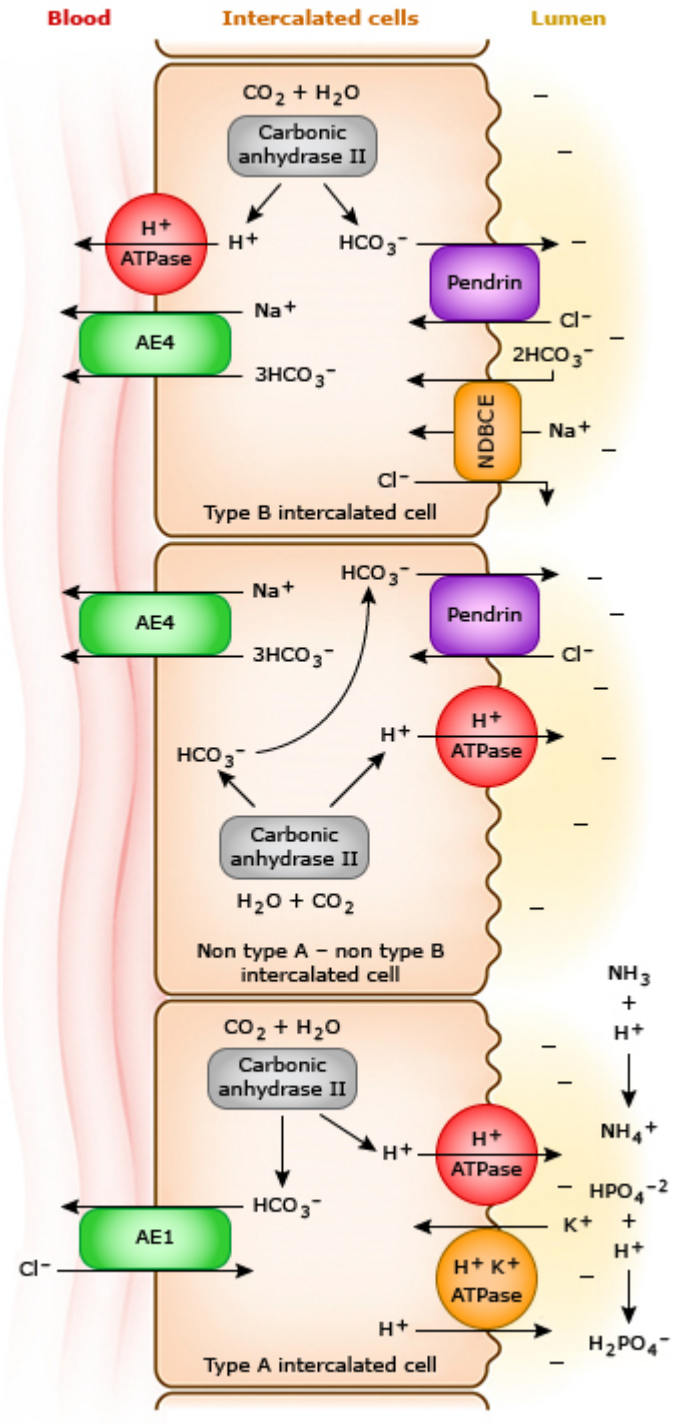
Major causes of metabolic alkalosis

Gastrointestinal hydrogen loss
Vomiting or nasogastric suction
Congenital chloride diarrhea (congenital chloridorrhea)
Renal hydrogen loss
Primary mineralocorticoid excess (primary hyperaldosteronism, Cushing syndrome [usually associated with ectopic ACTH] exogenous mineralocorticoids)
Mineralocorticoid excess-like states
▪ Licorice ingestion
▪ Liddle syndrome
▪ Apparent mineralocorticoid excess
Loop or thiazide diuretics
Bartter or Gitelman syndrome
Status post chronic hypercarbia
Severe hypokalemia causing both intracellular hydrogen shift and renal hydrogen excretion
Villous adenoma (may manifest metabolic alkalosis, metabolic acidosis, or both)
Laxative abuse (may manifest metabolic alkalosis, metabolic acidosis, or both)
Alkali administration with reduced renal function
Calcium-alkali syndrome*
Bicarbonate ingestion/infusion with impaired kidney function
Contraction alkalosis

* Formerly called the milk-alkali syndrome. Now more commonly generated by ingestion of calcium carbonate rather than the historic combination of milk, cream, and "sippy powders" (sodium bicarbonate and alkaline calcium and bismuth salts).

Graphic 57489 Version 6.0

Mechanisms of hydrogen ion or bicarbonate secretion by intercalated cells



3 different types of intercalated cells have been identified: type A, type B, and nontype A/nontype B. Each of these cells is rich in carbonic anhydrase II and is capable of generating abundant intracellular HCO_3^- and H^+ from the dehydration of H_2CO_3.

Type A intercalated cells: The H^+ that is generated from the "splitting" of H_2CO_3 is secreted into the lumen mainly via V-type H^+ ATPase and to a smaller extent via H^+ K^+ ATPase. The cytoplasmic HCO_3^- is secreted into the interstitial space/peritubular capillary via AE1 (a product of the solute carrier family 4 member 1 [*SLC4A1*] gene).

Type B intercalated cells: The H^+ that is generated from the "splitting" of H_2CO_3 is secreted into the interstitial space/peritubular capillary by V-type H^+ ATPase in the basolateral membrane (this H^+ transporter is identical to the transporter in the type A intercalated cells, but in the type A cells it is located on the luminal membrane). The cytoplasmic HCO_3^- generated in this cell is secreted into the lumen via the anion exchanger pendrin (a product of the solute carrier family 26 member 4 [*SLC26A4*] gene) that exchanges 1 HCO_3^- for 1 Cl^-. Pendrin is distinctly different from AE1 in the type A cells that are present in the basolateral membrane. AE4 (a product of the *SLC4A4* gene) is present in the basolateral membrane. Type B intercalated cells also have an NDBCE (a product of the solute carrier family 4 member 8 [*SLC4A8*] gene) in the luminal membrane. This transporter plays an important role in NaCl reabsorption. (Refer to discussion below.)

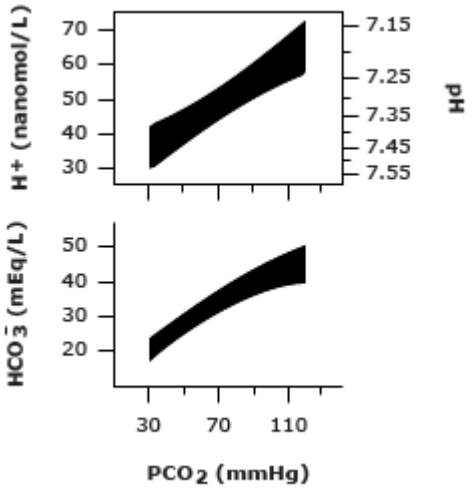
Nontype A/nontype B intercalated cells: This is the third type of intercalated cell. Both a V-type H^+ ATPase, which pumps H^+, and pendrin, which exchanges HCO_3^- for Cl^-, coexist in the lumen membrane. In the basolateral membrane, AE4 (a product of the *SLC4A4* gene) is present. This is a major $Na^+/3HCO_3^-$ cotransporter, which moves these ions into the interstitial space/peritubular capillary.

Role in salt balance: In addition to their major role in renal acid-base regulation in the distal nephron, intercalated cells have an important role in salt and volume regulation. NDBCE (a product of the *SLC4A8* gene), which is present in the luminal membrane of the type B intercalated cells, moves 1 Na^+ and 2 HCO_3^- ions into the cell while secreting 1 Cl^- into the lumen. Consequently it is an electrically neutral ion exchanger. These 2 HCO_3^- ions then reenter the lumen in exchange for 2 Cl^- ions via pendrin. The net result of these coupled exchanges will be the absorption of 1 molecule of NaCl. The NDBCE exchanger is inhibited by thiazide diuretics.

CO_2: carbon dioxide; H_2O: water; H^+: hydrogen ion; HCO_3^-: bicarbonate; Na^+: sodium ion; Cl^-: chloride ion; AE4: anion exchanger 4; NDBCE: sodium-driven bicarbonate chloride ion exchanger; AE1: anion exchanger 1; NH_3: ammonia; NH_4^+: ammonium ion; HPO_4^{-2}: hydrogen phosphate ion; $H_2PO_4^-$: dihydrogen phosphate ion; K^+: potassium ion; NaCl: sodium chloride.

Graphic 62465 Version 8.0

Compensation to chronic respiratory acidosis



95% significance bands for plasma pH and H^+ and HCO_3^- concentrations in chronic hypercapnia. Because of the compensatory rise in the plasma HCO_3^- concentration, there is much less change in H^+ concentration and pH than in acute hypercapnia.

Graphic 63315 Version 4.0