Causes of metabolic alkalosis

AUTHORS: Michael Emmett, MD, Harold Szerlip, MD, MACP, FCCP, FASN, FNKF
SECTION EDITOR: Richard H Sterns, MD
DEPUTY EDITOR: John P Forman, MD, MSc

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Jan 2024.**
This topic last updated: **Feb 06, 2022.**

INTRODUCTION

Metabolic alkalosis, a disorder that elevates the serum bicarbonate, can result from several mechanisms: intracellular shift of hydrogen ions; gastrointestinal loss of hydrogen ions; excessive renal hydrogen ion loss; administration and retention of bicarbonate ions; or volume contraction around a constant amount of extracellular bicarbonate (contraction alkalosis) (table 1) [1-5].

Hydrogen ions are derived from the dissociation of water into hydrogen and hydroxyl ions; therefore, when hydrogen ions are removed from the extracellular fluid, the remaining hydroxyl ion combines with carbon dioxide to form bicarbonate. Gastrointestinal and renal hydrogen loss is usually accompanied by the loss of chloride and potassium, resulting in hypochloremia and hypokalemia.

Patients with preserved kidney function should be able to rapidly excrete excess bicarbonate in the urine. Thus, metabolic alkalosis can only persist if the ability to excrete excess bicarbonate in the urine is impaired due to one of the following causes: hypovolemia; reduced effective arterial blood volume (due, for example, to heart failure or cirrhosis); chloride depletion; hypokalemia; reduced glomerular filtration rate; hyperaldosteronism or similar disorders; or combinations of these factors [3,6,7].

The causes of metabolic alkalosis will be reviewed here. The pathogenesis, evaluation, and treatment of this disorder are discussed separately:

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

INTRACELLULAR SHIFT OF HYDROGEN

Metabolic alkalosis can be generated by a shift of hydrogen ions into the cells. This most often occurs in patients with potassium deficits and hypokalemia. This may be an important contributory pathophysiologic mechanism in patients with metabolic alkalosis due to vomiting or nasogastric suction [8]. (See "Potassium balance in acid-base disorders".)

Hypokalemia — Hypokalemia occurs frequently in patients with metabolic alkalosis. It is an important contributor to both the development and maintenance of the alkalosis. The potassium loss and hypokalemia interact with metabolic alkalosis in multiple ways [1]:

- Many causes of metabolic alkalosis (vomiting, diuretics, mineralocorticoid excess) directly or indirectly induce renal potassium loss. (See "Causes of hypokalemia in adults".)
- Potassium depletion causes potassium to move from cells into the extracellular fluid, and this transcellular potassium flux causes extracellular hydrogen ions to move into cells to maintain electroneutrality [1]. These ion fluxes simultaneously increase the plasma bicarbonate concentration and lower the intracellular pH. To the extent that this occurs in renal tubular cells, the ensuing intracellular acidosis promotes hydrogen secretion into the lumen, which results in the addition of bicarbonate to the blood [9]. (See "Potassium balance in acid-base disorders" and "Pathogenesis of metabolic alkalosis".)
- Hypokalemia also increases renal ammoniagenesis and ammonium excretion, which can both generate and help to maintain metabolic alkalosis.

GASTROINTESTINAL HYDROGEN LOSS

Gastrointestinal hydrogen loss can result from the loss of gastric secretions (vomiting or nasogastric suction) or from diarrhea in patients with rare disorders that block intestinal chloride absorption (such as congenital chloridorrhea), and in some patients with villous adenomas.

Loss of gastric secretions — Gastric contents usually have a high concentration of hydrogen chloride and lower concentrations of potassium chloride and sodium chloride. Under normal conditions, gastric hydrogen ion secretion does not lead to metabolic alkalosis, since the hydrogen ions are not lost from the body, but instead are neutralized by bicarbonate secreted by the pancreas, liver, and intestines in response to the acid that enters the small bowel. Within the intestinal lumen, the hydrogen and bicarbonate ions combine to form carbonic acid and water, and the secreted chloride, sodium, and potassium ions are reabsorbed into the systemic circulation. When vomiting or nasogastric tube suction removes hydrogen chloride from the body and prevents it from reaching the duodenum, the bicarbonate that is added to the extracellular fluid is not balanced by the subsequent secretion of bicarbonate into the more distal gastrointestinal lumen [10-12].

The administration of poorly absorbed antacids, such as magnesium hydroxide or calcium carbonate, does not usually generate metabolic alkalosis. Although the hydroxide or carbonate component of the antacid combines with gastric hydrogen ions to generate carbon dioxide and water, the cation component of the antacid (magnesium, aluminum, or calcium) combines with bicarbonate in the more distal gastrointestinal lumen and is excreted in the stool [13]. The net effect is that the ingestion of poorly absorbed alkali is matched by a virtually equimolar excretion of alkali in the stool. However, this may not occur if a patient is treated simultaneously with both a poorly absorbed antacid and a cation-exchange resin such as sodium polystyrene sulfonate. Usually, this cation-exchange resin releases sodium and binds potassium, but if given with an antacid, the cation-exchanger also binds magnesium, aluminum, or calcium from the antacid in addition to potassium. The sodium released from the cation-exchange resin and the carbonate or hydroxide released from the antacid are systemically absorbed, while the cation-exchange resin is excreted in the stool combined with the magnesium, aluminum, or calcium [14]. If the patient has a low glomerular filtration rate, the alkalosis persists because the absorbed sodium bicarbonate cannot be rapidly excreted into the urine.

Diarrhea — Diarrheal stool typically has a relatively high alkali concentration (the alkali is usually present in the form of potassium and sodium salts of organic anions such as propionate and butyrate, which represent "potential bicarbonate"). As a result, large-volume diarrhea typically generates metabolic acidosis. (See "Acid-base and electrolyte abnormalities with diarrhea".)

However, in rare instances, diarrhea can produce metabolic alkalosis [11]. This may occur in some patients with a villous adenoma and in some who abuse laxatives. The mechanism responsible for the metabolic alkalosis in such patients is not well understood, but hypokalemia is invariably prominent and probably plays a major pathophysiologic role [15]. The concurrent

surreptitious use of diuretics as well as surreptitious vomiting may also contribute. (See "Factitious diarrhea: Clinical manifestations, diagnosis, and management" and 'Hypokalemia' above.)

Another form of diarrhea that consistently generates metabolic alkalosis is congenital chloride diarrhea, or chloridorrhea, which is due to a mutation in the solute carrier family 26 member 3 (*SLC26A3*) gene. This gene directs synthesis of an intestinal chloride-bicarbonate exchanger located in the apical mucosa of the lower intestinal tract. It normally reabsorbs chloride and secretes bicarbonate into the intestinal lumen. The exchanger has several different names including the "intestinal chloride-bicarbonate exchanger," the "chloride diarrhea anion exchanger (CLD)," and the "downregulated-in-adenoma (DRA) transporter." The diarrheal stool of these patients contains a very high concentration of chloride in contradistinction to virtually all other forms of diarrhea, in which the stool chloride concentration is relatively low. (See "Approach to chronic diarrhea in neonates and young infants (<6 months)".)

EXCESSIVE RENAL HYDROGEN LOSS

Urinary hydrogen ion losses increase when relatively generous sodium and water delivery to the distal nephron combines with increased mineralocorticoid activity at this site.

Three important actions of mineralocorticoids enhance hydrogen ion secretion by the distal renal tubule:

- Direct stimulation of the secretory H-ATPase pump (figure 1)
- Increased number of open epithelial sodium channels (ENaC)
- Increased activity of Na-K-ATPase

These actions combine to enhance the movement of sodium from the distal tubule lumen across the cell and into the extracellular fluid (figure 2). Because sodium is reabsorbed more readily than luminal anions, its reabsorption generates an electronegative charge in the tubular lumen. The electronegative lumen reduces back-diffusion of secreted hydrogen ions from the lumen into the tubular cells and also increases distal tubule hydrogen and potassium secretion, resulting in kidney bicarbonate generation, hypokalemia, and total body potassium depletion [16,17].

Primary mineralocorticoid excess — Any cause of primary and inappropriate hypersecretion of mineralocorticoids (independent of the volume status) can lead to metabolic alkalosis, which is generally accompanied by hypertension and hypokalemia. (See "Diagnosis of primary aldosteronism".)

By contrast, patients with secondary hyperaldosteronism due to reduced effective arterial blood volume (as in hypovolemia, heart failure, or cirrhosis) usually do not develop metabolic alkalosis or hypokalemia. In the absence of diuretic therapy, such patients have avid proximal tubule sodium reabsorption that markedly reduces distal sodium delivery and tubular flow rates. When distal delivery of sodium and water are low, even high levels of aldosterone cannot generate a large amount of distal sodium reabsorption or potassium and hydrogen ion secretion. However, administration of loop or thiazide diuretics to patients with secondary hyperaldosteronism markedly increases distal sodium delivery and tubular flow, which together with high aldosterone levels generates marked metabolic alkalosis and hypokalemia.

The combination of high mineralocorticoid levels and generous distal sodium and water delivery occurs with:

- Primary hypersecretion of endogenous mineralocorticoids (eg, primary aldosteronism) (see "Pathophysiology and clinical features of primary aldosteronism")
- Exogenous mineralocorticoids (eg, fludrocortisone)
- Ingestion of compounds that enhance endogenous mineralocorticoids (inhibitors of 11-beta hydroxysteroid dehydrogenase [ie, licorice]) (see "Apparent mineralocorticoid excess syndromes (including chronic licorice ingestion)")
- Genetic disorders such as "apparent mineralocorticoid excess syndrome" (see "Apparent mineralocorticoid excess syndromes (including chronic licorice ingestion)")
- Genetic disorders such as Liddle's syndrome, which mimics primary hyperaldosteronism as a result of persistently inserted and open distal epithelial sodium channels (see "Genetic disorders of the collecting tubule sodium channel: Liddle syndrome and pseudohypoaldosteronism type 1", section on 'Liddle syndrome')
- Secondary mineralocorticoid secretion plus thiazide and/or loop diuretics
- Genetic disorders that mimic chronic and persistent diuretic action (such as Bartter or Gitelman syndrome) (see "Inherited hypokalemic salt-losing tubulopathies: Pathophysiology and overview of clinical manifestations")

Loop or thiazide diuretics — These classes of diuretics increase distal sodium and water delivery and also elevate renin, angiotensin II, and aldosterone levels. In this form of secondary hyperaldosteronism, the diuretic-induced increase in distal sodium and water delivery enhances urinary hydrogen and potassium secretion, which results in metabolic alkalosis and

hypokalemia. Relative extracellular fluid volume contraction and hypokalemia also increase proximal tubule sodium bicarbonate reclamation.

If the diuresis reduces the volume of the extracellular fluid, this also contracts the bicarbonate space, which contributes to the elevation of the serum bicarbonate concentration [18-20]. (See 'Contraction alkalosis' below.)

Bartter and Gitelman syndromes — Metabolic alkalosis and hypokalemia are characteristic features of Bartter and Gitelman syndromes. These disorders are produced by genetic defects in ion transporters. The defect in Bartter syndrome impairs sodium chloride reabsorption in the loop of Henle and mimics the action of a persistent loop diuretic effect. Gitelman syndrome impairs sodium chloride reabsorption in the "diluting segment" of the distal convoluted tubule and mimics the action of a persistent thiazide diuretic effect. (See "Inherited hypokalemic salt-losing tubulopathies: Pathophysiology and overview of clinical manifestations".)

Pendred syndrome — Stimulation of pendrin, the sodium-independent chloride-bicarbonate exchanger found on the apical membrane of type B intercalated cells in the distal nephron (connecting tubule and collecting duct) [21,22], can increase neutral sodium chloride reabsorption in at least two ways:

- The sodium ion is reabsorbed via ENaC. Then the chloride ion can be reabsorbed transcellularly by a combination of a type A and B intercalated cells. The type A intercalated cell secretes a proton. Then a type B intercalated cell secretes a bicarbonate ion in exchange for reabsorption of a chloride ion. Net effect is reabsorption of sodium chloride.

- The other mechanism of sodium chloride reabsorption by intercalated cells via pendrin is two cycles of pendrin reabsorb two chloride ions in exchange for secretion of two bicarbonate ions. This is linked with one cycle of the NDBC exchanger also in type B intercalated cells, which reabsorbs two bicarbonate ions plus one sodium ion and secretes one chloride ion. The net effect is reabsorption of one sodium ion and one chloride ion.

Pendrin also probably plays an important role in the net secretion of bicarbonate to prevent or reverse the development of metabolic alkaloses [23]. Pendred syndrome is an autosomal recessive disorder that results in the reduced activity of pendrin. Under normal conditions, patients with Pendred syndrome do not exhibit any electrolyte disturbances. However, if treated with a thiazide diuretic that inhibits NCC, severe hypovolemia and metabolic alkalosis develop. Due to the importance of pendrin for iodide transport in the thyroid gland and electrolyte homeostasis in the inner ear, patients with Pendred syndrome also have sensorineural hearing

loss and hypothyroidism with goiter. (See "Approach to congenital goiter in newborns and infants", section on 'Inborn errors of thyroid hormone production'.)

Posthypercapnic alkalosis — Chronic respiratory acidosis increases renal hydrogen excretion (ammonium chloride loss) and bicarbonate reabsorption. The ensuing rise in the plasma bicarbonate concentration will return the pH toward normal [24]. The elevation in the serum bicarbonate concentration is associated with hypochloremia [25]. A detailed discussion of metabolic and respiratory compensation in simple and mixed acid-base disorders is presented elsewhere. (See "Simple and mixed acid-base disorders".)

If a chronically elevated PCO2 is rapidly lowered, usually by mechanical ventilation, the plasma bicarbonate concentration may remain elevated for a period of time, especially if the patient has a low effective arterial blood volume, has a reduced glomerular filtration rate, and/or is chloride deficient. Reduction of the PCO2 with a persistently elevated bicarbonate concentration results in a form of metabolic alkalosis that is called "posthypercapnic" metabolic alkalosis. This alkalosis will persist until enough sodium chloride is ingested or infused to replete the extracellular fluid volume and chloride deficit [25].

A rapid fall in PCO2 leading to a posthypercapnic alkalosis may acutely raise the cerebral intracellular pH. Although this has been reported to produce serious neurologic abnormalities and death, there are insufficient data to confirm that the alkalosis itself is responsible for the morbidity and mortality [26]. Most experts recommend that the PCO2 gradually be reduced in patients with chronic hypercapnia.

Hypercalcemia and the milk (or calcium)-alkali syndrome — The milk (or calcium)-alkali syndrome is an important cause of metabolic alkalosis and is usually associated with hypercalcemia. (See "The milk-alkali syndrome".)

The milk (or calcium)-alkali syndrome was initially described as a complication of aggressive milk and antacid therapy for peptic ulcer disease. However, calcium supplements (with or without vitamin D) have replaced milk as the calcium source in most patients with this syndrome. Many patients with the syndrome also have vomiting, which, in addition to the exogenous alkali, contributes to the generation of metabolic alkalosis. The bicarbonate cannot be excreted because of hypovolemia, reduced glomerular filtration rate (which results from both hypovolemia and hypercalcemia), and the hypercalcemia itself (which promotes hydrogen ion secretion) [27-30]. Alkalosis also enhances renal calcium reabsorption, thereby exacerbating the hypercalcemia [30]. The pathophysiology of the milk (or calcium)-alkali syndrome is presented in detail separately. (See "The milk-alkali syndrome".)

ALKALI ADMINISTRATION

The short-term administration of even large amounts of sodium bicarbonate to normal individuals usually results in very rapid renal excretion of the entire alkali load with minimal increase in the bicarbonate concentration. It is therefore difficult to produce more than a modest increase in plasma bicarbonate by chronically administering alkali to normal individuals. In one study, for example, administration of between 1000 to 1400 mEq per day to a 70 kg individual (a very large quantity) for as long as two to three weeks only raised the serum bicarbonate concentration to a maximum of 36 mEq/L because most of the ingested sodium bicarbonate was rapidly eliminated in the urine [31].

Although more pronounced metabolic alkalosis can occur if large quantities of sodium bicarbonate (or sodium salts of organic anions that are metabolized to bicarbonate such as lactate, citrate, or acetate) are given over a short period of time, this usually requires the simultaneous existence or development of hypovolemia, reduced effective arterial blood volume, or kidney function impairment.

Examples of metabolic alkalosis induced by alkali administration include:

- The administration of sodium bicarbonate to treat lactic acidosis or ketoacidosis may produce a post-correction metabolic alkalosis. In these settings, the administered bicarbonate represents "excess" alkali since reversal of the underlying disorder will regenerate bicarbonate from the metabolism of lactate or beta-hydroxybutyrate, both of which represent "potential bicarbonate" [32]. Such patients typically have hypovolemia and reduced glomerular filtration rate, which impair the excretion of the excess bicarbonate. (See "Pathogenesis of metabolic alkalosis" and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment", section on 'Bicarbonate and metabolic acidosis' and "Bicarbonate therapy in lactic acidosis".)

- Administration of large quantities of blood or blood products that are anticoagulated with citrate salts can produce a metabolic alkalosis. This becomes more likely when more than 8 units of blood are transfused. The sodium citrate is a metabolizable sodium salt that is converted to sodium bicarbonate. Infusion of large amounts of fresh frozen plasma (for example, during plasmapheresis) can generate the same type of alkalosis as a result of sodium citrate anticoagulant. The use of citrate salts rather than heparin as an anticoagulant in hemodialysis patients or during continuous kidney replacement therapy also represents an alkali load. In each of these scenarios, the alkali load is not readily excreted because of reduced effective arterial blood volume or kidney function

impairment [1,33-37]. (See "Anticoagulation for continuous kidney replacement therapy", section on 'Monitoring'.)

- Freebase and crack cocaine may be produced in illicit laboratories using a strong base such as household drain cleaner. Although the dominant acid-base disturbances associated with cocaine abuse are metabolic and/or respiratory acidoses, some cases of metabolic alkalosis have been reported when large amounts of freebase cocaine are used by patients with poor kidney function [37].

- The intentional induction of metabolic alkalosis in athletes has been studied as a method to improve exercise performance [38,39]. The presumptive mechanism of action may be related to 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 fluid that has a high sodium chloride concentration but a low bicarbonate concentration (lower than the extracellular fluid bicarbonate concentration) [19,20]. The plasma bicarbonate concentration rises in this setting because there is contraction of the extracellular volume around a relatively constant quantity of extracellular bicarbonate (and the chloride concentration simultaneously falls). The degree to which this occurs is offset by the release of hydrogen ions from cell buffers, which acts to stabilize the plasma bicarbonate concentration at its baseline level [20].

As an example, administration of intravenous loop diuretics to induce rapid fluid removal in a markedly edematous patient often generates a metabolic alkalosis. The etiology of this metabolic alkalosis is multifactorial and includes stimulation of distal tubule hydrogen ion secretion and hypokalemia-related acid-base effects, but one component of the alkalosis is contraction [19,40]. Other disorders in which contraction alkalosis may be a major contributor to the acid-base derangement include sweat losses in cystic fibrosis, congenital chloride diarrhea, and, possibly, the loss of gastric secretions in patients with achlorhydria [11,41-43]. (See "Approach to chronic diarrhea in neonates and young infants (<6 months)", section on 'Evaluation for suspected congenital diarrheas and enteropathies'.)

Although contraction of the extracellular volume can, by itself, theoretically raise the serum bicarbonate, the pathophysiology of the alkalosis in disorders associated with a contraction alkalosis is always multifactorial and complicated. In addition to contraction alkalosis, such

patients often have renal bicarbonate generation due to elevated aldosterone levels, combined with generous distal tubule salt and water delivery. Hypokalemia frequently contributes to accelerated renal bicarbonate generation and/or reduced renal bicarbonate excretory capacity; in addition, hypokalemia generates extracellular fluid bicarbonate when protons enter cells in exchange for potassium ions exiting the cells. (See "Potassium balance in acid-base disorders".)

The glomerular filtration rate is almost invariably reduced, and this also restricts the renal capacity to excrete bicarbonate.

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

- Metabolic alkalosis, which produces an elevation of the serum bicarbonate, is a relatively frequent clinical problem that is most commonly generated by excess loss of hydrogen ions from the gastrointestinal tract or in the urine, and/or by hydrogen ion movement into cells (table 1). An increased serum bicarbonate concentration may also result from alkali administration or extracellular fluid volume contraction around a relatively constant amount of extracellular bicarbonate (called a "contraction alkalosis"). Most patients with preserved renal function and normal volume status will rapidly excrete excess bicarbonate in the urine. Thus, for metabolic alkalosis to persist, there must be a reduction in the kidney's ability to excrete the excess bicarbonate into the urine. (See 'Introduction' above.)

- Metabolic alkalosis can result from the shift of hydrogen ions into cells. This most often occurs in patients with hypokalemia and potassium deficits. (See 'Intracellular shift of hydrogen' above.)

- Gastrointestinal hydrogen loss can result from the removal of gastric secretions (vomiting or nasogastric suction) or, rarely, from the loss of acid-rich stool as in congenital chloridorrhea and villous adenoma. (See 'Gastrointestinal hydrogen loss' above.)

- An increase in renal acid excretion is usually due to sodium and water delivery to the distal nephron combined with increased mineralocorticoid activity. This occurs with primary mineralocorticoid excess, use of loop or thiazide diuretics, Bartter and Gitelman

syndromes, and, to a lesser extent, with hypercalcemia due to the milk (or calcium)-alkali syndrome. (See 'Excessive renal hydrogen loss' above and 'Primary mineralocorticoid excess' above and 'Loop or thiazide diuretics' above and 'Bartter and Gitelman syndromes' above and 'Hypercalcemia and the milk (or calcium)-alkali syndrome' above.)

- Individuals with Pendred syndrome may develop severe metabolic alkalosis if treated with a thiazide diuretic. (See 'Pendred syndrome' above.)

- Chronic respiratory acidosis should generate an appropriate increase in renal hydrogen secretion and bicarbonate reabsorption. The ensuing increase in the plasma bicarbonate concentration will raise the arterial pH toward normal. If the chronically elevated PCO2 is rapidly lowered, usually by mechanical ventilation, the plasma bicarbonate concentration may remain elevated, producing a posthypercapnic alkalosis. (See 'Posthypercapnic alkalosis' above.)

- Alkali loads administered to a patient with an impaired renal capacity to excrete the bicarbonate (due to low effective arterial blood volume, chloride depletion, hypokalemia, or intrinsic renal disease) may produce metabolic alkalosis. The rapid administration of large alkali loads can cause short-term metabolic alkalosis. (See 'Alkali administration' above.)

- A contraction alkalosis occurs when there is loss of large volumes of fluids containing high concentrations of sodium chloride but relatively low concentrations of bicarbonate. The plasma bicarbonate concentration rises in this setting because there is contraction of the extracellular volume around a relatively constant quantity of extracellular bicarbonate. (See 'Contraction alkalosis' above.)

REFERENCES

1. Rose BD, Post TW. Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed, McGraw-Hill, New York 2001. p.559.
2. Palmer BF, Alpern RJ. Metabolic alkalosis. J Am Soc Nephrol 1997; 8:1462.
3. Galla JH. Metabolic alkalosis. J Am Soc Nephrol 2000; 11:369.
4. Khanna A, Kurtzman NA. Metabolic alkalosis. J Nephrol 2006; 19 Suppl 9:S86.
5. Emmett M. Metabolic Alkalosis: A Brief Pathophysiologic Review. Clin J Am Soc Nephrol 2020; 15:1848.

6. Seldin DW, Rector FC Jr. Symposium on acid-base homeostasis. The generation and maintenance of metabolic alkalosis. Kidney Int 1972; 1:306.
7. Luke RG, Galla JH. It is chloride depletion alkalosis, not contraction alkalosis. J Am Soc Nephrol 2012; 23:204.
8. Halperin ML, Scheich A. Should we continue to recommend that a deficit of KCl be treated with NaCl? A fresh look at chloride-depletion metabolic alkalosis. Nephron 1994; 67:263.
9. Capasso G, Jaeger P, Giebisch G, et al. Renal bicarbonate reabsorption in the rat. II. Distal tubule load dependence and effect of hypokalemia. J Clin Invest 1987; 80:409.
10. Kassirer JP, Schwartz WB. The response of normal man to selective depletion of hydrochloric acid. Factors in the genesis of persistent gastric alkalosis. Am J Med 1966; 40:10.
11. Perez GO, Oster JR, Rogers A. Acid-base disturbances in gastrointestinal disease. Dig Dis Sci 1987; 32:1033.
12. Giovannini I, Greco F, Chiarla C, et al. Exceptional nonfatal metabolic alkalosis (blood base excess +48 mEq/l). Intensive Care Med 2005; 31:166.
13. Stemmer CL, Oster JR, Vaamonde CA, et al. Effect of routine doses of antacid on renal acidification. Lancet 1986; 2:3.
14. Madias NE, Levey AS. Metabolic alkalosis due to absorption of "nonabsorbable" antacids. Am J Med 1983; 74:155.
15. Gennari FJ, Weise WJ. Acid-base disturbances in gastrointestinal disease. Clin J Am Soc Nephrol 2008; 3:1861.
16. Khadouri C, Marsy S, Barlet-Bas C, Doucet A. Short-term effect of aldosterone on NEM-sensitive ATPase in rat collecting tubule. Am J Physiol 1989; 257:F177.
17. Harrington JT, Hulter HN, Cohen JJ, Madias NE. Mineralocorticoid-stimulated renal acidification: the critical role of dietary sodium. Kidney Int 1986; 30:43.
18. Hropot M, Fowler N, Karlmark B, Giebisch G. Tubular action of diuretics: distal effects on electrolyte transport and acidification. Kidney Int 1985; 28:477.
19. CANNON PJ, HEINEMANN HO, ALBERT MS, et al. "CONTRACTION" ALKALOSIS AFTER DIURESIS OF EDEMATOUS PATIENTS WITH ETHACRYNIC ACID. Ann Intern Med 1965; 62:979.
20. Garella S, Chang BS, Kahn SI. Dilution acidosis and contraction alkalosis: review of a concept. Kidney Int 1975; 8:279.
21. Yamazaki O, Ishizawa K, Hirohama D, et al. Electrolyte transport in the renal collecting duct and its regulation by the renin-angiotensin-aldosterone system. Clin Sci (Lond) 2019;

133:75.

22. Wall SM. Regulation of Blood Pressure and Salt Balance By Pendrin-Positive Intercalated Cells: Donald Seldin Lecture 2020. Hypertension 2022; 79:706.
23. Wall SM, Lazo-Fernandez Y. The role of pendrin in renal physiology. Annu Rev Physiol 2015; 77:363.
24. POLAK A, HAYNIE GD, HAYS RM, SCHWARTZ WB. Effects of chronic hypercapnia on electrolyte and acid-base equilibrium. I. Adaptation. J Clin Invest 1961; 40:1223.
25. SCHWARTZ WB, HAYS RM, POLAK A, HAYNIE GD. Effects of chronic hypercapnia on electrolyte and acid-base equilibrium. II. Recovery, with special reference to the influence of chloride intake. J Clin Invest 1961; 40:1238.
26. ROTHERAM EB Jr, SAFAR P, ROBIN E. CNS DISORDER DURING MECHANICAL VENTILATION IN CHRONIC PULMONARY DISEASE. JAMA 1964; 189:993.
27. Hulter HN, Sebastian A, Toto RD, et al. Renal and systemic acid-base effects of the chronic administration of hypercalcemia-producing agents: calcitriol, PTH, and intravenous calcium. Kidney Int 1982; 21:445.
28. Orwoll ES. The milk-alkali syndrome: current concepts. Ann Intern Med 1982; 97:242.
29. Abreo K, Adlakha A, Kilpatrick S, et al. The milk-alkali syndrome. A reversible form of acute renal failure. Arch Intern Med 1993; 153:1005.
30. Patel AM, Goldfarb S. Got calcium? Welcome to the calcium-alkali syndrome. J Am Soc Nephrol 2010; 21:1440.
31. VAN GOIDSENHOVEN GM, GRAY OV, PRICE AV, SANDERSON PH. The effect of prolonged administration of large doses of sodium bicarbonate in man. Clin Sci 1954; 13:383.
32. Máttar JA, Weil MH, Shubin H, Stein L. Cardiac arrest in the critically ill. II. Hyperosmolal states following cardiac arrest. Am J Med 1974; 56:162.
33. Levin T. What this patient didn't need: a dose of salts. Hosp Pract (Off Ed) 1983; 18:95.
34. Kelleher SP, Schulman G. Severe metabolic alkalosis complicating regional citrate hemodialysis. Am J Kidney Dis 1987; 9:235.
35. Pearl RG, Rosenthal MH. Metabolic alkalosis due to plasmapheresis. Am J Med 1985; 79:391.
36. Gupta M, Wadhwa NK, Bukovsky R. Regional citrate anticoagulation for continuous venovenous hemodiafiltration using calcium-containing dialysate. Am J Kidney Dis 2004; 43:67.

37. Diskin CJ, Stokes TJ, Dansby LM, et al. Recurrent metabolic alkalosis and elevated troponins after crack cocaine use in a hemodialysis patient. Clin Exp Nephrol 2006; 10:156.
38. Bishop D, Claudius B. Effects of induced metabolic alkalosis on prolonged intermittent-sprint performance. Med Sci Sports Exerc 2005; 37:759.
39. Street D, Nielsen JJ, Bangsbo J, Juel C. Metabolic alkalosis reduces exercise-induced acidosis and potassium accumulation in human skeletal muscle interstitium. J Physiol 2005; 566:481.
40. Miller PD, Berns AS. Acute metabolic alkalosis perpetuating hypercarbia. A role for acetazolamide in chronic obstructive pulmonary disease. JAMA 1977; 238:2400.
41. Kennedy JD, Dinwiddie R, Daman-Willems C, et al. Pseudo-Bartter's syndrome in cystic fibrosis. Arch Dis Child 1990; 65:786.
42. Sweetser LJ, Douglas JA, Riha RL, Bell SC. Clinical presentation of metabolic alkalosis in an adult patient with cystic fibrosis. Respirology 2005; 10:254.
43. Augusto JF, Sayegh J, Malinge MC, et al. Severe episodes of extra cellular dehydration: an atypical adult presentation of cystic fibrosis. Clin Nephrol 2008; 69:302.

Topic 2331 Version 19.0

GRAPHICS

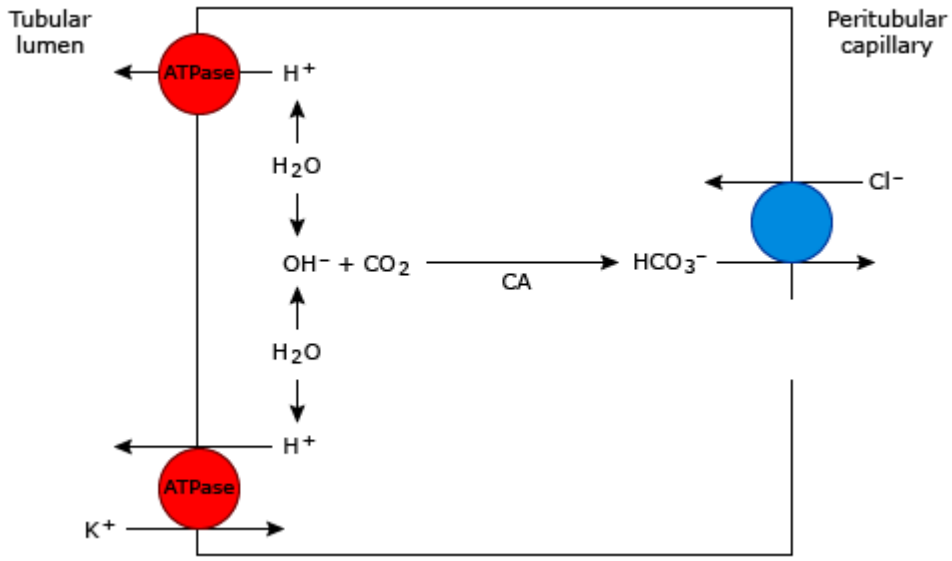
Major causes of metabolic alkalosis

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

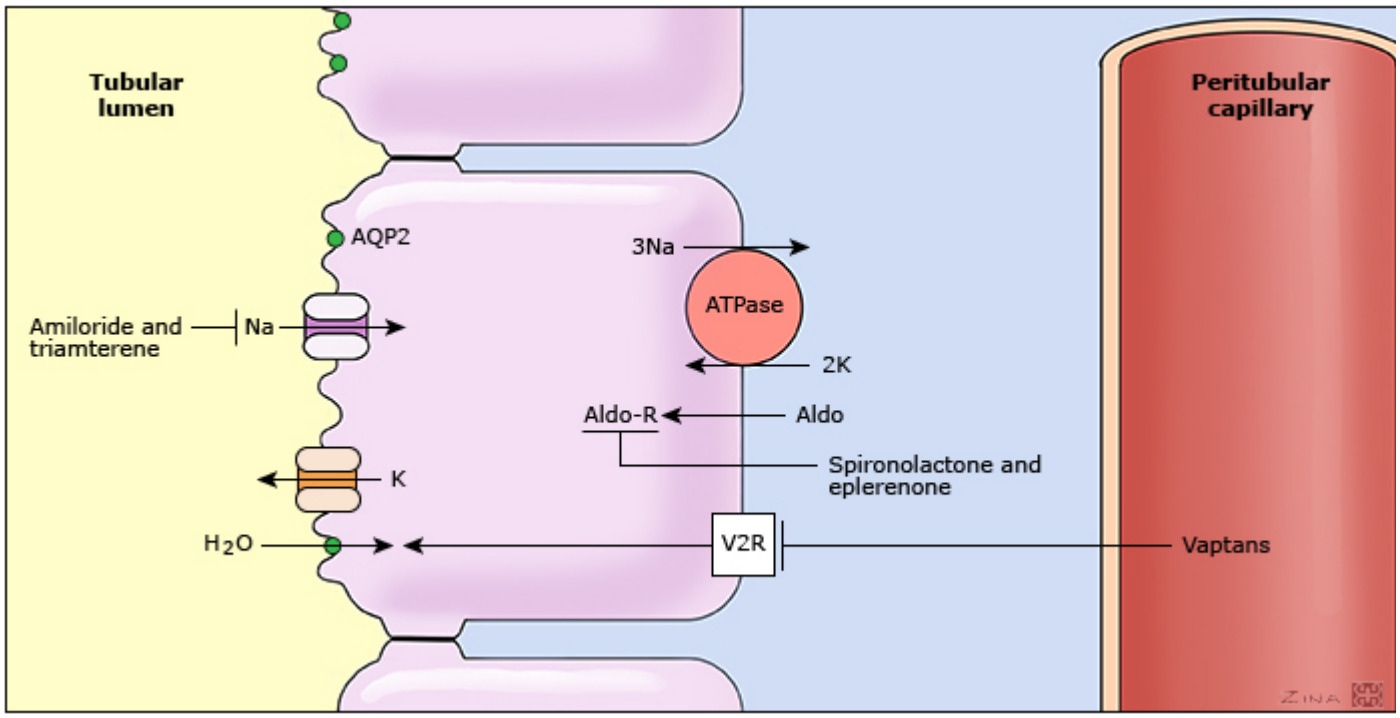
Acid-secreting type A intercalated cells



Transport mechanisms involved in hydrogen secretion and HCO_3^- and K^+ reabsorption in type A intercalated cells, which are present from the late distal convoluted tubule to the initial portion of the inner medullary collecting duct. Water within the cell dissociates into H^+ and OH^- ions. The former are secreted into the lumen by H-ATPase pumps in the luminal membrane, where they combine with urinary buffers to generate titratable acid (eg, convert HPO_4^{-2} to $H_2PO_4^-$) and convert NH_3 to NH_4^+. The OH^- ions in the cell combine with CO_2 to form HCO_3^- in a reaction catalyzed by carbonic anhydrase (CA). Driven by their electrochemical concentration gradients, cellular bicarbonate enters the peritubular capillaries in exchange for extracellular chloride via Cl-HCO_3 exchangers on the basolateral membrane. H-K-ATPase pumps, which secrete H^+ and reabsorb K^+, are also present in the luminal membrane of the type A intercalated cells. The number and activity of these pumps are increased by K^+ depletion, suggesting that they may be important for K^+ conservation.

Graphic 51361 Version 9.0

Ion transport in collecting tubule principal cells



Schematic representation of sodium (Na) and potassium (K) transport in the sodium-reabsorbing principal cells in the collecting tubules. The entry of filtered sodium into these cells is mediated by selective sodium channels in the apical (luminal) membrane (ENaC); the energy for this process is provided by the favorable electrochemical gradient for sodium (cell interior electronegative and low cell sodium concentration). Reabsorbed sodium is pumped out of the cell by the Na-K-ATPase pump in the basolateral (peritubular) membrane. The reabsorption of cationic sodium makes the lumen electronegative, thereby creating a favorable gradient for the secretion of potassium into the lumen via potassium channels (ROMK and BK) in the apical membrane. Aldosterone (Aldo), after combining with the cytosolic mineralocorticoid receptor (Aldo-R), leads to enhanced sodium reabsorption and potassium secretion by increasing both the number of open sodium channels and the number of Na-K-ATPase pumps. The potassium-sparing diuretics (amiloride and triamterene) act by directly inhibiting the epithelial sodium channel; spironolactone acts by competing with aldosterone for binding to the mineralocorticoid receptor.

Graphic 60693 Version 16.0