

Metabolic Alkalosis Pathogenesis, Diagnosis, and Treatment: Core Curriculum 2022

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Metabolic alkalosis is a widespread acid-base disturbance, especially in hospitalized patients. It is characterized by the primary elevation of serum bicarbonate and arterial pH, along with a compensatory increase in P_{CO_2} consequent to adaptive hypoventilation. The pathogenesis of metabolic alkalosis involves either a loss of fixed acid or a net accumulation of bicarbonate within the extracellular fluid. The loss of acid may be via the gastrointestinal tract or the kidney, whereas the sources of excess alkali may be via oral or parenteral alkali intake. Severe metabolic alkalosis in critically ill patients—arterial blood pH of 7.55 or higher—is associated with significantly increased mortality rate. The kidney is equipped with sophisticated mechanisms to avert the generation or the persistence (maintenance) of metabolic alkalosis by enhancing bicarbonate excretion. These mechanisms include increased filtration as well as decreased absorption and enhanced secretion of bicarbonate by specialized transporters in specific nephron segments. Factors that interfere with these mechanisms will impair the ability of the kidney to eliminate excess bicarbonate, therefore promoting the generation or impairing the correction of metabolic alkalosis. These factors include volume contraction, low glomerular filtration rate, potassium deficiency, hypochloremia, aldosterone excess, and elevated arterial carbon dioxide. Major clinical states are associated with metabolic alkalosis, including vomiting, aldosterone or cortisol excess, licorice ingestion, chloruretic diuretics, excess calcium alkali ingestion, and genetic diseases such as Bartter syndrome, Gitelman syndrome, and cystic fibrosis. In this installment in the AJKD Core Curriculum in Nephrology, we will review the pathogenesis of metabolic alkalosis; appraise the precipitating events; and discuss clinical presentations, diagnoses, and treatments of metabolic alkalosis.

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Introduction

A gain of base or a loss of acid from extracellular fluid is fundamental to the pathogenesis of metabolic alkalosis. The loss of acid may be via the gastrointestinal (GI) tract or by the kidney. Excess base may accumulate from oral or parenteral bicarbonate (HCO_3^-) administration or by lactate, acetate, or citrate supplementation. The loss of acid from the GI tract or the kidney is directly coupled to the generation of intracellular HCO_3^- , which is then transported to the blood, thus increasing the blood HCO_3^- concentration and pH.

The kidney is well equipped to eliminate excess HCO_3^- in order to maintain systemic acid-base status within a narrow physiological range. Any increase in blood HCO_3^- concentration (generation phase) will elicit a series of adaptive mechanisms that enhance HCO_3^- excretion by the kidney. Thus, significant metabolic alkalosis will not persist so long as the kidney's ability to enhance HCO_3^- excretion remains intact irrespective of the source of new HCO_3^- .

The pathogenesis of metabolic alkalosis encompasses 2 distinct phases, generation and maintenance, first conceptualized by Seldin in

1972 although there may be some overlap in certain disease states. The generation phase is defined as the period that is manifested by the initial loss of H^+ (acid) and chloride (Cl^-) either through the GI tract (eg, via vomiting) or via the kidney (eg, from chloruretic diuretics). The maintenance phase refers to the period when the active loss of acid has subsided or is subsiding (ie, the vomiting or diuretic usage has stopped), but metabolic alkalosis persists due to impairment of kidney HCO_3^- excretion. The correction (recovery) phase follows the maintenance phase and is achieved when the existing volume and electrolyte deficits (hypokalemia and hypochloremia) are corrected and the inciting event (GI or kidney acid loss) is treated. This installment of the AJKD Core Curriculum in Nephrology will try to incorporate the knowledge gained on this topic over the last 6 decades into a comprehensive description of the pathophysiology, diagnosis, and treatment of metabolic alkalosis.

To better understand the underlying mechanisms facilitating the generation, maintenance, or recovery from metabolic alkalosis, a detailed understanding of pathways and molecules regulating acid secretion and HCO_3^-

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

reabsorption in kidney tubules is essential. This issue will be discussed in the following section.

Bicarbonate Absorption, Secretion, and Generation in the Kidney: A Coordinated Interaction

Acid Secretion and Bicarbonate Reabsorption (Reclamation) by the Proximal Tubule

Approximately 85% to 90% of filtered HCO_3^- is reabsorbed in the proximal tubule, with the remaining being absorbed by the thick ascending limb of the loop of Henle,

distal convoluted tubule, and the collecting ducts. Reabsorption of HCO_3^- in the proximal tubule is mediated via H^+ secretion into the lumen principally through Na^+/H^+ exchanger 3 (NHE3) and the H^+ -transporting adenosine triphosphatase (H^+ -ATPase). Secreted H^+ reacts with luminal HCO_3^- and rapidly dissociates to carbon dioxide (CO_2) and H_2O , catalyzed by the luminal membrane carbonic anhydrase (CAIV). The CO_2 enters proximal tubule cells where it is converted to HCO_3^- by cytosolic carbonic anhydrase (CAII) before transportation to the blood via the basolateral $\text{Na}^+/\text{HCO}_3^-$ cotransporter (NBCe1). Figure 1 includes a depiction of the role of apical NHE3 and H^+ -ATPase,

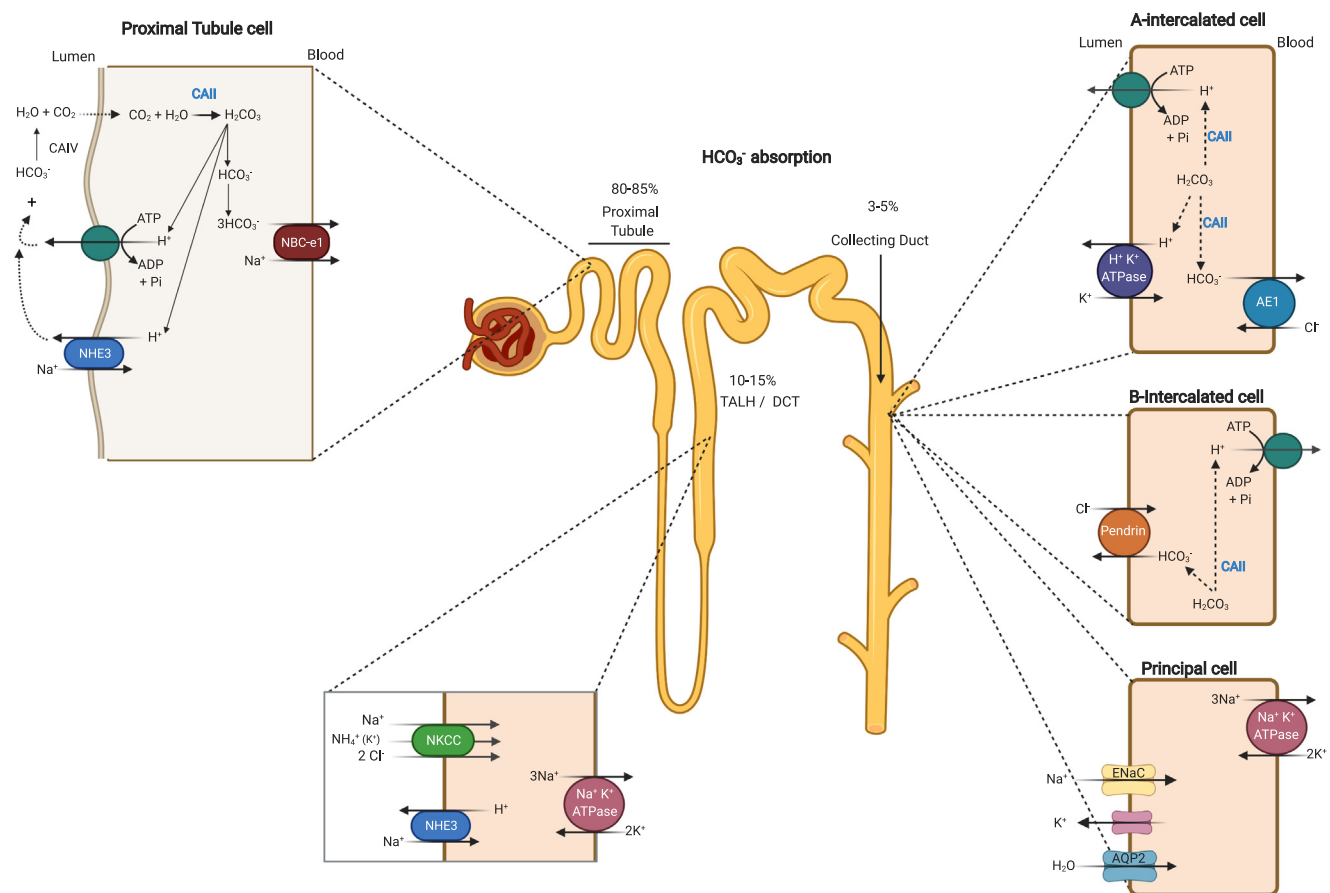


Figure 1. Schematic depiction of the localization and role of acid-base transporters and carbonic anhydrases in acid (H^+) and bicarbonate (HCO_3^-) transport in kidney tubules. The majority of filtered HCO_3^- is reabsorbed in the proximal tubule via the coordinated actions of Na^+/H^+ exchanger 3 (NHE3; encoded by *SLC9A3*) and H^+ -transporting adenosine triphosphatase (H^+ -ATPase) on the apical membrane working in tandem with the $\text{Na}^+/\text{HCO}_3^-$ cotransporter (NBCe1; encoded by *SLC4A4*) on the basolateral membrane. This process is facilitated by the actions of carbonic anhydrases IV and II (CAIV and CAII) on the apical membrane and in the cytoplasm, respectively. In the cortical collecting duct (CCD), H^+ -ATPase and H^+/K^+ -ATPase on the apical membrane of A-intercalated cells mediate H^+ secretion into the lumen, resulting in the generation of intracellular HCO_3^- that is transported to the blood via the basolateral $\text{Cl}^-/\text{HCO}_3^-$ AE1 (encoded by *SLC4A1*). The $\text{Cl}^-/\text{HCO}_3^-$ exchanger pendrin (encoded by *SLC26A4*) on the apical membrane of non-A-intercalated cells mediates HCO_3^- secretion into the lumen of the CCD in exchange for Cl^- absorption. Sodium (Na^+) and H_2O are absorbed by the epithelial sodium channel (ENaC) and aquaporin 2 (AQP2), respectively, in principal cells. Abbreviations: ADP, adenosine diphosphate; AE1, anion exchange protein 1; AQP2, aquaporin 2; ATP, adenosine triphosphate; CAII, carbonic anhydrase; CCD, cortical collecting duct; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; NBCe1, basolateral $\text{Na}^+/\text{HCO}_3^-$ cotransporter; NHE3, Na^+/H^+ exchanger 3; NKCC, $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter; PCT, proximal convoluted tubule; Pi, inorganic phosphate; TALH, thick ascending limb of Henle. Created with BioRender.com.

basolateral NBCe1, and CAIV and CAII in H^+ secretion and HCO_3^- reabsorption in the kidney proximal tubule.

Bicarbonate Absorption and Secretion in the Distal Nephron (Including the Collecting Duct)

The collecting duct plays a major role in systemic acid-base homeostasis by fine-tuning the excretion of acid and base. The cortical collecting duct comprises 3 cell types: A-intercalated cells, which secrete H^+ (acid); B-intercalated cells, which secrete HCO_3^- (base); and principal cells, which absorb Na^+ and water and secrete potassium ion (K^+). H^+ secretion by A-intercalated cells is primarily by apical H^+ -ATPases (and H^+/K^+ -ATPases), generating new HCO_3^- under the control of cytosolic CAII. This HCO_3^- is delivered to the blood in exchange for Cl^- by the basolateral Cl^-/HCO_3^- anion exchange protein 1 (AE1).

As opposed to A-intercalated cells, which occur along the length of the cortical and medullary collecting ducts, B-intercalated cells are primarily localized to the cortical collecting duct and are rarely found in the medullary collecting duct. Thanks mostly to the apical Cl^-/HCO_3^- exchanger pendrin, B-intercalated cells secrete HCO_3^- into the cortical collecting duct lumen in exchange for luminal Cl^- . The intracellular acid that results from HCO_3^- secretion in B-intercalated cells is transported into the blood by the basolateral H^+ -ATPase. The 3 major cell types in the cortical collecting duct (CCD) along with their apical and basolateral transporters involved in H^+ , HCO_3^- , or electrolyte transport are shown in Figure 1.

Ammoniogenesis and Its Role in New Bicarbonate Generation

Ammonia (NH_3) is generated in the proximal tubule from metabolism of glutamine through the process of ammoniogenesis (Fig 2). As a weak base, NH_3 acquires H^+ from H_2O to yield NH_4^+ (ammonium) at physiologic pH. NH_3/NH_4^+ is then secreted into the proximal tubule lumen, either as NH_3 , which is then trapped by H^+ (secreted by H^+ -ATPase or NHE3), or is transported as NH_4^+ by NHE3, which can function as a Na^+/NH_4^+ exchanger. Enzymes responsible for ammoniogenesis are regulated by intracellular pH (and indirectly by intracellular K^+). NH_4^+ is transported along the length of the proximal tubule to the medullary thick ascending limb, where it is absorbed into the medullary interstitium principally via the apical $Na^+/K^+/2Cl^-$ cotransporter (NKCC2). The secretion of NH_4^+ into the lumen of the collecting duct involves parallel H^+ and NH_3 secretion. Once in the collecting duct lumen, NH_3 is trapped as NH_4^+ by H^+ secreted through intercalated cells by H^+ -ATPase (and H^+/K^+ -ATPase). Collecting duct NH_4^+ excretion is in part dependent on the presence of nonerythroid Rh protein, RhCG, which is present on both the apical and basolateral membrane of A-intercalated cells of the connecting tubule and collecting duct. NH_4^+ excretion by the kidney leads to the elimination of acid in the collecting duct, thus allowing the gain of new HCO_3^-

in the proximal tubule. By regulating K^+ homeostasis as well as H^+ secretion into the lumen of the collecting duct, aldosterone plays a pivotal role in NH_4^+/NH_3 generation.

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Pathogenesis of Metabolic Alkalosis

Case 1: A 47-year-old man is brought to the emergency department with altered mental state after being found unresponsive at home by his neighbors. Little is known about his medical history except for a few medications found in his home, including over-the-counter antacids and ibuprofen. His neighbors indicated the patient had a history of heavy smoking and noticed some weight loss over the last 6 months. On arrival, his blood pressure was 95/57 mm Hg, pulse rate was 96 beats/min, and he was afebrile. The oxygen saturation by pulse oximetry was 92%. Basic chemistry laboratory testing showed Na^+ , 142 mEq/L; K^+ , 2.9 mEq/L; Cl^- , 90 mEq/L; HCO_3^- , 45 mEq/L; total calcium, 9.1 mg/dL; serum urea nitrogen (SUN), 38 mg/dL; and serum creatinine (Scr), 1.7 mg/dL. An arterial blood gas (ABG) revealed pH, 7.48; $Paco_2$, 52 mm Hg; and Pao_2 , 70 mm Hg. The nephrology service was consulted for the workup and management of the acid-base and electrolyte abnormalities.

Question 1: The differential diagnosis of metabolic alkalosis and hypokalemia in this patient should include (select the best answer):

- a) Excessive use of the carbonic anhydrase inhibitor acetazolamide
- b) Ectopic corticotropin production due to possible lung malignancy
- c) Intake of HCO_3^- -containing antacid for heartburn in the setting of pre-existing chronic kidney disease (CKD)
- d) Gastric outlet obstruction with vomiting

For the answer to the question, see the following text.

Box 1 displays the major causes of metabolic alkalosis, which are divided into 2 distinct categories based on

A

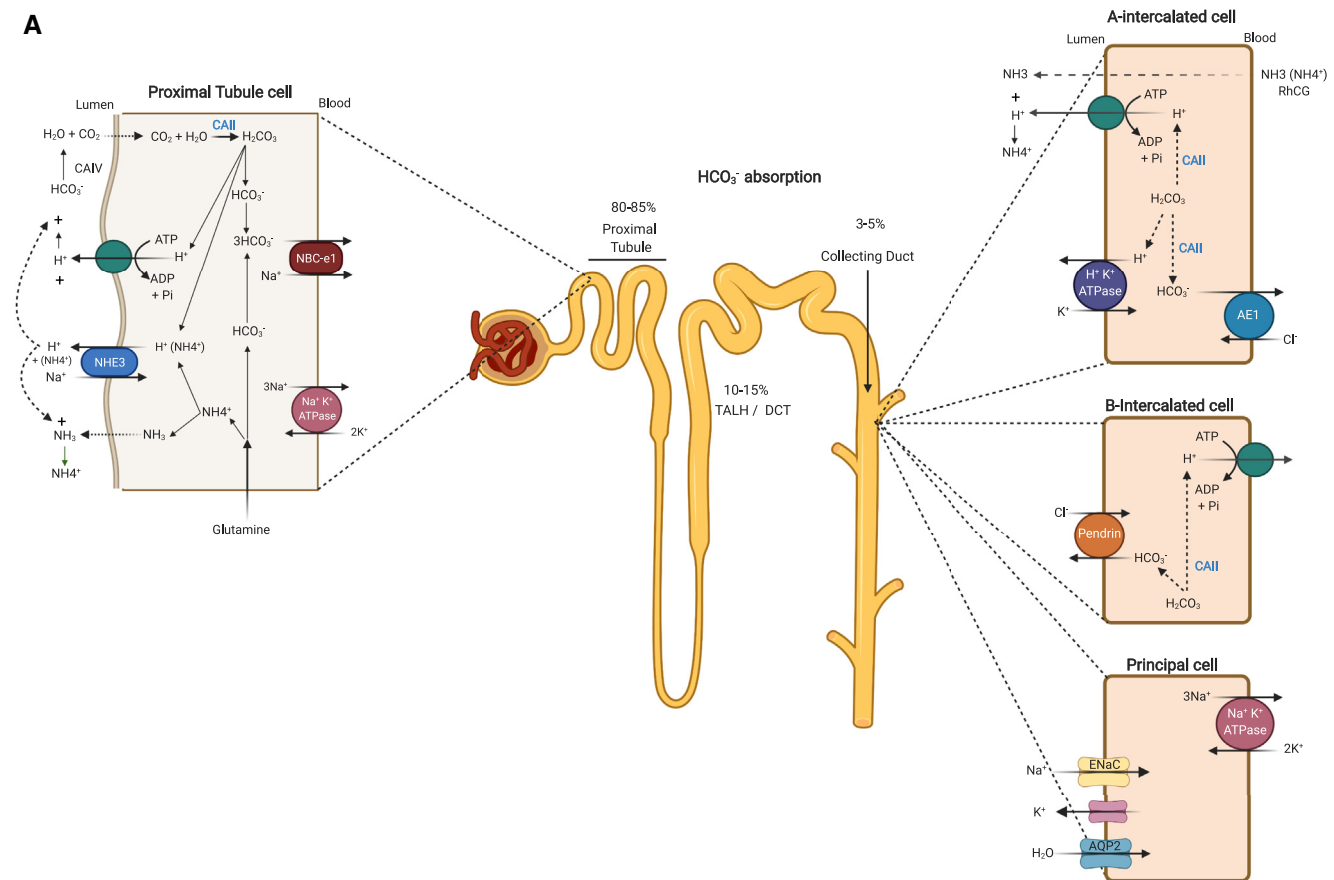


Figure 2. Schematic depiction of the mechanisms and nephron segments responsible for ammoniogenesis and ammonium/ammonia transport. Ammonium (NH_4^+) is generated from glutamine in the proximal tubule. Glutamine is converted to α -ketoglutarate (and eventually HCO_3^-) and NH_4^+ by glutaminase and glutamate dehydrogenase. NH_4^+ is transported into the lumen via the luminal NHE3 as well as being trapped by H^+ -ATPase-mediated H^+ secretion. The NH_4^+ is reabsorbed in the TAL via the apical $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter (NKCC2; encoded by *SLC12A1*) and secreted into the lumen of the collecting duct predominantly in the form of NH_3 , which is then trapped by the H^+ secreted via H^+ -ATPase to form NH_4^+ . NH_4^+ is then excreted into the urine with filtered Cl^- as its anion. This generates new HCO_3^- (via glutamine metabolism), while excreting an acid (ammonium chloride). The HCO_3^- is returned to the blood via NBCe1. Compared with the baseline state (A), hypokalemia (B) enhances ammoniogenesis in the proximal tubule, stimulates H^+ secretion and HCO_3^- reabsorption in the proximal tubule, activates H^+ -ATPase and $\text{Cl}^-/\text{HCO}_3^-$ AE1 in A-intercalated cells, induces the expression and activity of the nongastric H^+/K^+ -ATPase in the collecting duct, and downregulates the expression of the HCO_3^- -secreting transporter pendrin in B-intercalated cells. Bold arrows indicate activated pathways and molecules; thin arrows denote inactive processes and molecules in hypokalemia. Abbreviations: ADP, adenosine diphosphate; AE1, anion exchange protein 1; AQP2, aquaporin 2; ATP, adenosine triphosphate; CAII, carbonic anhydrase; CCD, cortical collecting duct; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; NBCe1, basolateral $\text{Na}^+/\text{HCO}_3^-$ cotransporter; NHE3, Na^+/H^+ exchanger 3; NKCC, $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter; PCT, proximal convoluted tubule; Pi, inorganic phosphate; TALH, thick ascending limb of Henle. Created with BioRender.com.

intravascular volume status. The following sections will review the pathogenesis of metabolic alkalosis in gastric acid loss and diuretic overuse as the 2 prototypes of GI and kidney acid loss with volume depletion. We will then discuss the role of mineralocorticoid excess in the generation and maintenance of metabolic alkalosis in both volume-depleted and volume-expanded states.

Gastric Alkalosis

Vomiting due to gastric outlet obstruction or nasogastric tube suctioning can lead to metabolic alkalosis consequent to the loss of gastric acid and fluid through the acid-

producing activity of the parietal cell. Parietal cells secrete H^+ along with Cl^- into the gastric lumen to produce hydrochloric acid (HCl) needed for digestion as shown in Figure 3. The generation of intracellular H^+ in parietal cells is coupled to the production of HCO_3^- facilitated by the CAII activity. The H^+ is extruded into the gastric lumen via the gastric H^+/K^+ -ATPase, whereas the HCO_3^- ion is transported to the blood predominantly via the basolateral $\text{Cl}^-/\text{HCO}_3^-$ anion exchange protein 2 (AE2), “generating” base excess that is referred to as “alkaline tide.” The secretion of H^+ into the gastric lumen and transport of HCO_3^- to the blood is the initial step in

B

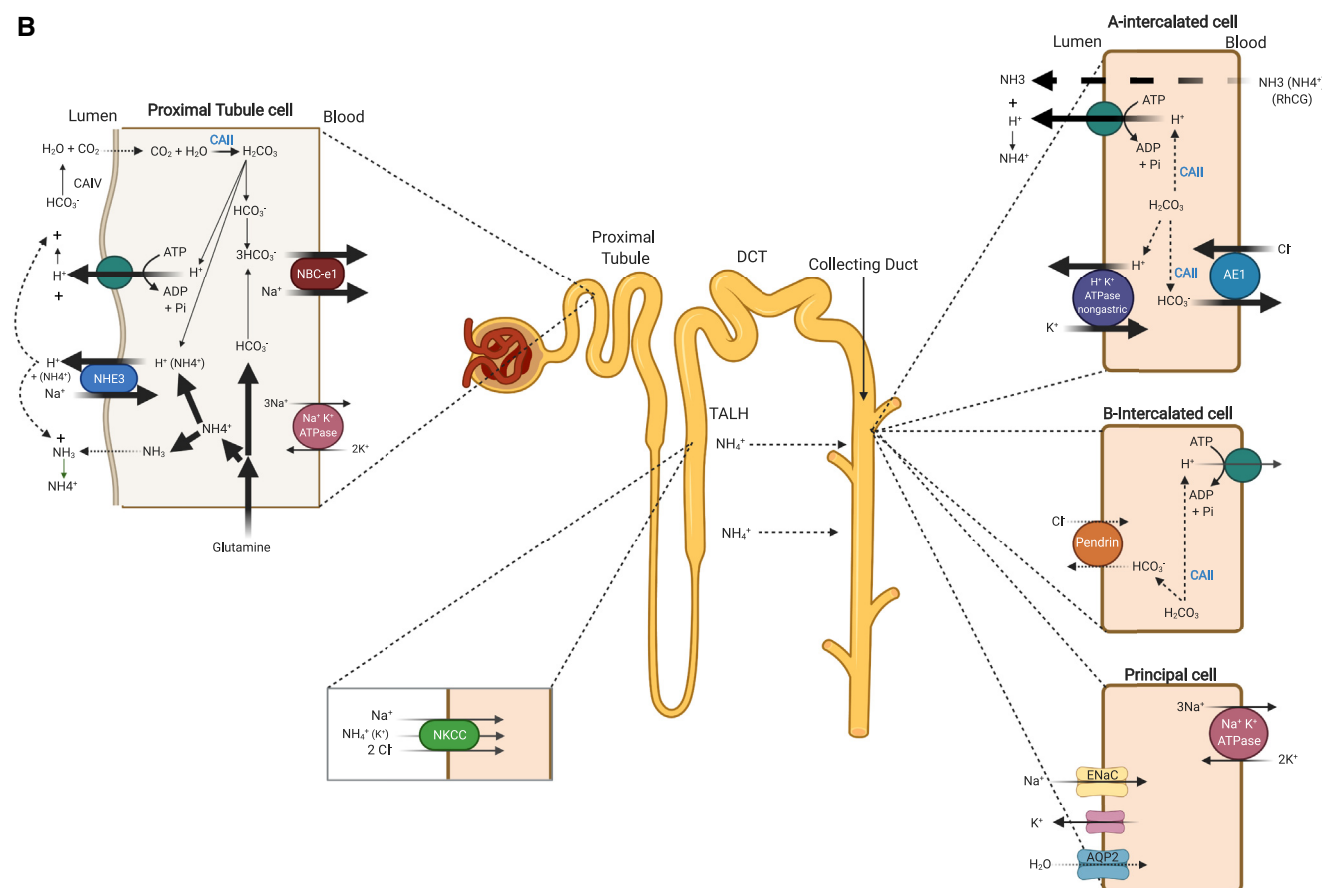


Figure 2. Continued

both the physiologic digestion process and gastric fluid loss due to vomiting. The initial increase in serum HCO_3^- concentration will be short-lived as long so the individual remains euvoletic, normochloremic, and normokalemic. However, significant gastric fluid loss (as in nasogastric suctioning or severe vomiting) will result in extracellular fluid (ECF) contraction and hypochloremia due to the direct loss of HCl from the gastric lumen. In addition, the resulting volume depletion will activate the renin-angiotensin-aldosterone system (RAAS), thus generating hypokalemia consequent to enhanced renal K^+ wasting. Together these factors are critical to the maintenance of metabolic alkalosis especially after the cause of the gastric fluid loss has ceased.

Diuretic-Induced Metabolic Alkalosis

Inhibitors of Cl^- absorption in both the kidney's thick ascending limb and the distal convoluted tubule can generate metabolic alkalosis subsequent to the loss of salt (NaCl) and fluid. Thiazides (inhibitors of the Na^+/Cl^- cotransporter [NCC]) produce a mild metabolic alkalosis. By contrast, loop diuretics (furosemide and its analogs) can produce severe metabolic alkalosis consequent to the inhibition of NKCC2. The generation of metabolic alkalosis with loop diuretics is due to the

combination of several sequential steps. It starts primarily with salt wasting, resulting in volume depletion and activation of the renin-aldosterone system (RAS). Next, the salt wasting increases the delivery of Na^+ (and Cl^-) to the more distal segments, such as the connecting tubule and collecting duct, where Na^+ will be absorbed via the epithelial sodium channel (ENaC) in exchange for K^+ (predominantly via the renal outer medullary K^+ channel [ROMK]) and H^+ secretion (via H^+ -ATPase and in part H^+/K^+ -ATPase) (Fig 4A). These processes are significantly amplified in the presence of aldosterone (Fig 4B), which also has a direct effect on H^+ secretion in the medullary collecting duct.

Carbonic anhydrase inhibitors (such as acetazolamide) are used as diuretics in patients with congestive heart failure. In addition, they are also used for the treatment of various disorders including certain types of seizures, glaucoma, mountain sickness, and idiopathic intracranial hypertension. They cause HCO_3^- wasting by inhibiting HCO_3^- absorption in the proximal tubule and the collecting duct, resulting in nongap (hyperchloremic) metabolic acidosis. In addition, they also cause K^+ wasting, which leads to hypokalemia. The patient in case 1 has metabolic alkalosis and not acidosis, so for Question 1, option (a) is not correct. Glucocorticoids at

Box 1. Etiologies of Metabolic Alkalosis

1. Intravascular volume depletion with hyponatremia.
 - i. Gastric acid (HCl) loss: vomiting, nasogastric drainage
 - ii. Renal chloride wasting
 - a. Loop diuretics (eg, furosemide, bumetanide, etc), thiazides (eg, hydrochlorothiazide)
 - b. Inherited disorders: Bartter syndrome; Gitelman syndrome
 - iii. Laxative overuse
 - iv. Chloride-losing diarrhea (acquired or inherited)
 - v. Cystic fibrosis
 - vi. Posthypercapnic state
 - vii. High-volume ileostomy output
 - viii. Hyponatremia without volume depletion?
2. Intravascular volume expansion with potassium depletion
 - i. Primary aldosteronism
 - ii. Renin-secreting tumors
 - iii. Renal artery stenosis: unilateral or bilateral
 - iv. Pseudohyperaldosteronism or apparent mineralocorticoid excess syndrome
 - a. Mutations in MR
 - b. Mutations in *HSD11B2*: leads to cortisol stimulation of MR
 - c. Altered activity of 11-hydroxysteroid dehydrogenase type 2 (excessive intake of carbenoxolone, licorice, or grapefruit)
 - d. Primary deoxycorticosterone excess: deficiency of 17 α -hydroxylase and 11 β -hydroxylase genes
 - v. Liddle syndrome: gain-of-function mutations in ENaC
 - vi. Cushing syndrome: excess cortisol production by adrenal gland due to adrenal tumors or consequent to ectopic corticotropin production (excess cortisol occupies and activates the MR; ectopic corticotropin is a more potent cause of hypokalemic metabolic alkalosis than adrenal or pituitary tumors)
 - vii. Glucocorticoid-remediable aldosteronism

Abbreviations: ENaC, epithelial sodium channel; MR, mineralocorticoid receptor.

high concentrations, like those in ectopic corticotropin production, can bind and activate the mineralocorticoid receptor in principal cells, leading to the stimulation of salt absorption via ENaC and generation of hypertension. The absorption of Na⁺ will increase K⁺ and H⁺ secretion into the urine, promoting hypokalemia and enhanced HCO₃⁻ absorption. The presence of hypertension is detected in the majority of patients with ectopic corticotropin secretion. The patient in case 1 presents with low blood pressure and tachycardia suggestive of intravascular volume depletion, so option (b) is not correct.

Ingestion of absorbable antacids such as those containing HCO₃⁻ or CO₃²⁻ (carbonate) in the setting of diminished kidney function can lead to the generation of metabolic alkalosis due to impaired kidney excretion of HCO₃⁻. Absorbable HCO₃⁻-containing medications, such as sodium bicarbonate, are usually used as a treatment to correct metabolic acidosis in CKD patients. The presence of significant hypokalemia and hypotension makes option (c) implausible for Question 1.

Many of the diseases that present with metabolic alkalosis are accompanied with K⁺ depletion. Vomiting due to gastric outlet obstruction can lead to metabolic alkalosis due to large gastric fluid losses via parietal cells as discussed under the gastric alkalosis section (Fig 3). Excessive loss of gastric fluid causes hyponatremia and ECF volume contraction, activates the RAS, and leads to hypokalemia due to renal K⁺ wasting. The net effect of these factors is a significant elevation of serum HCO₃⁻ and arterial pH along with hypokalemia and hyponatremia. Vital signs (low blood pressure and tachycardia due to vascular volume depletion) and laboratory results (hypokalemia and metabolic alkalosis) in case 1 fit this category of gastric loss-induced metabolic alkalosis; thus, the best answer to Question 1 is (d).

Question 2: Match each diagnosis with the correct clinical and laboratory presentation:

Clinical diagnosis:

- a) Overuse of the loop diuretic furosemide
- b) Ectopic corticotropin due to a lung malignancy
- c) Gastric outlet obstruction with vomiting

Presentation:

- 1) Blood pressure, 160/100 mm Hg; serum K⁺, 2.9 mEq/L; serum HCO₃⁻, 45 mEq/L; urine Na⁺, 40 mEq/L; Cl⁻, 45 mEq/L; and urine K⁺, 38 mEq/L
- 2) Blood pressure, 95/57 mm Hg; serum K⁺, 2.9 mEq/L; serum HCO₃⁻, 45 mEq/L; urine Na⁺, 40 mEq/L; urine Cl⁻, 45 mEq/L; and urine K⁺, 38 mEq/L
- 3) Blood pressure, 95/57 mm Hg; serum K⁺, 2.9 mEq/L; serum HCO₃⁻, 45 mEq/L; urine Na⁺, <10 mEq/L; urine Cl⁻, <20 mEq/L; and urine K⁺, 23 mEq/L

For the answer to the question, see the following text.

The overuse of loop diuretics is associated with volume contraction, which is consistent with a blood pressure of 95/57 mm Hg and with increased urine electrolytes. Ectopic corticotropin production presents with hypertension (blood pressure of 160/100 mm Hg) and increased urine electrolytes. Gastric outlet obstruction with vomiting presents with volume contraction (blood pressure of 95/57 mm Hg) and low urine Na⁺ and Cl⁻ excretion. Thus, the correct pairs are (a) and (2); (b) and (1); and (c) and (3).

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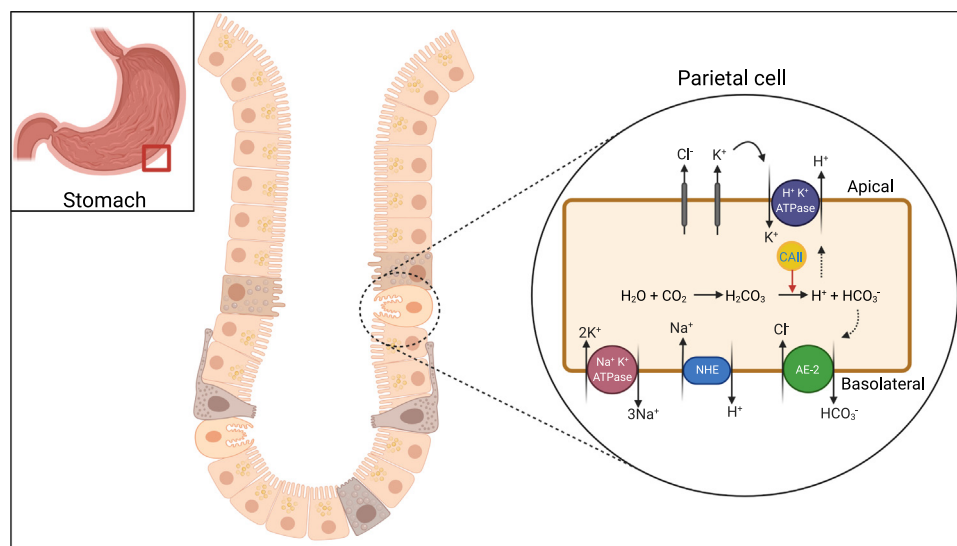


Figure 3. Schematic depiction of the localization and role of apical gastric H^+/K^+ -ATPase, cytoplasmic CAII, and the basolateral $\text{Cl}^-/\text{HCO}_3^-$ anion exchange protein 2 (AE2; encoded by *SLC4A2*) in acid secretion and bicarbonate absorption in gastric parietal cells. Excessive gastric loss of HCl results in the addition of new HCO_3^- to the blood. Abbreviations: AE-2, anion exchange protein 2; CAII, carbonic anhydrase; NHE, Na^+/H^+ exchanger. Created with BioRender.com.

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★**ESSENTIAL READING**

Mineralocorticoid Excess and Metabolic Alkalosis

Almost all cases of metabolic alkalosis present with an excess of mineralocorticoids. Most represent RAS stimulation consequent to decreased intravascular volume, which encompasses conditions with either true vascular volume deficit (ie, vomiting, excessive use of laxatives, or overuse of diuretics) or decreased effective vascular volume (ie, congestive heart failure). The other major category of metabolic alkalosis with increased mineralocorticoids encompasses patients with normal or expanded vascular volume such as in primary aldosteronism. The role of mineralocorticoid excess in the generation and or the maintenance of metabolic alkalosis in volume-depleted or volume-expanded states will be discussed in the following sections.

Maintenance Phase of Metabolic Alkalosis in Volume-Depleted States

The maintenance phase of metabolic alkalosis in disease states associated with ECF volume contraction refers to a period after the generation phase where the initiating factors responsible for increased arterial pH and HCO_3^- concentration (vomiting or diuretic overuse) may have abated but the metabolic alkalosis persists. Factors that impair the elimination of excess serum HCO_3^- will prevent the correction of metabolic alkalosis. The most important among these factors are decreased glomerular filtration rate

(GFR) consequent to volume contraction, hypochloremia, K^+ deficiency, and steroid (aldosterone) excess. The role of these factors in the maintenance of gastric alkalosis and diuretic-induced alkalosis will be discussed in the following sections.

Decreased Kidney Perfusion

Both vomiting (or nasogastric suctioning) and chloruretic diuretic overuse are associated with ECF volume contraction consequent to the loss of Cl^- -rich fluid in the stomach or kidney tubules, respectively, resulting in decreased kidney perfusion and GFR. The reduction in GFR reduces the amount of filtered HCO_3^- , preventing effective removal of excess HCO_3^- from the blood compartment.

Hypochloremia

Almost all patients with metabolic alkalosis and vascular volume depletion display both hypochloremia and kidney hypoperfusion (low GFR). Low serum Cl^- directly results from the loss of Cl^- into the lumen of the stomach and kidney tubules. This interferes with renal HCO_3^- excretion via several mechanisms, one of which is the impairment of HCO_3^- secretion in B-intercalated cells via pendrin (Fig 5A), which is inactivated both due to the low luminal Cl^- concentration and the transcriptional downregulation consequent to K^+ depletion (Fig 5B).

Aldosterone Excess

Volume depletion stimulates the RAAS, which mitigates sodium loss by increasing Na^+ absorption in exchange for K^+ and H^+ secretion. Increased H^+ secretion into the collecting duct lumen leads to enhanced HCO_3^-

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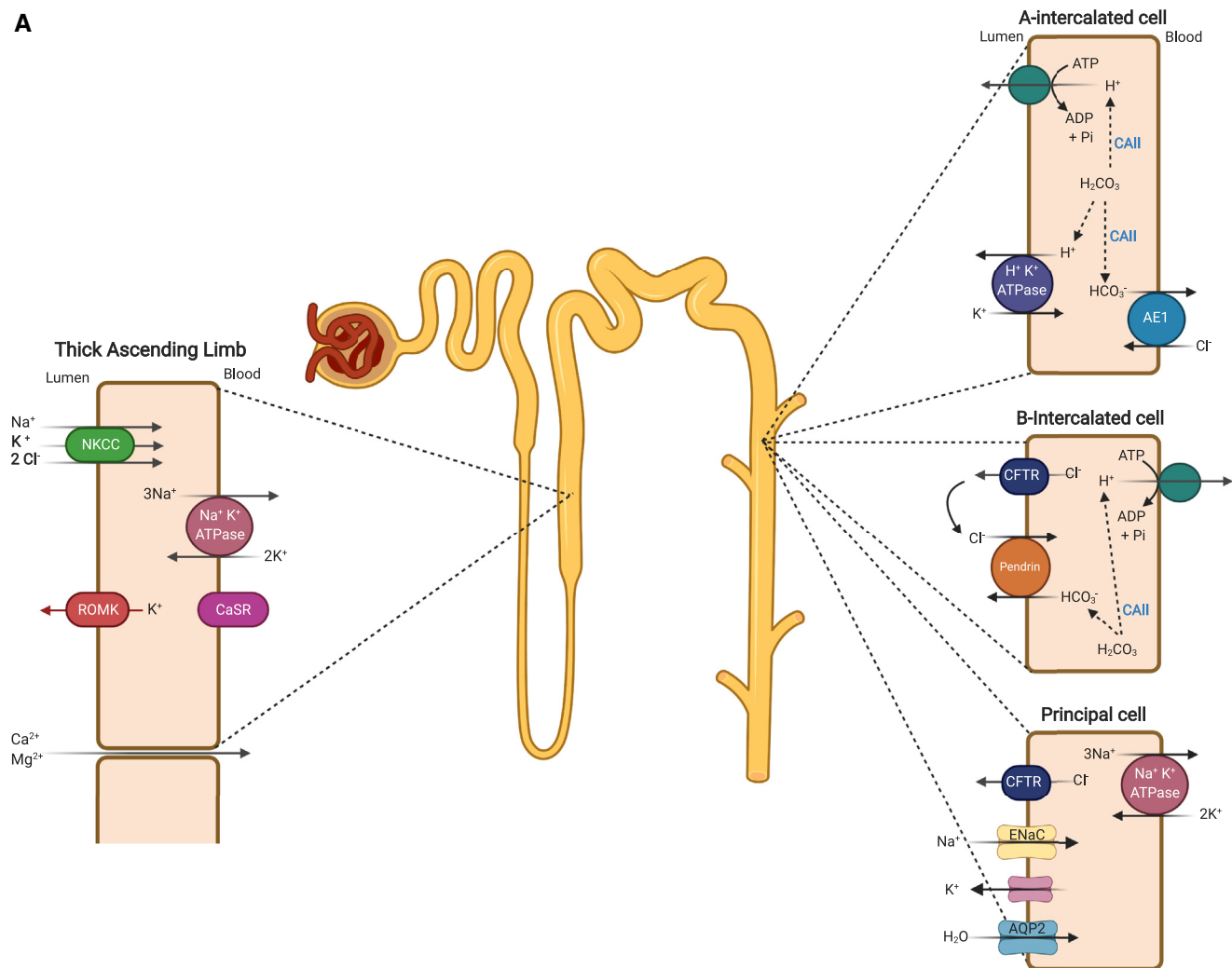


Figure 4. Schematic depiction of the mechanism of salt absorption in the thick ascending limb of Henle and salt absorption and acid secretion in the collecting duct. (A) With normal vascular volume, the inhibition of NKCC will increase the delivery of salt to the distal segments such as the collecting duct, where Na^+ is absorbed via ENaC in exchange for K^+ (via ROMK) and H^+ secretion (via H^+ -ATPase and in part H^+/K^+ -ATPase). The increase in bicarbonate absorption will be offset by enhanced HCO_3^- secretion via pendrin, mitigating the impact of acid secretion on systemic acid-base homeostasis. (B) When loop diuretic use causes volume depletion, the RAAS is activated. Na^+ absorption and K^+ and H^+ secretion processes in the collecting duct are significantly amplified in the presence of aldosterone. The resulting volume depletion and hypochloremia as well as RAAS activation and hypokalemia will enhance bicarbonate absorption and inhibit bicarbonate secretion in the collecting duct cells. Bold arrows indicate activated pathways and molecules. Abbreviations: ADP, adenosine diphosphate; AE1, anion exchange protein 1; Aldo, aldosterone; AQP2, aquaporin 2; ATP, adenosine triphosphate; CAII, carbonic anhydrase; CaSR, calcium-sensing receptor; CCD, cortical collecting duct; CFTR, cystic fibrosis transmembrane conductance regulator; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; K^+ , potassium ion; MR, mineralocorticoid receptor; NCC, Na^+/Cl^- cotransporter; NCX, sodium-calcium exchanger; NKCC, $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter; PCT, proximal convoluted tubule; Pi, inorganic phosphate; RAAS, renin-angiotensin-aldosterone system; ROMK, renal outer medullary K^+ channel; TAL, thick ascending limb; TRPV5, transient receptor potential vanilloid member 5. Created with BioRender.com.

absorption through A-intercalated cells and contributes to metabolic alkalosis (Fig 4B). The stimulation of K^+ secretion into the collecting duct in exchange for Na^+ absorption via ENaC leads to K^+ depletion, which impairs the correction of alkalosis by several mechanisms (see the following section). Angiotensin II has a direct effect on H^+ secretion in the proximal and distal nephron segments, contributing to enhanced absorption

of HCO_3^- and the maintenance of metabolic alkalosis in volume-depleted states.

Potassium Deficiency (or Hypokalemia)

Hypokalemia exerts multiple effects on kidney tubules with a net effect of maintaining the alkalosis, both in gastric or diuretic-induced alkalosis in volume depleted states, as well as in volume expanded states.

B

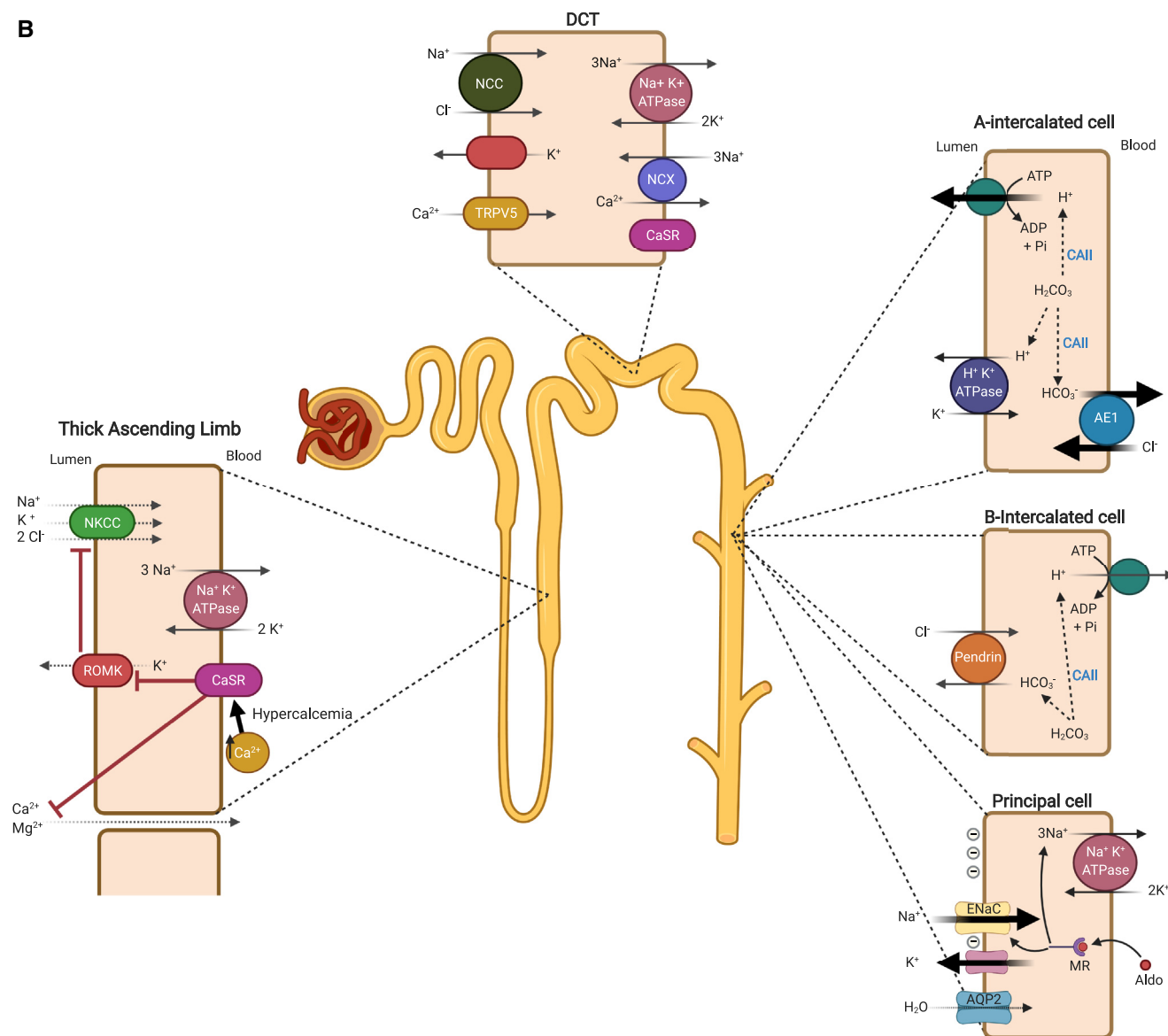


Figure 4. Continued.

Hypokalemia, as well as metabolic acidosis, is a potent stimulator of ammoniogenesis by increasing glutamine uptake and enhancing the expression of ammoniagenic enzymes in the proximal tubule, ultimately resulting in the generation and addition of new HCO₃⁻ to the blood (Fig 2B). This added HCO₃⁻ may be maladaptive because it can either contribute to the generation of metabolic alkalosis (primary aldosteronism) or impede the correction of alkalosis in volume-depleted states with secondary hyperaldosteronism (vomiting or loop diuretic-induced alkalosis).

Hypokalemia stimulates HCO₃⁻ reabsorption by activating apical NHE3 and basolateral NBCe1 in the proximal tubule, enhancing H⁺-ATPase and AE1 activities in A-intercalated cells, and inducing the expression and activity of the nongastric H⁺/K⁺-ATPase in the

collecting duct (Fig 2B). Furthermore, hypokalemia downregulates the expression of the HCO₃⁻-secreting transporter pendrin in B-intercalated cells (Fig 2B). Collectively, these effects blunt the elimination of excess HCO₃⁻ in volume-depleted states (vomiting, overuse of loop diuretics, etc) or contribute to the generation of metabolic alkalosis in volume-expanded states (primary aldosteronism).

In brief, hypokalemia is a critical contributor to the worsening of metabolic alkalosis, specifically in volume-depleted states, by (1) enhancing ammoniogenesis in proximal tubule cells, leading to new HCO₃⁻ generation; (2) increasing proximal tubular reabsorption of filtered HCO₃⁻; (3) increasing HCO₃⁻ generation and absorption in the collecting duct A-intercalated cells; and (4) decreasing HCO₃⁻ secretion in the collecting duct B-intercalated cells.

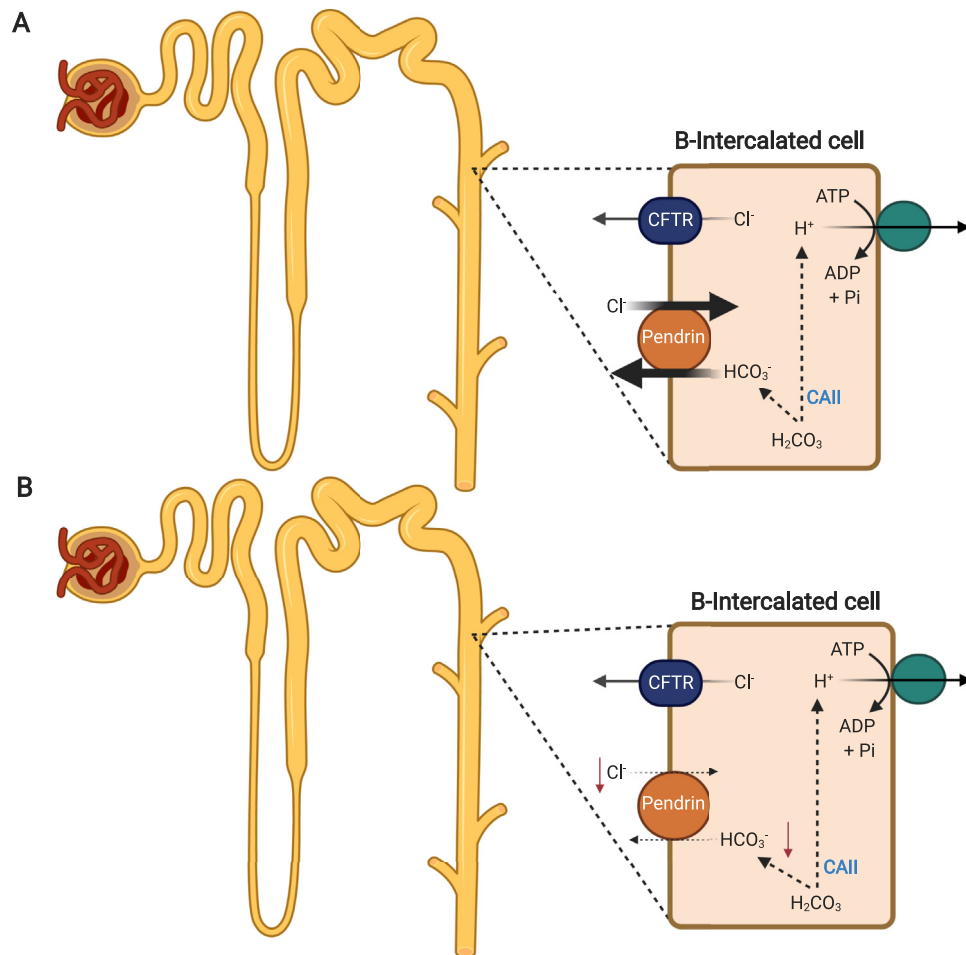


Figure 5. The impact of hypochloremia on HCO_3^- secretion in the cortical collecting duct. (A) In the baseline state the apical $\text{Cl}^-/\text{HCO}_3^-$ exchanger pendrin in B-intercalated cells is the only known HCO_3^- -secreting molecule along the length of the kidney tubule. Pendrin mediates the secretion of HCO_3^- in exchange for the luminal Cl^- under physiologic conditions. (B) In hypochloremia, the absence of luminal chloride impairs the HCO_3^- secretion via pendrin. The presence of hypokalemia independently downregulates pendrin, further blocking HCO_3^- secretion via this exchanger. Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; CFTR, cystic fibrosis transmembrane conductance regulator; CAII, cytosolic carbonic anhydrase. Created with BioRender.com.

Elevated Pco_2

The compensatory alveolar hypoventilation in metabolic alkalosis leads to hypercapnia (elevated arterial carbon dioxide; Paco_2), which blunts the rise in arterial pH due to elevated HCO_3^- concentration. Although hypercapnia occurs gradually as a respiratory compensation for metabolic alkalosis, it enhances the HCO_3^- reabsorptive capacity of the kidney tubules and thus prevents HCO_3^- excretion. Hypercapnia together with vascular volume depletion, hypochloremia, hypokalemia, and mineralocorticoid excess contribute to the maintenance of metabolic alkalosis.

Maintenance Phase of Metabolic Alkalosis in Volume-Expanded States

In conditions associated with the primary increase in circulating mineralocorticoids or glucocorticoids, the

vascular volume is increased due to augmented salt absorption in the collecting duct (Fig 4B). The initiation of metabolic alkalosis in the aforementioned states is gradual and is primarily due to enhanced H^+ excretion in A-intercalated cells. This process is driven by increased luminal negative electrogenicity consequent to aldosterone-dependent Na^+ absorption via the apical sodium channel, ENaC (Fig 4B). A similar driving force enhances K^+ secretion into the lumen of the collecting duct, creating a state of K^+ wasting. The aldosterone-induced hypokalemia plays a critical role in the generation and maintenance of metabolic alkalosis by increasing acid secretion and HCO_3^- absorption in several nephron segments as discussed previously (Fig 2B). Diseases such as primary aldosteronism and Cushing syndrome present with this abnormality, as does excess licorice ingestion. In conditions associated with primary stimulation of the

RAAS (renal artery stenosis, renin-producing tumors, etc), increased angiotensin II levels intensify net acid excretion in the distal nephron, hence contributing to the generation and maintenance of metabolic alkalosis.

Recovery Phase of Metabolic Alkalosis

The recovery phase occurs when the existing deficits (volume, Cl^- , or K^+) are corrected, and the continued losses (via kidney or GI tract) are halted. Agents that are responsible for the loss of acid (ie, loop diuretics, licorice, etc) or gain of alkali (oral bicarbonate or citrate) need to be discontinued.

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Workup and Treatment of Metabolic Alkalosis

Case 2: A 65-year-old woman with a history of hypertension, coronary artery disease, osteoporosis, and gastroesophageal reflux disease was brought to the emergency department with altered mental status. Her son reported that she started to experience decreased appetite several weeks ago. She had been reporting epigastric pain for the past several months. The

patient's home medications include antihypertensives and over-the-counter medications for pain and heartburn. Her vital signs showed temperature, 37.3°C; blood pressure, 108/62 mm Hg; pulse rate, 96 beats/min; and oxygen saturation of 93% on room air. The patient is somnolent but arousable on examination. Her laboratory tests are significant for Na^+ , 144 mEq/L; K^+ , 3.4 mEq/L; Cl^- , 92 mEq/L; HCO_3^- , 37 mEq/L, SUN, 28 mg/dL; and Scr, 2.7 mg/dL. Her serum calcium is 15.1 mEq/L; phosphorus, 3.0 mEq/L; and glucose, 130 mg/dL. Albumin is 3.8 g/dL. Venous blood gas (VBG) shows a pH of 7.47. You are asked to evaluate the patient for the acid-base abnormalities, hypercalcemia, and kidney failure. Further workup on blood drawn on admission showed parathyroid hormone (PTH) level of 10 pg/mL; undetectable PTH-related peptide; 1,25-dihydroxyvitamin D, 20 pg/mL.

Question 3: Which one of the following conditions is the best explanation for the development of hypercalcemia and metabolic alkalosis in this patient?

- a) Thiazide diuretic use for hypertension
- b) Primary hyperparathyroidism
- c) Sarcoidosis
- d) Calcium-alkali (milk alkali) syndrome
- e) Hypercalcemia of malignancy

For the answer to the question, see the following text.

The impact of metabolic alkalosis on the body is diverse and includes effects on the central nervous system (ranging from confusion to coma), peripheral nervous system (neuropathic symptoms such as tingling and numbness), myocardium (arrhythmia), and skeletal muscle (weakness and twitching), among others. Some of these signs and symptoms could be due to severe electrolyte derangements either consequent to transcellular shifts (hypokalemia and hypophosphatemia) or secondary to altering the ratio of free to bound ions (calcium). Metabolic alkalosis is divided into 2 major categories based on whether ECF volume status is contracted or expanded (**Box 1**). Diagnosis of metabolic alkalosis is established by elevation in blood pH above 7.44 in the setting of high serum HCO_3^- concentration. Arterial blood gas (ABG), or a VBG at a minimum, is required if the diagnosis is in doubt (**Fig 6**).

A comprehensive patient history can uncover potential causes of metabolic alkalosis such as vomiting or excessive intake of diuretics, laxatives, exogenous HCO_3^- , or licorice. The history can also provide clues toward the presence of diseases such as primary aldosteronism, cystic fibrosis, or possible alkalosis-provoking medications (penicillin, carbenicillins, etc). Physical examination can help in establishing ECF volume contraction. A basic chemistry profile for Na^+ , K^+ , Cl^- , Mg^{2+} , SUN, and Scr assists in evaluating kidney function and may provide clues toward the causes of alkalosis.

Based on the systemic blood pressure and urine electrolytes, patients with metabolic alkalosis are divided into chloride-sensitive (urine $\text{Cl}^- < 20$ mmol/L) and chloride-resistant (urine $\text{Cl}^- > 20$ mmol/L) groups (**Fig 6**).

Some important causes of metabolic alkalosis with variable volume status include hypokalemia, hypomagnesemia, refeeding syndrome, alkali loading in individuals with reduced GFR, and nonreabsorbable anions such as penicillin and carbenicillin.

Patients suspected of having primary aldosteronism require measurements of renin and aldosterone at baseline and, if necessary, following the saline suppression test. The diagnosis of Bartter, Gitelman, cystic fibrosis, and Pendred syndromes necessitates genetic testing. Diagnosing congenital adrenal hyperplasia due to 11 β - or 17 α -hydroxylase deficiency requires specific tests measuring the blood concentration of 11-deoxycorticosterone, corticosterone, renin, and aldosterone, as well as cortisol and its 17-hydroxylated precursors.

Returning to case 2, thiazide overuse can produce hypercalcemia due to increased calcium reabsorption in the proximal tubule, but will also cause other electrolyte disturbances such as profound hypokalemia and hyponatremia, which are not observed in this patient. Further, the magnitude of hypercalcemia by thiazides is not expected to exceed levels above 14 mg/dL. Thus, option (a) is not the correct answer to Question 3.

Because the patient's PTH level is borderline low, primary hyperparathyroidism as a cause of hypercalcemia is unlikely. Further, a majority of patients with primary hyperparathyroidism develop nongap metabolic acidosis due to the direct inhibitory effects of PTH on proximal tubule function, hence option (b) is not correct. In hypercalcemia caused by granulomatous diseases such as sarcoidosis, vitamin D levels are significantly increased, which is not the case in this patient; thus, option (c) is not correct. Because the PTH-related peptide levels are undetectable, option (e) is incorrect.

The patient's findings of hypercalcemia (PTH-independent), metabolic alkalosis, and decreased kidney function are most likely caused by calcium alkali (milk alkali) syndrome. This condition is triggered by the ingestion of calcium along with an absorbable alkali. The disease was initially described in patients treated for peptic ulcer disease who used milk and sodium bicarbonate for symptomatic relief, but the current dominant etiology is associated with the use of over-the-counter calcium-containing medications for the prevention and treatment of osteoporosis or heartburn. Because of the change in the causative agents over the years, several scholars have suggested changing the name to calcium-alkali syndrome to accurately reflect the current pathogenesis of this disorder. Thus, the correct answer to Question 3 is (d).

Question 4: The most critical step contributing to this patient's metabolic alkalosis and kidney failure is:

- a) Decreased kidney perfusion due to vasoconstriction of afferent arterioles
- b) Activation of the RAAS

- c) Downregulation of the water channel aquaporin (AQP2) in the collecting duct
- d) Inhibition of NKCC2 due to calcium-sensing receptor (CaSR) activation in the loop of Henle

For the answer to the question, see the following text.

The patient in case 2 presented with metabolic alkalosis, kidney failure, and profound hypercalcemia. Hypercalcemia can cause vasoconstriction of the afferent renal arterioles, which decreases GFR. The vasoconstriction could contribute to a decline in kidney function but does not play any significant role in salt wasting or metabolic alkalosis, making option (a) implausible.

The ECF volume contraction due to salt wasting activates the RAS, which stimulates H⁺ secretion in the collecting duct in an attempt to blunt the Na⁺ loss. This enhances HCO₃⁻ absorption and may increase arterial HCO₃⁻ concentration and pH. However, RAS activation per se does not lead to salt wasting and kidney failure, making option (b) incorrect.

Inhibition of the antidiuretic hormone-dependent apical water channel (AQP2) activity in hypercalcemia causes the inability to concentrate urine (nephrogenic diabetes insipidus), which may increase fluid loss. However, the increase in water diuresis per se should not cause metabolic alkalosis or kidney failure, so option (c) is not correct.

Studies on the impact of hypercalcemia on kidney physiology show the activation of the CaSR in the thick ascending limb, which inhibits NKCC2 and as a consequence produces salt wasting and volume contraction (Fig 7). For individuals consuming large amounts of calcium and alkali mixtures (calcium carbonate, etc), the generation of hypercalcemia and its attendant salt wasting and volume contraction (Fig 7) will precipitate kidney failure and exacerbate the magnitude of metabolic alkalosis due to the impaired excretion of consumed bicarbonate, making (d) the best answer for Question 4. In addition, the presence of volume contraction activates the RAS, which could exacerbate the magnitude of metabolic alkalosis (Fig 4).

More prolonged hypercalcemia, specifically in metastatic diseases such as multiple myeloma, could release calcium carbonate and calcium phosphate buffers from the bone, contributing to elevated serum HCO₃⁻ concentration even in the absence of exogenous alkali intake.

Case 2, continued: The patient's urinalysis demonstrated no protein, glucose, red blood cells, or white blood cells. Her urine osmolality is 180 mOsm/L.

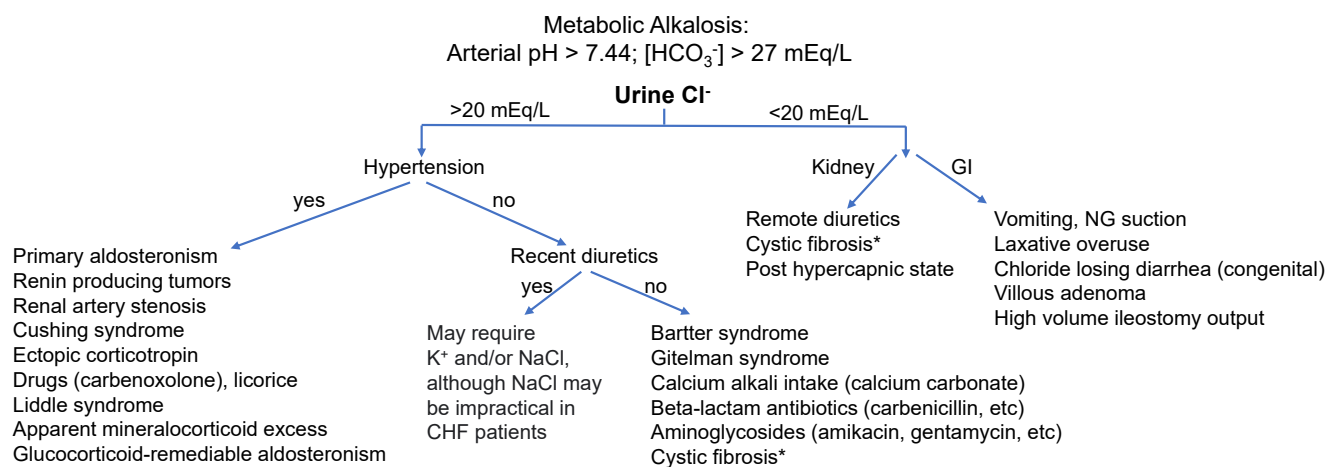


Figure 6. Algorithm for an approach to metabolic alkalosis based on urine chloride. Abbreviations: AME, apparent mineralocorticoid excess; CHF, congestive heart failure; GI, gastrointestinal; GRA, glucocorticoid-remediable aldosteronism; NG, nasogastric. *Cystic fibrosis may present with either low (<20 mmol/L) or high (>20 mmol/L) urine chloride.

Question 5: What would be the best first-line treatment in order to correct this patient's hypercalcemia and metabolic alkalosis?

- a) Intravenous loop diuretics alone
- b) The carbonic anhydrase inhibitor acetazolamide
- c) Aggressive volume resuscitation
- d) The bisphosphonate pamidronate
- e) Calcitonin

For the answer to the question, see the following text.

Intravenous loop diuretics could increase calcium excretion but will exacerbate the volume depletion in this patient who already has ECF volume contraction. Loop diuretics can specifically promote cast formation and obstruction of nephrons with cast-forming Bence Jones proteins in patients with multiple myeloma. Therefore, loop diuretics should be used with extreme caution as the initial treatment for hypercalcemia in volume-depleted patients, especially if the etiology of hypercalcemia has not been ascertained. Thus, option (a) is not correct.

Acetazolamide could increase the renal excretion of HCO₃⁻, potentially correcting her alkalosis, but will not help to correct this patient's hypercalcemia and volume depletion. Further, the beneficial effect of acetazolamide in enhancing HCO₃⁻ excretion is partly blunted in patients with ECF volume contraction. Finally, the use of acetazolamide is relatively contraindicated in kidney failure and should be used with extreme caution to avoid acetazolamide neurotoxicity consequent to impaired renal excretion. Thus, option (b) is not correct.

Aggressive volume expansion not only enhances calcium excretion but also increases HCO₃⁻ wastage. The improvement in the severity of metabolic alkalosis in the setting of hypercalcemia has significant therapeutic ramifications on both the salt wasting (from the thick limb), as

well as the calcium excretion. The increase in extracellular pH due to metabolic alkalosis independently activates basolateral CaSR in the thick ascending limb of Henle and apical/basolateral CaSR in the distal convoluted tubule. Together, these processes initiate a self-perpetuating cycle by inhibiting salt absorption in the thick ascending limb and activating calcium absorption (via calcium transporter 2 [TRPV5]) in the distal convoluted tubules. For this reason, patients with hypercalcemia and metabolic alkalosis tend to recover relatively fast when this vicious circle is interrupted by the administration of high volumes of isotonic solutions. Aggressive volume expansion is the most important initial therapeutic maneuver in hypercalcemia and metabolic alkalosis, making (c) the best answer to Question 4. Reports of aggressive volume expansion in conjunction with loop diuretics for the treatment of hypercalcemia with volume contraction have been published.

Even though bisphosphonates and occasionally calcitonin are considered first-line treatment in hypercalcemia, correction of volume depletion should be the first choice in the setting of hypercalcemia, volume depletion, and metabolic alkalosis, which is why options (d) and (e) are not correct.

The patient was started on a normal saline infusion at 200 mL/h and her calcium level and mental status improved 24 hours after admission.

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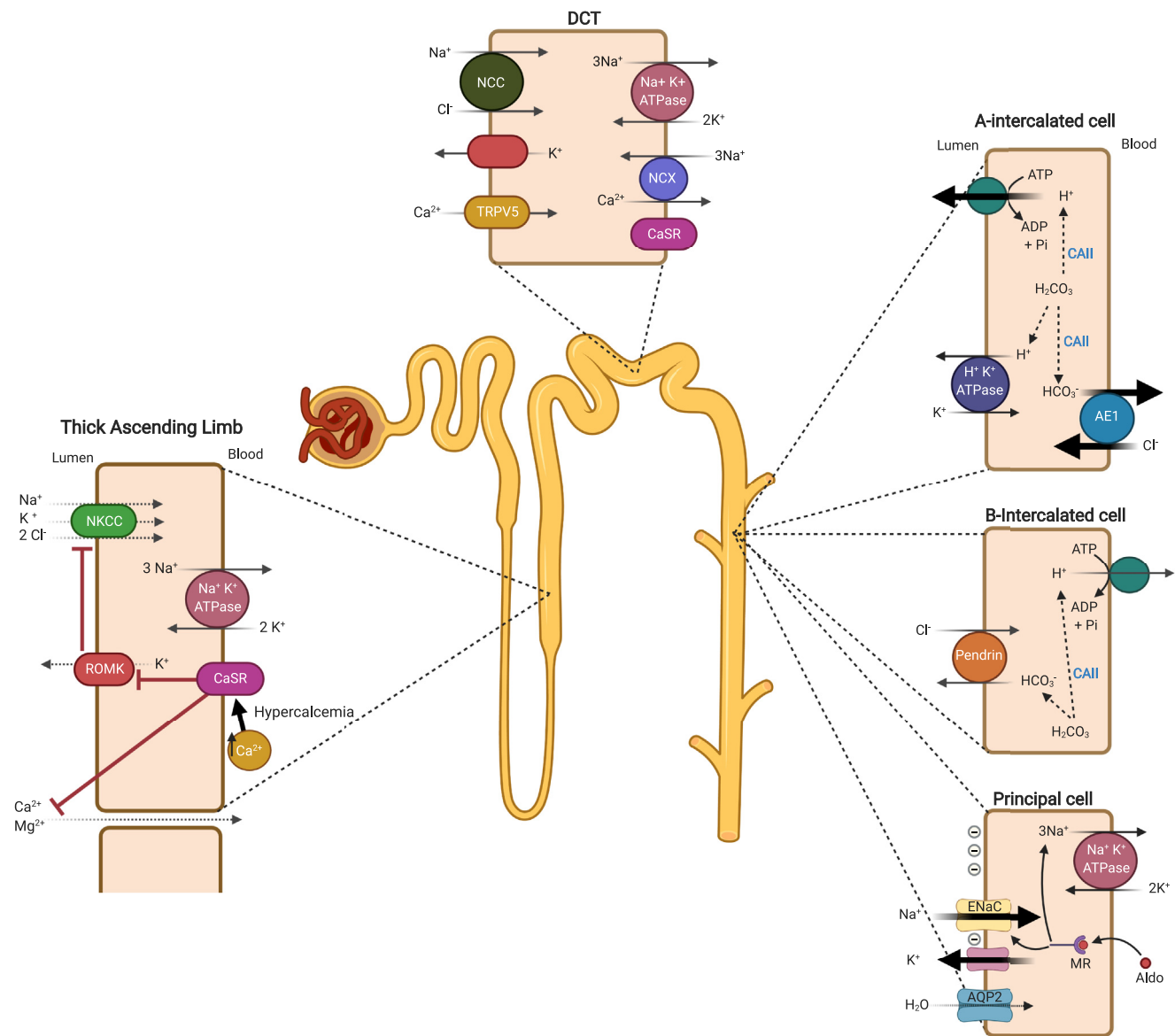


Figure 7. Schematic depiction of the role of hypercalcemia in salt wasting and metabolic alkalosis in calcium alkali syndrome. Hypercalcemia activates CaSR on the basolateral membrane of the thick ascending limb, leading directly to the inhibition of the ROMK-mediated K^+ secretion into the lumen, consequently inactivating NKCC on the apical membrane. This mimics the effect of furosemide, resulting in salt wasting and volume contraction; thereby enhancing the RAAS (renin-angiotensin-aldosterone system). The increased delivery of salt to the collecting duct increases the absorption of Na^+ and secretion of H^+ and K^+ into the lumen, provoking hypokalemia and exacerbating the alkalosis. Abbreviations: ADP, adenosine diphosphate; AE1, anion exchange protein 1; AQP2, aquaporin 2; ATP, adenosine triphosphate; CAII, carbonic anhydrase; CaSR, calcium-sensing receptor; DCT, distal convoluted tubule; NCX, sodium-calcium exchanger; NKCC, $Na^+/K^+/2Cl^-$ cotransporter; RAAS, renin-angiotensin-aldosterone system; ROMK, renal outer medullary K^+ channel; TRPV5, transient receptor potential vanilloid member 5. Created with BioRender.com.

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Case 3: A 28-year-old woman with cystic fibrosis has been followed up in the adult outpatient clinic for the past 12 years. Last year she was admitted to the hospital with severe weakness and lethargy after an episode of upset stomach associated with nausea and loss of appetite. There was no vomiting or diarrhea. Her vital signs on admission showed a blood pressure of 90/55 mm Hg and pulse rate of 90 beats/min. Blood chemical analysis showed Na^+ , 134 mEq/L; K^+ , 2.4 mEq/L; HCO_3^- , 35 mEq/L; Cl^- , 88 mEq/L; SUN , 38 mg/dL; and Scr , 1.4 mg/dL. She is not on any diuretics. VBG indicated a pH of 7.48 and PCO_2 of 48 mm Hg. Urine electrolyte profile showed Na^+ , 35 mEq/L; Cl^- , 30 mEq/L; and K^+ , 28 mEq/L.

Question 6: The generation of metabolic alkalosis, volume depletion, and renal Cl^- loss in this patient could be best explained by:

- Severe volume depletion due to the excessive loss of Na^+ and Cl^- in sweat
- Kidney salt wasting due to excessive consumption of electrolyte replacement solutions
- Posthypercapnic metabolic alkalosis after the treatment for respiratory acidosis
- The inability to conserve Cl^- in the kidney during volume depletion

For the answer to the question, see the following text.

Chloride-Responsive Alkalosis

The treatment of metabolic alkalosis with volume contraction (urine $\text{Cl}^- < 20$ mmol/L) targets the factors that maintain the alkalotic state: decreased GFR due to volume depletion, Cl^- deficiency, and hypokalemia. Administration of Cl^- -based intravenous fluids expands intravascular volume, restores GFR, and disrupts the avid reabsorption of Na^+ , K^+ , HCO_3^- , Cl^- , and water, as well as facilitating HCO_3^- excretion. Rising urinary Cl^- indicates adequate volume expansion. Repletion of K^+ to address hypokalemia decreases ammoniagenesis and the generation of new HCO_3^- as well as reducing the absorption of HCO_3^- . Restoring K^+ reestablishes pendrin expression and activity, thereby enhancing the secretion of HCO_3^- . Altogether, this treatment with Cl^- -based intravenous fluid and K^+ repletion corrects multiple pathogenic factors that maintain volume-depleted metabolic alkalosis.

Chloride-Resistant Alkalosis

The treatment of metabolic alkalosis with volume expansion (urine $\text{Cl}^- > 20$ mmol/L and elevated blood pressure) is mainly directed at modification of the primary cause when associated with high mineralocorticoid states, and the correction of hypokalemia. Removing the source of mineralocorticoid excess, as in adrenal or pituitary tumors, is the cornerstone of this therapy. In other cases, such as in primary hyperaldosteronism, treatment could be pursued via direct hormone blockade with the use of mineralocorticoid receptor antagonists (eg, spironolactone, eplerenone) or via amiloride, an ENaC blocker. The effect of this blockade will enhance NaCl excretion and K^+

retention, thereby improving the patient's alkalosis and hypertension.

It is critical to identify and remove exogenous factors that could potentially contribute to mineralocorticoid stimulation (ie, licorice, carbenoxolone). Almost all cases of Cl^- -resistant alkalosis are associated with hypokalemia; therefore, the correction of K^+ deficiency is essential to diminish the severity of metabolic alkalosis. The judicious use of oral or intravenous K^+ supplementation is advised, depending on the severity of the hypokalemia. Restriction of Na^+ and the addition of K^+ in the diet could help in improving the alkalosis. NCC will become active during hypokalemia, thus enhancing the salt absorption in the distal convoluted tubule (DCT) and worsening the hypertension. Correction of hypokalemia will restore NCC activity toward normal, and could potentially mitigate the severity of hypertension in individuals with Cl^- -resistant metabolic alkalosis with hypokalemia.

The patient in case 3 exhibits signs of volume depletion, along with hypokalemia and metabolic alkalosis. In addition, she displays inability to conserve chloride. Common causes of volume contraction with metabolic alkalosis and hypokalemia include vomiting, excessive use of loop or thiazide diuretics, or an inordinate consumption of laxatives. It can also be caused by genetic disorders such as congenital chloride-losing diarrhea, Gitelman syndrome, or Bartter syndrome. This patient does not fit into any of these categories. Loss of electrolytes in sweat, specifically in hot weather, can lead to significant volume depletion and RAAS activation, leading to hypokalemia and alkalosis. The urine chloride in nonrenal causes of volume depletion and metabolic alkalosis should be very low. However, the urine chloride in this patient is elevated, meaning option (a) is not correct for Question 6.

Salt wasting due to excessive consumption of electrolyte-containing solutions should not lead to volume depletion and metabolic alkalosis, so option (b) is not correct. This patient's history did not support the presence of respiratory acidosis before or on admission, and she was not treated for it before the admission to the hospital, ruling out option (c).

Recent studies have identified kidney-specific mechanisms that contribute to the generation of metabolic alkalosis in the setting of volume contraction. These reports demonstrated that pendrin, which is critical to Cl^- absorption (and HCO_3^- secretion) by B-intercalated cells in volume-depleted states, is profoundly downregulated in cystic fibrosis.^a Pendrin downregulation impairs the ability

^aIn patients with cystic fibrosis, metabolic alkalosis could be the initial presentation in infants and children. Very recent studies have indicated that similar to the pancreatic duct, the hormone secretin can function as an agonist to activate renal HCO_3^- secretion via the $\text{Cl}^-/\text{HCO}_3^-$ exchanger pendrin in B-intercalated cells. Given the specific role of pendrin downregulation in the pathogenesis of metabolic alkalosis in cystic fibrosis, the term "distal renal tubular alkalosis" was proposed to encompass those disturbances that cause metabolic alkalosis through reduced HCO_3^- secretion from the collecting duct.

of the kidney collecting duct to absorb salt and enhance HCO_3^- secretion (Fig 1). This further exacerbates the magnitude of volume contraction and metabolic alkalosis due to renal Cl^- loss and impaired HCO_3^- secretion into the collecting duct, respectively. The loss of Cl^- in the urine consequent to the inactivation of pendrin in the setting of volume depletion mimics a pseudo-Bartter picture, which has been described in cystic fibrosis patients, thus option (d) is the best answer to Question 6. The patient was admitted for the evaluation and treatment of hypokalemic metabolic alkalosis with volume contraction, and received 6 liters of saline along with 120 mEq of KCl over 48 hours. She was discharged with a serum HCO_3^- of 27 and K^+ of 3.8 mEq/L, and a venous blood gas of 7.41.

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