

SIGNS AND SYMPTOMS OF METABOLIC ALKALOSIS

Central Nervous System	Cardiovascular System	Respiratory System	Neuromuscular System	Metabolic Effects	Renal (Associated Potassium Depletion)
Headache	Supraventricular and ventricular arrhythmias	Hypoventilation with attendant hypercapnia and hypoxemia	Chvostek's sign	Increased organic acid and ammonia production	Polyuria
Lethargy	Potential of digitalis toxicity		Trousseau's sign	Hypokalemia	Polydipsia
Stupor	Positive inotropic ventricular effect		Weakness (severity depends on degree of potassium depletion)	Hypocalcemia	Urinary concentration defect
Delirium				Hypomagnesemia	Cortical and medullary renal cysts
Tetany				Hypophosphatemia	
Seizures					
Potential of hepatic encephalopathy					

FIGURE 6-38

Signs and symptoms of metabolic alkalosis. Mild to moderate metabolic alkalosis usually is accompanied by few if any symptoms, unless potassium depletion is substantial. In contrast, severe metabolic alkalosis ($[\text{HCO}_3^-] > 40 \text{ mEq/L}$) is usually a symptomatic disorder. Alkalemia, hypokalemia, hypoxemia, hypercapnia, and decreased plasma ionized calcium concentration all contribute to

these clinical manifestations. The arrhythmogenic potential of alkalemia is more pronounced in patients with underlying heart disease and is heightened by the almost constant presence of hypokalemia, especially in those patients taking digitalis. Even mild alkalemia can frustrate efforts to wean patients from mechanical ventilation [23,24].

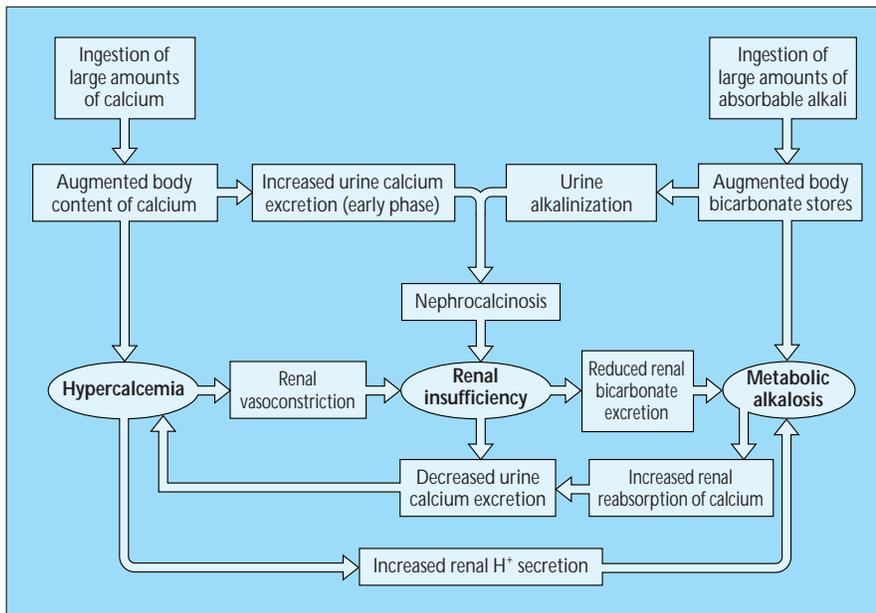


FIGURE 6-39

Pathophysiology of the milk-alkali syndrome. The milk-alkali syndrome comprises the triad of hypercalcemia, renal insufficiency, and metabolic alkalosis and is caused by the ingestion of large amounts of calcium and absorbable alkali. Although large amounts of milk and absorbable alkali were the culprits in the classic form of the syndrome, its modern version is usually the result of large doses of calcium carbonate alone. Because of recent emphasis on prevention and treatment of osteoporosis with calcium carbonate and the availability of this preparation over the counter, milk-alkali syndrome is currently the third leading cause

of hypercalcemia after primary hyperparathyroidism and malignancy. Another common presentation of the syndrome originates from the current use of calcium carbonate in preference to aluminum as a phosphate binder in patients with chronic renal insufficiency. The critical element in the pathogenesis of the syndrome is the development of hypercalcemia that, in turn, results in renal dysfunction. Generation and maintenance of metabolic alkalosis reflect the combined effects of the large bicarbonate load, renal insufficiency, and hypercalcemia. Metabolic alkalosis contributes to the maintenance of hypercalcemia by increasing tubular calcium reabsorption. Superimposition of an element of volume contraction caused by vomiting, diuretics, or hypercalcemia-induced natriuresis can worsen each one of the three main components of the syndrome. Discontinuation of calcium carbonate coupled with a diet high in sodium chloride or the use of normal saline and furosemide therapy (depending on the severity of the syndrome) results in rapid resolution of hypercalcemia and metabolic alkalosis. Although renal function also improves, in a considerable fraction of patients with the chronic form of the syndrome serum creatinine fails to return to baseline as a result of irreversible structural changes in the kidneys [27].

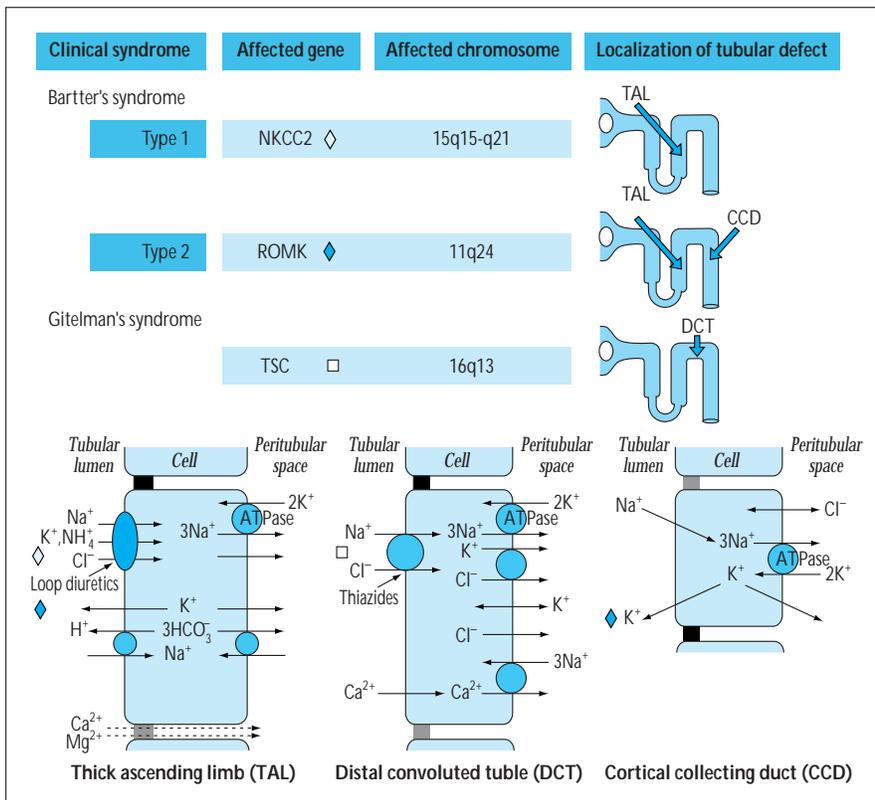
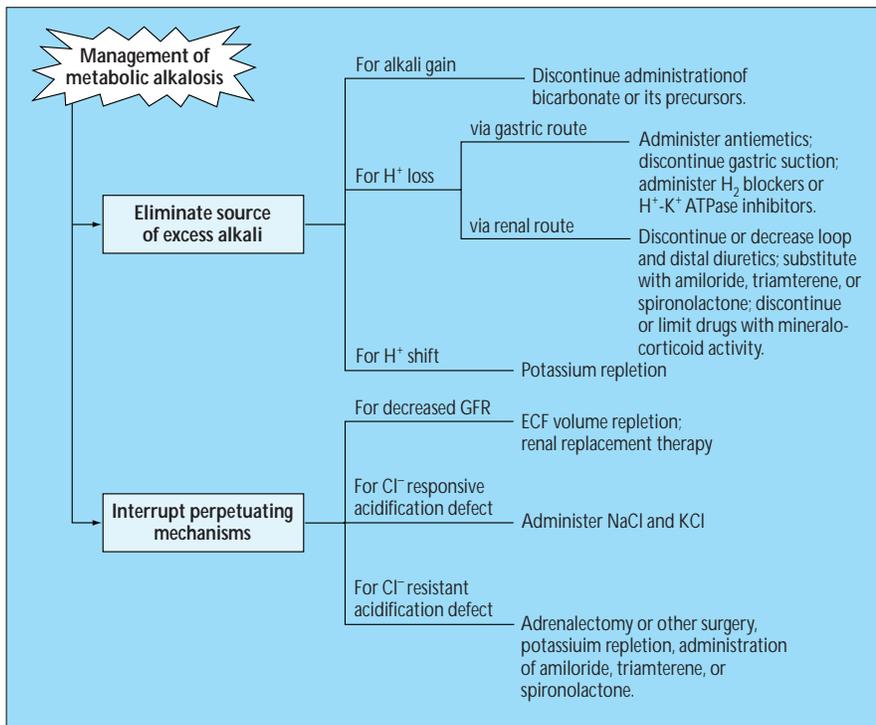


FIGURE 6-40

Clinical features and molecular basis of tubular defects of Bartter's and Gitelman's syndromes. These rare disorders are characterized by chloride-resistant metabolic alkalosis, renal potassium wasting and hypokalemia, hyperreninemia and hyperplasia of the juxtaglomerular apparatus, hyperaldosteronism, and normotension. Regarding differentiating features, Bartter's syndrome presents early in life, frequently in association with growth and mental retardation. In this syndrome, urinary concentrating ability is usually decreased, polyuria and polydipsia are present, the serum magnesium level is normal,

and hypercalciuria and nephrocalcinosis are present. In contrast, Gitelman's syndrome is a milder disease presenting later in life. Patients often are asymptomatic, or they might have intermittent muscle spasms, cramps, or tetany. Urinary concentrating ability is maintained; hypocalciuria, renal magnesium wasting, and hypomagnesemia are almost constant features. On the basis of certain of these clinical features, it had been hypothesized that the primary tubular defects in Bartter's and Gitelman's syndromes reflect impairment in sodium reabsorption in the thick ascending limb (TAL) of the loop of Henle and the distal tubule, respectively. This hypothesis has been validated by recent genetic studies [28-31]. As illustrated here, Bartter's syndrome now has been shown to be caused by loss-of-function mutations in the loop diuretic-sensitive sodium-potassium-2chloride cotransporter (NKCC2) of the TAL (type 1 Bartter's syndrome) [28] or the apical potassium channel ROMK of the TAL (where it recycles reabsorbed potassium into the lumen for continued operation of the NKCC2 cotransporter) and the cortical collecting duct (where it mediates secretion of potassium by the principal cell) (type 2 Bartter's syndrome) [29,30]. On the other hand, Gitelman's syndrome is caused by mutations in the thiazide-sensitive Na-Cl cotransporter (TSC) of the distal tubule [31]. Note that the distal tubule is the major site of active calcium reabsorption. Stimulation of calcium reabsorption at this site is responsible for the hypocalciuric effect of thiazide diuretics.

**FIGURE 6-41**

Metabolic alkalosis management. Effective management of metabolic alkalosis requires sound understanding of the underlying pathophysiology. Therapeutic efforts should focus on eliminating or moderating the processes that generate the alkali excess and on interrupting the mechanisms that perpetuate the hyperbicarbonatemia. Rarely, when the pace of correction of metabolic alkalosis must be accelerated, acetazolamide or an infusion of hydrochloric acid can be used. Treatment of severe metabolic alkalosis can be particularly challenging in patients with advanced cardiac or renal dysfunction. In such patients, hemodialysis or continuous hemofiltration might be required [1].

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