9 Diagnosis and Treatment of Metabolic Alkalosis

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Key Points

1. Primary metabolic alkalosis should be distinguished from metabolic compensation to respiratory acidosis.
2. Measurement of urine chloride concentration is essential for diagnosis and treatment.
3. Metabolic alkalosis with low urine chloride (chloride responsive) represents an appropriate renal response to H^+ and Cl^- losses from non-renal sites (GI, skin).
4. Metabolic alkalosis with high urine chloride (chloride unresponsive) should prompt an evaluation for renal and endocrine disorders and can be further evaluated by the presence or absence of hypertension, renal and adrenal imaging, and the relative concentrations of plasma renin activity and serum aldosterone.

Key Words: Metabolic alkalosis; urine chloride; hypokalemia; hypochloremia; bicarbonate; Bartter syndrome; Gitelman syndrome; aldosterone; loop diuretic; thiazide diuretic

1. DEFINITION

Metabolic alkalosis is defined as a primary increase in both plasma pH and plasma bicarbonate concentration. It is associated with a compensatory decrease in ventilation and increased $PaCO_2$ (Table 1). Typically, $PaCO_2$ increases 0.5–0.7 mmHg to compensate for each 1 mM increase in plasma HCO_3^-. For example, in a patient whose serum $[HCO_3^-]$ has increased from 22 to 30 mEq/L, the expected respiratory compensation will be approximately 0.7 times the difference between the normal serum $[HCO_3^-]$ and the alkalotic serum $[HCO_3^-]$, in this case 0.7×8, or 5.6. When added to a normal $PaCO_2$ of 40 mmHg, the expected $PaCO_2$ is 45.6 mmHg. A more rapid method to estimate the expected respiratory compensation to metabolic alkalosis is to add 15 to the patient's serum bicarbonate level for bicarbonate values ranging from 25 to 40 *(1)*. For example, for a patient with a serum $[HCO_3^-]$ of 30, add 15 to give an estimated $PaCO_2$ of 45 mmHg. If the actual respiratory compensation is less than estimated, consider a mixed respiratory and metabolic disorder. Also, remember that an increased serum $[HCO_3^-]$ also occurs in metabolic compensation to respiratory acidosis, but this can be

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Table 1
Estimated Respiratory Compensation to Primary Metabolic Alkalosis

Method 1:
Compensated $PaCO_2 = 40 + [0.7 (\text{patient } [HCO_3^-] - \text{normal } [HCO_3^-])]$
Example: a patient's serum $[HCO_3^-]$ has increased from 22 to 30 mEq/L:
Compensated $PaCO_2 = 40 + [0.7 (30–22)]$
Compensated $PaCO_2 = 40 + 5.6$
Compensated $PaCO_2 = 45.6$
Method 2:
Compensated $PaCO_2 = \text{patient } [HCO_3^-] + 15$
Example: a patient has a serum $[HCO_3^-] = 30$
Compensated $PaCO_2 = 30 + 15$
Compensated $PaCO_2 = 45$

distinguished from metabolic alkalosis by looking at plasma pH. In this case, the pH will generally be <7.35, as the metabolic compensation is not sufficient to over-correct the respiratory acidosis into the alkalotic range.

2. ETIOLOGY

How might you make someone alkalotic? While most of the disease states that lead to metabolic alkalosis result from varying combinations of the mechanisms discussed below, it is helpful to consider the influence of specific single perturbations and their impact on the generation and maintenance of alkalosis. This section will discuss primarily net effects of the various mechanisms, with more specific details of the physiology found in several comprehensive reviews *(1–4)*.

Because the kidney can normally excrete large bicarbonate loads, the finding of persistent metabolic alkalosis requires first an initial insult (generation phase), followed by a maintenance phase. Initial insults that contribute to the generation of alkalosis include HCl depletion, potassium depletion, volume depletion, or mineralocorticoid excess (described below). The maintenance phase occurs when renal mechanisms perpetuate the alkalotic state. These renal mechanisms include decreased glomerular filtration rate, development of intracellular acidosis, increased proximal tubule H^+ secretion (with subsequent HCO_3^- reabsorption), and increased distal tubule H^+ secretion, again with subsequent distal HCO_3^- reabsorption, and generation.

Infuse Bicarbonate or Other Alkali: Exogenous bicarbonate infusion is not an effective method of generating metabolic alkalosis. The kidney responds quickly and effectively to large bicarbonate loads. As long as the ECF volume (and the accompanying glomerular filtration rate) is adequate, the proximal tubule threshold for bicarbonate reabsorption is exceeded, and distal nephron mechanisms are inadequate to handle the load. However, in patients with significantly decreased glomerular filtration rates (GFR), either due to severe volume depletion or intrinsic renal disease, renal excretion

of bicarbonate is impaired and exogenous loads can cause significant alkalosis. Examples of bicarbonate or other alkali administration causing metabolic alkalosis in patients with decreased GFR include milk–alkali syndrome (often discussed but rarely seen), oral or IV $NaHCO_3$ administration, acetate loads in parenteral nutrition solutions, citrate from blood transfusions or from regional anticoagulation during continuous renal replacement or other extracorporeal therapies, and the combination of antacids plus cation exchange resins.

Remove HCl from the Gastrointestinal Tract: As both H^+ and Cl^- are lost from the GI tract or other sites, plasma [HCO_3^-] increases, increasing the renal filtered load. The net negative charge in the distal nephron caused by excess bicarbonate leads to increased tubular sodium and potassium losses, with accompanying water loss. Chloride, on the other hand, is avidly retained by the kidney to compensate for the high amount of GI (or other non-renal) loss. The resulting electrolyte profile is one of a hypochloremic (from GI loss) hypokalemic (from renal loss) metabolic alkalosis, with a decreased ECF volume because of both GI and renal volume losses. This state is also referred to as a contraction alkalosis, because the ECF volume is relatively contracted, with HCO_3^- as a more significant contributor to the overall anion concentration than in the normal state. The renin–angiotensin–aldosterone axis becomes more active, with a net effect of increasing sodium and water reabsorption, improving ECF volume but with a cost of contributing further to hypokalemia.

At this point, even if HCl losses stop, alkalosis is maintained until total body chloride content is replenished and ECF volume is restored. As long as the plasma chloride concentration is low, very little will show up in the distal nephron, and the primary anion in the distal nephron will be HCO_3^-, thus any tubular reabsorption of anion necessary to maintain electroneutral plasma will be of HCO_3^-. In addition, increased aldosterone activity and the high [HCO_3^-] in the tubular lumen will promote Na^+–H^+ exchange and even further H^+ loss into the urine. During the initial period of GI HCl losses, the urine pH is typically alkaline (6.5–7), but as HCl losses stop but renal mechanisms maintain the alkalosis, the urine pH can decrease (5.5–6). Once plasma Cl^- is restored and some appears in the lumen of the distal nephron, selective reabsorption of Cl^-, with subsequent excretion of HCO_3^- can occur, and alkalosis can be corrected. As ECF volume improves, aldosterone effects diminish, and net H^+ loss decreases, further contributing to the resolution alkalosis.

Create a State of Hypokalemia: Hypokalemia contributes to the generation and maintenance of alkalosis through several mechanisms:

- At the glomerulus, hypokalemia produces a reduction in glomerular filtration rate, although precise mechanisms have not been described.
- In the proximal nephron, hypokalemia increases net proximal tubule bicarbonate reabsorption. This proximal net bicarbonate reabsorption probably occurs when hypokalemia causes proximal tubule cells to develop an intracellular acidosis, created by exchange of extracellular H^+ for intracellular K^+ in an effort to maintain normal plasma potassium levels.
- Also, in the proximal nephron, hypokalemia enhances renal ammoniagenesis, increasing the amount of NH_3 in the tubule lumen available to bind secreted H^+, with net acid subsequently lost in the urine.

- In the distal nephron, hypokalemia impairs renal chloride reabsorption in a way that enhances secretion of H^+ into the tubular lumen.
- Additionally, hypokalemia creates intracellular acidosis in the distal nephron, which results in mechanisms similar to those seen in the proximal tubule.
- Finally, hypokalemia increases H^+–K^+ ATPase activity in the collecting duct.

Create a State of Hyperaldosteronism: The physiologic effect of mineralocorticoids, primarily aldosterone, is to respond to conditions of decreased intravascular volume by stimulating the apical sodium channel and the basolateral Na, K-ATPase of the principal cell of the cortical collecting duct, resulting in increased sodium reabsorption and increased urinary potassium secretion. Furthermore, mineralocorticoids directly increase tubular H^+ excretion through stimulation of Na^+–H^+ exchange. The systemic result is the development of increased intravascular volume (from Na retention), with hypokalemia and metabolic alkalosis. When mineralocorticoid effects go unchecked, as in states of mineralocorticoid excess, volume-overload hypertension, hypokalemia, and metabolic alkalosis are generated and maintained. Hypokalemia is particularly important for the maintenance of metabolic alkalosis in mineralocorticoid excess states. Note that while there is a phenomenon of escape from the Na-retaining effects of excess mineralocorticoid, permitting diuresis and natriuresis, no such mechanisms exist to prevent chronic loss of potassium. So, while generation of alkalosis occurs because of increased tubular excretion of both H^+ and K^+, the maintenance of alkalosis is driven by hypokalemia (discussed above).

3. CLINICAL PRESENTATION

Clinically relevant metabolic alkalosis arises from various combinations of the physiologic perturbations discussed above. The relative contributions of decreased intravascular volume, hypokalemia, Cl^- and H^+ loss, exogenous or endogenous HCO_3^-, and mineralocorticoids can be difficult to sort out, and one is often unsure what caused what. Fortunately, both the diagnosis and treatment can be pinned down with a careful history and physical exam and a few simple and inexpensive laboratory tests (Fig. 1).

Metabolic alkalosis is typically seen in patients with serious illness, either acute or chronic, at times making it difficult to separate symptoms specific to alkalosis from those of underlying illnesses. Significant alkalosis may manifest with serious CNS and cardiac complications; patients may develop stupor, confusion, lethargy, muscle weakness, and/or cramping. The frequent finding of hypokalemia with alkalosis predisposes patients to cardiac arrhythmias and sudden death. EKG findings include QT interval prolongation, ST segment depression, a flat or low amplitude T-wave, prominent U-wave, AV dissociation, torsade de pointes, ventricular tachycardia, and ventricular fibrillation *(5)*. Cardiac arrhythmias can be life threatening and refractory to treatment unless alkalosis and, equally importantly, hypokalemia are corrected. An alkalosis-induced shift of the oxygen-hemoglobin dissociation curve to the left, combined with relative hypoxia related to compensatory hypoventilation, can lead to decreased tissue delivery of oxygen. Also seen are decreased ionized calcium concentrations, increased lactate production, elevated anion gap, and decreased urinary calcium excretion *(6)*.

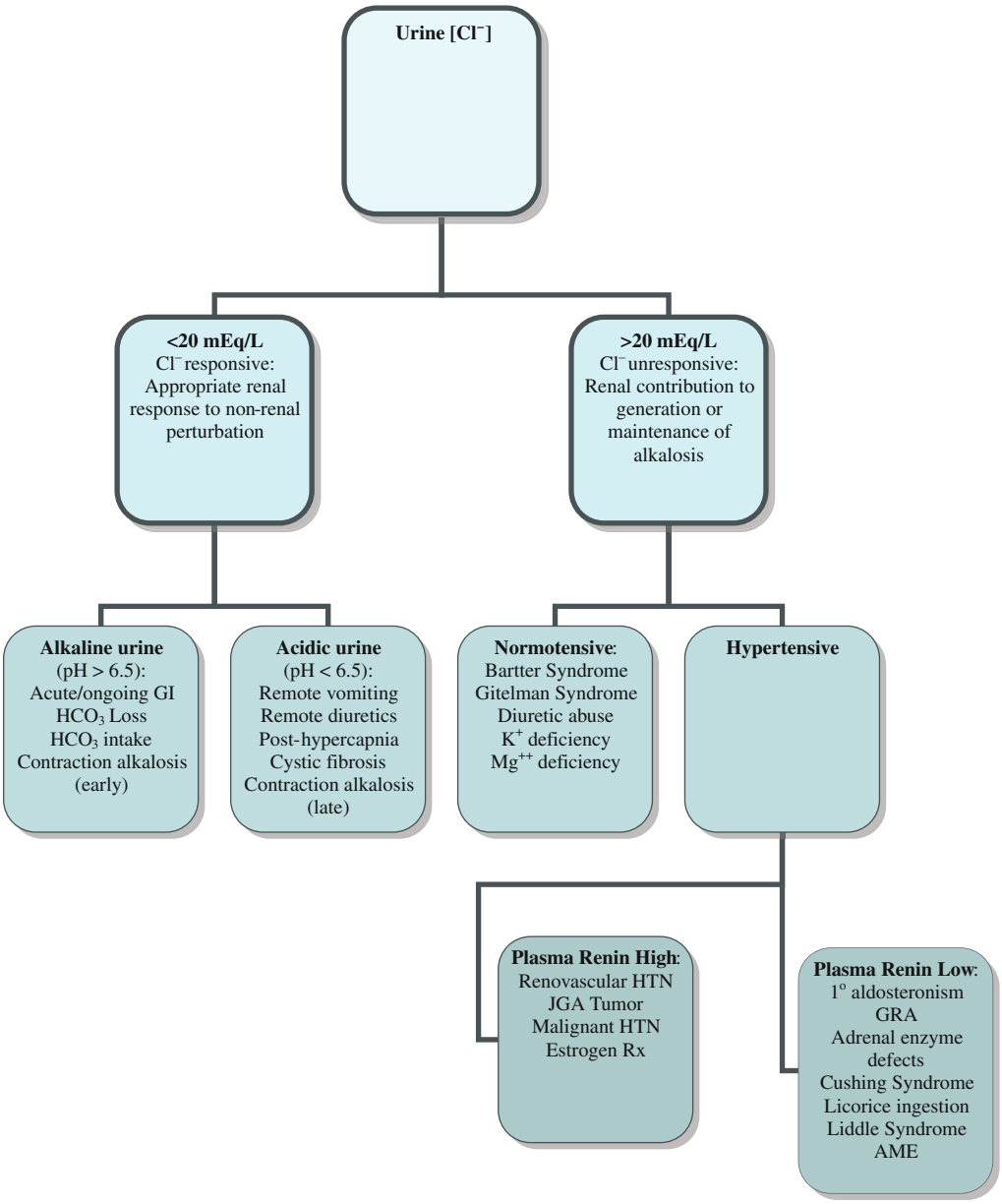

Fig. 1. Diagnostic algorithm for metabolic alkalosis (HTN: hypertension, JGA: juxtaglomerular apparatus, GRA: glucocorticoid remediable aldosteronism, AME: apparent mineralocorticoid excess).

In the acute care setting, it is important to review the patient's history for significant sources of GI loss, including nasogastric suction, surgical drains, and ostomies. Current and past history of diuretic use should also be obtained. Careful evaluation of enteral and parenteral nutrition may reveal potential sources of exogenous alkali administration. In the chronic setting, an evaluation for failure to thrive should include investigation

for alkalosis and hypokalemia. For infants, an assessment of feeding, particularly in formula-fed infants, may contribute. In older children, particularly adolescents, eating disorders may present with alkalosis either because of diuretic abuse or chronic vomiting. This history may be particularly difficult to elicit, and index of suspicion should be high. Patients with chronic fatigue, particularly muscle weakness or muscle spasm, should also be evaluated for alkalosis.

4. EVALUATION

Figure 1 is a diagnostic algorithm for patients with metabolic alkalosis. In addition to patient history and physical exam findings, key factors in guiding diagnosis and treatment include measurement of urine [Cl^-], assessment of blood pressure and intravascular volume, assessment of renal function, and assessment of plasma electrolytes including K^+, Cl^-, Ca^{++} (including ionized Ca), and Mg^{++}, plasma renin activity, and serum aldosterone.

Most importantly, urine chloride measurement simplifies differential diagnosis and guides treatment. Metabolic alkalosis can be divided into chloride responsive and chloride unresponsive types. If urine Cl^- is less than 20 mEq/L, the kidneys are responding appropriately to HCl losses from non-renal sites [most commonly GI, skin (in cystic fibrosis patients) or posthypercapnia]. If urine Cl^- is greater than 20 mEq/L, the kidneys are the site of excessive Cl^- loss, either in response to endogenous or exogenous hormone effects, drugs (diuretics), or due to primary renal tubular defects.

Urine potassium measurement helps differentiate a primary renal defect from an appropriate renal response to extrarenal potassium loss. Urine [K^+] > 30 mEq/L in a hypokalemic patient demonstrates inappropriate renal losses as seen in intrinsic renal defects (Bartter and Gitelman syndromes), diuretic use, or high circulating aldosterone levels. A urine [K^+] < 20 mEq/L denotes an appropriate renal response to extrarenal loss.

For patients with chloride unresponsive alkalosis, renal and adrenal imaging studies, particularly ultrasound or CT imaging, may aid in differential diagnosis. A finding of nephrocalcinosis in an infant may point to a diagnosis of neonatal Bartter syndrome. Renal size discrepancy or, more specifically, asymmetrical blood flow to the kidneys may prompt further evaluation for renal artery stenosis. A finding of a renal or adrenal mass may suggest, respectively, a renin-producing or aldosterone-producing tumor. While a complete discussion is beyond the scope of this section, measurement of plasma renin, plasma aldosterone, and calculation of a plasma aldosterone to plasma renin ratio can assist in sorting through the differential diagnosis of chloride unresponsive alkalosis *(7)*. Rarely, evaluation for congenital adrenal enzymatic defects or parathyroid hormone function may be required.

5. CAUSES

Table 2 summarizes the differential diagnosis of metabolic alkalosis. Most cases of metabolic alkalosis are acquired in the hospital setting, including prolonged nasogastric suctioning, contraction alkalosis from aggressive diuresis, posthypercapnia, recovery from lactic acidosis or ketoacidosis, or carbohydrate refeeding after starvation. These

Table 2
Differential Diagnosis of Metabolic Alkalosis

Mechanism	*Disorder*	*Urine [Cl^-]*
Exogenous alkali	Acute alkali administration	↓
	Regional citrate anticoagulation	?
	Milk–alkali syndrome	↓
Intravascular volume contraction, Normotension, K^+ deficiency, 2^o Hyperreninemic hyperaldosteronism	*Gastrointestinal or other (non-renal)*	
	Pyloric stenosis	↓
	Vomiting	↓
	Bulimia	↓
	Gastric aspiration	↓
	Gastrocystoplasty	↑
	Congenital chloride diarrhea	↓
	Villous adenoma	↓
	Cystic fibrosis (sweat Cl^-) loss	↓
	Renal	
	Diuretics (especially thiazide and loop diuretics)	↑ or ↓
	Edematous states	↓
	Posthypercapnia	↓
	Hypercalcemia–hypoparathyroidism	?
	Recovery from lactic acidosis or ketoacidosis	↓
	Nonreabsorbable anions such as penicillin, carbenicillin	↓
	Mg^{2+} deficiency	↑
	K^+ depletion	↑ or ↓
	Bartter Syndrome	↑
	Gitelman Syndrome	↑
	Carbohydrate refeeding after starvation	?
Intravascular volume expansion, hypertension, K^+ deficiency, hypermineralocorticoidism	*Associated with high renin*	
	Renal artery stenosis	↑
	Accelerated hypertension	↑
	Renin-secreting tumor	↑
	Estrogen therapy	↑
	Associated with low renin	
	Primary aldosteronism	
	Adenoma	↑
	Hyperplasia	↑
	Carcinoma	↑
	Glucocorticoid suppressible	↑
	Adrenal enzymatic defects	
	11β-Hydroxylase deficiency	↑
	17α-Hydroxylase deficiency	↑

Table 2
(Continued)

Mechanism	*Disorder*	*Urine [Cl^-]*
	Cushing syndrome or disease	
	Ectopic corticotropin	↑
	Adrenal carcinoma	↑
	Adrenal adenoma	↑
	Primary pituitary	↑
	Other	
	Licorice	↑
	Carbenoxolone	↑
	Chewing tobacco	↑
Intravascular volume expansion hypertension	Liddle syndrome	↑
K^+ deficiency hyporeninemic hypoaldosteronism	Apparent mineralocorticoid excess syndrome	↑

presentations will respond to early recognition and treatment of alkalosis and resolve with improvement in the underlying disease process.

Critical Care: Circumstances unique to the critical care setting may lead to alkalosis and contribute significantly to morbidity in critically ill patients. In patients recovering from respiratory acidosis, an appropriate renal response to acidosis may persist for several days after hypercapnia has resolved. The resulting avid retention of bicarbonate by the kidneys, often exacerbated by decreased intravascular volume and hypokalemia created by the necessary use of diuretics, creates a state of metabolic alkalosis. Once recognized, attention to restoring intravascular volume, potassium and chloride stores is usually sufficient to correct alkalosis. Alkalosis is a frequent complication of cardiac surgery and is strongly associated with younger age, cardiopulmonary bypass, preoperative ductal dependency, and perioperative hemodilution *(8)*. The use of regional citrate anticoagulation in patients requiring continuous renal replacement therapies can lead to alkalosis through its metabolism in Krebs cycle to bicarbonate *(9)*. This phenomenon is often referred to as citrate loc or citrate gap. Citrate-induced alkalosis responds to decreased citrate infusion rates, increased clearance rates, and/or saline infusion *(10, 11)*.

Chloride Responsive Alkalosis: While most cases of chloride responsive alkalosis are acquired in the hospital setting as a result of nasogastric suctioning, drainage, or emesis, several diseases should be considered in the differential diagnosis. Alkalosis is a classic presentation of pyloric stenosis in infants. Infants with a recent history of emesis and presence of alkalosis should be evaluated by abdominal ultrasound, and fluid resuscitation with correction of alkalosis should precede surgical correction when possible to minimize surgical and anesthetic morbidity *(12–15)*. Cystic fibrosis is unique among diseases that may present with chloride responsive alkalosis because chloride

loss is through the skin, via excessive sweat chloride loss, rather than through the GI tract *(16–18)*. Patients with eating disorders frequently present with alkalosis as a result of bulimia. However, measurement of urine chloride is particularly important. If urine chloride is excessive in a patient with a history of eating disorder, diuretic abuse should be considered *(19)*. Congenital chloride diarrhea is frequently listed in the differential diagnosis, but rarely seen. While congenital chloride diarrhea can be fatal if not recognized, once identified treatment consists of NaCl and KCl replacement, with an excellent long-term prognosis *(20, 21)*. Villous adenoma is often listed in the differential diagnosis of alkalosis, but no reports of this association were found in a review of the pediatric literature.

Chloride Unresponsive Alkalosis: A finding of chloride unresponsive alkalosis should prompt studies for primary renal and endocrine disorders once acquired alkalosis from diuretic use/abuse or glycyrrhizic acid (licorice, licorice root) *(22)* has been ruled out. The differential diagnosis of chloride unresponsive alkalosis can be refined by consideration of blood pressure. Disorders in which the primary defect is renal chloride wasting such as Bartter syndrome, Gitelman syndrome, and diuretic abuse present with hypotension and secondary (compensatory) increases in aldosterone activity. Alternatively, disorders in which increased mineralocorticoid production or renal tubular activity mimicking increased mineralocorticoid activity present with hypertension.

Three renal tubular disorders account for most cases of renal-mediated alkalosis: Bartter syndrome, Gitelman syndrome, and Liddle's syndrome. Both Bartter and Gitelman syndromes present with normotension or hypotension, while Liddle syndrome presents with hypertension. While molecular diagnostic techniques continue to clarify the transport mechanisms involved in these disorders, considering each by its site of action in the nephron can help us understand the various clinical presentations and guide therapy. Bartter syndrome and its variants arise from mutations in electrolyte transporters in the thick ascending limb (TAL) of the loop of Henle, Gitelman syndrome from electrolyte transport defects in the distal convoluted tubule, and Liddle syndrome from a defective transporter in the collecting duct.

Bartter Syndrome: To date, four types of Bartter syndrome have been identified based on molecular identification of mutations in TAL transmembrane proteins *(23–25)*. These defective proteins include an electroneutral bumetanide-sensitive luminal Na–2Cl–K cotransporter (NKCC2) (type 1), a luminal potassium channel: ROMK (type 2), a basolateral membrane chloride channel: CLCNKB (type 3), and a subunit of two basolateral chloride channels (CLCNKA and CLCNKB): Barttin (type 4 also associated with sensorineural deafness). Molecular characterization has significantly improved our understanding of these disorders but has not, to date, led to specific therapies. Description of Bartter-like or Gitelman-like syndromes whose physiology and genetics have not yet been described *(26)* suggests that additional mutations might be found. A rare genetic Bartter-like syndrome with hypocalcemia due to activation of the calcium sensing receptor *(27)* and an acquired Bartter-like syndrome following the use of gentamicin *(28)* have been reported.

Despite the various mutations, it is helpful to think of all Bartter syndrome types as a genetic model resembling loop diuretic abuse. All the mutations above lead to urine chloride wasting, with resulting hypovolemia and hypotension. Secondary aldosterone

release to compensate for the hypovolemia leads to further potassium and proton loss and maintenance of a chronic hypokalemic, hypochloremic metabolic alkalosis. Types 1, 2, and 4 typically present in newborns (neonatal Bartter), often with a history of polyhydramnios and premature birth. Classic Bartter syndrome (Type 3) may present at birth, but can also present later in infancy. On occasion, patients with neonatal Bartter (usually type 2) may present initially with a hyperkalemic metabolic acidosis and hyponatremia before developing the classic picture of hypokalemic metabolic alkalosis *(29)*. Clinical and laboratory features of Bartter syndrome include: polydipsia, polyuria, salt craving, growth retardation, dehydration, nephrocalcinosis (in neonatal types), high urine NaCl excretion, increased urine calcium excretion (in most cases), impaired urine concentrating ability, hyperreninism/hyperaldosteronism with normo- to hypotension, increased prostaglandin production, and hypertrophy of the juxtaglomerular apparatus.

Gitelman Syndrome: If loop diuretic abuse serves as a pharmacologic analogy for Bartter syndrome, Gitelman syndrome can be understood as analogous to thiazide diuretic abuse. Distal convoluted tubule (DCT) mutations account for the clinical findings. In particular, impaired sodium reabsorption by a thiazide-sensitive NaCl cotransporter (NCCT) is responsible. While both Bartter syndrome and Gitelman syndrome present with metabolic alkalosis, patients with Gitelman syndrome typically present later in childhood or adolescence, usually complaining of fatigue, weakness, muscle cramps, seizures, or tetany. Other features that help to distinguish Gitelman from Bartter include the absence of polyuria/polydipsia, the absence of growth retardation, the absence of nephrocalcinosis and associated hypercalciuria, and the presence of hypomagnesemia.

Liddle syndrome: Unlike the tubular defects in Bartter and Gitelman syndromes, which cause chronic salt-wasting and hypotension, the defect in Liddle syndrome causes sodium and volume retention, and hypertension, mimicking states of aldosterone excess. The disease is caused by mutations in the distal tubule amiloride-sensitive epithelial Na channel (ENaC), resulting in a sodium channel that is essentially "always open." The resulting excess reabsorption of sodium leads to volume overload, with secondary increased loss of potassium and protons in the urine, leading to hypokalemic metabolic alkalosis. Liddle syndrome is often found during evaluations for secondary hypertension, with initial findings of hypokalemic alkalosis, very low plasma renin activity and serum aldosterone, and a family history of hypertension in younger individuals following an autosomal dominant pattern.

Apparent Mineralocorticoid Excess Syndrome (AME): AME is a rare inherited disorder that, like Liddle syndrome, presents with hypokalemic metabolic alkalosis and low-renin, low aldosterone hypertension mimicking hyperaldosteronism. It is caused by a deficiency of a renal isozyme of 11β-hydroxysteroid dehydrogenase. In the absence of this enzyme, cortisol is not being oxidized to cortisone. Cortisol, unlike cortisone, binds to the renal mineralocorticoid receptors. Since cortisol binds as avidly as aldosterone to the mineralocorticoid receptor but its serum level is 100 times higher than that of aldosterone, the end result is very excessive mineralocorticoid activity, causing sodium retention, hypertension, and hypokalemic alkalosis *(30)*. The pharmacologic analog to AME is chronic glycyrrhizic acid (licorice, licorice root) ingestion, which competitively inhibits the 11β-hydroxysteroid dehydrogenase.

AME is usually transmitted as an autosomal recessive trait. It is characterized by low birth weight, failure to thrive, very early onset of hypertension, and damage to end organs. Those with the more severe form of AME also exhibit hypercalciuria, nephrocalcinosis, and renal failure. A milder phenotype was reported in adults with compound heterozygous mutations.

Glucocorticoid-Remediable Aldosteronism (GRA): GRA is typically diagnosed during evaluations for low-renin hypertension in families with a strong history of childhood hypertension in an autosomal-dominant pattern. Nevertheless, it may present additionally with laboratory features of hypokalemia and metabolic alkalosis. The somewhat awkward (but physiologically appropriate) name of this disorder provides insight into the pathophysiology: patients with GRA have a chimeric gene in the adrenal zona fasciculata linking the promoter sequence of the 11β-hydroxylase gene (which normally promotes cortisol synthesis in response to ACTH) to the coding sequence of aldosterone synthase. With this mutation, aldosterone is produced in response to ACTH (instead of by angiotensin II and potassium in the zona glomerulosa, as in unaffected individuals), resulting in adrenal hyperplasia and excessive aldosterone production. Glucocorticoid administration reduces ACTH production, thus decreasing aldosterone production by the chimeric gene *(31)* and improvement in hypertension, hypokalemia, and alkalosis. Interestingly some patients with GRA are normokalemic probably due to the circadian rhythm of ACTH secretion and lack of effect of dietary potassium on aldosterone secretion. Patients with GRA respond by profound hypokalemia to thiazide administration. GRA has also been called Familial Hyperaldosteronism Type I. A form of Familial Hyperaldosteronism (Type II) that is not responsive to glucocorticoids has also been described, and its genomics and proteomics are currently being investigated *(32)*.

Mineralocorticoid Receptor Gain of Function: A recently described mutation adds to the mechanisms related to increased aldosterone activity and chloride-resistant hypertensive metabolic alkalosis *(33)*. In this disorder, the aldosterone receptor itself is mutated and is activated by not only aldosterone, but also by cortisol, cortisone, and progesterone.

Primary hyperreninemia: States of primary renin overproduction leading to significant hypertension and metabolic alkalosis are rare in children, and usually are secondary to renal artery stenosis. Several types of renin-producing tumors have been described in children and adults, including tumors of the juxtaglomerular apparatus, Wilms' tumor, and a rhabdoid tumor of the kidney *(34, 35)*.

Primary Aldosteronism: In adults, increasing attention is being paid to states of increased aldosterone activity as a cause of hypertension *(7, 36)*. In children, adrenocortical adenoma, adrenocortical carcinoma, and bilateral nodular hyperplasia have been described *(37–41)*, but are quite rare. Renal and adrenal imaging, along with measurement of plasma renin and aldosterone levels (see "Section 4") can aid in the diagnosis.

Adrenal Enzyme Defects: Although one usually thinks of congenital adrenal hyperplasia (CAH) presenting as classic 21-hydroxylase deficiency (salt wasting, hypotension, hyperkalemia), two autosomal recessive rare variants of CAH may present with hypertension, hypokalemia, metabolic alkalosis, and low plasma renin activity: 11β-hydroxylase deficiency and 17α-hydroxylase deficiency *(42)*. 11β-Hydroxylase

deficiency is the second most common form of CAH, accounting for 5–8% of cases of CAH. Virilization secondary to excess adrenal androgen secretion is a characteristic finding. 17α-Hydroxylase deficiency accounts for approximately 1% of CAH. Underproduction of testosterone leads to undervirilized genitalia in males, and in girls who fail to develop secondary sex characteristics at puberty. In both disorders, overproduction of deoxycorticosterone (DOC), an aldosterone precursor, is responsible for hyperreninemic, hypervolemic hypertension, hypokalemia, and metabolic alkalosis.

Cushing Syndrome: Hypertension is common in patients receiving exogenous corticosteroids and in those with Cushing's disease. The mechanisms contributing to metabolic alkalosis in patients with states of glucocorticoid excess probably include the mineralocorticoid effects of glucocorticoids and, in patients with endogenous overproduction of glucocorticoids, the concomitant overproduction of aldosterone precursors with mineralocorticoid effects.

6. TREATMENT

6.1. Chloride Responsive Alkalosis

Chloride responsive alkalosis is characterized by intravascular volume contraction, hypo- or normotension, chloride deficiency, potassium deficiency, and secondary hyperreninemic hyperaldosteronism. Once alkalosis is established, correction of intravascular volume, chloride deficit, and potassium deficit is necessary to reverse the alkalosis. In severe, symptomatic, or life-threatening cases, urgent correction of alkalosis with acid administration may be required. Ultimately, identification and, if possible, removal or treatment of the underlying cause is the goal.

Restoring Intravascular Volume: Assessment of intravascular volume and calculation of fluid deficit has been addressed elsewhere in this volume. To facilitate correction of alkalosis, the fluid deficit should be replaced with isotonic saline: the administered chloride is necessary to facilitate renal tubular exchange of bicarbonate for chloride, and the correction of volume deficit is necessary to reverse the secondary hyperaldosteronism, which contributes to ongoing potassium and proton loss if not corrected. Once intravascular volume is restored and additional maintenance and ongoing losses are provided for, attention can then focus on whether chloride and potassium deficits still exist.

Restoring Chloride Deficit: Once euvolemia has been restored, total body chloride deficit can be calculated using the formula

$$\mathrm{Cl^-\,deficit\,(mEq)} = 0.2 \times \mathrm{Body\,Weight\,(kg)} \times (100 - \mathrm{patient\,[Cl^-]})$$

For example, for a 20 kg patient with a $[Cl^-] = 90$ mEq/L,

$$\begin{aligned}\mathrm{Cl^-\,deficit\,(mEq)} &= 0.2 \times 20 \times (100 - 90)\\ &= 4 \times 10\\ &= 40\,\mathrm{mEq}\end{aligned}$$

Thus, for the above example, an additional 40 mEq of Cl^- should be added to calculations of the patient's maintenance and ongoing losses (if any). Whether to give the Cl^- as NaCl or as KCl will depend on whether the patient also has an accompanying potassium deficit. When in doubt, assume that patients with metabolic alkalosis have a total body potassium deficit unless there is decreased GFR and provide the bulk of chloride deficit replacement as KCl.

Restoring Potassium Deficit: Correction of intravascular volume with isotonic saline and subsequent correction of chloride deficit with KCl is usually sufficient to correct total body potassium deficit. After initial fluid resuscitation, KCl in concentrations of 10–20 mEq/L should be added to maintenance fluids. In cases of severe hypokalemia, particularly those associated with cardiac arrhythmias or neuromuscular complications, additional oral or intravenous potassium may be needed.

Urgent Correction of Alkalosis: When alkalosis contributes to deteriorating clinical status in critically ill patients (for example, cardiac arrhythmia, digitalis cardiotoxicity, altered mental status, hepatic encephalopathy), typically when serum pH > 7.55, intravenous administration of acid, either as HCl or NH_4Cl may be considered. HCl, administered as an isotonic solution (150 mEq/L HCl) must be given through a central venous catheter with demonstrated good flow. The infusion rate should not exceed 25 mEq/h. The dose of HCl, in mEq, is calculated as follows:

$$\text{HCl dose (mEq)} = 0.5 \times \text{Body Weight (kg)} \times (\text{patient } [HCO_3^-] - 24\,\text{mEq/L})/2$$

Note (at the end of the equation) that for an initial correction, the difference between the patient $[HCO_3^-]$ and a normal $[HCO_3^-]$ (24 mEq/L) is divided by 2 to provide a "1/2" correction. The goal is to decrease symptoms of sever alkalosis, and rapid correction to a "normal" value may increase the risk of complications, particularly in patients whose course is complicated by chronic respiratory acidosis. For example, for a 20 kg patient with an $HCO_3^- = 34$ mEq/L,

$$\begin{aligned}\text{HCldose} &= 0.5 \times 20\,\text{kg} \times (34\,\text{mEq/L} - 24\,\text{mEq/L})2\\ &= 10 \times 10/2\\ &= 50\,\text{mEq}\end{aligned}$$

HCl should be infused over 8–24 h. In this example, 50 mEq of a 150 mEq/L solution of HCl yields a volume of 333 ml. For an 8 h infusion, the rate would be 42 ml/h (6.3 mEq/h), and for a 24 h infusion, the rate would be 14 ml/h (2.25 mEq/h). The expected $[HCO_3^-]$ from this "1/2 correction" would be 29–30 mEq/L.

NH_4Cl has been used as an alternative to HCl particularly when no central venous access is available, as it may be given through a peripheral line. NH_4Cl is contraindicated in patients with severe hepatic or renal disease. There is little pediatric experience with this therapy, and use should be limited to the critical care setting. Dose (in mEq) is calculated using the same formula as that for HCl. Typical administration is to prepare a 200 mEq/L solution and infuse over 3–6 h, with a maximum infusion rate of 1 mEq/kg/h. Monitor serum electrolytes and ammonia levels during therapy.

In patients with edematous states, particularly those with decreased GFR and oliguria, administration of NaCl or KCl may be contraindicated. NaCl administration can contribute to volume overload and edema, while KCl administration may lead to life-threatening hyperkalemia. If some residual renal function is present (GFR > 20–30 ml/min), acetazolamide, a carbonic anhydrase inhibitor, may increase urinary bicarbonate losses in exchange for increased acid reabsorption. Careful attention should be paid to serum electrolytes, as acetazolamide may contribute to hypovolemia and hypokalemia. Chronic use of carbonic-anhydrase inhibitors can result in nephrocalcinosis and urolithiasis.

In patients with renal failure (GFR < 20 ml/min) dialysis against a high-chloride dialysis bath will exchange bicarbonate for chloride and correct alkalosis.

Correcting the Underlying Cause: If ongoing gastric loss of HCl is identified, gastric HCl production can be decreased with H_2-receptor blockers or proton pump inhibitors. If possible, diuretics particularly loop or thiazide diuretics should be decreased or discontinued and if their use is obligatory, it should be supplemented by KCl or K-sparing diuretics.

6.2. Chloride Unresponsive Alkalosis

Chloride unresponsive forms of alkalosis are less common than chloride responsive types. With the exception of diuretic abuse and licorice ingestion, which resolve with discontinuation of the offending substance, treatment of other forms of chloride unresponsive alkalosis requires recognition of the underlying diagnosis and specific treatment for that disorder.

Bartter Syndrome: No mechanism-specific treatment for Bartter syndrome has yet been identified. Treatment consists of decreasing the fluid and electrolyte losses as much as possible and replacement of remaining deficits. Current therapy consists primarily of prostaglandin synthesis inhibition and potassium replacement. Most clinical experience is with indomethacin (2–5 mg/kg daily) or ibuprofen (30 mg/kg daily). A specific COX-2 inhibitor, rofecoxib, has also been used with good results *(24)*, but experience is limited and further trials needed. With chronic use of any NSAID, careful attention should be paid to symptoms suggestive of toxicity. In addition to prostaglandin synthesis inhibition, potassium supplementation, in the form of KCl, is usually required, with patients typically requiring 1–5 mEq/kg daily. Spironolactone and amiloride have also been used; they have the advantage of Mg-sparing but also carry the risk of worsening intravascular volume depletion, particularly in infants and young children.

Spironolactone may be superior to amiloride, as it blocks the effect of high serum levels of aldosterone *(43)*. Enalapril and other angiotensin converting enzyme inhibitors have also been used with some success, but no clear recommendation has yet emerged. Their introduction should be gradual due to the risk of hypotension. No treatment for nephrocalcinosis has been described. The use of thiazide diuretics to reduce urinary calcium excretion is contraindicated, as thiazides exacerbate the tubule defects seen in Bartter syndrome. Children with Bartter syndrome are particularly sensitive to dehydration during acute illnesses, and early evaluation for fluid and electrolyte problems should occur during times of decreased oral intake or increased GI losses.

Gitelman Syndrome: For Gitelman syndrome, like Bartter syndrome, no defect-specific therapy has yet been identified, and therapy consists of potassium and magnesium replacement. The roles of prostaglandin synthesis inhibitors and K-sparing diuretics need further investigation.

Liddle Syndrome: Early descriptions of Liddle syndrome, before the molecular mechanisms were identified, demonstrated that patients responded to amiloride, but not to spironolactone, suggesting that the defect was directly in the tubule, and not a tubular response to mineralocorticoid. Amiloride remains the drug of choice. Hypertension in Liddle syndrome is particularly salt sensitive, and dietary sodium restriction is also an important part of therapy.

Apparent Mineralocorticoid Excess Syndrome: Spironolactone, a mineralocorticoid receptor blocker, targets the defect in AME and is an effective treatment.

Glucocorticoid Remediable Aldosteronism (GRA): As the name implies, hypertension and hypokalemia in GRA respond to ACTH suppression with glucocorticoids. However, because of the side effects of chronic glucocorticoid use, spironolactone or amiloride may also be used.

Aldosterone Excess States: Inhibition of mineralocorticoid effects with spironolactone is useful as initial therapy in states of primary mineralocorticoid or glucocorticoid excess, but definitive diagnosis and treatment (beyond the scope of this section) are often curative.

CASE SCENARIOS

(a) Easy Fix or a Life-Long Problem?

A 3-month-old infant presents with a 1 week history of poor oral intake, vomiting, and increasing lethargy. Parents note decreased tears, one wet diaper over the past 24 h, and four to five episodes of emesis over the past 24 h. There is no history of diarrhea, no fever, and there are no ill contacts. On presentation, the heart rate is 140/min, the blood pressure is 80/45 mmHg, respiratory rate is 18/min, and temperature is 37°F. On physical exam, the child is difficult to arouse, the anterior fontanel is sunken, there are decreased tears, mucus membranes are sticky, eyes are slightly sunken, capillary refill is >2 s.

A. Initial therapy: Regardless of our ultimate findings, the child in this vignette is severely dehydrated, with a fluid deficit of 10–15%. Initial evaluation should include assessment of renal function, acid–base status, and electrolyte status. Because of the severe degree of dehydration, intravenous fluid resuscitation should begin immediately with 20 ml/kg boluses of isotonic saline.

B. Initial laboratory values: Just before a fluid bolus has been given, the initial laboratory values are as follows:

Na =	132 mEq/L
K =	2.5 mEq/L
Cl =	88 mEq/L
BUN =	30 mg/dL
Creatinine =	0.9 mg/dL

$pH =$ 7.50
$pCO_2 =$ 47 mmHg
$HCO_3^- =$ 36 mEq/L

A pH of 7.5 reflects alkalosis, not a typical finding since most infants with severe dehydration present with metabolic acidosis. Using the equations in Table 1 to determine if the alkalosis is primary metabolic with an appropriate respiratory compensation, or instead represents a mixed acid–base disorder:

Method 1: Compensated $PaCO_2 = 40 + [0.7 \text{ (patient } [HCO_3^-] - \text{normal } [HCO_3^-])]$
In this case the patient's serum $[HCO_3^-]$ has increased from normal for age of 22 mEq/L to 32 mEq/L:

Compensated $PaCO_2 = 40 + [0.7\ (32–22)]$
Compensated $PaCO_2 = 40 + 7$
Compensated $PaCO_2 = 47$

Method 2: Compensated $PaCO_2 =$ patient $[HCO_3^-] + 15$
In this case, the patient has a serum $[HCO_3^-] = 32$

Compensated $PaCO_2 = 32 + 15$
Compensated $PaCO_2 = 47$

Either equation can be used to demonstrate that the patient has a primary metabolic alkalosis with an appropriate respiratory compensation (decrease in ventilation to raise pCO_2).

C. Further diagnosis and treatment are guided by measurement of urine electrolytes, particularly urine $[Cl^-]$ (Fig. 1). We will consider two likely diagnostic possibilities based on the patient's urine $[Cl^-]$:

Case Scenario 1: The patient's urine $[Cl^-]$ is <5 mEq/L and urine pH is >6.5. The urine results reflect an appropriate renal response to HCl loss from a non-renal site, or exogenous HCO_3^- administration. The history of vomiting and poor oral intake point to gastric HCl loss (rather than alkali administration) as the alkalosis-generating step, with maintenance of alkalosis promoted by a decreased GFR from dehydration, and hypokalemia from both decreased oral intake and increased urine loss from secondary hyperaldosteronism (an appropriate response to volume depletion, but one which has an unintended consequence of maintaining alkalosis). The increased aldosterone activity also contributes to alkalosis by increasing urinary H^+ loss.

Investigation of causes for vomiting in a 3-month-old should include abdominal imaging, with ultrasound being the study of choice. In this case, a finding of pyloric stenosis explains the metabolic alkalosis. Pyloric stenosis is a surgically treatable lesion, but to minimize the chance of anesthetic and intraoperative complications, fluid deficit and alkalosis should be corrected prior to surgery. After initial fluid resuscitation, fluid deficit should again be estimated, with a goal to replace the fluid deficit over 24 h with isotonic saline. Potassium can be added to maintenance fluids at concentration of 10–20 mEq/L. If either potassium or chloride fails to correct with initial fluid therapy,

additional KCl can be added to replace the chloride deficit:

$$Cl^- \text{deficit (mEq)} = 0.2 \times \text{Body Weight (kg)} \times (100 - \text{patient } [Cl^-])$$

In this case, for patient with a $[Cl^-] = 90$ mEq/L and weight = 6 kg,

$$\begin{aligned} Cl^- \text{deficit (mEq)} &= 0.2 \times 6 \times (100 - 88) \\ &= 1.2 \times 12 \\ &= 14.4 \text{ mEq, or approximately } 2 - 3 \text{ mEq/kg of KCl in addition to maintenance KCl.} \end{aligned}$$

Case Scenario 2: While metabolic alkalosis secondary to gastric loss in pyloric stenosis is a classic presentation in pediatrics, measurement of urine $[Cl^-]$ can sometimes reveal surprises. In this scenario, urine $[Cl^-] = 35$ mEq/L. In a patient with a serum $[Cl^-] = 88$ mEq/L, this is an inappropriate renal loss, and reflects an underlying problem with renal mechanisms to preserve chloride. Since the patient is relatively hypotensive, with evidence of severe intravascular volume depletion, reference to Fig. 1 points to renal tubular defects, diuretic abuse, or severe K^+ or Mg^+ deficiency. The history in this case is not suggestive of dietary deficiency or medication administration, and the most likely diagnosis is Bartter syndrome or Gitelman syndrome. An ultrasound finding of nephrocalcinosis would suggest neonatal Bartter syndrome, but is not seen in all cases. To further differentiate Bartter from Gitelman syndromes, measurement of urine calcium excretion (usually high in Bartter, low in Gitelman is helpful). Serum magnesium is typically low in Gitelman, and normal in Bartter. While initial fluid resuscitation should follow guidelines for all dehydrated patients, once euvolemia has been established, disease-specific therapy must be initiated to prevent further serious decompensation.

(b) When metabolic alkalosis is combined with hypertension

A 3-year-old is brought to the Emergency Department for an ear infection. Vital signs show blood pressure of 150/100 mmHg, confirmed by repeat measurements. The family history is positive for the biological father having hypertension who since young age was treated by a medicine unknown to the mother. Besides the ear infection the rest of the physical examination is unremarkable. Blood work shows Na 136, K 2.8, Cl 86, HCO_3 34 mEq/l, creatinine 0.5, Ca 9.6, P 4.2 mg/dL. Urinalysis is normal.

What is your next step in evaluating the metabolic alkalosis?

As always, the first step is assessment of urine chloride, which is 38 mEq/L.

The child has chloride resistant metabolic alkalosis with hypertension.

As shown in Fig. 1 and Table 1, in such cases assessment of PRA and serum aldosterone is crucial in establishing the diagnosis. In this case, both were very low. The family history in this case indicates Liddle syndrome rather than AME. In the future, genetic studies will provide the definitive diagnosis.

Contrary to most cases of metabolic alkalosis, which are associated with hypovolemia, the rare situation of metabolic alkalosis combined with hypertension is caused by hypervolemia. Therefore, there is no indication to treat with NaCl, which may aggravate the hypertension. Treatment of Liddle syndrome requires the use of K-sparing diuretics as discussed above.

REFERENCES

1. DuBose TD. Acid–Base Disorders. In: Brenner BM, ed. Brenner and Rector's The Kidney. 7 ed. Philadelphia: W.B. Saunders Company; 2003:969–976.
2. Laski ME, Sabatini S. Metabolic alkalosis, bedside and bench. Seminars in Nephrology 2006;26: 404–421.
3. Galla JH. Metabolic alkalosis. American Journal of Nephrology 2000;11:369–375.
4. Rose BD, Post TW. Metabolic Alkalosis. In: Clinical Physiology of Acid–Base and Electrolyte Disorders. 5 ed. New York: McGraw Hill Medical Publishing Division; 2001:551–572.
5. Malafronte C, Borsa N, Tedeschi S, et al. Cardiac arrhythmias due to severe hypokalemia in a patient with classic Bartter disease. Pediatric Nephrology 2004;19:1413–1415.
6. Toto RD, Alpern, R.J. Metabolic acid–base disorders. In: Kokko JP, Tannen R.L., ed. Fluids and Electrolytes. 3 ed. Philadelphia: W.B. Saunders Company; 1996:241–256.
7. Pimenta E, Calhoun DA. Primary aldosteronism: diagnosis and treatment. Journal of Clinical Hypertension 2006;8:887–893.
8. van Thiel RJ, Koopman SR, Takkenberg JJM, Ten Harkel ADJ, Bogers AJJC. Metabolic alkalosis after pediatric cardiac surgery. European Journal of Cardio-Thoracic Surgery 2005;28:229–233.
9. Barletta G-M, Bunchman TE. Acute renal failure in children and infants. Current Opinion in Critical Care 2004;10:499–504.
10. Morgera S, Scholle C, Voss G, et al. Metabolic complications during regional citrate anticoagulation in continuous venovenous hemodialysis: single-center experience. Nephron 2004;97: c131–136.
11. Gabutti L, Marone C, Colucci G, Duchini F, Schonholzer C. Citrate anticoagulation in continuous venovenous hemodiafiltration: a metabolic challenge. Intensive Care Medicine 2002;28:1419–1425.
12. Blumer SL, Zucconi WB, Cohen HL, Scriven RJ, Lee TK. The vomiting neonate: a review of the ACR appropriateness criteria and ultrasound's role in the workup of such patients. Ultrasound Quarterly 2004;20:79–89.
13. MacMahon B. The continuing enigma of pyloric stenosis of infancy: a review [see comment]. Epidemiology 2006;17:195–201.
14. Dinkevich E, Ozuah PO. Pyloric stenosis. Pediatrics in Review 2000;21:249–250.
15. Hernanz-Schulman M. Infantile hypertrophic pyloric stenosis. Radiology 2003;227:319–331.
16. Bates CM, Baum M, Quigley R. Cystic fibrosis presenting with hypokalemia and metabolic alkalosis in a previously healthy adolescent. Journal of the American Society of Nephrology 1997;8: 352–355.
17. Fustik S, Pop-Jordanova N, Slaveska N, Koceva S, Efremov G. Metabolic alkalosis with hypoelectrolytemia in infants with cystic fibrosis. Pediatrics International 2002;44:289–292.
18. Salvatore D, Tomaiuolo R, Abate R, et al. Cystic fibrosis presenting as metabolic alkalosis in a boy with the rare D579G mutation. Journal of Cystic Fibrosis 2004;3:135–136.
19. Woywodt A, Herrmann A, Eisenberger U, Schwarz A, Haller H. The tell-tale urinary chloride [see comment]. Nephrology Dialysis Transplantation 2001;16:1066–1068.
20. Hihnala S, Hoglund P, Lammi L, Kokkonen J, Ormala T, Holmberg C. Long-term clinical outcome in patients with congenital chloride diarrhea. Journal of Pediatric Gastroenterology & Nutrition 2006;42:369–375.
21. Lok K-H, Hung H-G, Li K-K, Li K-F, Szeto M-L. Congenital chloride diarrhea: a missed diagnosis in an adult patient. American Journal of Gastroenterology 2007;102:1328–1329.

22. Lin S-H, Yang S-S, Chau T, Halperin ML. An unusual cause of hypokalemic paralysis: chronic licorice ingestion. American Journal of the Medical Sciences 2003;325:153–156.
23. Ellison DH. Divalent cation transport by the distal nephron: insights from Bartter's and Gitelman's syndromes. American Journal of Physiology - Renal Physiology 2000;279:F616–625.
24. Kleta R, Bockenhauer D. Bartter syndromes and other salt-losing tubulopathies. Nephron Physiology 2006;104:73–80.
25. Shaer AJ. Inherited primary renal tubular hypokalemic alkalosis: a review of Gitelman and Bartter syndromes. American Journal of the Medical Sciences 2001;322:316–332.
26. Laine J, Jalanko H, Alakulppi N, Holmberg C. A new tubular disorder with hypokalaemic metabolic alkalosis, severe hypermagnesuric hypomagnesaemia, hypercalciuria and cardiomyopathy. Nephrology Dialysis Transplantation 2005;20:1241–1245.
27. Watanabe S, Fukumoto S, Chang H, et al. Association between activating mutations of calcium-sensing receptor and Bartter's syndrome. Lancet 2002;360:692–694.
28. Chou C-L, Chen Y-H, Chau T, Lin S-H. Acquired Bartter-like syndrome associated with gentamicin administration. American Journal of the Medical Sciences 2005;329:144–149.
29. Rodriguez-Soriano J. Tubular Disorders of Electrolyte Regulation. In: Avner ED, Harmon WE, Niaudet P, ed. Pediatric Nephrology. 5 ed. Philadelphia: Lippincott Williams & Wilkins; 2004: 729–741.
30. Moudgil A, Rodich G, Jordan SC, Kamil ES. Nephrocalcinosis and renal cysts associated with apparent mineralocorticoid excess syndrome. Pediatric Nephrology 2000;15:60–62.
31. Williams SS. Advances in genetic hypertension. Current Opinion in Pediatrics 2007;19:192–198.
32. So A, Duffy DL, Gordon RD, et al. Familial hyperaldosteronism type II is linked to the chromosome 7p22 region but also shows predicted heterogeneity. Journal of Hypertension 2005;23:1477–1484.
33. Geller DS, Farhi A, Pinkerton N, et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy [comment]. Science 2000;289:119–123.
34. Friedman K, Wallis T, Maloney KW, Hendrickson RJ, Mengshol S, Cadnapaphornchai MA. An unusual cause of pediatric hypertension. Journal of Pediatrics 2007;151:206–212.
35. Markey RB, MacLennan GT. Juxtaglomerular cell tumor of the kidney. Journal of Urology 2006;175:730.
36. Mulatero P, Morello F, Veglio F. Genetics of primary aldosteronism. Journal of Hypertension 2004;22:663–670.
37. Abasiyanik A, Oran B, Kaymakci A, Yaar C, Calikan U, Erkul I. Conn syndrome in a child, caused by adrenal adenoma. Journal of Pediatric Surgery 1996;31:430–432.
38. Abdullah N, Khawaja K, Hale J, Barrett AM, Cheetham TD. Primary hyperaldosteronism with normokalaemia secondary to an adrenal adenoma (Conn's syndrome) in a 12 year-old boy. Journal of Pediatric Endocrinology 2005;18:215–219.
39. Baranwal AK, Singhi SC, Narshimhan KL, Jayashree M, Singhi PD, Kakkar N. Aldosterone-producing adrenocortical adenoma in childhood: a case report. Journal of Pediatric Surgery 1999;34:1878–1880.
40. Boushey RP, Dackiw AP. Adrenal cortical carcinoma. Current Treatment Options in Oncology 2001;2:355–364.
41. Rogoff D, Bergada I, Venara M, Chemes H, Heinrich JJ, Barontini M. Intermittent hyperaldosteronism in a child due to an adrenal adenoma. European Journal of Pediatrics 2001;160:114–116.
42. New MI, Ghizzoni, Lucia. Congenital Adrenal Hyperplasia. In: Lifshitz F, ed. Pediatric Endocrinology. 4 ed. New York: Marcel Dekker, Inc.; 2003:175–178.
43. Colussi G, Rombola G, De Ferrari ME, Macaluso M, Minetti L. Correction of hypokalemia with antialdosterone therapy in Gitelman's syndrome. American Journal of Nephrology 1994;14:127–135.