Metabolic disturbances of acid-base balance are associated with many disease states, and identification of the acid-base disturbance may facilitate diagnosis of the underlying disease process. For example, observation of hypochloremic metabolic alkalosis on a serum biochemical profile of a vomiting dog may lead to recognition of gastrointestinal obstruction as the cause. The regulation of normal acid-base balance is considered in detail in Chapter 9.

**METABOLIC ACIDOSIS**

Metabolic acidosis is characterized by a primary decrease in plasma HCO\(_3^-\)/CO\(_2\) concentration, increased [H\(^+\)], decreased pH, and a secondary, or adaptive, decrease in P\(_{CO_2}\). In one study, metabolic acidosis was the most common acid-base disturbance in dogs and cats.\(^{61}\)

Metabolic acidosis can be caused by loss of HCO\(_3^-\)-rich fluid from the body, addition of fixed acid to the body or its production by metabolism within the body, or failure of renal excretion of fixed acid. Loss of HCO\(_3^-\)-rich fluid usually occurs via the gastrointestinal tract (e.g., small bowel diarrhea), but it also may occur via the kidneys (e.g., carbonic anhydrase inhibitors, proximal renal tubular acidosis). The HCO\(_3^-\) concentration of diarrheal fluid exceeds that of plasma, whereas its Cl\(^-\) concentration is lower. The loss of such fluid results in a hyperchloremic metabolic acidosis. Examples of the addition of fixed acid to the body include toxins (e.g., ethylene glycol, salicylate) and compounds used therapeutically (e.g., ammonium chloride, cationic amino acids). Examples of metabolic production of fixed acid within the body include lactic acidosis and diabetic ketoacidosis. Renal failure, hypoadrenocorticism, and distal renal tubular acidosis are examples of impaired urinary excretion of fixed acid. Small bowel diarrhea, renal failure, hypoadrenocorticism, diabetic ketoacidosis, and lactic acidosis during cardiovascular collapse are the most common causes of metabolic acidosis in small animal practice.

**BODY BUFFER RESPONSE TO AN ACUTE ACID LOAD**

When HCl was infused acutely into nephrectomized dogs, approximately 40% of the acid was buffered by extracellular HCO\(_3^-\), 10% by red cell buffers (primarily hemoglobin), and 50% by intracellular buffers of soft tissues and bone (primarily proteins and phosphates).\(^{223}\)

In nonnephrectomized unanesthetized dogs infused intermittently with HCl, intracellular buffers contributed approximately 50% of the buffer response, regardless of the magnitude of the H\(^+\) load.\(^{210}\) Within a few minutes of an acute fixed acid load, administered H\(^+\) is buffered by HCO\(_3^-\) in plasma water. Plasma proteins and phosphates play a minor role in this acute response. Some of the administered acid enters red cells and is buffered by hemoglobin. The CO\(_2\) produced by the combination of the H\(^+\) with HCO\(_3^-\) ions is rapidly removed from the body by alveolar ventilation. Within 30 minutes, the acid load has been distributed to the interstitial fluid, where HCO\(_3^-\) again plays the dominant role in the acute buffer response. After several hours, H\(^+\) enters intracellular water in exchange for sodium and potassium ions. These hydrogen ions are buffered within cells by proteins and phosphates. In early studies,\(^{210,223}\) serum potassium concentration increased, but serum sodium concentration decreased after infusion of HCl. The relative roles of these buffers are depicted in Figure 10-1.

**RESPIRATORY RESPONSE TO AN ACUTE ACID LOAD**

A fixed acid load increases [H\(^+\)] and thereby stimulates peripheral and central chemoreceptors to increase alveolar ventilation. This effect begins within hours and is complete within 12 to 24 hours. In humans, there is an approximately 1.2-mm Hg reduction in P\(_{CO_2}\) for each 1-mEq/L decrement in plasma HCO\(_3^-\) concentration to a minimum P\(_{CO_2}\) of approximately 10 mm Hg.\(^{99,195}\) In dogs with uncomplicated metabolic acidosis induced by chronic feeding of HCl, the observed compensatory respiratory
response is an approximately 0.7-mm Hg decrement in $P_{CO_2}$ per 1-mEq/L decrement in plasma $HCO_3^-$ concentration. In these studies, the smallest observed respiratory response was an approximately 0.5-mm Hg decrement in $P_{CO_2}$ per milliequivalents per liter decrement in plasma $HCO_3^-$ concentration, and the largest response was a 1.1-mm Hg decrement in $P_{CO_2}$ per milliequivalents per liter decrement in plasma $HCO_3^-$ concentration. Data are limited on the respiratory response of cats to metabolic acidosis, but there is some evidence that the cat fails to develop respiratory compensation to the same extent as observed in the dog in spontaneous and NH$_4$Cl-induced metabolic acidosis.

The classic explanation of the respiratory response to metabolic acidosis is that the increase in [H$^+$] (decrease in pH) stimulates ventilation, and the resultant decrease in $P_{CO_2}$ returns the $HCO_3^- / P_{CO_2}$ ratio and pH toward normal. This is true in acute metabolic acidosis, but the resultant secondary hypocapnia has been observed to decrease plasma $HCO_3^-$ concentration further in chronic metabolic acidosis, presumably by reducing renal $HCO_3^-$ reabsorption. This secondary hypocapnia contributes to 40% of the observed decrease in plasma $HCO_3^-$ concentration during chronic HCl acidosis. Thus, chronic metabolic acidosis decreases plasma $HCO_3^-$. The role of the kidneys is to excrete the fixed acid load imposed by the underlying disease process responsible for metabolic acidosis. The kidneys accomplish this task primarily by augmenting its excretion of NH$_4^+$. Titratable acidity changes little unless there is a change in the filtered load of phosphate. Chloride ions accompany the NH$_4^+$ into urine while $HCO_3^-$ is regenerated and reabsorbed into extracellular fluid (ECF) to restore $HCO_3^-$ that was titrated during the acute fixed acid load. Within 48 hours of a fixed acid load, approximately 25% of the added acid has been excreted in the urine, and the remainder is excreted during the next 4 days. The kidney can increase its NH$_4^+$ excretion as much as fivefold to tenfold during chronic metabolic acidosis. There is some evidence that cats do not adapt to metabolic acidosis by enhanced renal ammoniagenesis. The role of the kidneys in regulation of acid-base balance is discussed further in Chapter 9.

**CLINICAL FEATURES OF METABOLIC ACIDOSIS**

The clinical signs in small animals with metabolic acidosis are more likely to be caused by the underlying disease responsible for metabolic acidosis than by the acidosis itself. In humans, respiratory compensation for metabolic acidosis leads to characteristic hyperventilation, recognized by a deep, rhythmic breathing pattern (i.e., Kussmaul respirations). Such a characteristic respiratory pattern has not been described in small animal patients, and metabolic acidosis is usually suspected by observation of a low total CO$_2$ content on a biochemical profile and confirmed by blood gas analysis.

Severe acidosis has serious detrimental effects on cardiovascular function, including decreased cardiac output, decreased arterial blood pressure, and decreased hepatic and renal blood flow. Myocardial contractility is decreased when blood pH falls below 7.20. Impaired contractility may result from a decrease in myocardial intracellular pH (pH$_i$) and displacement of calcium ions from critical binding sites on contractile proteins. Acidosis may predispose the heart to ventricular arrhythmias or ventricular fibrillation. Acidosis has a direct arterial vasodilating effect that is offset by increased release of endogenous catecholamines. However, the inotropic response to catecholamines is impaired, and this may be associated with a reduction in the number of
Acidemia produces insulin resistance that impairs peripheral uptake of glucose and inhibits anaerobic glycolysis by inhibiting phosphofructokinase. During severe acidosis, the liver may be converted from a consumer to a producer of lactate. Severe acidosis also impairs the ability of the brain to regulate its volume, leading to obtundation and coma. Acute mineral acidosis causes hyperkalemia by a transcellular shifting of potassium from intracellular fluid to ECF in exchange for hydrogen ions. This effect causes a very variable change in serum potassium concentration and is not observed with organic acidosis. Acute reduction in blood pH causes displacement of calcium ions from negatively charged binding sites (e.g., –COO⁻ groups) on proteins (primarily albumin) as these sites become protonated, and an increase in ionized serum calcium concentration results. Chronic metabolic acidosis leads to release of buffer (mainly calcium carbonate) from bone, and osteodystrophy and hypercalciuria result.

**DIAGNOSIS OF METABOLIC ACIDOSIS**

Metabolic acidosis is associated with several different diseases and should be considered in any severely ill patient. Oftentimes, the diagnosis is first suspected by review of the electrolyte and total CO₂ results on the patient’s biochemical profile. It is confirmed by blood gas analysis. The causes of metabolic acidosis may be divided into those associated with a normal anion gap (hyperchloremic metabolic acidosis) and those associated with an increased anion gap (normochloremic metabolic acidosis) (Box 10-1).

The anion gap represents the difference between the commonly measured plasma cations and the commonly measured anions. This concept is discussed in detail in Chapters 9 and 12. The normal electrolyte composition of canine plasma is compared with that in normal (hyperchloremic) and increased (normochloremic) anion gap metabolic acidosis in Figure 10-2. The anion gap concept is useful in the diagnostic approach to the patient with metabolic acidosis, but it must not be taken literally. In reality, electroneutrality is maintained, and there is no actual anion gap. Normally, the anion gap is made up of the net negative charge on sulfates, phosphates, plasma proteins, and organic anions (e.g., lactate, citrate). Recent studies have shown that in normal dogs and cats, a substantial portion of the anion gap arises from the negative charge on plasma proteins. The net protein charge of plasma at p. 7.40 was calculated to be 16.0 mEq/L in dogs, and this value was determined to be 13.7 mEq/L in cats. Factors other than metabolic acidosis may also affect the value of the anion gap, and these are discussed in Chapter 12.

When the anion gap is calculated as \[(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)\], normal values in dogs are in the range of 12 to 25 mEq/L. Values for the anion gap may be somewhat higher in cats (17 to 31 mEq/L) than in dogs (13 to 25 mEq/L) because of some unaccounted protein and phosphate charge. In other studies, the mean anion gap for normal cats (calculated as described above) was approximately 20 mEq/L. If the observed metabolic acidosis is characterized by a high anion gap, it is assumed to have arisen from an acid that does not contain chloride as its anion. Examples include some inorganic acids (e.g., phosphates, sulfates) or organic acids (e.g., lactate, ketoacids, salicylate, metabolites of ethylene glycol). In this setting, titration of body buffers by the acid results in accumulation of an anion other than chloride. If the observed metabolic acidosis is characterized by a normal anion gap, there is a reciprocal increase in the plasma chloride concentration.
to balance the decrease in plasma $\text{HCO}_3^-$ concentration.

In the following discussion, the causes of metabolic acidosis have been divided into those associated with a normal anion gap and those associated with an increased anion gap.

**DISORDERS ASSOCIATED WITH A NORMAL ANION GAP**

**Diarrhea**

The concentration of $\text{HCO}_3^-$ in intestinal fluid usually is higher than that of plasma, whereas its $\text{Cl}^-$ concentration is lower. This results from the addition of alkaline pancreatic and biliary secretions to luminal contents and from secretion of $\text{HCO}_3^-$ in exchange for $\text{Cl}^-$ in the ileum (Fig. 10-3 and Table 10-1). In some diseases of the small intestine, increased delivery of ileal contents to the colon may overwhelm the considerable capacity of the colon for reabsorption of fluid and electrolytes. As a result, severe acute small bowel diarrhea may cause loss of $\text{HCO}_3^-$ in excess of $\text{Cl}^-$ with resultant hyperchloremic metabolic acidosis. The acidosis is not purely hyperchloremic but

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**Figure 10-2** Theoretical examples of electrolyte distribution in (A) normal canine plasma, (B) a dog with pure hyperchloremic (normal anion gap) metabolic acidosis, and (C) a dog with normochloremic (increased anion gap) metabolic acidosis caused by lactate accumulation (i.e., lactic acidosis). (Adapted from Toto RD. Metabolic acid-base disorders. In: Kokko JP, Tannen RL, editors. Fluids and electrolytes, 2nd ed. Philadelphia: WB Saunders, 1990: 324.)

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**Figure 10-3** Influence of secretory rate on electrolyte composition of canine pancreatic juice. Note the inverse relationship between $\text{Cl}^-$ and $\text{HCO}_3^-$ concentrations and the relatively constant concentrations of $\text{Na}^+$ and $\text{K}^+$. (From Cohen JJ, Kassirer JP. Acid-base. Boston: Little, Brown, 1982: 135.)
rather is mixed if volume depletion and impaired tissue perfusion lead to lactic acid accumulation.

In one study of 134 dogs with gastroenteritis caused by parvoviral infection, only 13% had low total CO2 concentrations. In another study of 17 dogs with parvoviral gastroenteritis, 59% had normal pH at presentation. In the animals with abnormal blood gas results, alkalemia (6 of 17) was more common than acidemia (1 of 17). The majority (64%) of the dogs in this study were presented for both vomiting and diarrhea. Hypochloremia is more common than hyperchloremia in parvoviral gastroenteritis. In another study consisting of 25 puppies with parvoviral enteritis, plasma concentrations of sodium, potassium, chloride, and bicarbonate were lower than those of control dogs; however, increases in serum L-lactate concentration were uncommon, and increases in serum D-lactate concentration were not observed. Most dogs in this study had mild compensated metabolic acidosis.

**Renal Tubular Acidosis**

Renal tubular acidosis (RTA) is characterized by hyperchloremic metabolic acidosis caused by either decreased HCO3- reabsorption (proximal RTA) or defective acid excretion (distal RTA) in the presence of a normal glomerular filtration rate (GFR). RTA is uncommonly recognized in small animal practice.

**Distal Renal Tubular Acidosis**

In distal (classic or type 1) RTA, the urine cannot be maximally acidified because of impaired hydrogen ion secretion in the collecting ducts, and urine pH typically is above 6.0, despite moderately to markedly decreased plasma HCO3- concentration. Increased urine pH (>6.0) in the presence of acidosis is the hallmark of distal RTA. Urinary tract infection by a urease-positive organism (e.g., *Proteus* sp., *Staphylococcus aureus*) must be ruled out before considering distal RTA. Urinary net acid excretion is decreased, but bicarbonaturia usually is mild because urinary HCO3- concentration is only 1 to 3 mEq/L in the pH range of 6.0 to 6.5. Nephrolithiasis (usually calcium phosphate stones), nephrocalcinosis (resulting from alkaline urine pH and decreased urinary citrate concentration), bone demineralization (resulting from loss of bone buffer stores during chronic acidosis), and urinary potassium wasting with hypokalemia are features of distal RTA in human patients. Mutations in cytosolic carbonic anhydrase, the basolateral Cl-/HCO3- anion exchanger, and luminal H+-ATPase that affect function of the α-intercalated cells have been associated with inherited forms of distal renal tubular acidosis in humans. Urinary fractional excretion of HCO3- is normal (<5%) in distal RTA when plasma HCO3- concentration is increased to normal by alkali administration.

A diagnosis of distal RTA may be confirmed by an ammonium chloride tolerance test during which urine pH is monitored (using a pH meter) before and at hourly intervals for 5 hours after oral administration of 0.2 g/kg NH4Cl. Under such conditions, the urine pH of normal dogs decreased to a minimum value of 5.16 at 4 hours after administration of ammonium chloride. Dogs in this study also developed systemic acidosis (pH approximately 7.22 and HCO3- approximately 14 mEq/L at 2 hours after ammonium chloride administration). The amount of alkali required to correct the acidosis in human patients with distal RTA is variable but typically less than that required in proximal RTA. The required dosage of alkali in distal RTA may be as little as 1 mEq/kg/day (i.e., that required to offset daily endogenous acid production) or more than 2 to 4 mEq/kg/day. A combination of potassium and sodium citrate (depending on potassium balance) may be the preferred source of alkali.

**Proximal Renal Tubular Acidosis**

In proximal (type 2) RTA, renal reabsorption of HCO3- is markedly reduced and urinary fractional excretion of HCO3- is increased (>15%) when plasma HCO3- concentration is increased to normal. Bicarbonaturia is absent and urine pH is appropriately low when metabolic acidosis is present and plasma HCO3- concentration is decreased because distal acidifying ability is intact. When plasma HCO3- concentration is decreased, the filtered load of HCO3- is reduced, and almost all of the filtered HCO3- is reabsorbed in the distal tubules, despite the

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**TABLE 10-1 Electrolyte Composition of Luminal Fluid at the End of Individual Segments of the Gastrointestinal Tract**

<table>
<thead>
<tr>
<th>Segment End</th>
<th>Na (mEq/L)</th>
<th>K (mEq/L)</th>
<th>HCO3- (mEq/L)</th>
<th>Cl- (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>60</td>
<td>15</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>Jejunum</td>
<td>140</td>
<td>6</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>Ileum</td>
<td>140</td>
<td>8</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>Colon</td>
<td>40</td>
<td>90</td>
<td>30</td>
<td>15*</td>
</tr>
</tbody>
</table>


*The large anion gap in luminal fluid at the end of the colon is caused by the presence of organic anions resulting from bacterial metabolism. These organic anions represent functional base loss in the stool because they could have been metabolized in the body to yield HCO3-.*
presence of the proximal tubular defect. Thus, proximal RTA can be viewed as a “self-limited” disorder in which plasma HCO$_3^-$ stabilizes at a lower than normal concentration after the filtered load falls sufficiently enough that distal HCO$_3^-$ reabsorption can maintain plasma HCO$_3^-$ at a new but lower steady-state concentration. Mutations in renal tubular transport proteins, such as the electrogenic basolateral Na$^+$/3HCO$_3^-$ cotransporter, and one of the five forms of the luminal Na$^+$/H$^+$ antiporter, have been implicated in the pathogenesis of inherited forms of proximal renal tubular acidosis in humans. Other abnormalities of proximal tubular function typically accompany impaired HCO$_3^-$ reabsorption in proximal RTA, and these include defects in glucose, phosphate, sodium, potassium, uric acid, and amino acid reabsorption. This combination of proximal tubular defects is known as Fanconi syndrome. Serum potassium concentration usually is normal in affected human patients at the time of diagnosis, but alkali therapy may precipitate hypokalemia and aggravate urinary potassium wasting, presumably by increasing distal delivery of sodium and HCO$_3^-$.

The diagnosis of proximal RTA is made by finding an acid urine pH (5.5 to 6.0) in the presence of hyperchloremic metabolic acidosis and a normal GFR but an increased urine pH (>6.0) and increased urinary fractional excretion of HCO$_3^-$ (>15%) after plasma HCO$_3^-$ concentration has been increased to normal by alkali administration. If present, the detection of other defects in proximal tubular function (e.g., glucosuria with normal blood glucose concentration) establishes the diagnosis. Correction of metabolic acidosis by alkali therapy is more difficult in proximal RTA than in distal RTA because of the marked bicarbonaturia that occurs when plasma HCO$_3^-$ concentration is increased to normal. Alkali dosages in excess of 10 mEq/kg/day may be required to correct the plasma HCO$_3^-$ concentration, and such therapy may result in frank hypokalemia. Thus, potassium citrate may be the preferred source of alkali.

Multiple renal tubular reabsorptive defects resembling Fanconi syndrome have been reported in young basenji dogs. Clinical findings included polyuria, polydipsia, weight loss, dehydration, and weakness. Affected dogs had abnormal fractional reabsorption of glucose, bicarbonate, phosphate, sodium, potassium, and urate, and they had isolated cystinuria or generalized aminoaciduria. The renal tubular disorder in affected basenji dogs is thought to be the result of a metabolic or membrane defect affecting sodium movement or increased back leak or cell-to-lumen flux of amino acids. In one study, brush border membranes isolated from basenji dogs with Fanconi syndrome had decreased sodium-dependent glucose transport but no abnormality of cystine uptake despite the observed reabsorptive defect for cystine. Defective urinary concentrating ability leads to isostenuria or hypostenuria, and the GFR may be normal initially but decreased later in the course of the disease. Hypokalemia has also been observed late in the course of the disease. Death usually results from acute renal failure and papillary necrosis or acute pyelonephritis. A distinctive renal lesion is hyperchromatic karyomegaly of renal tubular cells.

Fanconi syndrome has been observed sporadically in other breeds and has been reported in association with administration of some drugs. In one case, Fanconi syndrome developed in association with primary hypoparathyroidism and resolved after treatment with calcium and calcitriol. In another case, Fanconi syndrome and proximal renal tubular acidosis also have been reported in a dog with high liver enzyme activities, and toxic exposure was considered as a possible explanation. Idiopathic transient renal tubular dysfunction also has been reported in a Labrador retriever and greyhound. Fanconi-like syndrome occurred in Australian dogs that had been fed dried chicken treats from China in 2007 and another product (not containing chicken and not from China) in 2009. Affected dogs had polyuria, polydipsia, glucosuria, acidosis, hypokalemia, hypophosphatemia, and azotemia. Most of them survived with conservative medical management. Finally, Fanconi syndrome has been reported in several dogs with copper storage hepatopathy, and tubular dysfunction resolved after copper chelation therapy.

In one report, an 8-year-old female German shepherd had hyperchloremic metabolic acidosis, polyuria, polydipsia, isostenuria, glucosuria, with normal blood glucose concentration, and alkaline urine pH (7.46) after oral administration of NH$_4$Cl. The metabolic acidosis was unresponsive to NaHCO$_3$ administration at dosages up to 4 mEq/kg/day. This dog appeared to have distal (type 1) RTA and renal glucosuria. In another case of apparent distal RTA, a 5-year-old mixed breed dog was presented for evaluation of anorexia and was determined to have alkaline urine pH with hyperchloremic metabolic acidosis. In another report, an 8-year-old female German shepherd was presented for polyuria, polydipsia, weight loss, and lethargy. It had a normal GFR, metabolic acidosis, hypostenuria, and intermittent glucosuria. Fractional reabsorption of sodium, glucose, and HCO$_3^-$ was decreased, but reabsorption of chloride, phosphate, potassium, urate, and amino acids was normal. The dog gained weight, and its clinical signs were reversed after treatment with NaHCO$_3$ at approximately 10 mEq/kg/day. This dog appeared to have proximal (type 2) RTA.
Distal RTA has been reported in two cats with pyelonephritis caused by *Escherichia coli*.\textsuperscript{77,236} Clinical signs included polyuria, polydipsia, anorexia, lethargy, enlarged kidneys, and isosthenuria. In one cat, urine pH was 5.0 at the time pyelonephritis was first diagnosed, but distal RTA was documented at a later time by the presence of hyperchloremic metabolic acidosis, alkaline urine pH, and failure to lower urine pH after oral administration of NH\textsubscript{4}Cl.\textsuperscript{77} Findings were similar for the other cat, but hyperphosphaturia and persistent hypokalemia also were detected.\textsuperscript{236} Distal RTA and hepatic lipidosis were reported in another cat without urinary tract infection\textsuperscript{29} and in a cat with concurrent hyperaldosteronism and severe hypokalemia.\textsuperscript{228} Distal renal tubular acidosis also has been reported in association with immune-mediated hemolytic anemia in three dogs.\textsuperscript{215} Distal renal tubular acidosis is associated with some immune-mediated diseases in human patients, but not specifically immune-mediated hemolytic anemia. The clinical features of proximal (type 2) and distal (type 1) RTA are summarized in Table 10-2.

Hyporeninemic hypoaldosteronism, characterized by hyperkalemia with decreased plasma renin and aldosterone, is associated with some immune-mediated diseases in human patients, but not specifically immune-mediated hemolytic anemia. The clinical features of proximal (type 2) and distal (type 1) RTA are summarized in Table 10-2.

### TABLE 10-2 Clinical Features of Proximal and Distal Renal Tubular Acidosis

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Proximal RTA</th>
<th>Distal RTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyperphosphaturia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Urinary citrate</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Bone disease</td>
<td>Less severe</td>
<td>More severe</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>No</td>
<td>Yes (calcium phosphate)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Mild</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Potassium wasting</td>
<td>Worsened by NaHCO\textsubscript{3}</td>
<td>Improved by NaHCO\textsubscript{3}</td>
</tr>
<tr>
<td>Alkali required for treatment</td>
<td>$&gt;10$ mEq/kg/day</td>
<td>$&lt;3$ mEq/kg/day</td>
</tr>
<tr>
<td>Other defects of proximal tubular function*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reduction in plasma HCO\textsubscript{3}$^-$</td>
<td>Moderate</td>
<td>Variable (can be severe)</td>
</tr>
<tr>
<td>FeHCO\textsubscript{3} at normal plasma HCO\textsubscript{3}$^-$ concentration</td>
<td>$&gt;15%$</td>
<td>$&lt;5%$</td>
</tr>
<tr>
<td>Urine pH during acidemia</td>
<td>$&lt;5.5$</td>
<td>$&gt;6.0$</td>
</tr>
<tr>
<td>Urine pH after NH\textsubscript{4}Cl</td>
<td>$&lt;5.5$</td>
<td>$&gt;6.0$</td>
</tr>
</tbody>
</table>

Fe, fractional excretion.

*Decreased fractional reabsorption of sodium, potassium, phosphate, urate, glucose, and amino acids.

TABLE 10-2 Clinical Features of Proximal and Distal Renal Tubular Acidosis

Ammonium chloride at a dose of 535 mg/kg/day significantly decreased blood HCO\textsubscript{3}$^-$ concentration during the course of the study.\textsuperscript{85} Ammonium chloride at a dosage of 535 mg/kg/day administered to dogs over 6 days caused hyperchloremic metabolic acidosis and was associated with hypokalemia, presumably related to increased aldosterone secretion.\textsuperscript{150} In another study of dogs, NH\textsubscript{4}Cl at 200 mg/kg/day reduced urine pH to approximately 5.0 and produced mild metabolic acidosis without change in serum potassium concentration.\textsuperscript{208}

### Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors, such as acetazolamide, decrease proximal tubular reabsorption of HCO\textsubscript{3}$^-$ in the kidneys by noncompetitive inhibition of luminal and cellular carbonic anhydrase. Hypokalemia is caused by increased sodium delivery to the distal nephron and its reabsorption in exchange for potassium. As hyperchloremic metabolic acidosis develops, the filtered load of HCO\textsubscript{3}$^-$ decreases and the effect of carbonic anhydrase inhibitors on HCO\textsubscript{3}$^-$ reabsorption is limited. Acetazolamide given at 7 to 10 mg/kg three times daily causes self-limited hyperchloremic metabolic acidosis, mild to moderate hypokalemia, and mild hypocapnia in dogs.\textsuperscript{107,201} The effects of acetazolamide were greatest after 3 days of administration, and blood chemistry results stabilized after 5 days of administration.\textsuperscript{201} Acetazolamide is used most commonly in small animal practice for the treatment of glaucoma.

### Ammonium Chloride

Administration of NH\textsubscript{4}Cl is equivalent to administration of HCl because the NH\textsubscript{4}$^+$ is converted in the liver to urica and H$^+$. Ammonium chloride has been used commonly as a urinary acidifier in dogs and cats. A study of cats receiving 800 mg of NH\textsubscript{4}Cl per day as a powder or tablet showed that venous blood pH and HCO\textsubscript{3}$^-$ concentrations were decreased to values at the lower end of the normal range.\textsuperscript{211} A combination product supplying 580 mg each of NH\textsubscript{4}Cl and D,L-methionine had a more notable effect on venous blood pH and HCO\textsubscript{3}$^-$ concentrations than that observed with 800 mg of NH\textsubscript{4}Cl alone, but results were still within the reported normal range.\textsuperscript{212} In another study of cats, NH\textsubscript{4}Cl at 300 mg/kg/day did not significantly alter venous blood pH, P\textsubscript{CO$_2$} or HCO\textsubscript{3}$^-$ concentration, but 400 mg/kg/day significantly decreased blood HCO\textsubscript{3}$^-$ concentration during the course of the study.\textsuperscript{85} Ammonium chloride at a dosage of 535 mg/kg/day significantly decreased blood HCO\textsubscript{3}$^-$ concentration during the course of the study.\textsuperscript{85}
In young, growing and adult dogs, the addition of NH₄Cl to the diet leads to demineralization of bone. Chronic acid feeding has also been reported to affect bone metabolism in cats. Diets containing 3% NH₄Cl sloved growth of young cats, decreased blood pH and HCO₃⁻ concentrations, and lowered urine pH. Urinary calcium excretion increased in these cats, and bone demineralization was observed on histologic examination of caudal vertebrae. Adult cats fed 1.5% NH₄Cl for 6 months developed hyperchloremic metabolic acidosis and negative balance for calcium and potassium, but no significant changes in trabecular bone remodeling or bone mineral density were found. In one study, administration of NH₄Cl to cats fed a potassium-restricted diet resulted in hypokalemia, possibly by reducing gastrointestinal absorption of potassium. Results of these studies indicate that NH₄Cl should be used with caution and blood gases should be monitored during therapy.

**Infusion of Cationic Amino Acids**

Metabolism of cationic amino acids (e.g., lysine, arginine, histidine) results in production of H⁺ as the NH₄⁺ from these amino acids is converted to urea in the liver. For this reason, amino acid-containing fluids used in total parenteral nutrition can contribute to hyperchloremic metabolic acidosis. Other contributing factors are the presence of sulfur-containing amino acids (e.g., methionine, cysteine) in the fluid and development of hypophosphatemia during refeeding, which may reduce renal excretion of titratable acid.

**Posthypocapnic Metabolic Acidosis**

During compensation for chronic respiratory alkalosis, renal net acid excretion decreases with consequent reduction in plasma HCO₃⁻ and increase in plasma Cl⁻ concentrations. When the stimulus for hyperventilation is removed and PₐCO₂ increases, pH decreases because it requires 1 to 3 days for the kidneys to increase net acid excretion and to increase plasma HCO₃⁻ concentration. Until this occurs, a state of “posthypocapnic” metabolic acidosis exists. Recovery is spontaneous as long as sodium and phosphate are available in the diet to allow the appropriate increase in renal net acid excretion.

**Dilutional Acidosis**

Dilutional acidosis refers to a decrease in plasma HCO₃⁻ concentration that occurs when extracellular volume is expanded using an alkali-free chloride-containing solution such as 0.9% NaCl. The high chloride concentration of 0.9% NaCl and the highly resorbable nature of the chloride ion in the renal tubules contribute to the decrease in plasma HCO₃⁻ concentration and the increase in Cl⁻ concentration. Dilutional acidosis can be corrected by substitution of a solution with a lower chloride concentration (e.g., lactated Ringer’s solution, 0.45% NaCl).

**Hypoadrenocorticism**

Aldosterone increases renal tubular lumen negativity by enhancing sodium reabsorption in the collecting duct and secondarily increases hydrogen ion secretion. It also directly stimulates H⁺ secretion by increasing the activity of the luminal H⁺-ATPase pump in the medullary collecting duct. These effects allow urinary excretion of H⁺ and K⁺ when distal delivery of sodium is decreased. Deficiency of aldosterone in hypoadrenocorticism results in metabolic acidosis and hyperkalemia. Metabolic acidosis of variable severity is common in dogs with hypoadrenocorticism. In one study, low total CO₂ concentration suggesting the presence of metabolic acidosis was found in 81 of 200 (41%) dogs with hypoadrenocorticism. Treatment of hypoadrenocorticism includes volume expansion with 0.9% NaCl and replacement of deficient mineralocorticoids and glucocorticoids.

**DISORDERS ASSOCIATED WITH AN INCREASED ANION GAP**

**Ethylene Glycol Ingestion**

Ethylene glycol (EG) is an organic solvent (molecular mass, 62 Da) used in commercial antifreeze solutions. Ingestion of antifreeze by dogs and cats is a common cause of oliguric acute renal failure in small animal practice, and mortality exceeds 80% in affected animals. EG itself is not toxic, but it is converted in the liver to several metabolites that cause severe metabolic acidosis and acute renal failure (Fig. 10-4). It is rapidly absorbed from the gastrointestinal tract and is undetectable in plasma of dogs 48 hours after administration.

**Pathophysiology**

EG is first metabolized in the liver to glycoaldehyde by alcohol dehydrogenase. Glycoaldehyde uncouples...
oxidative phosphorylation and may contribute to neurologic signs observed early in the course of intoxication. Subsequent steps in metabolism produce glycolic and glyoxylic acids. Glycolic acid is primarily responsible for the severe metabolic acidosis that occurs in animals poisoned by EG.50 Renal tubular injury results from glycoaldehyde, glycolic acid, and glyoxylic acids, and calcium oxalate crystals are deposited within renal tubules. The observation of these birefringent crystals in the presence of acute tubular necrosis confirms the diagnosis of EG intoxication.

Vomiting, polydipsia, and polyuria may occur soon after ingestion of EG, but the owners of poisoned animals often do not detect these signs. Within 12 hours of ingestion, neurologic signs (e.g., lethargy, ataxia, stupor, seizures, coma) may develop. Cardiac and pulmonary manifestations (e.g., tachypnea, tachycardia) occur 12 to 24 hours after ingestion but rarely are detected in clinical cases. Oxalate crystals may be detected in the urine as early as 3 to 6 hours after ingestion of EG.68,69 Renal failure occurs in dogs as early as 24 to 48 hours after ingestion and is manifested by anorexia, lethargy, vomiting, and oliguria or anuria.97 In cats, azotemia may develop within 12 to 24 hours after ingestion of EG.68 Unfortunately, most dogs and cats with EG poisoning are presented for veterinary attention after renal failure has already developed.

A severe normochloremic (i.e., high anion gap) metabolic acidosis occurs within 3 hours of EG ingestion and persists for at least 24 hours.68,69,97,227 Serum hyperosmolality and osmolar gap peak 1 to 6 hours after ingestion and persist for 12 to 24 hours,68,69,97 but the osmolar gap may be normal in animals presented later in the course of the disease.227 Activated charcoal preparations containing propylene glycol and glycerol can increase osmolality and osmolar gap, and potentially complicate the diagnosis of EG intoxication. Measured serum osmolality peaked at 4 hours (353 mOsm/kg), osmolar gap at 6 hours (52 mOsm/kg), and serum lactate concentration at 4 hours (4.5 mmol/L) after administration of 4 g/kg of an activated charcoal preparation containing propylene glycol and glycerol.35 Results returned to baseline 24 hours after administration of the activated charcoal preparation.

Calcium oxalate dihydrate crystals (“Maltese cross” or “envelope” forms) may be observed in the urine, but calcium oxalate monohydrate crystals (“picket fence” or “dumbbell” forms) are observed more commonly. Calcium oxalate dihydrate crystals occasionally are found in the urine of normal dogs and cats, whereas calcium oxalate monohydrate crystals rarely are seen except in animals that have ingested EG (Fig. 10-5).68,227 Crystals previously referred to as hippurates actually are calcium oxalate monohydrate crystals.134,226 Other laboratory findings include azotemia, isosthenuria, hypocalcemia, hyperphosphatemia, and hyperglycemia.227 Hyperphosphatemia observed very early in the course of EG intoxication (3 to 12 hours after ingestion) probably is the result of the high phosphorus content of rust-retardant antifreeze preparations.57,69 Hyperechogenicity of the renal cortex is observed on renal ultrasonography as early as 5 hours after ingestion of EG.2

### Treatment

The response to treatment depends on the amount of EG ingested and the amount of time that elapses before treatment. In early studies, dogs that ingested less than 10 mL/kg EG were saved if treated within 2 to 4 hours of ingestion,17,175,205 and cats survived up to 6 mL/kg EG if treated within 4 hours.187 Treatment consists of inducing vomiting with apomorphine or performing gastric lavage with activated charcoal if ingestion has been recent (<8 hours before presentation). Severe hypocalcemia is corrected with calcium gluconate, and NaHCO₃ is administered to combat metabolic acidosis. A NaHCO₃ dosage of 1 to 2 mEq/kg may be used empirically. Calcium gluconate and NaHCO₃ must not be given simultaneously because calcium carbonate crystals form, and the solution becomes turbid. Attempts to stimulate urine production with furosemide (2 to 4 mg/kg) or mannitol (1 g/kg) usually are futile.

Alcohol dehydrogenase has greater affinity for ethanol than EG. For this reason, 20% ethanol has been administered intravenously to affected dogs at a dosage of 5.5 mL/kg every 4 hours for five treatments and then every 6 hours for four additional treatments.96 Cats are treated with 20% ethanol at a dosage of 5 mL/kg every 6 hours for five treatments and then every 8 hours for four additional treatments. This treatment is unlikely to be of benefit if more than 12 to 24 hours have elapsed since ingestion of EG. Fomepizole (4-methylpyrazole) is a pharmacologic inhibitor of alcohol dehydrogenase that can be used to treat dogs with EG toxicosis.57,69 In dogs, it is superior to ethanol because it does not cause central nervous system (CNS) depression, but it must be administered within 8 hours of EG ingestion. The dosage of fomepizole used in dogs with EG intoxication is 20 mg/kg intravenously, followed by 15 mg/kg intravenously at 12 and 24 hours and 5 mg/kg intravenously at 36 hours.57,67,69 Unfortunately, fomepizole was not efficacious in EG-intoxicated cats unless administered at the same time as the EG was consumed.68 A study to investigate the difference in efficacy of fomepizole between dogs and cats found that the percentage inhibition of canine and feline alcohol dehydrogenase was similar when the concentration of fomepizole applied to feline liver homogenates was 6 times higher than that applied to canine liver homogenates.58 When cats that received lethal doses of EG were treated within 3 hours of ingestion using 125 mg/kg fomepizole followed by 31 mg/kg at 12, 24, and 36 hours, 5 of 6 survived.59 One cat developed acute renal failure but recovered. Cats treated with this high
dosage of fomepizole developed mild sedation, but no biochemical evidence of toxicity was identified.

Thiamine promotes conversion of glyoxylate to glycine, and pyridoxine promotes conversion of glyoxylate to \(\alpha\)-hydroxy-\(\beta\)-ketoadipate (see Fig. 10-4). These vitamins may be administered to promote alternative pathways of glyoxylate metabolism, but efficacy has not been demonstrated for such treatment. In one study, all nonazotemic dogs treated with fomepizole within 2 to 8.5 hours after EG ingestion survived, whereas only 1 of 21 azotemic dogs treated 8.5 to 38 hours after ingestion survived.\(^5\,\text{7}\,\text{,}2\text{2}\text{7}\)

Peritoneal dialysis or hemodialysis is necessary if the animal has anuric or oliguric renal failure at the time of presentation. Early dialysis may also be helpful to remove toxic intermediate metabolites. Despite dialysis, affected dogs may progress to end-stage renal disease and become dependent on dialysis. The prognosis for survival in adult dogs and cats with anuric or oliguric acute renal failure caused by EG intoxication is unfortunately very poor.\(^5\,\text{7}\,\text{,}2\text{2}\text{7}\)

**Salicylate Intoxication**

Aspirin (acetylsalicylic acid) is hydrolyzed to salicylic acid (pK\(_a\) = 3.0) in the liver. Salicylate intoxication is uncommon in small animal practice and is an example of a mixed acid-base disturbance characterized by metabolic acidosis and respiratory alkalosis. Salicylate intoxication in anesthetized, spontaneously breathing dogs resulted in a mixed respiratory alkalosis and metabolic acidosis.\(^2\text{1}\text{8}\)

The stimulation of ventilation is caused by a direct effect of salicylate on the medullary respiratory center. Salicylate also uncouples oxidative phosphorylation in mitochondria, and the associated disturbances in carbohydrate metabolism lead to metabolic acidosis characterized by an increased anion gap associated with accumulation of lactic acid, ketoacids, and other organic acids. Salicylate usually makes a minor contribution to the observed increase in unmeasured anions.

Gastric lavage with activated charcoal should be performed if ingestion occurred less than 6 to 12 hours before admission. Administration of NaHCO\(_3\) promotes removal of salicylate from tissues and enhances its urinary excretion by the mechanism of diffusion trapping. Alkalinization of ECF and urine increases the proportion of drug present in the ionized form and thus favors diffusion of more nonionized salicylic acid from cells into ECF and urine, where it can be trapped as the poorly diffusible ionized form. An attempt should be made to maintain urine pH above 7.5 during alkaline diuresis with NaHCO\(_3\), especially if metabolic acidosis is the predominant acid-base disturbance. Alkalinization should be carried out with caution, if at all, when respiratory alkalosis is the predominant acid-base disturbance. Glucose infusion is recommended to prevent reduction in CNS glucose concentration. Hypokalemia may develop during treatment as a result of NaHCO\(_3\) administration and diuresis, and parenteral fluids should be supplemented with potassium as needed.

**Metaldehyde Intoxication**

Metaldehyde is a tetramer of acetaldehyde used as a snail and slug bait that can cause seizures and hyperthermia in dogs that ingest it.\(^2\text{4}\text{1}\)

It is hydrolyzed to acetaldehyde in the stomach, which then is absorbed and metabolized to acetic acid (pK\(_a\) = 4.75). Acidemia was present in 6 of 11 intoxicated dogs in which arterial blood gas analysis was performed. Three dogs had metabolic acidosis and three had mixed acid-base disturbances that were not further characterized. Conversion of acetaldehyde to acetic acid could explain development of metabolic acidosis, and ventilatory disturbances associated with generalized seizures (either respiratory alkalosis or acidosis) could have contributed to development of mixed acid-base disturbances.
disorders. With supportive care, blood gas abnormalities resolve within 24 to 48 hours.

**Diabetic Ketoacidosis**

**Pathophysiology**

Overproduction of acetoacetic acid (pK_a = 3.58) and β-hydroxybutyrate (pK_a = 4.70) by the liver occurs in diabetes mellitus because of a deficiency of insulin and relative excess of glucagon. An increase in glucagon and a decrease in insulin shift the liver from its normal role in esterification of fatty acids into triglycerides to β-oxidation of fatty acids into ketoacids. At the normal pH of ECF (7.40), these organic acids are completely dissociated, and the hydrogen ions that are released titrate HCO_3^- and other body buffers. Acetone is formed by the nonenzymatic decarboxylation of acetoacetate and does not contribute additional fixed acid. The pathophysiology and treatment of diabetic ketoacidosis are discussed in detail in Chapter 20.

Metabolic acidosis is common in dogs and cats with diabetic ketoacidosis. In one series, mean plasma HCO_3^- concentration in 72 dogs with diabetic ketoacidosis was approximately 11 mEq/L at the time of diagnosis with a range of 4 to 20 mEq/L, whereas the mean HCO_3^- concentration in 20 affected cats was 13 mEq/L with a range of 8 to 22 mEq/L. In an early study of dogs with diabetes mellitus, mean plasma HCO_3^- concentration was 13.7 mEq/L in eight survivors (range, 9.3 to 21.0 mEq/L) and 18.1 mEq/L in five nonsurvivors (range, 13.4 to 30.2 mEq/L). In another study of dogs with diabetic ketoacidosis, mean arterial pH and HCO_3^- concentration were 7.201 (range, 6.978 to 7.395) and 11.1 mEq/L (range, 4.1 to 19.7 mEq/L) before treatment and 7.407 ± 0.053 and 18.2 ± 0.7 mEq/L 24 hours after treatment. Only three dogs (those with pH < 7.1) received sodium bicarbonate treatment. Metabolic acidosis with median pH of 7.14 (range, 7.04 to 7.24) and HCO_3^- concentration of 10 mEq/L (range, 6 to 15 mEq/L) was found in 25 of 33 cats evaluated by venous blood gas analysis in a survey of cats with diabetic ketoacidosis. Cats with HCO_3^- concentrations below 14 mEq/L received bicarbonate supplementation of their fluids. In another series of diabetic cats, median total CO_2 was 13 mEq/L in ketoacidotic cats and 15 mEq/L in nonketoacidotic cats. In a study of 116 dogs with diabetes mellitus, 43 (37%) had diabetic ketoacidosis with median venous blood pH of 7.228 (range, 6.979 to 7.374) and median bicarbonate concentration of 10.1 mEq/L (range, 4.0 to 19.3 mEq/L). In a study of 127 dogs with ketoacidosis, acid-base status at presentation had substantial impact on outcome. Nonsurvivors had lower venous pH and larger base deficits, and for each unit improvement in base deficit there was a 9% increase in likelihood of discharge from the hospital.

The nitroprusside reagent (e.g., Acetest, Bayer, Tarrytown, N.Y.) detects only ketone (–C=O) groups (e.g., acetoacetate, acetone). The concentration of β-hydroxybutyrate typically exceeds that of acetoacetate in uncontrolled diabetic ketoacidosis, and the dipstick reaction underestimates the degree of ketonuria. This problem can be overcome by adding a few drops of hydrogen peroxide to urine, which nonenzymatically converts β-hydroxybutyrate to acetoacetate. When insulin is administered and metabolism of ketones proceeds, there is a shift toward acetoacetate, and the dipstick reaction transiently becomes more strongly positive. This possibility should be recognized by the clinician and should not cause concern. In a study of 116 diabetic dogs (of which 88 had not previously received insulin), all ketotic and ketoacidotic dogs and 21 of 32 (66%) "nonketotic" dogs (i.e., negative urine dipstick test for ketones) had abnormally high serum β-hydroxybutyrate concentrations (>0.15 mmol/L) at presentation. Although not as readily available, measurement of plasma β-hydroxybutyrate concentrations is more valuable than use of dipstick tests in the characterization of ketonemia in diabetic dogs and cats. The increase in unmeasured anions (as reflected in the anion gap) gives a rough estimate of the concentration of ketoanions in serum. However, this estimate is inaccurate if lactic acidosis develops because lactate also is an unmeasured anion. In one study of diabetic dogs, however, acidosis was correlated primarily with serum ketone concentration, and not with serum lactate concentration.

To some extent, the anions of these ketoacids are excreted in urine along with sodium and potassium for electroneutrality. These organic anions are lost from the body and cannot be metabolized to HCO_3^- after correction of diabetic ketoacidosis with insulin therapy. Their loss thus contributes to depletion of body buffer and cation stores. Osmotic diuresis is induced by hyperglycemia and also contributes to the whole-body cation deficit. The extent of impairment in renal function may determine whether patients with diabetic ketoacidosis have an increased anion gap metabolic acidosis or hyperchloremic metabolic acidosis at the time of presentation. Patients with severe volume depletion have an increased anion gap because of retention of ketoanions, whereas those without volume depletion have hyperchloremia as a result of increased urinary excretion of the sodium and potassium salts of ketoanions and retention of chloride.

**Treatment**

The best treatment for the acidosis of uncontrolled diabetes mellitus is fluid therapy and insulin. Insulin administration allows glucose use by skeletal muscle and adipose tissue, decreases hepatic glucose production, prevents lipolysis and ketogenesis, and permits peripheral metabolism of ketoacids. Several regimens for administration of insulin to ketoacidotic dogs and cats have been...
The metabolic acidosis of chronic renal failure is usually mild to moderate in severity (plasma HCO$_3^-$ concentration, 12 to 15 mEq/L) and may be hyperchloremic early in the course of the disease process. Later in the course of the disease, the anion gap increases because of retention of phosphates, sulfates, and organic anions. Acid-base status is usually well preserved in chronic renal failure until GFR decreases to 10% to 20% of normal. In retrospective studies of small animal patients with chronic renal failure, plasma HCO$_3^-$ concentrations were less than 16 mEq/L in 40% of dogs with chronic renal failure caused by amyloidosis and less than 15 mEq/L in 63% of cats with chronic renal failure of various causes. A high anion gap was observed in 43% of affected dogs (>25 mEq/L) and in 19% of affected cats (>35 mEq/L) in these studies. In acute renal failure, there has been insufficient time for the kidneys to adapt to the disease state, and the metabolic acidosis of acute renal failure is usually more severe than that observed in chronic renal failure. Complications such as sepsis and marked tissue catabolism may contribute to the severity of metabolic acidosis in acute renal failure.

Delivery of HCO$_3^-$ from the proximal tubules to the distal nephron is increased in chronic renal failure. In dogs with experimentally induced unilateral renal disease, renal HCO$_3^-$ reabsorption was not different in the diseased and control kidneys, but bicarbonaturia developed when the normal kidney was removed, and the contralateral diseased kidney was forced to function in a uremic environment. The osmotic diuresis characteristic of uremia may thus contribute to the increased delivery of HCO$_3^-$ to the distal tubules. Increased parathyroid hormone concentration as a result of renal secondary hyperparathyroidism does not seem to have important adverse effects on HCO$_3^-$ reabsorption in experimentally induced
renal disease in dogs. The ability to lower urine pH maximally is preserved in chronic renal failure.

The main method by which the diseased kidney responds to chronic retention of fixed acid is by enhanced renal ammoniagenesis. Total ammonium excretion decreases during progressive chronic renal disease, but ammonium excretion is observed to be markedly increased when expressed per 100 mL GFR or per remnant nephron. On a per nephron basis, the diseased kidney can increase its ammonium excretion threefold to fivefold. This adaptive mechanism seems to be fully expended when the GFR decreases to less than 20% of normal. At this point, the diseased kidneys can no longer effectively cope with the daily fixed acid load, and a new steady state is established at a lower than normal plasma HCO\textsubscript{3}\textsuperscript{−} concentration. The relatively mild decrease in plasma HCO\textsubscript{3}\textsuperscript{−} concentration that is observed in chronic renal failure has been attributed to the contribution of the large reservoir of buffer (e.g., calcium carbonate) in bone. However, the capacity of the skeleton to buffer the amount of acid that accumulates in long-standing chronic renal failure has been questioned. The decrease in total ammonium excretion that occurs in chronic renal failure may be counterbalanced by decreased urinary excretion of organic anions (e.g., citrate, lactate, pyruvate, ketoanions). Metabolism of these retained organic anions would result in a net gain of HCO\textsubscript{3}\textsuperscript{−} that would offset the decreased excretion of H\textsuperscript{+} in the form of NH\textsubscript{4}\textsuperscript{+}.

The amount of phosphate buffer available in urine in chronic renal failure is relatively fixed and likely to be at its maximum because of hyperphosphatemia and the effects of increased plasma parathyroid hormone concentration. Furthermore, phosphorus binders and dietary phosphorus restriction are commonly used to treat chronic renal failure and may limit the amount of phosphate that can contribute to titratable acidity. When expressed on a per nephron basis, however, titratable acidity is increased in chronic renal failure.

### Treatment

Whether to treat well-compensated mild to moderate metabolic acidosis in adult patients with chronic renal failure is controversial. The potential benefits of such treatment include minimizing potential depletion of bone buffers, preventing the catabolic effects of uremic acidosis on muscle protein, preventing tubulointerstitial damage resulting from complement activation by ammonia, and improving the patient’s ability to combat a superimposed acidotic crisis (e.g., acute diarrhea). Thus, treatment with oral NaHCO\textsubscript{3} at a dosage of 0.5 to 1.0 mEq/kg/day or an amount sufficient to maintain plasma HCO\textsubscript{3}\textsuperscript{−} concentration at 15 mEq/L or above is reasonable if the patient can tolerate the associated sodium load. One teaspoon of baking soda contains 5 g NaHCO\textsubscript{3} (1.3 g of which is sodium). An advantage of using calcium carbonate (e.g., Tums [GlaxoSmithKline, Brentford, UK], Os-Cal [GlaxoSmithKline]) as a phosphorus binder in chronic renal failure is that this compound can serve as both a source of alkali and a source of calcium, if small amounts of calcitriol (2 to 3 ng/kg/day) are also provided. The patient should be monitored for development of hypercalcemia when calcium carbonate and calcitriol are administered concurrently. Potassium and sodium citrate should not be used for alkali therapy in chronic renal failure patients that also are being treated with aluminum-containing phosphorus binders (e.g., aluminum hydroxide, aluminum carbonate) because citrate can increase aluminum absorption from the gastrointestinal tract in this clinical setting.

### Lactic Acidosis

Lactic acidosis is characterized by an accumulation of lactate in body fluids and a plasma lactate concentration greater than 5 mEq/L. The pK\textsubscript{\textsuperscript{a}} of lactic acid is 3.86, and it is completely dissociated at the normal pH of ECF (7.40). Lactic acidosis has been divided into two categories (Box 10-2). In type A (hypoxic) lactic acidosis, mitochondrial function is normal but O\textsubscript{2} delivery to tissues is inadequate. In type B (nonhypoxic) lactic acidosis, there is adequate O\textsubscript{2} delivery to tissues but defective mitochondrial oxidative function and abnormal carbohydrate metabolism. Inborn errors of metabolism affecting gluconeogenesis and mitochondrial oxidative function are documented to cause type B lactic acidosis in humans. Defects in mitochondrial oxidative function are called mitochondrial myopathies and are caused by hereditary defects in specific mitochondrial enzyme systems. A number of case reports suggest that similar defects occur in dogs.

Pyruvate dehydrogenase deficiency is suspected to occur in clumber spaniels. This discussion focuses on type A (hypoxic) lactic acidosis.

### Normal Physiology

Lactate is a metabolic end product. Its production allows regeneration of cytosolic nicotinamide adenine dinucleotide (NAD\textsuperscript{+}) during anaerobic metabolism, and its ultimate fate is reoxidation back to pyruvate:

\[ \text{CH}_3\text{COCO}_2^- + \text{NADH} + \text{H}^+ \xrightarrow{\text{lactate dehydrogenase}} \text{CH}_3\text{CHOHCO}_2^- + \text{NAD}^+ \]  

The equilibrium of this reaction is far to the right, and the normal ratio of lactate to pyruvate is 10:1. The main determinants of cytosolic lactate concentration are the...
concentration of pyruvate and the NADH/NAD\(^+\) ratio, both of which are affected by mitochondrial oxidative function.

Pyruvate is produced in the cytosol by anaerobic glycolysis (Embden-Meyerhof pathway). Under aerobic conditions, NADH is oxidized to NAD\(^+\) in the mitochondria and pyruvate enters the mitochondria for conversion to acetylcoenzyme A (CoA) and use in the tricarboxylic acid (Krebs) cycle, or it is converted to oxaloacetate and used for gluconeogenesis in the liver and renal cortex. Under anaerobic conditions (e.g., tissue hypoxia), oxidative pathways in the mitochondria are disrupted, and NAD\(^+\) must be replenished by reduction of pyruvate to lactate in the cytosol. Thus, lactate accumulation is the price to be paid for maintaining energy production under anaerobic conditions.

At rest, skin, red cells, brain, skeletal muscle, and gut all produce lactate. During tissue hypoxia, skeletal muscle and gut become the major producers of lactate. The liver and kidneys are the main consumers of lactate, using it for gluconeogenesis (primarily in the liver) or oxidizing it to CO\(_2\) and water. Protons are consumed when lactate is metabolized:

\[
2\text{CH}_3\text{CHOHCOO}^- + 2\text{H}^+ \rightarrow \text{C}_6\text{H}_{12}\text{O}_6
\]

Oxidative metabolism

\[
\text{CH}_3\text{CHOHCOO}^- + \text{H}^+ + 3\text{O}_2 \rightarrow 3\text{CO}_2 + 3\text{H}_2\text{O}
\]

Both of these reactions require normal mitochondrial oxidative function. The protons are consumed when adenosine triphosphate (ATP) is synthesized from adenosine diphosphate (ADP) and when NADH is oxidized to NAD\(^+\) in the mitochondria.\(^{136,144}\) Protons are released by hydrolysis of ATP to ADP and by reduction of NAD\(^+\) to NADH, reactions that occur mainly in the cytosol. The protons do not arise from dissociation of lactic acid because the anion lactate is the predominant metabolite at normal hepatocyte pH\(_i\) (pH\(_i\) = 7.00 to 7.20). Thus, lactic acidosis reflects the imbalance between ATP hydrolysis and synthesis and between reduction and oxidation of NAD\(^+\). The protons produced during anaerobic glycolysis are buffered by bicarbonate and nonbicarbonate buffers. Protons are consumed and the buffers replenished when lactate is metabolized to glucose or oxidized to CO\(_2\) and water.

**Pathophysiology**

Lactic acidosis occurs when production of lactate by muscle and gut exceeds its use by liver and kidneys. Both pathways of lactate use depend on intact mitochondrial oxidative function, and clinical settings characterized by tissue hypoxia are the most common causes of lactic acidosis (see Box 10-2). Hepatic uptake of lactate is decreased when arterial PO\(_2\) decreases to approximately 30 mm Hg.\(^{225}\) Severe acidosis further impairs hepatic uptake of lactate, and the liver eventually becomes a producer rather than a consumer of lactate.\(^{140}\)

In an experimental model of hypoxic lactic acidosis (type A) induced by ventilating dogs with 8% O\(_2\), lactate concentration was more than 5 mEq/L, pH was less than 7.2, HCO\(_3^-\) concentration was less than 12 mEq/L, PO\(_2\) was less than 30 mm Hg, and hepatocyte pH\(_i\) was less than 7.00.\(^{11}\) When a similar degree of acidosis was created by infusing lactic acid into dogs with normal PO\(_2\), hepatocyte pH\(_i\) was less than 7.03.\(^{225}\) These findings led to the hypothesis that the liver has the capacity to convert lactate into glucose via gluconeogenesis, an ability that is lost when arterial oxygenation is decreased.\(^{140}\)

**BOX 10-2** Causes of L-Lactic Acidosis*

<table>
<thead>
<tr>
<th>Type A: Hypoxic</th>
<th>Type B: Nonhypoxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased oxygen demand</td>
<td>Drugs and toxins</td>
</tr>
<tr>
<td>Severe exercise</td>
<td>Phenformin</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Decreased oxygen availability</td>
<td>Ethylene glycol</td>
</tr>
<tr>
<td>Reduced tissue perfusion</td>
<td>Many others(^{144})</td>
</tr>
<tr>
<td>Cardiac arrest, cardiopulmonary resuscitation</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Shock</td>
<td>Liver failure</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>Neoplasia (e.g., lymphosarcoma)</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Low cardiac output</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Reduced arterial oxygen content</td>
<td>Hereditary defects</td>
</tr>
<tr>
<td>Hypoxemia (PO(_2) (&lt;) 30 mm Hg)</td>
<td>Mitochondrial myopathies</td>
</tr>
<tr>
<td>Extremely severe anemia (packed cell volume &lt;10%)</td>
<td>Defects in gluconeogenesis</td>
</tr>
</tbody>
</table>

*D-Lactic acidosis occurs with short bowel syndrome in humans and has been reported in a cat with intestinal bacterial overgrowth secondary to pancreatic insufficiency.\(^{184}\) It also has been observed in cats with diabetic ketoacidosis\(^{47}\) and in those fed propylene glycol.\(^{45,46}\)
pH$_i$ remained greater than 7.00, and hepatic extraction of lactate (as a percentage of the delivered load) was approximately three times higher than that observed in the hypoxic animals. Hypoxemia reduces hepatic O$_2$ uptake, and hepatocyte pH$_i$ decreases, presumably as a result of CO$_2$ accumulation within cells. This study demonstrated that impaired hepatic extraction of lactate is related to decreased hepatic O$_2$ uptake and pH$_i$ but not to arterial pH. During severe hypoxia, increased lactate production by gut and muscle and decreased hepatic extraction of lactate lead to progressive lactic acidosis. Impaired hepatic extraction of lactate and increased splanchnic production also contribute to the lactic acidosis of sepsis in dogs.\textsuperscript{48}

**Clinical Features**

Lactic acidosis may occur in several clinical settings, especially those associated with poor perfusion and tissue hypoxia (e.g., cardiac arrest and cardiopulmonary resuscitation, shock, left ventricular failure). The clinician should strongly consider the possibility of lactic acidosis in such settings (see Box 10-2). Usually, lactic acidosis results from accumulation of the L isomer of lactate. D-Lactic acidosis, characterized by the accumulation of the D isomer, is rare but has been reported in human patients with “short-bowel syndrome” in whom gut bacteria metabolize glucose to D-lactate. Increased concentrations of D-lactate have been observed in cats fed propylene glycol\textsuperscript{45,46} and in cats with diabetic ketoacidosis, possibly as a result of hepatic ketone metabolism.\textsuperscript{47} Severe D-lactic acidosis has been documented in a cat with pancreatic insufficiency, likely as a consequence of intestinal bacterial overgrowth.\textsuperscript{184}

Lactic acidosis should be suspected whenever there is an unexplained increase in unmeasured anions (i.e., an unexplained increase in the anion gap). Confirmation requires measurement of plasma lactate concentration, which has not been performed commonly in small animal practice. Care should be taken to prevent vascular stasis when collecting venous blood for lactate determinations, and blood samples should be centrifuged immediately after collection to prevent a spurious increase in lactate concentration related to anaerobic glycolysis by red cells. Lactate concentrations in dogs have been reported in many experimental studies.\textsuperscript{9} From results of these studies, normal plasma lactate concentrations in dogs are expected to be less than 2 mEq/L. Control plasma lactate concentrations in cats were 1.46 mEq/L in one study.\textsuperscript{13} In an experimental model of hemorrhagic shock in dogs, plasma lactate concentration increased from 1.5 to 5.5 mEq/L but did not completely account for the observed increases in anion gap and strong ion gap.\textsuperscript{30} Other organic anions (especially acetate and citrate) also contributed to the changes in the anion gap and strong ion gap.

Racing caused venous lactate concentrations in greyhounds to increase from 0.57 to 28.93 mEq/L, but lactate concentrations returned to 0.53 mEq/L 3 hours after exercise.\textsuperscript{119} Arterial pH decreased from 7.365 to 6.997 and returned to 7.372 3 hours after exercise, and HCO$_3^-$ concentration decreased from 21.1 to 3.1 mEq/L and returned to 20.5 mEq/L 3 hours after exercise. Plasma potassium concentration does not increase in response to organic acidosis as it does in acute mineral acidosis.\textsuperscript{6} In the racing greyhounds, there was no change in plasma potassium concentration despite severe lactic acidosis.

**Cardiac Arrest and Cardiopulmonary Resuscitation**

Oxygen delivery to, and CO$_2$ removal from, tissues are dependent on adequate tissue perfusion. Cardiac arrest is an extreme example of impaired tissue perfusion. During cardiopulmonary resuscitation (CPR), reduced tissue perfusion and reduced O$_2$ delivery cause anaerobic metabolism and lactic acidosis. In dogs, lactate concentrations increased linearly during the time between cardiac arrest and the onset of CPR.\textsuperscript{38} Lactate concentrations increased progressively during closed-chest CPR in dogs\textsuperscript{39} and remained stable but did not decrease during 30 minutes of open-chest CPR.\textsuperscript{38} In this model, closed-chest CPR did not provide adequate tissue perfusion and O$_2$ delivery to halt anaerobic metabolism.

During CPR, arterial blood gases reflect alveolar-arterial gas exchange, whereas mixed venous blood gases reflect tissue acid-base status and oxygenation.\textsuperscript{154} Respiratory alkalosis develops in arterial blood as a result of mechanical ventilation, whereas respiratory acidosis develops in venous blood because of poor tissue perfusion and impaired transport of accumulated CO$_2$ to the lungs. In one study of human patients undergoing CPR, average arterial pH was 7.41, whereas average mixed venous pH was 7.15.\textsuperscript{237} Arterial P$_{CO_2}$ averaged 32 mm Hg and mixed venous P$_{CO_2}$ was 74 mm Hg, whereas arterial and venous HCO$_3^-$ concentrations were similar.

Closed-chest CPR, initiated after 6 minutes of cardiac arrest, was studied in dogs.\textsuperscript{204} Sodium bicarbonate (2 mEq/kg) was administered after 20 minutes of cardiac arrest. Administration of NaHCO$_3$ increased both arterial and venous pH. Before NaHCO$_3$, arterial P$_{CO_2}$ was approximately 40 mm Hg, and with CPR it decreased to 20 mm Hg as a result of mechanical ventilation. After NaHCO$_3$, arterial P$_{CO_2}$ increased to 30 mm Hg. Venous P$_{CO_2}$ was nearly 50 mm Hg, and it slowly increased during 30 minutes of cardiac arrest to 60 mm Hg in untreated dogs. Bicarbonate treatment caused venous P$_{CO_2}$ to increase transiently to 100 mm Hg, and it decreased to 70 mm Hg 10 minutes after NaHCO$_3$ administration. The pH of CSF was not changed by NaHCO$_3$ administration.

The normal arteriovenous pH gradient in dogs is 0.01 to 0.04.\textsuperscript{8,20,152} Reduced cardiac output increases arteriovenous pH and P$_{CO_2}$ gradients as a result of arterial
hypocapnia and venous hypercapnia. The ventilation-to-perfusion ratio is increased because of decreased pulmonary blood flow, accounting for the observed arterial hypocapnia. Venous hypercapnia results from anaerobic metabolism and a greater than normal addition of CO₂ to venous blood from hypoperfused tissues and diminished CO₂ excretion in the lungs because of pulmonary hypoperfusion. These increases in arteriovenous pH and P_CO₂ gradients occur only if pulmonary ventilation continues. Respiratory arrest abolishes arteriovenous pH and P_CO₂ gradients. In summary, arterial P_CO₂ is not an accurate reflection of CO₂ removal from tissues during CPR, and analysis of mixed venous P_CO₂ is recommended.

During CPR and ventilation with 100% O₂, arterial PO₂ may be normal, but tissue perfusion is low (20% to 25% of normal). After NaHCO₃ administration, additional CO₂ is produced, and venous hypercapnia persists if ventilation is inadequate. Improving tissue perfusion is much more important during CPR than is NaHCO₃ administration. Effective cardiac compression and adequate perfusion allow delivery of O₂ to and removal of CO₂ from tissues. Conversely, tissue acidosis is aggravated and pHᵢ is decreased by NaHCO₃ administration if the CO₂ generated cannot be removed from the tissues by the lungs. The increase in tissue CO₂ decreases pHᵢ because CO₂ diffuses more rapidly into cells than does the charged HCO₃⁻, thereby lowering the intracellular HCO₃⁻/P_CO₂ ratio. Intracellular acidosis of the myocardium leads to impaired cardiac contractility, decreased cardiac output, and aggravation of lactic acidosis. Thus, the main goals of CPR are to provide adequate tissue perfusion by effective cardiac compression and to ventilate the patient with 100% O₂. In one study of short (5 minutes) and prolonged (15 minutes) cardiac arrest in dogs, NaHCO₃ administration improved acidosis without a significant increase in P_CO₂. The authors concluded that NaHCO₃ might be useful to reverse the acidosis of cardiac arrest if ventilation is adequate and NaHCO₃ is administered in a reasonable therapeutic window.

Lymphosarcoma in Dogs

Dogs with lymphosarcoma had higher lactate concentrations than control animals, and their lactate concentrations increased significantly 30 minutes after administration of 500 mg/kg dextrose. Blood lactate concentrations were higher before and 1 hour after infusion of lactated Ringer’s solution in dogs with lymphosarcoma as compared with control animals. Blood lactate concentration returned to baseline during the second hour of the 6-hour infusion. The authors concluded that dogs with stage III or IV lymphosarcoma might have abnormal carbohydrate metabolism and a transient inability to handle lactate loads. Tumors may produce increased amounts of lactate as a result of excessive anaerobic metabolism and possibly as a result of less than normal hepatic extraction of lactate. Induction of remission with doxorubicin chemotherapy did not improve hyperlactatemia in dogs with lymphosarcoma.

Treatment

The outcome of lactic acidosis depends on the severity and reversibility of the underlying disease process responsible for the acid-base disturbance. If treatment of lactic acidosis is to be successful, prompt diagnosis and correction of the underlying disease state are crucial. Tissue perfusion and oxygen delivery should be improved by aggressive fluid therapy to expand ECFV. Ventilation with O₂ should be considered if the patient’s spontaneous ventilation is inadequate. Infections should be treated with appropriate antimicrobial agents, and cardiac output should be improved, if necessary, by administration of inotropic agents. If the underlying disease cannot be corrected, the prognosis for patients with lactic acidosis is very poor. If the underlying disease can be corrected, the accumulated lactate is metabolized, yielding an equivalent amount of HCO₃⁻, and the acidosis is reversed.

When the pH of the patient’s blood decreases to below 7.1 to 7.2, administration of alkali is justified to prevent the detrimental effects of severe acidosis on the cardiovascular system (e.g., impaired myocardial contractility, impaired cardiovascular responsiveness to catecholamines, increased susceptibility to ventricular arrhythmias). Small doses of NaHCO₃ should be administered to increase the patient’s pH to 7.2. Approximately 10% to 15% of administered NaHCO₃ is converted immediately to CO₂. It is essential that ventilation increase to allow removal of accumulated CO₂ from the body. It is probably safe to administer NaHCO₃ if the patient can reasonably be expected to increase ventilation spontaneously. If not, administration of NaHCO₃ may be detrimental. In any case, NaHCO₃ should be administered slowly to minimize the increase in mixed venous P_CO₂.

The volume of distribution (Vₐ) of administered HCO₃⁻ is variable, depending on the severity of the acidosis. Thus, there is no simple way to calculate the dosage of NaHCO₃ required to increase the pH to 7.2. Volumes of distribution of 0.21 and 0.5 have been recommended for calculation of the bicarbonate space. Sodium bicarbonate should be used cautiously and only in amounts necessary to increase the pH to 7.2. It should be administered slowly over several minutes to a few hours, and at least 30 minutes should be allowed to elapse after the infusion before judging its effect.

The use of NaHCO₃ in lactic acidosis is controversial. Using the canine model of hypoxic lactic acidosis described above, affected dogs were left untreated, treated with 2.5 mEq/kg NaHCO₃, or treated with 2.5
mEq/kg 1 M NaCl. Animals treated with bicarbonate showed a greater decrease in pH and HCO$_3^-$ concentration and higher lactate concentration than the other groups. Gut lactate production was greater in dogs that received NaHCO$_3$ than in dogs that received NaCl, and portal vein $P_{CO_2}$ was higher in the group that received NaHCO$_3$. Arterial blood pressure and cardiac output declined in the untreated group and the group that received NaHCO$_3$ but were higher in the group that received NaCl. Increased portal vein $P_{CO_2}$ and hepatic accumulation of lactate presumably caused hepatocyte pH to decrease. The ability of the liver to extract lactate depends on adequate hepatic blood flow and normal hepatocyte pH, both of which are decreased in this model. During hypoxia ($PO_2 < 30$ mm Hg), the liver is unable to increase its lactate extraction, despite an increased load delivered from the ischemic gut. The investigators concluded that use of NaHCO$_3$ during lactic acidosis might not be effective and might even be detrimental.

Dichloroacetate (DCA) stimulates the enzyme pyruvate dehydrogenase, which converts pyruvate to acetyl CoA. In the canine model of hypoxic lactic acidosis described before, DCA was compared with NaCl. DCA increased pH and HCO$_3^-$ concentration and maintained a constant lactate concentration, whereas NaCl treatment was associated with a decrease in pH and HCO$_3^-$ concentration and an increase in lactate concentration. Hepatic lactate extraction increased with DCA, whereas liver and muscle accumulation of lactate decreased. Muscle pH$_i$ increased with DCA, but neither treatment changed arterial blood pressure or cardiac output. DCA was also studied in a cardiac arrest model in dogs. This study compared DCA, DCA and NaHCO$_3$, NaHCO$_3$, and no treatment. Bicarbonate treatment increased arterial pH, but DCA did not. DCA did not decrease lactate concentration or increase pH in either the peripheral circulation or CNS. In a canine model of hemorrhagic shock, DCA administration decreased arterial lactate concentrations but was associated with decreased cardiac stroke volume, decreased myocardial efficiency, and reduced myocardial lactate consumption. Thus, there are conflicting results regarding the usefulness of DCA in canine models of lactic acidosis.

Carbicarb is an equimolar mixture of Na$_2$CO$_3$ and NaHCO$_3$ that limits the generation of CO$_2$ during the buffering process:

$$Na_2CO_3 + H_2O + CO_2 \rightarrow 2HCO_3^- + 2Na^+$$

However, some of the HCO$_3^-$ generated from this reaction can buffer H$_2$ derived from nonbicarbonate buffers and generate CO$_2$ in the presence of carbonic anhydrase:

$$2HCO_3^- + 2H^+ \rightarrow 2H_2CO_3 \rightarrow 2H_2O + 2CO_2$$

In the canine model of hypoxic lactic acidosis described earlier, 2.5 mEq/kg Carbicarb was compared with 2.5 mEq/kg NaHCO$_3$. Arterial pH increased after administration of Carbicarb but decreased after NaHCO$_3$. Mixed venous $P_{CO_2}$ was unchanged after Carbicarb administration but increased after NaHCO$_3$. Arterial lactate concentration increased after administration of NaHCO$_3$ but stabilized after Carbicarb, whereas lactate use by the gut, muscle, and liver improved with Carbicarb but decreased after NaHCO$_3$. Hepatocyte pH$_i$ increased after Carbicarb and decreased after NaHCO$_3$. Arterial blood pressure decreased to a lesser extent and cardiac output stabilized with Carbicarb, whereas cardiac output decreased with NaHCO$_3$. It was concluded that Carbicarb had a beneficial effect on myocardial contractility. Myocardial contractility may decrease after NaHCO$_3$ administration as a result of increased venous $P_{CO_2}$ and decreased myocardial pH. Decreased cardiac output follows and leads to decreased blood flow and decreased O$_2$ delivery to gut, muscle, and liver, resulting in decreased lactate use and increased production. Carbicarb improved arterial pH without impairing myocardial contractility, presumably because it did not increase venous $P_{CO_2}$. This study suggests that Carbicarb is superior to NaHCO$_3$ in the treatment of lactic acidosis in dogs.

In another study, Carbicarb was compared with sodium bicarbonate and hypertonic saline in a canine model of hemorrhagic shock. All dogs received identical sodium loads. Groups that received Carbicarb and sodium bicarbonate experienced similar increases in serum bicarbonate, but arterial $P_{CO_2}$ increased more in bicarbonate-treated dogs than in those treated with Carbicarb. Hemodynamics, oxygen delivery, and oxygen consumption improved in all three groups, and these effects were attributed to the sodium load. Carbicarb, NaHCO$_3$, and NaCl were compared in a model of hypoxic lactic acidosis in anesthetized, mechanically ventilated dogs. Carbicarb increased arterial pH$_i$, base excess, and cardiac index without an increase in lactate. Bicarbonate increased $P_{CO_2}$, but no adverse effects of NaHCO$_3$ on hemodynamics or pH$_i$ were detected.

A sodium-free 0.3 N solution of tromethamine (THAM) is another CO$_2$-consuming alkalinizing agent that is capable of buffering both nonvolatile (H$^+$) and volatile (H$_2$CO$_3$ derived from CO$_2$) acid. THAM and sodium bicarbonate had similar buffering ability when evaluated in dogs with experimentally induced metabolic acidosis. Dogs treated with THAM did not experience the transient hypernatremia and hypercapnia that were observed in bicarbonate-treated dogs.

**TREATMENT OF METABOLIC ACIDOSIS**

The main goal in the treatment of metabolic acidosis is prompt diagnosis and specific treatment of the underlying cause of the acid-base disorder. Correction of the underlying disease that is responsible for the patient's
metabolic acidosis may be all that is necessary (e.g., fluids and insulin in diabetic ketoacidosis). In some instances, however, the underlying disease cannot be corrected (e.g., chronic renal failure), and alkali therapy must be considered.

In general, administration of NaHCO$_3$ should be reserved for clinical settings in which the patient’s blood pH is less than 7.1 to 7.2, and NaHCO$_3$ should be administered only in amounts necessary to increase the pH to 7.2. Therapy with sodium bicarbonate is less likely to be harmful in animals with simple hyperchloremic metabolic acidosis (normal anion gap) because of the absence of unmeasured organic anions. In patients with normochloremic metabolic acidosis (increased anion gap), unmeasured organic anions (e.g., ketoacids, lactate) are present and can be metabolized to HCO$_3^-$ during recovery. Administration of NaHCO$_3$ in such a setting may result in late development of metabolic alkalosis. This complication should not be serious if renal function is normal because the kidneys can excrete the excess HCO$_3^-$. Severe acidosis may lead to life-threatening cardiovascular complications (e.g., impaired cardiac contractility, impaired pressor response to catecholamines, sensitization to ventricular arrhythmias).

Thus, if blood pH is less than 7.1 to 7.2, judicious treatment with NaHCO$_3$ is justified. The aim of therapy should be to increase the patient’s pH to 7.2 ([H$^+$] = 63 nEq/L), at which point the risk of life-threatening hemodynamic complications is reduced.

For example, consider a 10-kg dog with a pH of 7.000, [H$^+$] = 100 nEq/L, [HCO$_3^-$] = 6 mEq/L, and P$_{CO_2}$ = 25 mm Hg. We assume that normal values are a pH of 7.387, [H$^+$] = 41 nEq/L, [HCO$_3^-$] = 21 mEq/L, and P$_{CO_2}$ = 36 mm Hg and that the normal compensatory respiratory response to metabolic acidosis is a 0.7-mm Hg decrement in P$_{CO_2}$ per 1.0 mEq/L decrement in [HCO$_3^-$]. How much NaHCO$_3$ must be administered to increase the dog’s pH to 7.200 ([H$^+$] = 63 nEq/L)? This may be determined using the Henderson equation:

$$[\text{H}^+] = \frac{24P_{CO_2}}{HCO_3^-}$$

Thus, the desired [HCO$_3^-$] would be 24(25)/63 or 9.5 mEq/L. If we assume that the P$_{CO_2}$ will not change. However, alveolar hyperventilation is likely to subside somewhat as the acidemia is partially corrected. If we assume that the P$_{CO_2}$ will increase to 28 mm Hg, the required [HCO$_3^-$] is 24(28)/63 or 10.7 mEq/L. Thus, we want to increase the dog’s [HCO$_3^-$] to 9.5 to 10.7 mEq/L.

We still must determine how much NaHCO$_3$ to administer. This can be calculated using the formula:

$$\text{mEq HCO}_3^- = V_d \times \text{weight (kg)} \times \text{HCO}_3^- \text{deficit}/L$$

where $V_d$ is the volume of distribution for HCO$_3^-$. However, the volume of distribution of HCO$_3^-$ varies inversely with the initial HCO$_3^-$ concentration and changes for at least 90 minutes after HCO$_3^-$ administration to dogs. In this study, dogs with chronic metabolic acidosis and initial plasma HCO$_3^-$ concentrations of 10 mEq/L were given 5 mEq/kg NaHCO$_3$ and had average $V_d$ values of 60% at 30 minutes and 76% at 90 minutes. This increase in $V_d$ represents distribution of administered HCO$_3^-$ from extracellular to intracellular sites. Bicarbonate distributes to ECF within 15 minutes and to intracellular and bone buffers within 2 to 4 hours. Thus, it is impossible to assign a single value for the $V_d$ of NaHCO$_3$ administered to dogs with metabolic acidosis. Any dosage recommendations must be considered only rough guidelines to treatment.

The dogs in this study had ECFVs equal to approximately 24.5% of body weight as measured by radiosulfate space. If we arbitrarily choose 0.5, a value approximately twice ECFV:

$$\text{HCO}_3^- (\text{mEq}) = 0.5 \times 10 \times (9.5 - 6) = 17.5 \text{ mEq}$$

Thus, the desired amount of NaHCO$_3$ is between 17.5 and 23.5 mEq. The NaHCO$_3$ should be administered over the first few hours of therapy and blood gases reevaluated before making a decision about additional alkali administration. This amount of NaHCO$_3$ represents a dose of 1.7 to 2.3 mEq/kg, and an empirical dose of 2 mEq/kg could safely have been used.

In patients with severe acidosis, any additional small reduction in plasma HCO$_3^-$ concentration represents a large percentage change and can markedly increase [H$^+$] (and reduce pH). For example, consider a normal dog with a pH of 7.387, [H$^+$] = 41 nEq/L, P$_{CO_2}$ = 36 mm Hg, and [HCO$_3^-$] = 21 mEq/L that sustains a peracute reduction in [HCO$_3^-$] of 2 mEq/L (new [HCO$_3^-$] = 19 mEq/L) before respiratory compensation can develop. The new [H$^+$] can be calculated from the Henderson equation as 24(36)/19 = 45 nEq/L (p. 7.347). This represents a 0.04-U change in pH and a 4-nEq/L change in [H$^+$]. Now consider a dog with a pH of 7.102,[H$^+$] = 79 nEq/L, P$_{CO_2}$ = 23 mm Hg, and [HCO$_3^-$] = 7 mEq/L, that sustains a peracute reduction in [HCO$_3^-$] of 2 mEq/L (new [HCO$_3^-$] = 5 mEq/L) before respiratory compensation can develop. The dog’s new [H$^+$] is 24(23)/5 = 110 nEq/L (p. 6.959). This represents a 0.14-U change in pH and a 31-nEq/L change in [H$^+$]. This change in [H$^+$] is almost eight times greater than that observed in the previous example. Thus, a small change in [HCO$_3^-]$
has a much more dramatic effect on \([H^+]\) and pH when the initial \([HCO_3^-]\) concentration is very low. For this reason, patients with very low plasma \(HCO_3^-\) concentrations and pH values less than 7.1 to 7.2 should be treated promptly with small amounts of \(NaHCO_3\) to increase their pH to the hemodynamically safe value of 7.2.

Potential complications of \(NaHCO_3\) therapy include volume overload caused by administered sodium, tetany resulting from decreased serum ionized calcium concentration caused by increased binding of calcium to plasma proteins, decreased \(O_2\) delivery to tissues because of increased affinity of hemoglobin for \(O_2\), paradoxical CNS acidosis as hyperventilation abates and \(CO_2\) diffuses into CSF, late development of alkalosis as metabolism of organic anions (e.g., ketoanions, lactate) replenishes body \(HCO_3^-\) stores, and hypokalemia as potassium ions enter and \(H^+\) ions exit intracellular fluid in response to alkalization of ECF.\textsuperscript{109}

**METABOLIC ALKALOSIS**

Metabolic alkalosis is characterized by a primary increase in plasma \(HCO_3^-\) concentration, decreased \([H^+]\), increased pH, and a secondary or adaptive increase in \(PCO_2\). Metabolic alkalosis was the third most common acid-base disturbance in dogs and cats in one study.\textsuperscript{61}

Metabolic alkalosis can be caused by loss of chloride-rich fluid from the body via either the gastrointestinal tract or kidneys or by chronic administration of alkali. In the normal animal, renal excretion of exogenously administered alkali is very efficient, and it is difficult to create metabolic alkalosis by administration of alkali unless there is some factor preventing renal \(HCO_3^-\) excretion. Most cases of metabolic alkalosis in small animal practice are caused either by vomiting of stomach contents or by administration of diuretics. In a review of 962 dogs evaluated by blood gas determinations, 20 (2%) were found to be alkalemic.\textsuperscript{194} Of these 20 dogs, 13 had metabolic alkalosis and 7 had respiratory alkalosis. Of the 13 dogs with metabolic alkalosis, 10 had a history of gastrointestinal disease. In a study of 138 dogs with gastrointestinal foreign bodies, 77.5% of which were located in the stomach or duodenum, hypochloremia (51.2%), metabolic alkalosis (45.2%), hypokalemia (25%), and hyponatremia (20.5%) were commonly observed laboratory abnormalities.\textsuperscript{22}

**CLASSIFICATION OF METABOLIC ALKALOSIS**

Patients with metabolic alkalosis may be divided into two groups.\textsuperscript{101,122,123,200,229} One group has ECFV depletion and avid renal retention of sodium and chloride. These patients respond to chloride administration and are said to have chloride-responsive metabolic alkalosis. The other group has normal or increased ECFV, and all sodium chloride ingested on a daily basis is excreted in the urine. These patients do not respond to chloride administration and are said to have chloride-resistant metabolic alkalosis.

In most instances of chloride-responsive metabolic alkalosis, the chloride concentration of the fluid lost from the body is greater than that of the ECF, so there has been a disproportionate loss of chloride. For example, the chloride concentration of gastric fluid is approximately 150 mEq/L, whereas serum chloride concentration is approximately 110 mEq/L in the dog and 120 mEq/L in the cat. Chloride-responsive metabolic alkalosis is much more common in small animal practice than is chloride-resistant metabolic alkalosis.

**DEVELOPMENT OF CHLORIDE-RESPONSIVE METABOLIC ALKALOSIS**

The pathophysiology of chloride-responsive metabolic alkalosis can be understood by considering the events associated with selective removal of gastric \(HCl\).\textsuperscript{131,132,172} Loss of \(H^+\) from the stomach is associated, milliequivalent for milliequivalent, with an increase in the concentration of \(HCO_3^-\) in ECF. Plasma \(HCO_3^-\) concentration and the filtered load of \(HCO_3^-\) in the kidneys increase. Natriuresis, kaliuresis, suppression of net acid excretion with bicarbonaturia, increased urine flow rate, and renal water loss follow, but bicarbonaturia is transient and insufficient to return plasma \(HCO_3^-\) concentration to normal.\textsuperscript{172} These events occurred without any change in the GFR in a study of dogs made alkalemic by hemofiltration and replacement of ECF with a solution containing \(HCO_3^-\) as the only anion.\textsuperscript{28} It is believed that the abatement of bicarbonaturia was caused by renal sodium avidity, engendered by the volume deficit that developed as a result of the initial natriuresis and diuresis. Renal sodium avidity is thus established and contributes to perpetuation of the alkalosis and development of a potassium deficit as long as chloride intake remains deficient. These events constitute the development phase of chloride-responsive metabolic alkalosis.

Probably the most important factors in the maintenance phase of chloride-responsive metabolic alkalosis are ECFV depletion and the chloride deficit, two factors that are difficult to separate experimentally.\textsuperscript{51,98,124,174,203} Other factors that contribute to perpetuation of metabolic alkalosis are the effects of aldosterone and the potassium deficit. Aldosterone concentration is increased by ECFV depletion and results in increased distal renal \(Na^+\cdotH^+\) and \(Na^+\cdotK^+\) exchange. This results in perpetuation of alkalosis and development of a potassium deficit. Potassium depletion leads to a transcellular shift of \(H^+\) from ECF to intracellular fluid in exchange for potassium ions. When this shift occurs in renal tubular cells, it decreases pH and enhances \(H^+\) secretion by the renal tubular cells, further aggravating
the alkalosis. Hypokalemia also stimulates renal ammoniagenesis, presumably through stimulation of glutaminase via decreased pH. The increase in renal ammonium excretion enhances renal acid excretion and contributes to increased plasma HCO$_3^-$ concentration. Hypokalemia also may decrease the GFR as a consequence of glomerular hemodynamic changes and may directly impair chloride reabsorption in the distal nephron, resulting in enhanced lumen electronegativity and facilitation of H$^+$ secretion into tubular fluid.

**RESPONSE OF THE BODY TO METABOLIC ALKALOSIS**

The body’s response to metabolic alkalosis is the reverse of its response to administration of a mineral acid such as HCl. The kidneys are more effective in excreting an alkaline load than an acid load, provided that the subject is not sodium avid and sufficient chloride is provided.

**Acute Buffer Response**

In an early study of the buffer response to alkali, nephrectomized dogs were given 20 mEq/kg NaHCO$_3$ with a resultant increase in plasma HCO$_3^-$ concentration to approximately 60 mEq/L. Of the administered HCO$_3^-$, almost one third (32%) was titrated by intracellular buffers. Of this 32%, 4% was converted to carbonic acid by H$^+$ from lactic acid released into ECF from cells. Increased pH$_i$ enhances cellular production of lactic acid by stimulation of phosphofructokinase. Approximately 2% entered red cells in exchange for chloride (so-called chloride shift), and 26% was titrated by H$^+$ released from intracellular proteins and phosphates while sodium and potassium ions entered cells to maintain electroneutrality. By comparison, intracellular buffers handle approximately 50% of a mineral acid load.

Approximately two thirds (68%) of the HCO$_3^-$ load was confined to ECF. In response to the increase in pH$_i$, plasma proteins buffered 1% of this HCO$_3^-$, that is, plasma proteins released hydrogen ions in numbers sufficient to convert 1% of the infused HCO$_3^-$ to carbonic acid. The remaining 67% was retained in the ECF compartment and contributed to the observed increase in plasma HCO$_3^-$ concentration. These buffer reactions are summarized in Figure 10-6.

**Respiratory Response to Metabolic Alkalosis**

The decrease in [H$^+$] that accompanies chronic metabolic alkalosis stimulates chemoreceptors and is responsible for the observed decrease in alveolar ventilation. Secondary or adaptive alveolar hypoventilation protects pH in the presence of increased plasma HCO$_3^-$ concentration (Fig. 10-7). A review of studies of dogs with experimentally induced metabolic alkalosis suggests that for each 1.0-mEq/L increase in plasma HCO$_3^-$ concentration, there is an adaptive 0.55- to 0.77-mm Hg increase in P$_{CO_2}$. This adaptive hypoventilation is associated with some degree of hypoxemia. Arterial PO$_2$ decreased to 60 to 70 mm Hg in dogs made alkalotic by feeding a diet with a chloride deficit and administering furosemide.

The ventilatory response to metabolic alkalosis usually is considered to be less marked than the response to metabolic acidosis (i.e., a 0.6-mm Hg increase in P$_{CO_2}$ for each 1-mEq/L increase in plasma HCO$_3^-$ concentration in metabolic alkalosis as compared with a 1.2-mm Hg decrease in P$_{CO_2}$ for each 1-mEq/L decrease in plasma HCO$_3^-$ concentration in metabolic acidosis). This view has been challenged by a study of the ventilatory response of dogs to HCl acidosis and metabolic alkalosis induced by diuretics, removal of gastric acid, or mineralocorticoid administration. The ventilatory responses to all of these experimental acid-base disturbances were not significantly different from one another, and it was concluded that an average change of 0.74 mm Hg P$_{CO_2}$ can be expected for each 1.0-mEq/L change of plasma HCO$_3^-$ concentration of metabolic origin. In one study, the respiratory compensation for metabolic alkalosis ranged from a 0.4- to 0.6-mm Hg increment in P$_{CO_2}$ for each 1-mEq/L increment in HCO$_3^-$ for

![Mechanism of buffering](image)

**Figure 10-6** Distribution of buffer response to a fixed alkaline load. (Drawing by Tim Vojt. Adapted from Pitts RF. Physiology of the kidney and body fluids, 2nd ed. Chicago: Year Book Medical, 1968: 173.)
arterial, mixed venous, and jugular venous samples in dogs made alkalotic by the administration of furosemide. As a rule, a 1-mEq/L increase in plasma HCO$_3^-$ concentration is expected to be associated with an adaptive 0.7-mm Hg increase in P$_{CO_2}$ in dogs with metabolic alkalosis.

Renal Response to Metabolic Alkalosis

In the normal animal, the kidneys rapidly and effectively excrete administered alkali. Metabolic alkalosis persists only if renal excretion of HCO$_3^-$ is impaired. This may occur if GFR is decreased (i.e., decreased filtered load of HCO$_3^-$), a continued high rate of alkali administration, or some stimulus for the kidneys to retain sodium in the presence of a relative chloride deficit. In most dogs and cats with metabolic alkalosis, a combination of renal sodium avidity and diminished chloride availability is responsible for perpetuation of the alkalosis. A potassium deficit and hypokalemia develop as the kidneys increase Na$^+$-K$^+$ exchange in the distal nephron.

When sodium, chloride, and water are removed in proportion to their concentrations in ECF, sodium avidity develops but alkalosis does not. When the sodium deficit in an alkalotic animal is repaired by infusing a fluid identical in composition to the alkalotic ECF, metabolic alkalosis is corrected by selective retention of chloride. This occurs even when the filtered load of chloride is kept constant during the infusion of fluid. Thus, both sodium avidity and decreased chloride availability seem to be necessary for the perpetuation of metabolic alkalosis.

Potassium deficiency does not cause alkalosis but rather is a result of the alkalotic state. In fact, isolated potassium deficiency in dogs leads to mild metabolic acidosis. When potassium retention is prevented but sodium chloride is supplied, alkalosis is corrected despite a persisting potassium deficit. If potassium is supplied but chloride is not, alkalosis cannot be corrected. Administration of potassium chloride leads to complete correction of both alkalosis and the potassium deficit.

The renal response to hypercapnia in metabolic alkalosis was studied in normal unanesthetized dogs made alkalotic by dietary chloride restriction and administration of ethacrynic acid. Adaptive hypercapnia was allowed to develop and then prevented by exposure to hypoxia. During development of metabolic alkalosis, serum sodium concentration remained unchanged, but serum chloride, potassium, and phosphorus concentrations decreased, and lactate and unmeasured anion (i.e., anion gap) concentrations increased. With hypercapnia, plasma HCO$_3^-$ concentration was maintained at 7.7 mEq/L above control values, whereas without hypercapnia it was maintained at 4.5 mEq/L above control values. Thus, approximately 60% of the increase in plasma HCO$_3^-$ concentration was caused by the renal response to chloride and volume depletion, whereas 40% of the increase could be attributed to adaptive hypercapnia. This response appeared to be a direct effect of P$_{CO_2}$ on renal acid excretion and HCO$_3^-$ reabsorption and was not related to any change in extracellular pH because the degree of alkalemia remained unchanged throughout the experiment. This portion of the increase in plasma HCO$_3^-$ concentration (40%) may be considered maladaptive because it contributes to a higher extracellular pH. When metabolic alkalosis persists, this indiscriminate renal response to hypercapnia results in a further increase in plasma HCO$_3^-$ concentration and abrogates the original beneficial effect of the increased plasma HCO$_3^-$ concentration on extracellular pH.
The curve back to the right.

8 hours of metabolic alkalosis and results in a shift of diphosphoglycerate concentration occurs after 6 to clinically relevant because an increase in red cell 2,3-RH release from hemoglobin. This effect probably is not sociation curve to the left (Bohr effect) and impairs oxy-

Clinical signs also may result from the accompanying potassium depletion. Signs of potassium depletion include muscle weakness of varying severity, cardiac arrhythmias, alterations in renal function (e.g., defective concentrating ability), and gastrointestinal motility disturbances (e.g., ileus). These complications are discussed in Chapter 5.

Muscle twitching may occur as a result of decreased serum ionized calcium concentration because alkalosis increases the number of negative charges on proteins, allowing more calcium ions to be bound (Fig. 10-8). Serum ionized calcium concentration decreases and may account for neuromuscular irritability by rendering the threshold potential of cells more negative (i.e., bringing the resting potential closer to the threshold potential) (Fig. 10-9). Administration of a single dose (4 mEq/kg) of sodium bicarbonate to normal cats resulted in a 10% decrease in serum ionized calcium concentration and an 8% decrease in serum total calcium concentration. These changes persisted for 3 hours, but no clinical signs were observed.

Metabolic alkalosis shifts the oxygen-hemoglobin dissocation curve to the left (Bohr effect) and impairs oxygen release from hemoglobin. This effect probably is not clinically relevant because an increase in red cell 2,3-diphosphoglycerate concentration occurs after 6 to 8 hours of metabolic alkalosis and results in a shift of the curve back to the right.

**DIAGNOSIS OF METABOLIC ALKALOSIS**

Specific clinical manifestations of metabolic alkalosis have not been reported in dogs and cats. The clinician must have a high index of suspicion for this disorder when presented with an animal having compatible clinical signs, usually chronic vomiting of stomach contents. Thus, an accurate history is the key to suspecting the diagnosis. Metabolic alkalosis also can be suspected from the results of routine serum biochemical tests. Blood gas analysis should be performed if decreased serum chloride and potassium concentrations are observed and total CO₂ content is increased. Blood gas analysis allows the clinician to determine whether primary metabolic alkalosis is present and whether the magnitude of respiratory compensation is as predicted (see earlier). The concentration of unmeasured anions (i.e., anion gap) in metabolic alkalosis may increase because of loss of hydrogen ions from nonbicarbonate buffers. The increased anion gap is primarily caused by increased numbers of negative charges on proteins and partially the result of the increase in plasma protein concentration that occurs as a consequence of ECFV depletion.

Urine pH is low during the maintenance phase of metabolic alkalosis because of enhanced distal Na⁺-H⁺ exchange and reabsorption of all filtered HCO₃⁻. However, urine pH is alkaline during development of and recovery from metabolic alkalosis. Thus, urinary pH is of little diagnostic significance in metabolic alkalosis.
Causes of Metabolic Alkalosis

Metabolic alkalosis can be caused by continuous administration of alkali, disproportionate loss of chloride (chloride-responsive alkalosis), or excessive mineralocorticoid effect (chloride-resistant alkalosis). In some instances, the mechanism of metabolic alkalosis is unknown, and these examples are classified as miscellaneous. Most dogs with gastric dilatation-volvulus have metabolic acidosis or normal blood gas values at presentation, but, uncommonly, metabolic alkalosis and hypokalemia have been reported. The causes of metabolic alkalosis are listed in Box 10-3, and the pathophysiology of the major types of metabolic alkalosis is considered further here.

Chloride-Responsive Metabolic Alkalosis

Chronic vomiting of stomach contents and administration of diuretics are the most common causes of chloride-responsive metabolic alkalosis in dogs and cats.

Administration of Alkali

Acute administration of 4 mEq/kg NaHCO₃ to normal unanesthetized cats resulted in mild increases in venous blood pH and HCO₃⁻ concentration lasting 180 minutes. A slight decrease in serum chloride concentration persisted for 30 minutes, whereas a mild increase in P₃CO₂ persisted for 60 minutes. A solution of NaHCO₃ (6.6 mEq/L) infused over 30 minutes into anesthetized dogs caused transient increases in arterial P₃CO₂, pH, base excess, and standard bicarbonate concentration. Prompt renal excretion of administered NaHCO₃ presumably prevented any persistent change in acid-base values in these acute studies. Renal acid excretion decreases, urine pH increases, and administered NaHCO₃ is excreted within hours. There is an acute increase in carbonic acid and P₃CO₂ as body buffers release H⁺ to combine with the administered HCO₃⁻. The excess NaHCO₃ is excreted in the urine, increased ventilation occurs in response to increased P₃CO₂, and acid-base balance is restored to normal.

When alkali is administered chronically, plasma HCO₃⁻ concentration becomes a function of the daily dosage administered but returns to normal within a few days after alkali administration is discontinued. If alkali is given to subjects rendered sodium avid by previous dietary salt restriction, smaller dosages of alkali result in greater increases in plasma HCO₃⁻ concentration than are observed when higher alkali dosages are used in subjects receiving normal amounts of dietary salt.

Sources of alkali other than NaHCO₃ may also contribute to metabolic alkalosis. Such organic anions include lactate that has accumulated during lactic acidosis, ketoacids in uncontrolled diabetes mellitus, and citrate in banked blood or that administered in an attempt to prevent recurrence of calcium oxalate urolithiasis. These organic anions yield HCO₃⁻ when metabolized:

Anion⁻ + O₂ → HCO₃⁻ + CO₂ + H₂O

This reaction often serves to replace the HCO₃⁻ titrated during development of the acidosis (e.g., lactic acidosis, diabetic ketoacidosis). If NaHCO₃ has been administered during treatment, however, metabolism of the organic anion after correction of the acidosis can result in metabolic alkalosis. If renal function is normal and volume depletion is not present, the kidneys promptly excrete the excess HCO₃⁻ and restore normal acid-base balance.

Administration of nonabsorbable alkali (e.g., aluminum hydroxide used as a phosphorus binder in patients with renal failure) usually does not cause metabolic alkalosis. Neutralization of H⁺ by Al(OH)₃ in the stomach results in the net addition of HCO₃⁻ to ECF. Combination of Al³⁺ with HCO₃⁻ secreted by the pancreas produces insoluble Al₂(CO₃)₃ in the duodenum, and there is no net increase in HCO₃⁻ ions in ECF. If, however, Al(OH)₃ is administered concurrently with a cationic exchange resin (e.g., polystyrene sulfonate), the resin can bind Al³⁺, leaving HCO₃⁻ secreted by the pancreas to be reabsorbed in the small intestine, thus resulting in alkalinization of ECF. When renal failure is present, the kidneys have reduced capacity to excrete retained HCO₃⁻, and metabolic alkalosis could result. This sequence of events is most likely to occur in an animal with oliguric renal failure that is treated concurrently with Al(OH)₃ for hyperphosphatemia and with polystyrene sulfonate for hyperkalemia.

<table>
<thead>
<tr>
<th>BOX 10-3 Causes of Metabolic Alkalosis</th>
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<tr>
<td><strong>Chloride Responsive</strong></td>
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<tr>
<td>Vomiting of stomach contents</td>
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<tr>
<td>Diuretic therapy</td>
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<td>Posthypercapnia</td>
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<tr>
<td><strong>Chloride Resistant</strong></td>
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<tr>
<td>Primary hyperaldosteronism</td>
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<td>Hyperadrenocorticism</td>
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<tr>
<td><strong>Alkali Administration</strong></td>
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<tr>
<td>Oral administration of sodium bicarbonate or other organic anions (e.g., lactate, citrate, gluconate, acetate)</td>
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<tr>
<td>Oral administration of cation exchange resin with nonabsorbable alkali (e.g., phosphorus binder)</td>
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<tr>
<td><strong>Miscellaneous</strong></td>
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<tr>
<td>Refeeding after fasting</td>
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<td>High-dose penicillin</td>
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<td>Severe potassium or magnesium deficiency</td>
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**Gastric Fluid Loss**

The H⁺ and Na⁺ concentrations of gastric fluid are inversely related to one another, whereas the K⁺ concentration is relatively stable (approximately 10 mEq/L). The Cl⁻ concentration is very high (approximately 150 mEq/L) and remains remarkably constant even when hypochloremia develops. Subtracting the sum of the Na⁺ and K⁺ concentrations of gastric fluid from the Cl⁻ concentration yields an approximation of the H⁺ concentration. The composition of gastric fluid is compared with that of other body fluids in Figure 10-10.

When a dog or cat vomits stomach contents, water is lost along with large amounts of HCl and small amounts of potassium and sodium.

The H⁺ produced during gastric acid secretion originates from the dissociation of carbonic acid; thus an equal number of HCO₃⁻ ions are generated in ECF. In the normal animal, gastric acid secretion does not disturb acid-base balance because the increase in ECF HCO₃⁻ concentration that accompanies parietal cell H⁺ secretion is balanced by pancreatic HCO₃⁻ secretion in the duodenum, and Cl⁻ secreted into the stomach is recaptured lower in the gastrointestinal tract. When stomach contents are lost, H⁺ and Cl⁻ are removed from this system, and HCO₃⁻ secreted into the duodenum by the pancreas is no longer titrated by gastric H⁺ but is reabsorbed farther down in the gastrointestinal tract in place of Cl⁻. The normal relationship between gastric and pancreatic secretions in the gastrointestinal tract is shown in Figure 10-11. Continued loss of gastric fluid can result in marked increases in plasma HCO₃⁻ concentration, and chronic vomiting of stomach contents is the most common cause of metabolic alkalosis in small animal practice.

In studies of gastric alkalosis, experimental subjects are rendered sodium avid by feeding a low-salt diet. Gastric fluid is then continuously removed by nasogastric suction, and fluid and electrolyte losses other than HCl are quantitatively replaced. The effects of repeated gastric drainage over 3 days on plasma HCO₃⁻ and chloride concentrations and on potassium, sodium, and chloride balance in experimental dogs are shown in Figure 10-12. Note that the resulting metabolic alkalosis is corrected by provision of NaCl despite a progressively negative potassium balance. In the clinical setting, persistent vomiting of stomach contents leads to fluid and electrolyte losses (H⁺ and Cl⁻ > Na⁺ and K⁺), and anorexia prevents adequate dietary intake of electrolytes. In patients with pyloric obstruction, gastrin secretion is enhanced, and gastric acid secretion is stimulated further. Overproduction of gastrin by a gastrin-secreting tumor may also stimulate gastric acid secretion. In one dog with gastrinoma, severe metabolic alkalosis and hypokalemia were associated with a history of chronic vomiting.

Renal avidity for sodium and defense of the ECFV occur because of ongoing fluid and electrolyte losses in the vomiting animal or intake of a low-salt diet and nasogastric suction in the experimental setting. To maintain ECFV, the kidneys must reabsorb sodium by all available mechanisms. Because of ongoing loss of gastric HCl and
increased distal Na⁺. The low urine pH during the maintenance phase reflects perpetuation of the metabolic alkalosis and development of potassium depletion as shown in Figure 10-13. The critical factor in resolution of this form of alkalosis is the provision of chloride as a resorbable anion. Alkalosis can be corrected without provision of sodium or potassium as long as chloride is provided. Clinically, however, alkalosis is corrected by administering some combination of NaCl and KCl.

**Diuretic Administration**

Diuretics cause approximately equal losses of sodium and chloride in the urine, but the concentration of chloride in ECF is less than that of sodium by approximately 35 mEq/L. Thus, these drugs may cause chloride-responsive metabolic alkalosis by a disproportionate loss of chloride in urine and creation of a relative chloride deficit in ECF. Increased renal sodium avidity is also an important factor in development of the metabolic alkalosis and potassium depletion that may occur during diuretic administration.

Loop diuretics inhibit NaCl reabsorption in the thick ascending limb of Henle’s loop by competing with chloride for the Na⁺-K⁺-2Cl⁻ luminal carrier. This causes increased delivery of sodium to the distal nephron, where accelerated Na⁺-H⁺ and Na⁺-K⁺ exchange occurs as the kidneys attempt to retain more sodium. Increased reliance of the kidneys on these mechanisms for sodium reabsorption contributes to metabolic alkalosis and potassium depletion. These complications are less likely when thiazide diuretics are used. Thiazide diuretics inhibit NaCl transport in the distal tubule and connecting segment. They are less potent than the loop diuretics because their main effect occurs at sites in the nephron distal to those responsible for the majority of sodium reabsorption.

In response to hypokalemia, transcellular shifts of H⁺ from ECF into renal tubular cells may occur in exchange for K⁺. The resultant increase in intracellular H⁺ concentration facilitates renal Na⁺-H⁺ exchange and aggravates metabolic alkalosis. Stimulation of the renin-angiotensin-aldosterone system by decreased effective circulating volume also favors increased Na⁺-H⁺ and Na⁺-K⁺ exchange in the distal nephron. These latter effects are probably important in most forms of chloride-responsive metabolic alkalosis.

Many animals treated with diuretics have congestive heart failure as their primary disease process. If the treatment plan for the animal includes a low-sodium diet, renal sodium avidity is guaranteed and increases the tendency toward metabolic alkalosis and potassium depletion. Complications from diuretic therapy are unlikely if the animal is drinking water and eating a diet with adequate amounts of chloride. However, complications can develop if the animal becomes anorexic.
Posthypercapnia
Blood pH increases rapidly when P$_{CO_2}$ is suddenly reduced in patients with chronic hypercapnia. This has been called posthypercapnic metabolic alkalosis. In such patients, plasma HCO$_3^-$ concentration has previously been increased by adaptive changes in renal HCO$_3^-$ reabsorption. In response to the lowered P$_{CO_2}$, it takes several hours for the kidneys to decrease Na$^+$-H$^+$ exchange and begin to excrete the previously retained HCO$_3^-$. It may take several days for the kidneys to excrete all of the excess HCO$_3^-$. Chloride deficiency during recovery from chronic hypercapnia plays a role in sustaining posthypercapnic metabolic alkalosis. Provision of chloride allows the alkalosis to be corrected.

Chloride-Resistant Metabolic Alkalosis
Several disorders in human medicine may cause chloride-resistant metabolic alkalosis. Of these, primary hyperaldosteronism and hyperadrenocorticism may occur in small animal practice. However, chloride-resistant metabolic alkalosis is rare in dogs and cats.

Primary Hyperaldosteronism
In primary hyperaldosteronism, increased secretion of aldosterone, usually by an adrenocortical tumor, results in sodium retention, volume expansion, hypernatremia, mild to moderate hypertension, potassium deficiency, hypokalemia, and metabolic alkalosis resistant to chloride administration. Plasma renin activity is low, but plasma aldosterone concentration is high. Affected human patients are in salt balance at an expanded ECFV and excrete ingested NaCl in the urine. Stimulation of distal nephron Na$^+$-H$^+$ and Na$^+$-K$^+$ exchange by excess mineralocorticoids is probably the most important pathophysiologic feature of primary hyperaldosteronism.

Several dogs and cats with primary hyperaldosteronism caused by aldosterone-producing adenomas or adenocarcinomas of the adrenal gland have been reported in the veterinary literature. Clinical features in affected animals included polyuria, polydipsia, weakness, hypertension, hypokalemia, hypernatremia, mild metabolic alkalosis, dilute urine, and extremely high serum aldosterone concentrations (for additional information and references see Chapter 5).
Hyperadrenocorticism

Metabolic alkalosis occurs in approximately one third of human patients with Cushing’s syndrome. It is more common in patients with adrenocortical carcinomas and in those with ectopic production of ACTH by nonadrenal malignancies than in those with pituitary-dependent hyperadrenocorticism. The frequency of metabolic alkalosis and serum electrolyte disturbances in dogs with hyperadrenocorticism is uncertain. Serum sodium and potassium concentrations often are normal in dogs with hyperadrenocorticism. This may reflect the fact that 80% to 85% of dogs with hyperadrenocorticism have pituitary-dependent disease. In a large group of dogs with hyperadrenocorticism, 21 of 52 (40%) dogs had increased serum sodium concentrations and 25 of 52 (48%) had decreased serum potassium concentrations. The relative frequency of pituitary- and adrenal-dependent disease was not reported in this study. In another study, mild hypernatremia and hypokalemia were observed occasionally in dogs with hyperadrenocorticism, and total CO₂ content was increased in 33% of affected dogs.

In another report, hypokalemia was found in only 5% of dogs with pituitary-dependent hyperadrenocorticism but in 45% of those with adrenocortical neoplasia. A high rate of secretion of cortisol and other corticosteroids, such as desoxycorticosterone and corticosterone in patients with adrenocortical malignancies, could be responsible for hypernatremia, hypokalemia, and metabolic alkalosis in adrenal-dependent hyperadrenocorticism.

Miscellaneous

Large doses of penicillin, ampicillin, or carbenicillin administered as a sodium salt can lead to hypokalemia and metabolic alkalosis in human patients. The drug may increase lumen electronegativity in the distal nephron by acting as a nonresorbable anion and enhancing Na⁺-H⁺ and Na⁺-K⁺ exchange. “Refeeding” alkalosis can occur in human patients when glucose is administered after prolonged fasting. The mechanism for this type of alkalosis is unknown. These types of metabolic alkalosis have not been reported in the veterinary literature.

TREATMENT OF METABOLIC ALKALOSIS

Acid-base disturbances are secondary phenomena. Diagnosis and definitive treatment of the responsible disease process are integral to the successful resolution of acid-base disorders. However, it must be remembered that alkalosis persists until chloride is replaced if vomiting of stomach contents or diuretic administration is responsible for the metabolic alkalosis. The goal of treatment in chloride-responsive metabolic alkalosis is to replace the chloride deficit while providing sufficient potassium and sodium to replace existing deficits. Definitive treatment of the underlying disease process (e.g., removal of a gastric foreign body) prevents recurrence of the metabolic alkalosis.

Patients with chronic pulmonary disease that have hypoxemia and hypercapnia are at greater risk from metabolic alkalosis than others because superimposition of metabolic alkalosis can further reduce ventilation and lead to worsening of hypoxemia. Thus, metabolic alkalosis should be treated appropriately if present and avoided if not present. Giving oxygen to patients with metabolic alkalosis should also be avoided if possible because this may impair ventilation and further aggravate hypercapnia.

Potassium without chloride (e.g., potassium phosphate) corrects neither the alkalosis nor the potassium deficit because administered potassium is excreted in the urine. A chloride salt must be given for alkalosis to be resolved and potassium retention to occur. Provision of chloride as either the sodium or potassium salt corrects chloride-responsive metabolic alkalosis. This therapy allows the kidneys to reabsorb the sodium the body requires with chloride to maintain electroneutrality. Thus, a NaCl solution (0.45% or 0.9%) with added KCl is the fluid of choice for dogs and cats with chloride-
responsive metabolic alkalosis. It is best to use solutions containing NaCl and KCl because affected animals typically have been sick long enough to develop clinically relevant potassium deficits. Administering 0.9% NaCl without KCl can cause diuresis and increased urinary excretion of potassium, thus worsening any potassium deficit. As shown in Figure 10-12, provision of NaCl corrects metabolic alkalosis induced in dogs by gastric drainage, but the potassium deficit persists unless potassium is provided. A few days may be required to restore normal electrolyte and acid-base balance, but in nearly all instances, these measures are sufficient to resolve the alkalosis. In human patients with severe metabolic alkalosis or in those with severely impaired renal function, HCl or arginine HCl has been used for rapid correction of metabolic alkalosis, but there is no report of the use of these compounds in animals with metabolic alkalosis, and their use is not recommended.

H₂-blocking drugs such as cimetidine, ranitidine, or famotidine may be considered as adjunctive therapy if gastric losses are ongoing because this approach reduces gastric acid secretion. For the patient with heart failure receiving loop diuretics, oral KCl administration is the best way to provide chloride without sodium and prevent further retention of fluid and aggravation of edema. Even in the presence of sodium avidity, provision of chloride lessens Na⁺-H⁺ and Na⁺-K⁺ exchange at distal nephron sites and prevents development of alkalosis when loop diuretics are used. Simultaneous use of distal blocking agents such as spironolactone, triamterene, or amiloride may also be considered. These drugs work in the principal cells of the cortical collecting tubule and impair Na⁺-H⁺ and Na⁺-K⁺ exchange by inhibiting aldosterone-sensitive sodium channels. In metabolic alkalosis caused by chronic administration of alkali, discontinuation of the source of alkali results in correction of the alkalosis over a few days, provided that renal function is normal.

Chloride-resistant metabolic alkalosis is uncommon in comparison with chloride-responsive metabolic alkalosis. When present, its successful treatment requires that the underlying disease be diagnosed and treated before alkalosis can be resolved.

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