CHAPTER 8

Diabetic Ketoacidosis

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CHAPTER CONTENTS

Diabetic ketoacidosis (DKA) is a serious complication of diabetes mellitus. Before the availability of insulin in the 1920s, DKA was a uniformly fatal disorder. Even after the discovery of insulin, DKA continued to carry a grave prognosis with a reported mortality rate in humans ranging from 10% to 30%. However, with the expanding knowledge regarding the pathophysiology of DKA and the application of new treatment techniques for the complications of DKA, the mortality rate for this disorder has decreased to less than 5% in experienced human medical centers (Kitabchi et al, 2008). We have experienced a similar decrease in the mortality rate for DKA in our hospital over the past two decades. DKA remains a challenging disorder to treat, in part because of the deleterious impact of DKA on multiple organ systems and the frequent occurrence of concurrent often serious disorders that are responsible for the high mortality rate of DKA. In humans, the incidence of DKA has not decreased, appropriate therapy remains controversial, and patients continue to succumb to this complication of diabetes mellitus. This chapter summarizes current concepts regarding the pathophysiology and management of DKA in dogs and cats.

PATHOGENESIS AND PATHOPHYSIOLOGY

Generation of Ketone Bodies

Ketone bodies are derived from oxidation of nonesterified or free fatty acids (FFAs) by the liver and are used as an energy source by many tissues during periods of glucose deficiency. FFAs released from adipose tissue are assimilated by the liver at a rate dependent on their plasma concentration. Within the liver, FFAs can be incorporated into triglycerides, can be metabolized via the tricarboxylic acid (TCA) cycle to CO_2 and water, or can be converted to ketone bodies (Hood and Tannen, 1994; Kitabchi et al, 2001; Fig. 8-1). Oxidation of FFAs leads to the production of acetoacetate. In the presence of NADH, acetoacetate is reduced to β-hydroxybutyrate. Acetone is formed by spontaneous decarboxylation of acetoacetate (see Fig. 8-1). These ketone bodies—acetoacetate, β-hydroxybutyrate, and acetone—are substrates for energy metabolism by most tissues. The metabolism of ketone bodies is integrated with that of other substrates of energy metabolism, both in peripheral tissues and in the liver. However, excessive production of ketone bodies, as occurs in uncontrolled diabetes, results in their accumulation in the circulation and development of the ketosis and acidosis of ketoacidosis.

Role of Insulin Deficiency

The most important regulators of ketone body production are FFA availability and the ketogenic capacity of the liver (McGarry et al, 1989; Zammit, 1994). For the synthesis of ketone bodies to be enhanced, there must be two major alterations in intermediary metabolism: (1) increased mobilization of FFAs from triglycerides stored in adipose tissue and (2) a shift in hepatic metabolism from fat synthesis to fat oxidation and ketogenesis (Hood and Tannen, 1994; Kitabchi et al, 2001). Insulin is a powerful inhibitor of lipolysis and FFA oxidation (Groop et al, 1989). A relative or absolute deficiency of insulin results in increased activity of hormone sensitive lipase in adipocytes, which increases FFA release from adipocytes—thus increasing the availability of FFAs to the liver and in turn promoting ketogenesis. Insulin deficiency also reduces peripheral utilization of glucose and ketones. The combination of increased production and decreased utilization leads to an accumulation of glucose and ketones in blood. Virtually all dogs and cats with DKA have a relative or absolute deficiency of insulin (Fig. 8-2). In established diabetic animals after insulin is discontinued and in newly-diagnosed diabetic animals that are diagnosed with ketoacidosis on initial examination, circulating insulin levels are low or undetectable. Some dogs and cats have serum insulin concentrations similar to those observed in healthy, fasted dogs and cats (i.e., within the reference range; Durocher et al, 2008). However, such insulin concentrations are

inappropriately low ("relative" insulin deficiency) for the severity of hyperglycemia encountered.

Some diabetic dogs and cats develop ketoacidosis despite receiving daily injections of insulin, and circulating insulin concentrations may even be increased. Insulin deficiency per se cannot be the sole physiologic cause for the development of DKA. In this group, a "relative" insulin deficiency is present. Presumably these dogs and cats have insulin resistance potentially resulting from an increase in circulating glucose counterregulatory hormones (i.e., glucagon, epinephrine, cortisol, growth hormone), an increase in proinflammatory cytokines (e.g., tumor necrosis factor alpha [TNFα] and interleukin-6 [IL-6]), an increase in plasma FFAs and amino acids, and development of metabolic acidosis (Tilg and Moschen, 2006; Vick et al, 2008). The ability to maintain normal glucose homeostasis represents a balance between the body's sensitivity to insulin and the amount of insulin secreted by the beta-cell or injected exogenously. With the development of insulin resistance, the need for insulin may exceed the daily injected insulin dose, and this leads to a predisposition for the development of DKA (Fig. 8-3).

Role of Glucose Counterregulatory Hormones

Circulating levels of glucagon, epinephrine, cortisol, and growth hormone are typically markedly increased in humans with DKA, as are plasma FFA and amino acid concentrations (Luzi et al,

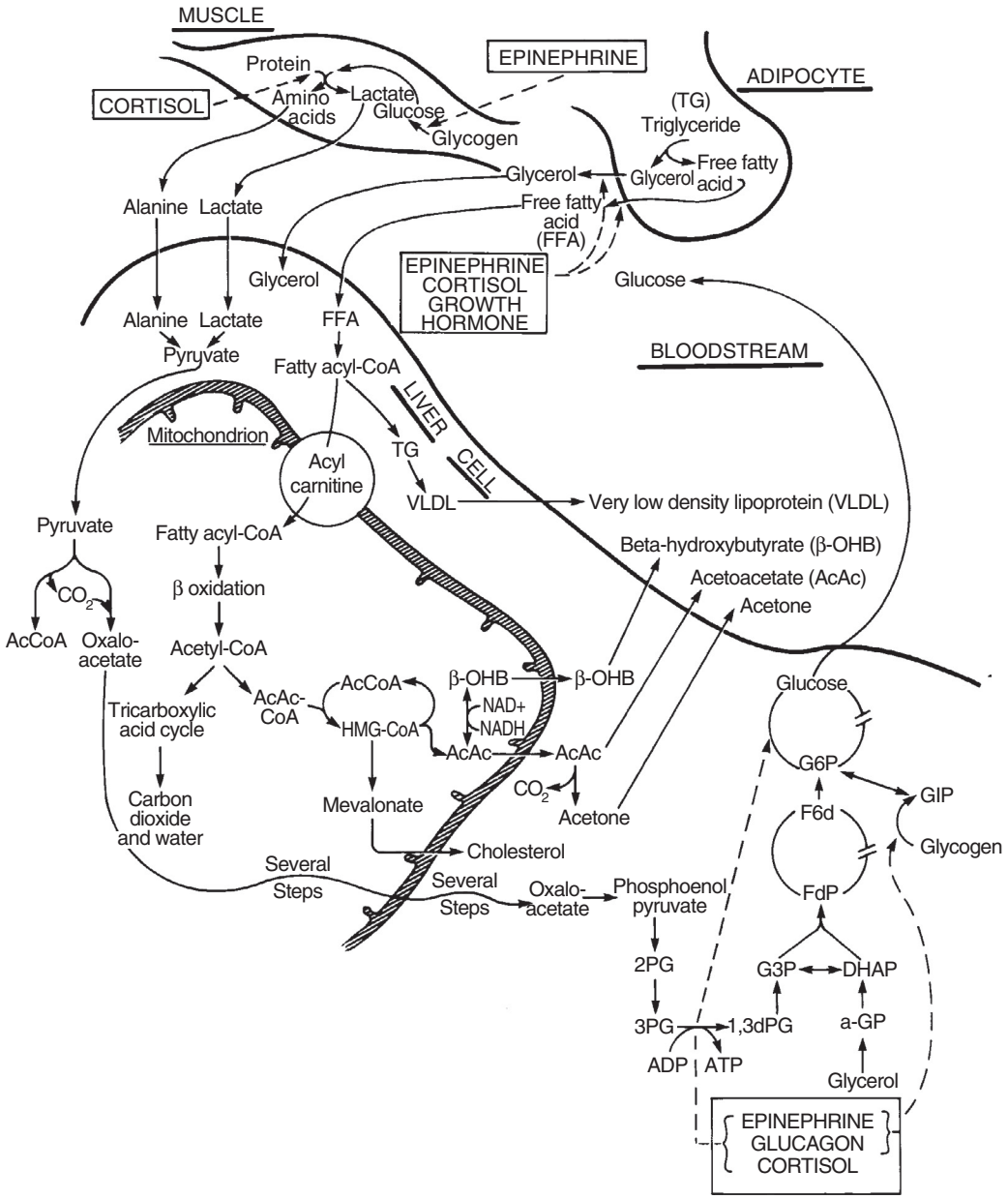

FIGURE 8-1 In response to a wide variety of stress situations (e.g., sepsis, heart failure, and pancreatitis), the body increases its production of the glucoregulatory hormones—insulin, glucagon, epinephrine, cortisol, and growth hormone. In diabetes, the lack of insulin allows the glucogenic effects of the stress hormones to be unopposed in liver, muscle, and adipose tissue. This results in excess ketone formation, fat and muscle breakdown, and a classic catabolic state. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate; *DHAP,* dihydroxyacetone phosphate; *GIP,* gastric inhibitory polypeptide; *HMG,* hydroxymethylglutaryl; *NAD+,* nicotinamide adenine dinucleotide; *NADH,* nicotinamide adenine dinucleotide (reduced form).

1988; Fig. 8-4). Increased circulating concentrations of these counterregulatory hormones cause insulin resistance, stimulate lipolysis and the generation of FFAs in the circulation, and shift hepatic metabolism of FFAs from fat synthesis to fat oxidation and ketogenesis (McGarry et al, 1989; Zammit, 1994). Glucagon is considered the most influential ketogenic hormone. Increased concentrations accompany ketotic states, and low concentrations blunt ketogenesis in ketogenic conditions (Hood and Tannen, 1994). Glucagon can directly influence hepatic ketogenesis. A low insulin-glucagon ratio has a direct effect on the liver that promotes increased production of ketones (Durocher et al, 2008). However, glucagon's effects still depend on substrate availability, and ketogenesis can occur in the absence of glucagon. Catecholamines are also important modulators of ketogenesis, primarily through stimulation of lipolysis. Both epinephrine and glucagon contribute to insulin resistance by inhibiting insulin-mediated glucose uptake in muscle and by stimulating hepatic glucose production through an augmentation of both glycogenolysis and gluconeogenesis (Cherrington et al, 1987; Cryer, 1993). Cortisol and growth hormone enhance lipolysis in the presence of a relative or absolute deficiency of insulin (see Fig. 8-1), block insulin action in peripheral tissues (Bratusch-Marrain, et al, 1982; Boyle, 1993), and potentiate the stimulating effect of epinephrine and glucagon on hepatic glucose output (Sherwin et al, 1980). An elevation in plasma FFA concentration and FFA oxidation inhibits insulin-mediated glucose uptake in muscle and stimulates hepatic gluconeogenesis (Thiebaud et al, 1982; Ferrannini et al, 1983). The combination of insulin deficiency and excesses in counterregulatory hormones also stimulates protein catabolism. Increased plasma amino acid concentrations impair insulin action in muscle and provide substrate to drive gluconeogenesis (Tessari et al, 1985). The net effect of these hormonal disturbances is accentuation of insulin deficiency through the development of insulin resistance, stimulation of lipolysis leading to ketogenesis, and stimulation of gluconeogenesis, which worsens hyperglycemia. All of these factors lead to the eventual onset of clinical manifestations associated with DKA.

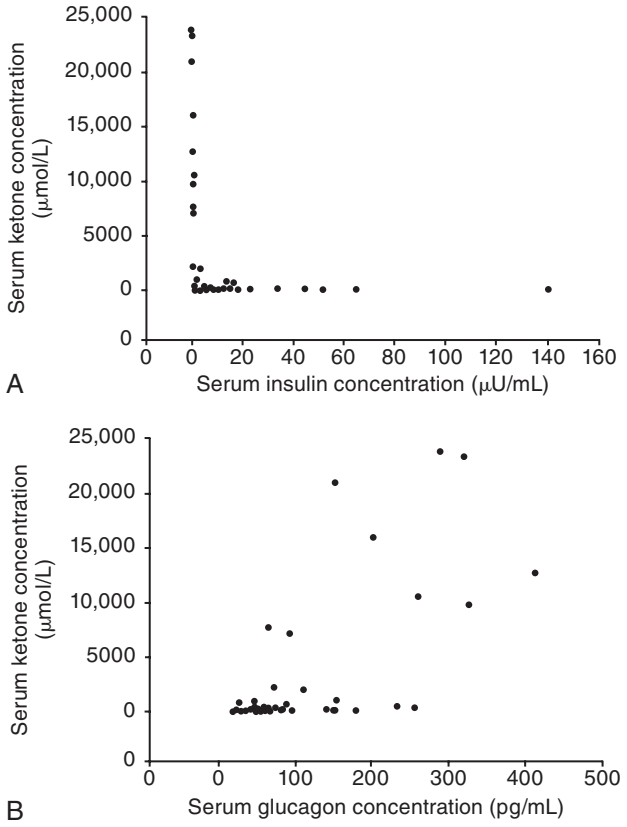

FIGURE 8-2 Scatterplots of serum ketone concentrations versus serum insulin concentration **(A)** and serum glucagon concentration **(B)** in 48 dogs with diabetes mellitus. There was a significant ($P < 0.001$) linear relationship between serum ketone concentration and serum glucagon concentration. (From Durocher LL, et al.: Acid-base and hormonal abnormalities in dogs with naturally occurring diabetes mellitus, *J Am Vet Med Assoc* 232:1310, 2008.)

The body increases its production of the glucose counterregulatory hormones in response to a wide variety of diseases and stress situations. Although this response is usually beneficial, in DKA the activity of these hormones as insulin antagonists usually worsens hyperglycemia and ketonemia, provoking acidosis, fluid depletion, and hypotension. This condition progresses in a self-perpetuating spiral of metabolic decompensation (Fig. 8-5). It is rare for the dog or cat with DKA not to have some coexisting disorder, such as pancreatitis, infection, chronic kidney disease, or concurrent hormonal disorder. These disorders have the potential for increasing glucose counterregulatory hormone secretion. For example, infection causes a marked increase in the secretion of cortisol and glucagon, heart failure and trauma result in increased circulating levels of glucagon and catecholamines, and fever induces secretion of glucagon, growth hormone, catecholamines, and cortisol (Kandel and Aberman, 1983; Feldman and Nelson, 1987). The recognition and treatment of disorders that coexist with DKA are critically important for successful management of DKA (see Fig. 8-3).

Physiologic Consequences of Enhanced Ketone Body Production

The physiologic derangements that accompany DKA are a direct result of relative or absolute insulin deficiency, hyperketonemia, and hyperglycemia (Box 8-1). In a short-term situation,

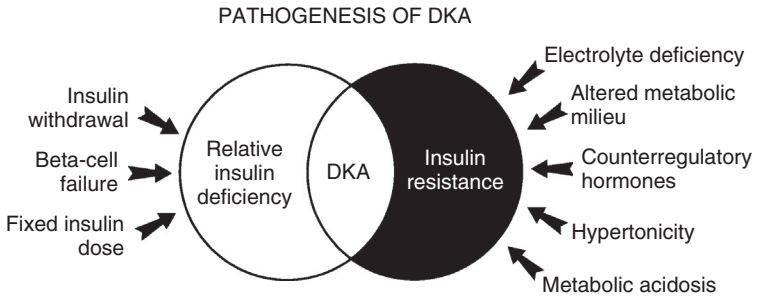

FIGURE 8-3 The pathogenesis of diabetic ketoacidosis *(DKA)*, illustrating the interaction of insulin deficiency and insulin resistance necessary in the development of the ketoacidotic state.

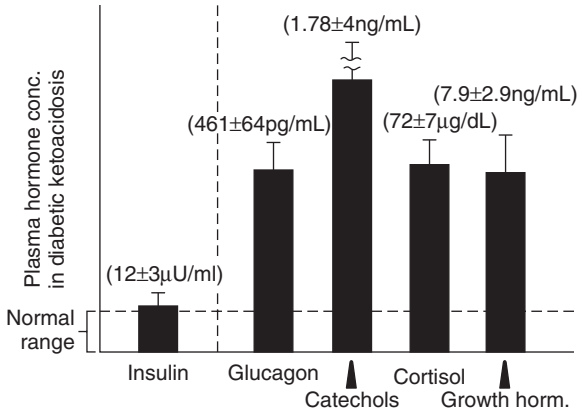

FIGURE 8-4 Plasma insulin and counterregulatory hormone concentrations in diabetic ketoacidosis (DKA) (mean ± standard error of the mean [SEM]). DKA is characterized by relative insulin deficiency and stress hormone excess. Plasma cortisol concentration is characteristically elevated in all humans admitted to the hospital in severe DKA. Although the mean growth hormone concentration also tends to be elevated in ketoacidosis, in many humans this hormone does not become elevated until therapy is begun with insulin and fluids. (Reprinted from Schade DS, et al.: Diabetic ketoacidosis: pathogenesis, prevention, and therapy. In Schade DS, et al, editors: *Diabetic coma,* Albuquerque, 1981, University of New Mexico Press, p. 84.)

the conversion of FFAs to ketone bodies is actually a positive metabolic development. Diabetes mellitus is interpreted physiologically as a state of starvation. With glucose deficiency, ketone bodies can be used as an energy source by many tissues. However, increasing plasma glucose and ketone concentrations eventually surpass the renal tubular threshold for complete reabsorption and spill into the urine, inducing an osmotic diuresis. Each gram of glucose excreted via the kidneys adds a solute load of approximately 6 mOsm. The lower molecular weight of ketones accounts for a greater osmotic load per gram, and excretion of ketones is responsible for one-third to one-half of the osmotic diuresis in humans with DKA (DeFronzo et al, 1994; Kitabchi et al, 2001). The anionic charge on the ketones, even at a maximally acid urine pH, obligates the excretion of positively charged ions (e.g., sodium, potassium, calcium, and magnesium) to maintain electrical neutrality. This increased solute excretion impairs the reabsorption of water throughout the proximal tubule and loop of Henle, lowering the concentration of sodium and chloride in the tubular lumen, creating an increased concentration gradient for their reabsorption, and thereby inhibiting their transport from lumen to blood. The result is an excessive loss of electrolytes and water with depletion of water roughly twice that of solutes, leading to volume contraction, underperfusion of tissues, and hypertonicity of the extracellular fluid (ECF) compartment. Insulin deficiency per se also contributes to the excessive renal losses of water and electrolytes. Physiologic increases in plasma insulin concentration augment salt and water reabsorption in both the proximal and distal portions of the nephron and enhance proximal tubular phosphate reabsorption (DeFronzo et al, 1994). Conversely, insulin deficiency leads to enhanced water and electrolyte excretion.

The formation of ketones by the liver is associated with the production of an equivalent number of hydrogen ions, which titrate the plasma bicarbonate concentration. As ketones continue to accumulate in the blood, the body's buffering system becomes overwhelmed, causing an increase in arterial hydrogen ion concentration, a decrease in serum bicarbonate, and development of metabolic acidosis. Further loss of water and electrolytes occurs as a result of repeated bouts of vomiting, diarrhea, or both combined with a lack of fluid intake; problems that often develop as the metabolic acidosis worsens (see Fig. 8-5). The excessive loss of electrolytes and water leads to further volume contraction, underperfusion of tissues, decline in the glomerular filtration rate (GFR), and worsening prerenal azotemia and dehydration. Hyperglycemic dogs and cats with reduced GFR lose the ability to excrete glucose and, to a lesser degree, hydrogen ions. Glucose and ketones then accumulate in the vascular space at a more rapid rate. The result is increasing hyperglycemia and ketonemia and worsening metabolic acidosis (see Fig. 8-5). The increase in blood glucose concentration increases plasma osmolality, and the resulting osmotic diuresis further aggravates the increase in plasma osmolality by causing water losses in excess of salt loss. The increase in plasma osmolality causes water to shift out of cells, leading to cellular dehydration and the eventual development of obtundation and coma. The severe metabolic consequences of DKA, which include severe acidosis, obligatory osmotic diuresis, hyperosmolality, dehydration, and electrolyte derangements, ultimately become life-threatening.

SIGNALMENT

DKA is a serious complication of diabetes mellitus that occurs most commonly in dogs and cats with previously undiagnosed diabetes. Less commonly, DKA develops in an insulin-treated diabetic dog or cat that is receiving an inadequate dosage of insulin, which is often in conjunction with a concurrent infectious, inflammatory, or insulin-resistant hormonal disorder. Because of the close association between DKA and newly-diagnosed diabetes mellitus, the signalment for DKA in dogs and cats is similar to that for non-ketotic diabetics (see Chapters 6 and 7). For the most part, DKA appears to be a disease of middle-aged and older dogs and cats, although DKA can be diagnosed at any age. In dogs, DKA is diagnosed more commonly in females, whereas in cats it is more common in males. Any breed of dog or cat can develop DKA.

HISTORY AND PHYSICAL EXAMINATION

The history and findings on physical examination are variable, in part because of the progressive nature of the disorder and the variable time between the onset of DKA and owner recognition of a problem. The spectrum ranges from ketonuric dogs and cats that are otherwise healthy, eating, and have not yet developed metabolic acidosis (i.e., diabetic ketosis [DK]) to ketonuric dogs and cats that have developed severe metabolic acidosis (i.e., DKA), have severe signs of illness, and are moribund.

Polyuria, polydipsia, polyphagia, and weight loss develop initially but are either unnoticed or considered insignificant by the owner. Systemic signs of illness (i.e., lethargy, anorexia, vomiting) ensue as progressive ketonemia and metabolic acidosis develop, the severity of systemic signs being directly related to the severity of metabolic acidosis, hyperosmolality, and dehydration and the nature of concurrent disorders (e.g., pancreatitis, infection) that are often present. The time interval from the onset of initial clinical signs of diabetes to development of systemic signs of illness caused by DKA is unpredictable and ranges from a few days to several months. Once ketoacidosis begins to develop, however, severe illness typically becomes evident within a week.

When a severely ill dog or cat is brought to a veterinarian, the owner may not mention signs that were present prior to those most

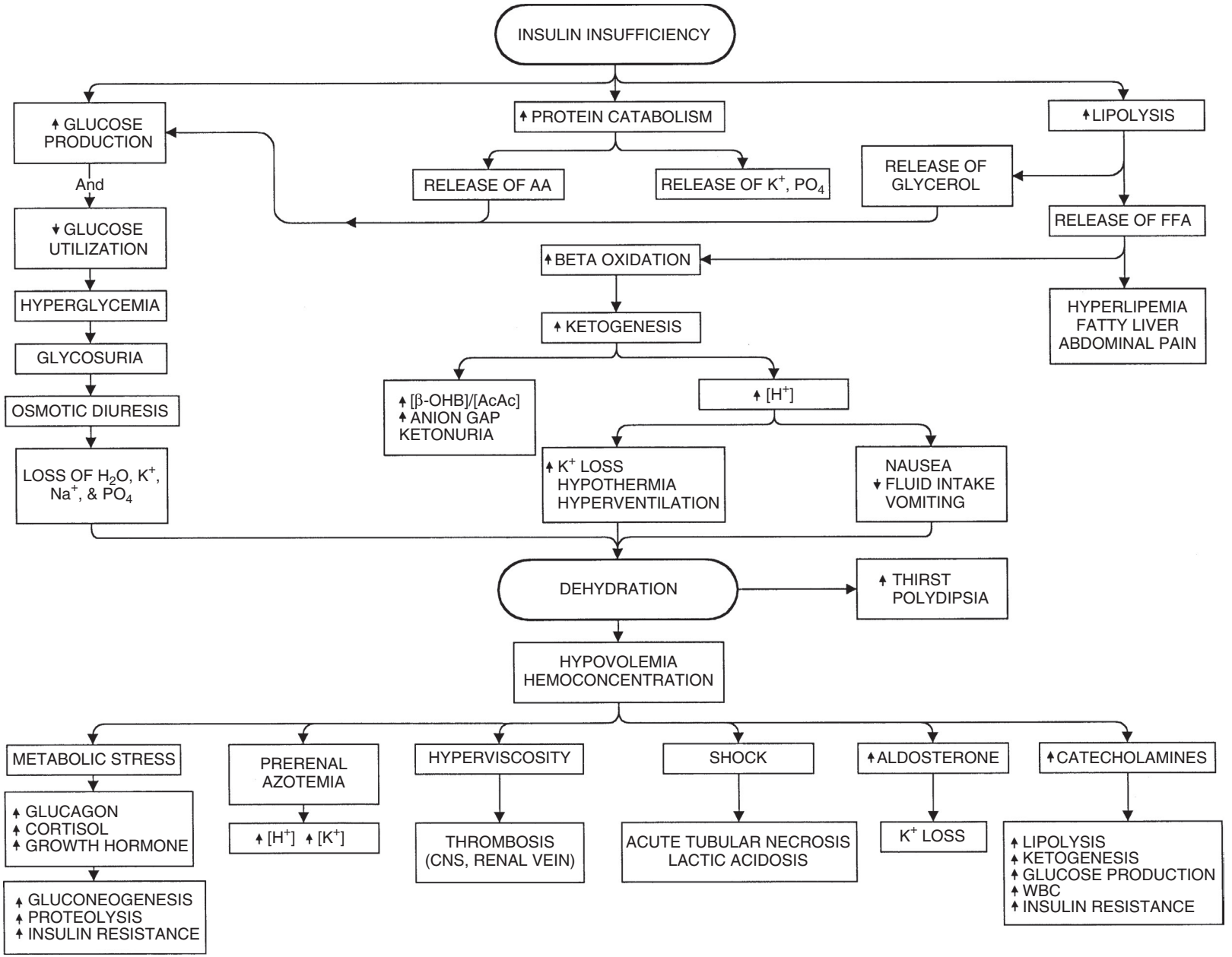

FIGURE 8-5 The interrelationship of the pathophysiologic mechanisms that result in diabetic ketoacidosis (DKA). *AA,* Amino acids; *AcAc,* acetoacetate; *β-OHB,* beta-hydroxybutyrate; *CNS,* central nervous system; *FFAs,* free fatty acids; *K,* potassium; *WBC,* white blood cells.

BOX 8-1 Pathophysiologic Derangements in Diabetic Ketoacidosis

Hyperglycemia	Hyperketonemia	Insulin Deficiency
Osmotic diuresis	Osmotic diuresis	Electrolyte and fluid losses
Sodium	Sodium	Sodium
Potassium	Potassium	Water
Water	Water	Phosphate
Calcium	Calcium	Negative nitrogen balance
Phosphate	Phosphate	
Intracellular dehydration	Metabolic acidosis	

obvious and worrisome at the moment. If the owner is questioned closely with regard to the past history, the changes noted before severe illness include the classic history for diabetes mellitus (i.e., polyuria, polydipsia, polyphagia, and weight loss). Because of the increased incidence of concurrent diseases, it is imperative that the clinician spend ample time obtaining a careful history concerning all organ systems. Some diseases (e.g., pyometra, kidney failure, and hyperadrenocorticism) have historical signs resembling DKA and can initiate the metabolic derangements leading to DKA in a previously unidentified or insulin-regulated diabetic.

A complete and careful physical examination is critically important in any ketoacidotic animal. The initial physical examination should focus on an evaluation of the status of hydration, on the extent of central nervous system (CNS) depression, and on a careful search for any initiating cause for diabetic decompensation and ultimate ketoacidosis. Diabetic dogs and cats frequently suffer from concurrent infections, pancreatitis, cholangiohepatopathy, kidney disease, cardiac disease, or other insulin-antagonistic disorders (Bruskiewicz et al, 1997; Hume et al, 2006). A careful history, physical examination, and judicious use of laboratory tests can, in most circumstances, identify underlying concurrent disorders, lead to appropriate treatment, and increase the likelihood of a successful outcome.

Common physical examination findings suggestive of DKA include lethargy, dehydration, tachypnea, tachycardia, weakness, and sometimes a strong odor of acetone on the breath. Slow deep breathing (i.e., Kussmaul respiration) may be observed in animals with severe metabolic acidosis. Gastrointestinal tract signs (e.g., vomiting and abdominal pain) are common in dogs and cats with DKA; this is in part because of the common concurrent occurrence of pancreatitis. Other intraabdominal disorders should also be considered and diagnostic tests (e.g., abdominal ultrasound) performed to help identify the cause of the gastrointestinal signs. Additional physical examination findings associated with uncomplicated diabetes mellitus (e.g., hepatomegaly, cataracts, peripheral neuropathy) may also be identified (see Chapters 6 and 7).

ESTABLISHING THE DIAGNOSIS OF DIABETIC KETOSIS AND KETOACIDOSIS

A diagnosis of diabetes mellitus requires the presence of appropriate clinical signs (i.e., polyuria, polydipsia, polyphagia, and weight loss) and documentation of persistent fasting hyperglycemia and glycosuria. Measurement of the blood glucose concentration using a portable blood glucose monitoring device (see Protocol for Generating the Serial Blood Glucose Curve in the Hospital in Chapter 6) and testing for the presence of glycosuria using urine reagent test strips (e.g., Keto-Diastix)

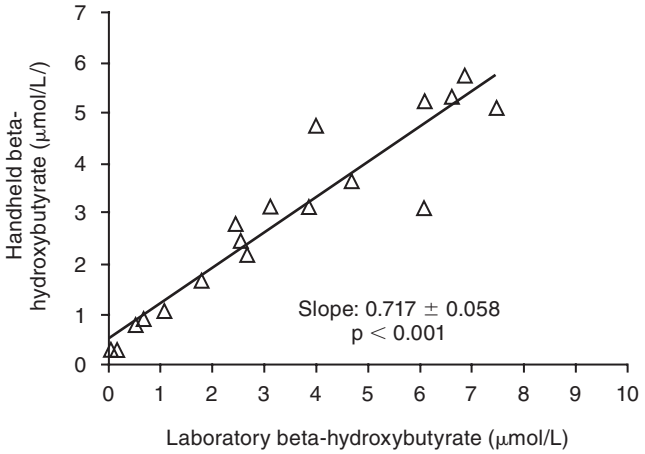

FIGURE 8-6 Comparison of β-hydroxybutyrate measurements using a laboratory-based enzymatic assay and a handheld ketone meter in 16 dogs and 3 cats. (From Hoenig M, et al.: Use of a hand-held meter for the measurement of blood beta-hydroxybutyrate in dogs and cats, *J Vet Emerg Crit Care* 18:86, 2008.)

allows the rapid confirmation of diabetes mellitus. The concurrent documentation of ketonuria establishes a diagnosis of DK or ketoacidosis. The subsequent documentation of metabolic acidosis differentiates DKA from DK. Commonly used nitroprusside reagent test strips for ketonuria (e.g., Keto-Diastix, Ketostix) measure only acetoacetate and its byproduct acetone. Beta-hydroxybutyrate has no ketone group and is therefore not detected by conventional nitroprusside tests. Beta-hydroxybutyrate is formed from acetoacetate in the presence of hydrogen ions; the more acidic the diabetic dog or cat is, the more β-hydroxybutyrate is formed. Urine ketone measurements do not reflect the severity of increase in blood β-hydroxybutyrate concentration, may not reflect the severity of the metabolic acidosis, and may be negative for ketones in dogs and cats in the early stages of DK and DKA. If ketonuria is not identified in a dog or cat with suspected DK or DKA, blood should be tested for the presence of β-hydroxybutyrate using a quantitative enzymatic assay or a portable blood glucose and ketone analyzer (e.g., Precision Xtra, Abbott Diagnostics; Fig. 8-6), or plasma from heparinized hematocrit tubes can be used to test for the presence of acetoacetate using urine reagent strips used to document ketonuria (Duarte et al, 2002; Brady et al, 2003; Hoenig et al, 2008; Di Tommaso et al, 2009; Zeugswetter and Pagitz, 2009).

In human diabetics, the predominate ketone body produced during DKA is β-hydroxybutyrate. The β-hydroxybutyrate-to-acetoacetate ratio can range from 3:1 to 20:1 depending on the severity of hypovolemia, tissue hypoxia, and lactic acidosis (Li et al, 1980; Goldstein, 1995). In the presence of circulatory collapse, an increase in lactic acid can shift the redox state to increase β-hydroxybutyrate at the expense of readily detectable acetoacetate. Severe hyperketonemia could be underestimated or even undetected if urine reagent test strips or blood tests that only measure acetoacetate and acetone are used to identify DK or DKA.

The predominate ketone body produced in diabetic dogs and cats is also believed to be β-hydroxybutyrate. Although serum β-hydroxybutyrate concentrations may be mildly increased in sick non-diabetic dogs and cats in a negative energy balance, documenting an increased serum β-hydroxybutyrate concentration in conjunction with hyperglycemia and glycosuria supports a diagnosis of DK or DKA, regardless of dipstick test

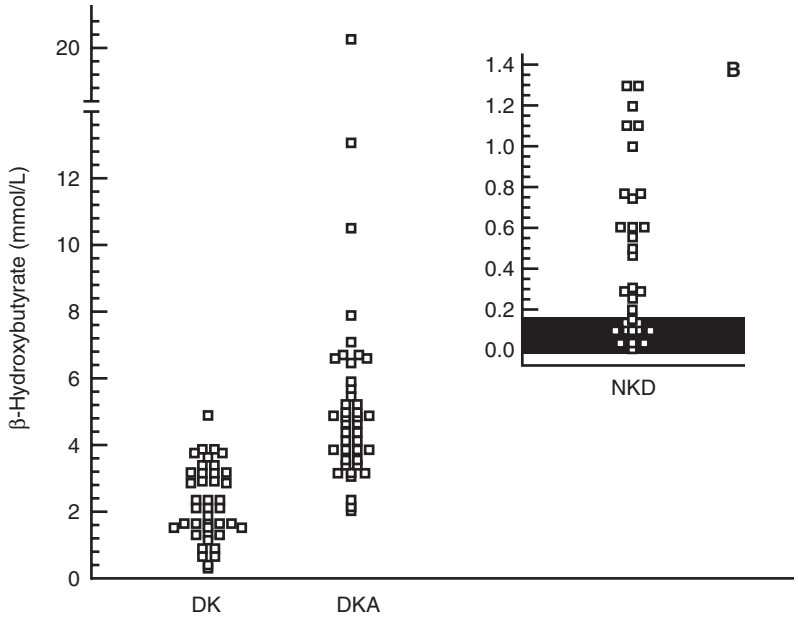

FIGURE 8-7 Serum beta-hydroxybutyrate (β-OHB) concentrations from dogs with diabetic ketoacidosis *(DKA)* and diabetic ketosis *(DK).* The small plot *(B)* is a graphic depiction of serum β-OHB concentrations from dogs with non-ketotic diabetes mellitus *(NKD)* compared to the reference interval *(shaded area).* (From Duarte R, et al.: Accuracy of serum β-hydroxybutyrate measurements for the diagnosis of diabetic ketoacidosis in 116 dogs. *J Vet Intern Med* 16:411, 2002.)

results for ketonuria (Di Tommaso et al, 2009; Zeugswetter et al, 2010; Aroch et al, 2012). The magnitude of increase in serum β-hydroxybutyrate concentration correlates with the severity of the metabolic acidosis with the highest concentrations identified in dogs with DKA (Duarte et al, 2002; Fig. 8-7). However, a recent study by Durocher, et al., (2008) suggested that acetoacetate may be the predominate ketone body in some dogs with DKA. Serum β-hydroxybutyrate and total ketone body concentrations were measured in 48 diabetic dogs. As expected, serum β-hydroxybutyrate concentrations were increased in the dogs, but when expressed as a percentage of total serum ketone concentration, serum β-hydroxybutyrate concentration decreased from approximately 60% to 20% as serum total ketone concentration (and presumably acetoacetate concentration) increased (Fig. 8-8). These findings suggest that the predominate ketone body (β-hydroxybutyrate versus acetoacetate) may differ between dogs. Regardless, measurement of β-hydroxybutyrate in blood is indicated whenever DK or DKA is suspected but ketonuria is absent.

In a recent study evaluating plasma and urine ketone measurements using dipstick methodology (Ketostix) in cats with DK and DKA based on increased plasma β-hydroxybutyrate concentrations, positive plasma and urine test results for acetoacetate were found in approximately 46% and 20% of the cats, respectively (Zeugswetter and Pagitz, 2009). The sensitivity of the plasma ketone dipstick test was 100%, and a negative plasma test result reliably excluded DKA, suggesting that the plasma ketone dipstick test may be a useful tool to rule out DKA in cats.

A subsequent study evaluating a hand-held glucose and ketone meter (Precision Xtra, Abbott) for measuring β-hydroxybutyrate in whole blood in diabetic cats showed a good linear correlation with a reference laboratory method at low to moderate β-hydroxybutyrate concentrations (Zeugswetter and Rebuzzi, 2012). Unfortunately, a significant negative bias was identified at high concentrations of β-hydroxybutyrate. Beta-hydroxybutyrate

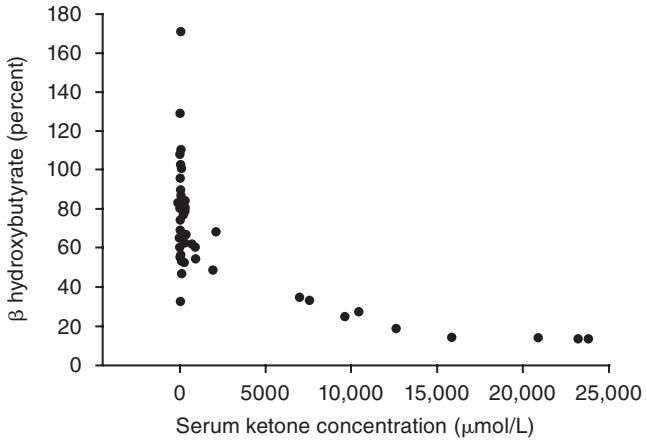

FIGURE 8-8 Scatterplot of serum β-hydroxybutyrate concentration, expressed as a percentage of serum ketone concentration, versus serum ketone concentration in 48 dogs with diabetes mellitus. (From Durocher LL, et al.: Acid-base and hormonal abnormalities in dogs with naturally occurring diabetes mellitus, *J Am Vet Med Assoc* 232:1310, 2008.)

concentrations greater than 2.55 mmol/L had a sensitivity of 94% but a specificity of 68% for diagnosing ketoacidemia. Many cats with high β-hydroxybutyrate concentrations and normal blood pH had an elevated chloride gap suggestive of superimposed hypochloremic metabolic alkalosis. The authors concluded that the ketone meter was a valid tool for excluding DKA in sick diabetic cats and for identifying resolution of ketonemia when treating a DKA cat.

The aggressiveness of the diagnostic evaluation and treatment of a dog or cat with DKA is dictated primarily by results of the history and physical examination. A diagnosis of severe DKA is indicated in dogs and cats with systemic signs of illness (i.e., lethargy, anorexia, and/or vomiting); a physical examination

revealing dehydration, depression, weakness, and/or Kussmaul respiration; blood glucose concentration greater than 600 mg/dL (34 mmol/L); and severe metabolic acidosis as diagnosed by a total venous CO_2 or arterial bicarbonate concentration less than 12 mEq/L. History and physical examination findings are subjective, however, and a veterinarian may not be able to obtain quick acid-base information. Therefore, a diagnosis of severe DKA is often initially based on having an *ill* dog or cat with glucose and ketones in the urine. Dogs and cats with severe DKA require hospitalization and immediate initiation of fluid therapy (see Fluid Therapy). Additional diagnostic tests are necessary to care for these animals properly (see the next section), but therapy should proceed while remaining tests are pending.

A tentative diagnosis of DK is reserved for diabetic dogs and cats that are apparently healthy but have both glucose and ketones present in the urine. Systemic signs of illness are absent or mild, serious abnormalities are not readily identifiable on physical examination, and metabolic acidosis has not yet developed or is mild (i.e., total venous CO_2 or arterial bicarbonate concentration greater than 16 mEq/L). Dogs and cats with DK are not in need of immediate aggressive therapy and must be distinguished from the pet with a critical metabolic emergency. The apparently healthy ketotic diabetic can often be managed conservatively, usually without fluid therapy, whereas the animal with severe DKA requires a much more intensive therapeutic plan involving treatments with a variety of contingency alternatives based on numerous assessments of related parameters.

IN-HOSPITAL DIAGNOSTIC EVALUATION

The laboratory evaluation of "healthy" ketotic diabetic dogs and cats is similar to that for non-ketotic diabetics (see Clinical Pathologic Abnormalities in Chapter 6 and Establishing the Diagnosis of Diabetes Mellitus in Chapter 7). The healthy ketotic diabetic can usually be managed conservatively, as contrasted with the needs of an extremely ill DKA pet. Critically important information for formulating the initial treatment protocol in the sick DKA pet include hematocrit and total plasma protein concentration; serum glucose, albumin, creatinine, and urea nitrogen concentrations; serum electrolytes; venous total CO_2 or arterial acid-base evaluation; and urine specific gravity. Abnormalities frequently associated with DKA are listed in Box 8-2. Once treatment for DKA is initiated, additional studies (e.g., a complete blood count [CBC], serum biochemistry panel, urinalysis, urine culture, thoracic radiographs, and abdominal ultrasound) or diagnostic tests for pancreatitis, diestrus in the female dog, and hyperthyroidism in the cat are usually warranted to identify underlying concurrent disorders (Box 8-3).

Urinalysis and Urine Culture

The urinalysis can serve several purposes simultaneously. The most obvious reason for obtaining a urine sample is to identify glycosuria and ketonuria. Urinary tract infection is a common and important contributing factor in DKA. The presence of bacteriuria, hematuria, and pyuria on urinalysis supports the presence of urinary tract infection and the need for culture of a urine sample. If possible, urine should be obtained by cystocentesis. Because of the high incidence of urinary tract infections in our cats and especially dogs with DKA, we routinely culture urine, regardless of findings on urinalysis (Bailiff et al, 2006). Proteinuria may be the result of urinary tract infection or glomerular damage secondary to disruption of the basement membrane. Evaluation of a urine protein-to-creatinine ratio performed on a urine sample void of infection or inflammation can help determine if the proteinuria is significant.

BOX 8-2 Common Clinicopathologic Abnormalities Identified in Dogs and Cats with Diabetic Ketoacidosis

- Neutrophilic leukocytosis, signs of toxicity if septic
- Hemoconcentration
- Hyperglycemia
- Hypercholesterolemia, lipemia
- Increased alkaline phosphatase activity
- Increased alanine aminotransferase activity
- Increased blood urea nitrogen (BUN) and serum creatinine concentrations
- Hyponatremia
- Hypochloremia
- Hypokalemia
- Metabolic acidosis
- Hyperosmolality
- Glycosuria
- Ketonuria
- Urinary tract infection

BOX 8-3 Diagnostic Tests for Insulin Resistance in Diabetic Dogs and Cats

- Complete blood count (CBC), serum biochemistry panel, and urinalysis
- Bacterial culture of the urine
- Serum canine/feline pancreatic-specific lipase (SPEC cPL/fPL) (pancreatitis)
- Serum trypsin-like immunoreactivity (TLI) (exocrine pancreatic insufficiency)
- Adrenocortical function tests
  - Urine cortisol-to-creatinine ratio (spontaneous hyperadrenocorticism)
  - Low-dose dexamethasone suppression test (spontaneous hyperadrenocorticism)
  - Adrenocorticotropic hormone (ACTH)-stimulation test (iatrogenic hyperadrenocorticism)
- Thyroid function tests
  - Baseline serum total and free thyroxine (hypothyroidism and hyperthyroidism)
  - Serum thyroid-stimulating hormone (TSH; hypothyroidism)
- Serum progesterone concentration (diestrus in intact female dog)
- Fasting serum triglyceride concentration (hyperlipidemia)
- Plasma growth hormone or serum insulin-like growth factor-1 (IGF-1) concentration (acromegaly)
- Serum insulin concentration 24 hours after discontinuation of insulin therapy (insulin antibodies)
- Abdominal ultrasonography (adrenomegaly, adrenal mass, pancreatitis, pancreatic mass, inflammatory bowel disease, neoplasia)
- Thoracic radiography (cardiomegaly, neoplasia)
- Computed tomography or magnetic resonance imaging (pituitary mass)

From Nelson RW, Couto CG: *Small animal internal medicine,* ed 5, St Louis, 2014, Elsevier/Mosby.

Azotemia is also common in DKA, and evaluation of urine specific gravity from a sample of urine obtained prior to initiation of fluid therapy is helpful in differentiating prerenal azotemia from primary kidney failure. Urine specific gravity must be assessed with the severity of glycosuria and the hydration status of the dog or cat kept in mind. If the animal is clinically dehydrated and has normal kidney function, its urine specific gravity should be greater than 1.030. Urine specific gravities that are less than 1.020 are suggestive of primary kidney disease or concurrent polyuria/polydipsia disorder (e.g., hyperadrenocorticism). Glycosuria will increase the urine specific gravity measured by refractometers and should be considered when interpreting urine specific gravity. As a general rule of thumb, 2% or 4+ glycosuria as measured on urine reagent test strips will increase the urine specific gravity 0.008 to 0.010 when urine specific gravity is measured by refractometry.

Oliguric and anuric kidney failure is an infrequent but grave complication of DKA. Severe hyperglycemia (> 600 mg/dL; 34 mmol/L) is not likely to occur without a significant reduction in the GFR due to primary kidney disease or severe dehydration and poor renal perfusion. It is critical that urine production be closely monitored in the severely ill DKA animal. Although diabetic dogs and cats are prone to develop infection, it is still strongly recommended that the animal with severe DKA and concurrent azotemia have an indwelling urinary catheter secured in the bladder and attached to a closed collection system. The urine volume produced over the initial 12 hours of therapy can be assessed and oliguric or anuric kidney failure quickly recognized. Rapid institution of appropriate measures to improve GFR and urine production can then be initiated. Urine production should increase once dehydration is corrected and normovolemia restored in the dog or cat with severe prerenal azotemia and decreased GFR. Once adequate urine production is confirmed, the indwelling urinary catheter can be removed.

The Minimum Data Base (Ketoacidosis Profile)

Blood Glucose

Although the average blood glucose concentration in dogs and cats with DKA is approximately 500 mg/dL (28 mmol/L), values can range from close to 200 mg/dL (11 mmol/L) to concentrations greater than 1000 mg/dL (56 mmol/L) (Fig. 8-9). Because hepatic production of glucose is excessive in dogs and cats with DKA and relative or absolute deficiencies of insulin always exist, it is likely that the degree of hyperglycemia is determined primarily by the severity of dehydration and corresponding decrease in GFR. Evidence suggests that blood glucose concentrations become extremely elevated (i.e., > 600 mg/dL; 34 mmol/L) only when the ECF volume has decreased to the point that urine flow and the capacity to excrete glucose are impaired. Studies have shown a marked reduction in the blood glucose concentration when humans with DKA were treated solely with fluids (i.e., no insulin) (Owen et al, 1981); these findings have also been seen clinically in diabetic dogs and cats (Fig. 8-10). An association has been made in diabetic humans between the maximum attainable blood glucose concentration and the severity of reduction in GFR (Kandel and Aberman, 1983). The initial blood glucose concentration also dictates, in part, how aggressive the initial fluid and insulin therapy should be. The higher the blood glucose concentration, the higher the plasma osmolality, and the more at-risk the animal is for developing cerebral edema following a sudden decrease in plasma osmolality; therefore the rate of blood glucose decline needs to be slower during the initial hours of treatment.

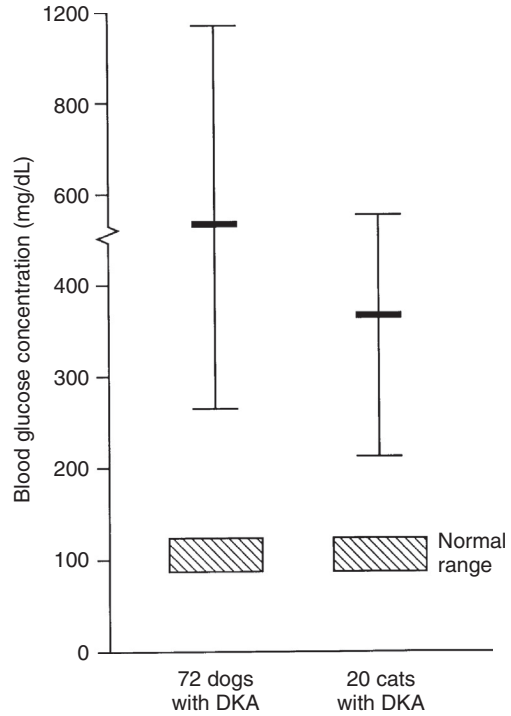

FIGURE 8-9 Mean and range of blood glucose concentration determined at the time diabetic ketoacidosis *(DKA)* was diagnosed in 72 dogs and 20 cats.

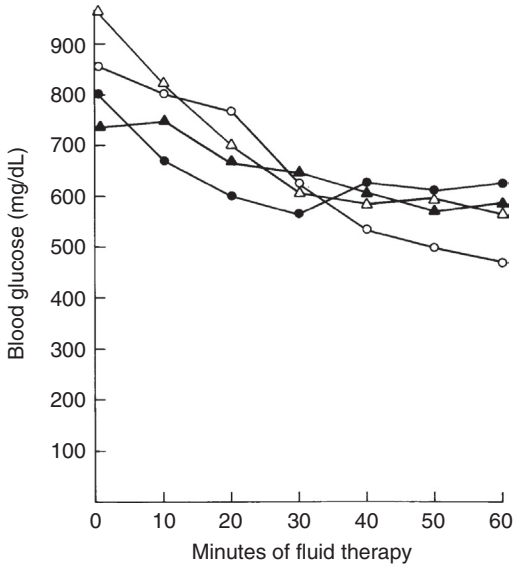

FIGURE 8-10 The effect of fluid therapy on four severely diabetic ketoacidotic dogs over a period of 1 hour, without insulin administration.

Acid-Base Status

Metabolic acidosis is one of the hallmark clinical pathologic changes in DKA and is the direct result of an excess accumulation of ketone bodies in the blood. Excessive serum ketones can overwhelm the body's buffering system, causing an increase in arterial

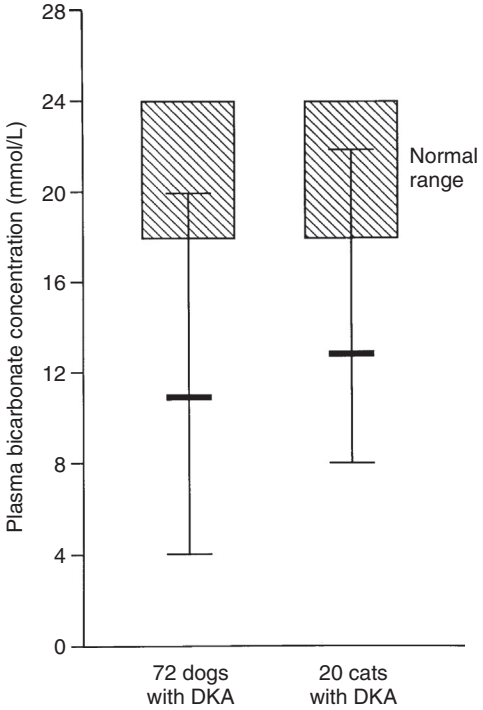

FIGURE 8-11 Mean and range of plasma bicarbonate concentration determined at the time diabetic ketoacidosis *(DKA)* was diagnosed in 72 dogs and 20 cats.

hydrogen ion concentration, a decrease in serum bicarbonate, and a progressively worsening metabolic acidosis (Fig. 8-11).

Failure of the kidneys to compensate adequately for the acid load in DKA is partly the result of the physicochemical properties of β-hydroxybutyrate and acetoacetate. The renal threshold for these acids is low, and appreciable excretion occurs at plasma concentrations only slightly above normal. Thus, the renal tubules are easily overwhelmed when these acids are synthesized in excessive quantities by the liver. This creates a situation in which the amount of acid present surpasses the renal capacity for urine acidification. Furthermore, β-hydroxybutyrate and acetoacetate are relatively strong acids (pKa 4.70 and 3.58, respectively). Even at the lowest urinary pH, they are excreted mostly as sodium and potassium salts, resulting in the concomitant loss of bicarbonate.

Recognition of acidosis is usually straightforward with the use of arterial blood gas or venous total CO_2 determinations (Table 8-1). In DKA, the severity of changes in arterial blood gas or venous total CO_2 depends on the duration and severity of hyperketonemia at the time of presentation to the veterinarian. Arterial pH can range from 7.2 to as low as 6.6. Dogs and cats with arterial blood pH values less than 7.0 have life-threatening DKA and are often difficult to treat successfully (Hume et al, 2006). A tremendous amount of controversy surrounds therapy directed specifically at the acidosis component of DKA. A discussion on the pros and cons of bicarbonate therapy for animals with severe DKA is found in the Bicarbonate Therapy section later in this chapter.

Serum Sodium Concentration

The serum sodium concentration is a reflection of the relative amounts of water and sodium present in the body. With rare exception, dogs and cats with DKA have significant deficits in total body sodium, regardless of the measured serum concentration. In 72 dogs with DKA, 62% were hyponatremic and only 7% were hypernatremic (Fig. 8-12). Similarly, in 42 cats with

TABLE 8-1 **ARTERIAL pH, PCO_2, AND HCO_3^- IN SIMPLE ACUTE ACID-BASE DISORDERS**

CONDITION	pH	ARTERIAL PCO_2	TOTAL VENOUS CO_2*
Acidosis			
Respiratory	↓	↑↑	↑
Metabolic	↓	↓	↓↓
Alkalosis			
Respiratory	↑	↓↓	↓
Metabolic	↑	↑	↑↑

Double arrows indicate primary change; HCO_3^-, bicarbonate ion; PCO_2, partial pressure of carbon dioxide.
*The total venous CO_2 concentration is equal to the arterial bicarbonate concentration.

DKA, 80% were hyponatremic and only 5% were hypernatremic (Bruskiewicz et al, 1997).

Hyponatremia results from excessive urinary sodium loss caused by the osmotic diuresis induced by glycosuria and ketonuria. Because insulin enhances renal sodium reabsorption in the distal portion of the nephron, its absence results in sodium wasting. Hyperglucagonemia, vomiting, and diarrhea also contribute to the sodium loss in DKA (Foster and McGarry, 1983).

It is important to consider the severity of hyperglycemia when assessing the severity of hyponatremia in the dog or cat with DKA. Because glucose penetrates cells poorly in the absence of insulin, an increase in ECF glucose concentration creates a transcellular osmotic gradient that results in the movement of water out of the cells, a corresponding reduction in the plasma sodium concentration, and a falsely decreased measured sodium value. In general, for every 100 mg/dL of plasma glucose above the reference range, plasma sodium concentration decreases by approximately 1.6 mEq/L (DiBartola, 2012). Conversely, as insulin therapy drives glucose into the cells, water will follow and the plasma sodium concentration will increase. The measured sodium value should be corrected to a sodium value that accounts for hyperglycemia by using the following formula:

$$\text{Corrected } Na^+ = 1.6 \times (\text{measured glucose [mg/dL]} - 100)/100 + \text{measured } Na^+$$

This reflects that the measured serum sodium value is decreased by approximately 1.6 mEq for every 100 mg/dL increase in glucose above 100 (Nugent, 2005).

Severe hypertriglyceridemia may occasionally cause factitious hyponatremia. Severe hypertriglyceridemia can be recognized by the presence of gross lipemia on visual inspection of serum or plasma or by the presence of lipemia retinalis on ophthalmoscopic examination and confirmed by measurement of triglyceride concentration in serum or plasma. Physiologic saline and Ringer's solutions have adequate sodium quantities for replacement of sodium deficiencies and are recommended as the initial fluids of choice for the treatment of severe DKA (see Fluid Therapy later in this chapter).

Serum Potassium Concentration

During DKA, intracellular dehydration occurs as hyperglycemia and water loss lead to increased plasma and ECF tonicity and a shift of water out of cells. This shift of water is also associated with a shift of potassium into the extracellular space (Kitabchi et al, 2001; Fig. 8-13). Potassium shifts are further enhanced by

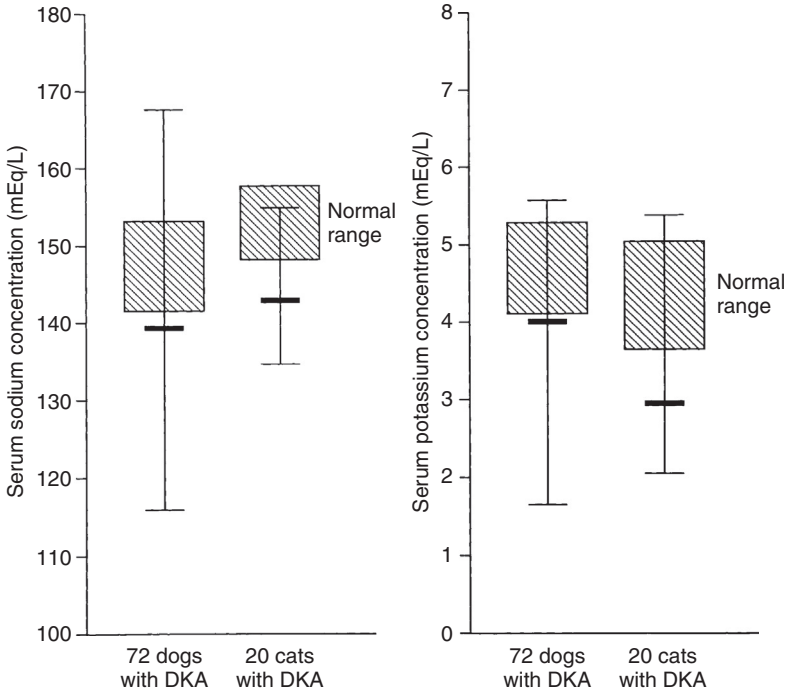

FIGURE 8-12 Mean and range of serum sodium and potassium concentrations determined at the time diabetic ketoacidosis *(DKA)* was diagnosed in 72 dogs and 20 cats.

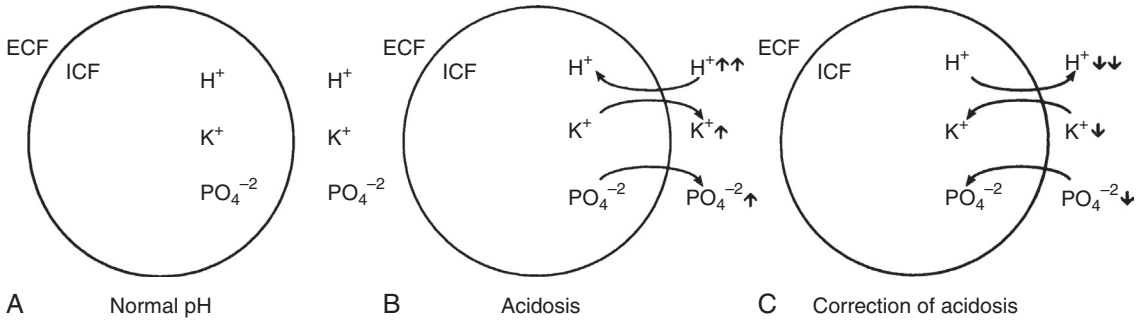

FIGURE 8-13 Redistribution of extracellular fluid *(ECF)* and intracellular fluid *(ICF)* hydrogen, potassium, and phosphate ions in response to a decrease in ECF pH (i.e., acidosis); an increase in ECF glucose and osmolality; and the translocation of water from the ICF to the ECF compartment and subsequent correction of acidosis and the intracellular shift of glucose and electrolytes with insulin treatment. **A,** Normal ECF pH. **B,** ECF H^+ concentration increases during acidosis, causing H^+ to move into cells and down its concentration gradient. Increase in ECF glucose and osmolality causes extracellular shift of water, K^+, and PO_4^{+2}. **C,** ECF H^+ concentration decreases during correction of acidosis, causing H^+ to move out of cells. Insulin administration and correction of acidemia cause an intracellular shift of glucose, K^+, and PO_4^{+2}, decreasing ECF K^+ and PO_4^{+2} concentration.

the presence of acidosis and the breakdown of intracellular protein secondary to insulin deficiency. Entry of potassium into cells is also impaired in the presence of insulinopenia. The osmotic diuresis induced by glycosuria and ketonuria causes marked urinary losses of potassium. Secondary hyperaldosteronism induced by plasma volume contraction, gastrointestinal losses, and decreased dietary intake augment the potassium deficiency (Kitabchi et al, 2001). As a consequence, most dogs and cats with DKA have a net deficit of total body potassium. Serum potassium concentrations can be decreased, normal, or increased, depending on the duration of illness, kidney function, and previous nutritional state of the dog or cat. Most dogs and cats with DKA have either normal or decreased serum potassium concentrations on pretreatment testing (see Fig. 8-12). In 72 dogs and 42 cats with DKA, 43% and 67% were hypokalemic and 10% and 7% were hyperkalemic, respectively, at the time DKA was diagnosed (Bruskiewicz et al, 1997).

Knowing the serum potassium concentration and status of kidney function is critical when deciding on the aggressiveness of potassium supplementation in the intravenous (IV) fluids. Polyuric DKA animals are predisposed to *severe* hypokalemia, and oliguric/anuric animals are predisposed to *severe* hyperkalemia. Insulin treatment causes a marked translocation of potassium from the ECF to the intracellular fluid (ICF) compartment, which when combined with continuing kidney and gastrointestinal loss, can cause severe hypokalemia during the initial 24 to 48 hours of treatment. DKA dogs and cats that are hypokalemic on initial evaluation require aggressive potassium supplementation to their IV fluids to replace deficits and to prevent worsening hypokalemia (see Monitoring Fluid Therapy later in this chapter).

Blood Urea Nitrogen and Creatinine

The blood urea nitrogen (BUN) and serum creatinine concentrations are commonly elevated in DKA (Fig. 8-14) and are useful indicators of the severity of volume depletion. When evaluated in conjunction with the urine specific gravity and serum calcium and phosphorus concentrations, they can also help to identify concurrent primary kidney failure versus prerenal azotemia. In addition, the initial BUN or serum creatinine concentration can serve as a measure of the success of fluid therapy. A rapidly falling BUN and serum creatinine concentration in an azotemic dog or cat is consistent with proper fluid therapy, good urine output, and prerenal azotemia. The increased BUN and serum creatinine concentration that is slowly declining or static suggests inadequate fluid therapy or primary kidney failure. Serum creatinine concentrations may also be falsely increased due to interference from acetoacetate with some automated creatinine assays (Molitch et al, 1980; Nanji and Campbell, 1981).

Serum Osmolality

Hyperosmolality is a potentially serious development in DKA, one that can have profound effects on CNS function and consciousness. Of all the factors related to stupor or altered consciousness, including the serum levels of glucose, ketones, or arterial pH, the serum osmolality correlates best with the level of consciousness in humans with DKA. "Clouded consciousness" is an extremely subjective finding in humans, making recognition of such a problem guesswork in dogs or cats. Nevertheless, veterinarians and owners can usually recognize "depression" in the dog and cat, and, in our experience, the severity of this sign roughly correlates with the severity of hyperosmolality.

Fortunately, severe hyperosmolality (> 350 mOsm/kg of H_2O) occurs infrequently in dogs and cats with DKA, in part because of the concurrent prevalence of hyponatremia (see Fig. 8-12). Serum sodium concentration and, to a lesser extent, glucose are the primary determinants of *effective* serum osmolality. Cell membranes are permeable to potassium and urea and, as such, these solutes are *ineffective* osmoles. Hyperosmolality, if present, usually resolves with IV isotonic fluid and insulin therapy, albeit correction of the hyperosmolar state must be done slowly to minimize the shift of water from the extracellular to the intracellular compartment.

Many veterinary hospitals, especially those with a large emergency case load, have the necessary equipment to measure serum or plasma osmolality directly. One can calculate the approximate *effective* osmolality of serum or plasma using the following formula:

$$\textit{Effective}\ \text{ECF Osmolality (mOsm/kg)} = 2\,(Na^+) + 0.05\,(\text{glucose [mg/dL]})$$

or

$$= 2\,(Na^+) + \text{glucose (mmol/L)}$$

In an insulin deficient state, the intracellular movement of glucose in insulin-dependent tissues is impaired and the increase in extracellular glucose creates an osmotic gradient between the ECF and ICF compartments. For this reason, glucose is included in calculations of *effective* osmolality. In contrast, potassium and urea remain freely permeable across cell membranes regardless of insulin concentrations and therefore are not included in calculations of *effective* serum osmolality. The approximate normal range for *effective* serum osmolality in the dog and cat is 280 to 300 mOsm/kg.

Anion Gap

The metabolic acidosis stemming from hyperketonemia is an anion gap acidosis, which must be differentiated from other causes of anion gap acidosis (e.g., lactic acidosis, kidney failure, and/or ethylene glycol intoxication) and from hyperchloremic acidosis (Narins et al, 1994). The anion gap is calculated by subtracting the negatively charged anions, chloride and bicarbonate, from the most important positively charged cations, sodium and potassium. The normal anion gap for dogs and cats is 12 to 16 mEq/L (Feldman and Rosenberg, 1981). Anything greater than 16 mEq/L indicates the presence of an anion gap acidosis. The

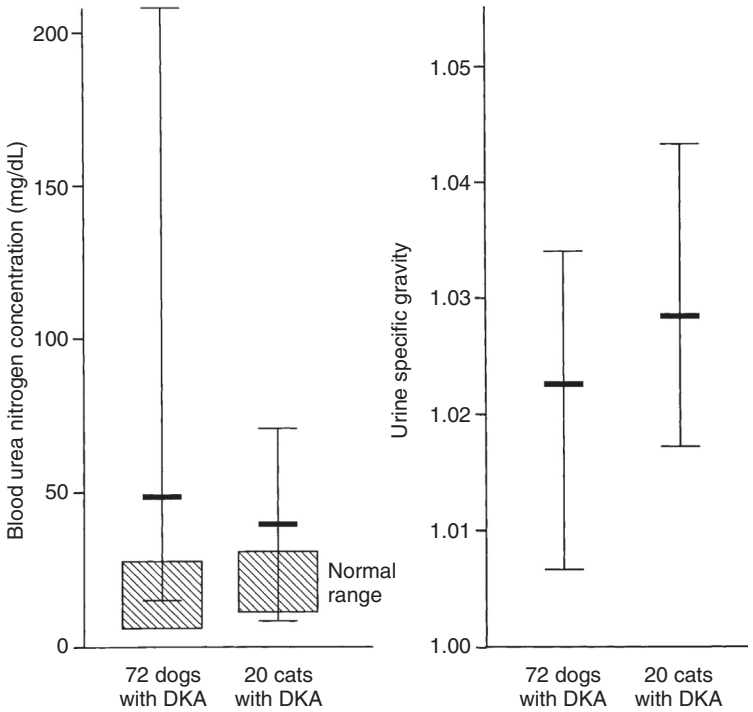

FIGURE 8-14 Mean and range of blood urea nitrogen (BUN) concentration and urine specific gravity determined at the time diabetic ketoacidosis *(DKA)* was diagnosed in 72 dogs and 20 cats.

unmeasured anions that comprise the normal anion gap include albumin and other circulating proteins, sulfate, phosphate, lactate, and a variety of organic acids.

The typical diabetic dog or cat in ketoacidosis has an anion gap that ranges from 20 to 35 mEq/L, and the increment in the anion gap above baseline approximates the decrement in serum bicarbonate concentration (Adrogué et al, 1982). A number of factors can disrupt the normal stoichiometry between acid retention, increment in the anion gap, and decrease in serum bicarbonate concentration (Box 8-4). Such disruption is common in DKA because urinary loss of ketoanions causes a disproportionately greater decrease in serum bicarbonate concentration compared with the increment in anion gap. In these cases, chloride replaces the missing ketoanion, and a component of hyperchloremic acidosis commonly accompanies the anion gap acidosis (Adrogué et al, 1982; 1984; Table 8-2). Dogs and cats that are volume contracted tend to have a pure anion gap acidosis, because the decrease in GFR and tubular avidity for sodium reabsorption limit the urinary loss of ketone bodies. Conversely, animals with DKA able to maintain salt and water intake avoid severe volume depletion. These animals have variable degrees of hyperchloremic acidosis due to the urinary excretion of ketone salts and a concomitant retention of chloride (see Table 8-2).

Completing the Data Base

Complete Blood Count

The CBC in uncomplicated DKA usually reveals a neutrophilic leukocytosis without evidence of toxic neutrophils (Bruskiewicz et al, 1997; Hume et al, 2006). The leukocytosis may occur secondary to the release of "stress" hormones or severe inflammation, especially if an underlying pancreatitis is present. White blood cell counts greater than 30,000/μL, the presence of toxic or degenerative neutrophils, or a significant left shift toward immaturity of the cells supports the presence of a severe inflammatory and/or infectious process as the cause of the leukocytosis. The red blood cell count and hematocrit should be consistent with hemoconcentration secondary to dehydration. A hematocrit below 35% in these typically volume-contracted animals should arouse suspicion that blood loss has occurred or that significant bone marrow suppression or another problem has resulted in anemia.

BOX 8-4 Influences of Common Metabolic Disorders on the Calculated Anion Gap*

Increased Anion Gap
Diabetic ketoacidosis (DKA)
Lactic acidosis
- Tissue ischemia and/or hypoxemia
- Sepsis
- Malignancy
- Drugs

Uremic acidosis
Ethylene glycol intoxication
Salicylate intoxication

Normal Anion Gap
Diarrhea
Renal tubular acidosis
Hypoadrenocorticism
Hyperchloremic acidosis
Ammonium chloride
Carbonic anhydrase inhibitors

*These disorders are frequently associated with metabolic acidosis.

Liver Enzymes and Total Bilirubin

Clinical pathologic abnormalities associated with the liver are common in dogs and cats with DKA and are usually caused by hepatic lipidosis, pancreatitis, severe acidosis, hypovolemia, hypoxia, sepsis, and, less commonly, extrahepatic biliary obstruction caused by acute severe pancreatitis, acute and chronic hepatitis, and cholangiohepatitis. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or alkaline phosphatase (ALP) are usually increased, even in a non-ketotic diabetic animal. A more worrisome hepatopathy and/or acute severe pancreatitis should be suspected when icterus, a marked increase in serum liver enzyme activities (higher than expected with hepatic lipidosis), or abnormalities involving endogenous liver function tests (e.g., hypoalbuminemia, hypocholesterolemia, increased bile acids) are identified. Acute and chronic hepatitis and cholangiohepatitis should also be considered in diabetic dogs and cats with persistent lethargy and anorexia despite correction of the metabolic derangements associated with DKA. Hepatitis and cholangiohepatitis often occur in conjunction with pancreatitis. When appropriate, abdominal ultrasound and histologic evaluation of a liver biopsy specimen may be indicated to establish concurrent liver disease.

Pancreatic Enzymes

Because acute and chronic pancreatitis is so common in dogs and cats with DKA, a diagnostic evaluation for its existence is always warranted (Bruskiewicz et al, 1997; Hume et al, 2006). In our experience, abdominal ultrasound is the single best diagnostic test for identifying acute and chronic pancreatitis in the dog or cat with DKA (Fig. 8-15); however, results are equipment and operator dependent. Blood tests to assess for the presence of pancreatitis should also be considered in the newly-diagnosed diabetic dog or cat with DKA and in dogs or cats with recurring bouts of DKA, especially if abdominal ultrasound is not available. Measurement of canine and feline pancreatic-specific lipase (SPEC cPL and SPEC fPL) is currently the blood test of choice for identifying pancreatitis (Forman et al, 2004; Trivedi et al, 2011; McCord et al, 2012). Preliminary studies evaluating a less expensive novel catalytic assay for colorimetric determination of serum

TABLE 8-2 EXAMPLES OF SERUM ELECTROLYTE CONCENTRATIONS AND THEIR ASSOCIATED ANION GAPS IN ACIDOSIS

	SODIUM (mEq/L)	POTASSIUM (mEq/L)	CHLORIDE (mEq/L)	BICARBONATE (mEq/L)	ANION GAP* (mEq/L)
Normal	142	4	108	22	12
Hyperchloremic acidosis	142	4	118	12	12
Anion gap acidosis	142	4	108	12	22

*Anion gap = (Na + K) − (Cl + bicarbonate); the normal anion gap is 12 to 16 mEq/L.

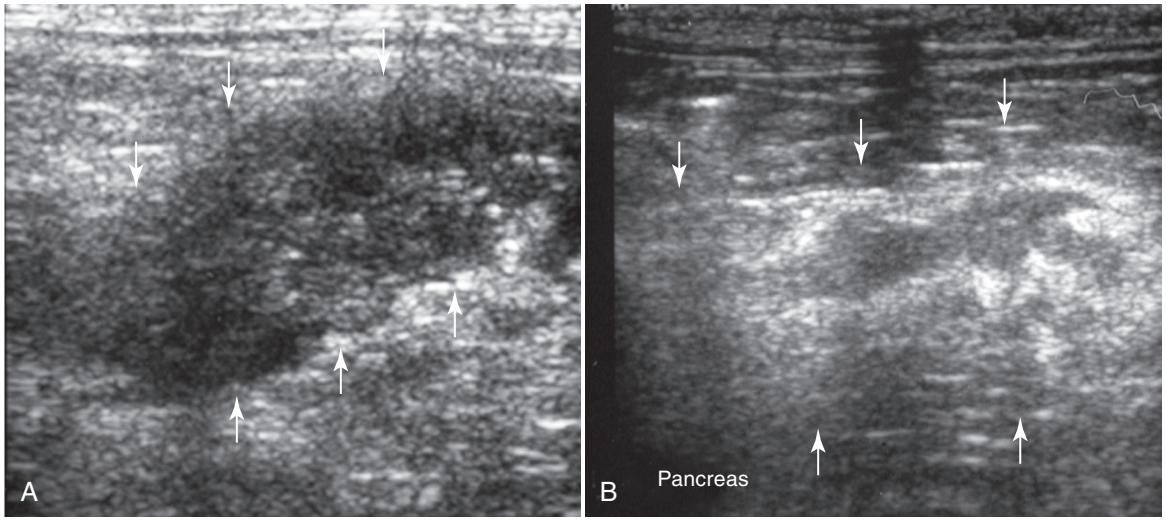

FIGURE 8-15 Abdominal ultrasound images of the pancreas *(arrows)* in a 10-year-old, spayed female Calico cat diagnosed with severe diabetic ketoacidosis (DKA) and acute pancreatitis. At presentation **(A),** the pancreas was enlarged and diffusely hypoechoic. On the fifth day of treatment **(B),** the pancreas was enlarged with a mixed echogenic pattern characterized by a hypoechoic center and a hyperechoic periphery, changes consistent with resolving pancreatitis. The cat underwent diabetic remission 5 weeks after discharge but was euthanized 2 years later because of reoccurring bouts of pancreatitis and insulin-requiring diabetes.

lipase activity in dogs and cats found substantial agreement with SPEC cPL and SPEC fPL results from the same blood samples, suggesting that the novel catalytic assay may offer a cost-effective alternative diagnostic test for pancreatitis in dogs and cats (Graca et al, 2005; Oppliger et al, 2013). Sensitivity and specificity of SPEC cPL and SPEC fPL varies between studies and is dependent on the severity of pancreatitis and the cutoff value (200 versus 400 µg/L in dogs; 6.8 versus 10 µg/L in cats) used to differentiate normal from pancreatitis (McCord et al, 2012; Bostrom et al, 2013). Serum SPEC cPL and SPEC fPL concentrations can be increased in dogs and cats with a histologically confirmed normal pancreas and normal in dogs and cats with histologically confirmed inflammation of the pancreas, especially when the inflammatory process is chronic and mild (Forman et al, 2004; McCord et al, 2012). Interpretation of serum SPEC cPL and SPEC fPL results should always be done in context with the history, physical examination, and additional findings on laboratory tests. Recognition of concurrent pancreatitis in the dog or cat with DKA has important implications regarding initial fluid therapy, subsequent dietary therapy, and prognosis. Fortunately, fluid therapy is the cornerstone of treatment for both DKA and pancreatitis.

Calcium and Phosphorus

The serum calcium and phosphorus concentrations are usually normal in the diabetic dog or cat with "uncomplicated" DKA. If concurrent primary kidney failure is present, the serum calcium concentration is typically normal, whereas the serum phosphorus concentration is increased. Hypocalcemia may occur in dogs and cats with concurrent pancreatitis, hypomagnesemia, or hypoproteinemia. The hypocalcemia is usually mild and does not require treatment per se. Hypercalcemia supports the existence of concurrent disease affiliated with the development of hypercalcemia (see Chapter 15).

Attention has been directed to serum phosphorus concentrations in dogs and cats with DKA, especially during the initial 24 hours of treatment. Phosphate, along with potassium, shifts from the intracellular to the extracellular compartment in response to hyperglycemia and hyperosmolality (Kitabchi et al, 2001; see Fig. 8-13). Osmotic diuresis subsequently leads to enhanced urinary phosphate loss. Serum phosphorus concentrations can be decreased, normal, or increased, depending on the duration of illness and kidney function. Most dogs and cats with DKA have either normal or decreased serum phosphorus concentrations on pretreatment testing. Hypophosphatemia (< 3.0 mg/dL) was identified at initial presentation in 24% of 72 dogs and 48% of 42 cats with DKA (Bruskiewicz et al, 1997). In contrast, hyperphosphatemia (> 6.0 mg/dL) was identified in 14% and 26% of DKA dogs and cats, respectively, and usually occurred in conjunction with kidney failure.

Insulin treatment causes a marked translocation of phosphorus from the ECF to the ICF compartment. Within 24 hours of initiating treatment for DKA, serum phosphorus concentration can decline to severe levels (i.e., < 1 mg/dL) as a result of the dilutional effects of fluid therapy, the intracellular shift of phosphorus following the initiation of insulin therapy, and continuing kidney and gastrointestinal loss (Willard et al, 1987). Clinical signs usually do not develop until the serum phosphorus concentration is less than 1.5 mg/dL, and even at these low levels many dogs and cats remain asymptomatic. Hypophosphatemia primarily affects the hematologic and neuromuscular systems in the dog and cat (Forrester and Moreland, 1989). Hemolytic anemia is the most common and serious sequela to hypophosphatemia. Hypophosphatemia may decrease erythrocyte concentration of adenosine triphosphate (ATP) and/or alter red blood cell membrane lipids, which increases erythrocyte fragility, leading to hemolysis (Shilo et al, 1985; Adams et al, 1993). Hemolysis is usually not identified until the serum phosphorus concentration is 1 mg/dL or less. Hemolytic anemia can be life threatening if not recognized and treated. Neuromuscular signs include weakness, ataxia, and seizures, as well as anorexia and vomiting secondary to intestinal ileus. Phosphate therapy is indicated if clinical signs or hemolysis are identified or if the serum phosphorus concentration is less than 1.5 mg/dL, especially if a further decrease is possible (see Phosphate Supplementation).

Magnesium

The osmotic diuresis of DKA may cause significant urinary losses of magnesium and the development of hypomagnesemia (serum total magnesium concentration < 1.5 mg/dL; serum ionized magnesium concentration measured by ion-selective electrode < 1.0 mg/dL; Norris et al, 1999a; Fincham et al, 2004). In addition, the nature of the translocation of magnesium between the ICF and ECF compartments is similar to potassium in that factors that promote a shift of potassium into the ICF compartment (e.g., alkalosis, insulin, and/or glucose infusion) promote a similar shift in magnesium. During therapy for DKA, the serum total and ionized magnesium concentration can decline to severely low levels (i.e., less than 1 mg/dL and 0.5 mg/dL, respectively) as a result of the dilutional effects of fluid therapy and the intracellular shift of magnesium after the initiation of insulin therapy (Norris et al, 1999a; Hume et al, 2006). Clinical signs of hypomagnesemia do not usually occur until the serum total magnesium concentration is less than 1.0 mg/dL, and even at these low levels, many animals remain asymptomatic.

A magnesium deficiency can result in several nonspecific clinical signs, including lethargy, anorexia, muscle weakness (including dysphagia and dyspnea), muscle fasciculations, seizures, ataxia, and coma (Abbott and Rude, 1993; Martin et al, 1993; Dhupa and Proulx, 1998). Concurrent hypokalemia, hyponatremia, and hypocalcemia occur in animals with hypomagnesemia, although the prevalence of these electrolyte abnormalities may differ between species. These electrolyte abnormalities may also contribute to the development of clinical signs. Magnesium is a cofactor for all enzyme reactions that involve ATP, most notably the sodium-potassium ATPase pump. Deficiencies in magnesium may cause potassium-losing nephropathy and potassium wastage from the body and the resultant hypokalemia may be refractory to appropriate potassium replacement therapy. Magnesium deficiency may inhibit parathyroid hormone (PTH) secretion from the parathyroid gland, resulting in hypocalcemia (Bush et al, 2001). Magnesium deficiency causes the resting membrane potential of myocardial cells to be decreased and leads to increased Purkinje fiber excitability, with the consequent generation of arrhythmias (Abbott and Rude, 1993). Electrocardiographic changes include a prolonged PR interval, widened QRS complex, depressed ST segment, and peaked T waves. Cardiac arrhythmias associated with magnesium deficiency include atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, and ventricular fibrillation. Hypomagnesemia also predisposes animals to digitalis-induced arrhythmias.

Unfortunately, assessing an animal's magnesium status is problematic because there is no simple, rapid, and accurate laboratory test to gauge total body magnesium status. Serum total magnesium represents 1% of the body's magnesium stores, and serum ionized magnesium represents 0.2% to 0.3% of total body magnesium stores. As a result, serum total and ionized magnesium concentrations do not always reflect total body magnesium status. A normal serum magnesium concentration may exist despite an intracellular magnesium deficiency. However, a low serum magnesium concentration would support the presence of a total body magnesium deficiency, especially when clinical signs or concurrent electrolyte abnormalities are consistent with hypomagnesemia. Magnesium exists in three distinct forms in serum: an ionized fraction, an anion-complexed fraction, and a protein-bound fraction. A serum ionized magnesium concentration determined using an ion-selective electrode more accurately assesses total body magnesium content than measurement of serum total magnesium and is recommended (Norris et al, 1999b). Fortunately, hypomagnesemia is not usually a clinically recognizable problem during management of DKA, and magnesium supplementation is not recommended unless hypomagnesemia is documented in dogs and cats with complications that have been associated with hypomagnesemia (e.g., persistent lethargy and anorexia; refractory hypokalemia, hypocalcemia, or both).

BOX 8-5 Electrocardiographic Alterations Associated with Hypokalemia and Hyperkalemia in the Dog and Cat

Hypokalemia
Depressed T-wave amplitude
Depressed ST segment
Prolonged QT interval
Prominent U wave
Arrhythmias
  Supraventricular
  Ventricular

Hyperkalemia
Spiked T waves
Flattened P waves
Prolonged PR interval
Prolonged QRS interval
Decreased R-wave amplitude
Bradycardia
Complete heart block
Ventricular arrhythmias
Cardiac arrest

Diagnostic Imaging

Concurrent disorders (e.g., acute or chronic pancreatitis, pyometra, cholangiohepatitis, heart failure, bacterial pneumonia, and concurrent endocrinopathies) are common in dogs and cats with DKA. Many of these disorders actually perpetuate the metabolic derangements of DKA. Successful treatment of DKA requires recognition and treatment of these concurrent disorders. Abdominal and thoracic radiographs as well as abdominal ultrasonography are invaluable in confirming problems suspected after a review of the history and physical examination and in identifying problems previously unsuspected. In our hospital, thoracic radiography and abdominal ultrasonography are routine components of the diagnostic evaluation of any sick DKA dog or cat. However, radiographs and ultrasound scans are not usually obtained until more critical laboratory data (i.e., the *ketoacidotic profile*) have been analyzed and appropriate treatment for DKA initiated.

Electrocardiogram

The electrocardiogram (ECG) can be used to document and characterize suspected cardiac arrhythmias and for monitoring changes in serum potassium concentration during treatment of DKA. Use of the ECG is especially helpful for recognizing severe hypokalemia or hyperkalemia in hospitals where frequent monitoring of the serum potassium concentration is difficult because of lack of a point-of-care chemistry analyzer or because of economic constraints. The primary concern prior to and during treatment of DKA is hypokalemia. It must be emphasized that hypokalemia usually causes *subtle* changes in the ECG, especially when the serum potassium concentration is above 3.0 mEq/L (Box 8-5; Fig. 8-16). Changes in the ECG are more obvious when the serum potassium concentration is between 2.5 and 3.0 mEq/L, and alterations invariably occur with serum potassium levels below 2.5 mEq/L.

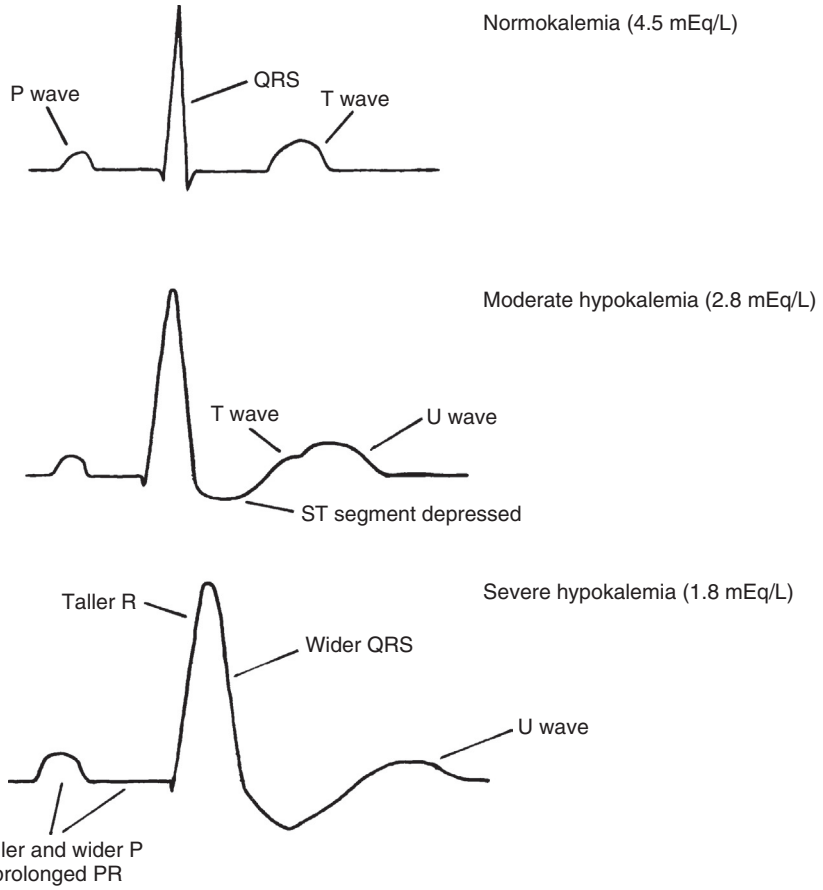

FIGURE 8-16 Profiles of serum potassium are reflected in the electrocardiogram (ECG). These changes are exaggerated here for illustration purposes. In practice, these changes can be quite subtle, indicating the necessity of a baseline ECG with simultaneous laboratory serum potassium.

The basic electrophysiologic alteration with hypokalemia is a gradual shift of the repolarization wave away from systole into diastole. The most consistent change on the ECG is prolongation of the QT interval. Additional findings include a progressive sagging of the ST segment, a decreased amplitude of the T wave, and a repolarization wave occurring after the T wave (U wave). In advanced hypokalemia, the amplitude and duration of the QRS complex are increased. It is believed that the QRS complex widens diffusely secondary to a generalized slowing of conduction in the ventricular myocardium or Purkinje fibers. The amplitude and the duration of the P wave increase, and the PR interval is slightly prolonged with hypokalemia. Atrial and ventricular premature contractions may also occur.

A complete description of the ECG findings in hyperkalemia is available in Chapter 12.

TREATMENT OF "HEALTHY" DOGS AND CATS WITH DIABETIC KETOSIS

Diabetic dogs and cats that have ketonuria but not metabolic acidosis (i.e., DK) are often relatively healthy aside from the typical clinical signs of uncontrolled diabetes mellitus. DK may be identified in newly-diagnosed diabetic dogs and cats or in diabetic dogs and cats that are being treated with insulin. Identification of ketonuria in insulin-treated diabetic dogs and cats indicates that insulin treatment has become ineffective, usually because of a problem with the insulin treatment regimen, development of a concurrent disorder causing insulin resistance, or both. Critical evaluation of the insulin treatment regimen and evaluation for concurrent disorders should be undertaken. If systemic signs of illness are absent or mild, inappetence is not present, serious abnormalities are not readily identifiable on physical examination, and metabolic acidosis is mild (i.e., total venous CO_2 or arterial bicarbonate concentration greater than 16 mEq/L), short-acting regular crystalline insulin can be administered subcutaneously three times daily until the ketonuria and ketonemia resolves. Fluid therapy and intensive care are usually not needed. Because regular crystalline insulin is potent insulin, the initial dosage (0.1 to 0.2 U/kg/injection) is lower than that recommended for longer-acting insulin preparations. To minimize hypoglycemia, the dog or cat should be fed one-third of its daily caloric intake at the time of each insulin injection. Subsequent adjustments in the insulin dose are based on clinical response and results of blood glucose measurements. Urine ketone concentrations should be monitored and, if available, blood glucose and β-hydroxybutyrate concentrations using a portable glucose and ketone meter (e.g., Precision Xtra, Abbott). A decrease in the blood glucose concentration implies a decrease in ketone production. This, in combination with metabolism of ketones and loss of ketones in urine, will usually correct ketosis within 48 to 96 hours of initiating insulin therapy. Prolonged ketonemia and ketonuria is suggestive of a significant concurrent illness (e.g., chronic pancreatitis) or inadequate blood insulin concentrations to suppress lipolysis and ketogenesis. Once the ketosis has resolved, insulin therapy may be initiated using longer-acting insulin preparations (see Chapters 6 and 7). As a general rule of thumb, the initial dosage of the longer-acting insulin preparation

BOX 8-6 Initial Management of the Dog or Cat with Severe Diabetic Ketoacidosis

Fluid Therapy

Type: 0.9% saline solution if hyponatremia is severe (< 130 mEq/L); isotonic crystalloid solution, such as Ringer's, lactated Ringer's solution, Plasma-Lyte 148, or Normosol-R if serum sodium concentration ≥ 130 mEq/L

Rate: 60 to 100 mL/kg/24 hours initially; adjust based on hydration status, urine output, persistence of fluid losses

Potassium supplement: Based on serum K^+ concentration (see Table 8-4); if unknown, initially add 40 mEq KCl to each liter of fluids

Phosphate supplement: Administer if serum phosphorus concentration < 1.5 mg/dL; initial IV infusion rate is 0.01 to 0.03 mmol phosphate/kg/hour in calcium-free IV fluids

Dextrose supplement: Not indicated until blood glucose concentration is less than 250 mg/dL (14 mmol/L), then begin 5% dextrose infusion

Bicarbonate Therapy

Indication: Administer if plasma bicarbonate concentration is less than 12 mEq/L or total venous CO_2 concentration is less than12 mmol/L; if not known, do not administer unless animal is severely ill and then only once

Amount: mEq HCO_3^- = body weight (kg) × 0.4 × (12 – animals HCO_3^-) × 0.5; if animal's HCO_3^- or total CO_2 concentration is unknown, use 10 in place of (12 – animal's HCO_3^-)

Administration: Add to IV fluids and give over 6 hours; do not give as bolus infusion

Retreatment: Only if plasma bicarbonate concentration remains less than 12 mEq/L after 6 hours of therapy

Insulin Therapy

Type: Regular crystalline insulin

Administration technique:

Intermittent IM technique: Initial dose, 0.1 to 0.2 U/kg IM; then 0.1 U/kg IM hourly until blood glucose concentration is less than 250 mg/dL (14 mmol/L), then switch to IM regular insulin every 4 to 6 hours or SC regular insulin every 6 to 8 hours

Low-dose IV infusion technique: To prepare infusion, add 2.2 U/kg (dogs) or 1.1 U/kg (cats) of regular insulin to 250 mL of 0.9% saline; run 50 mL through the drip set and discard; then administer via infusion or syringe pump through a line separate from that used for fluid therapy at an initial rate of 10 mL/hr; adjust infusion rate according to hourly blood glucose measurements; switch to SC regular insulin every 6 to 8 hours once blood glucose is less than 250 mg/dL or continue insulin infusion at a decreased rate to prevent hypoglycemia until the IV insulin preparation is exchanged for a longer-acting preparation

Goal: Gradual decline in blood glucose concentration, preferably around 50 mg/dL/hr (2.8 mmol/L/hr) until concentration is less than 250 mg/dL (14 mmol/L)

Ancillary Therapy

Concurrent pancreatitis is common in DKA; nothing by mouth and intensive fluid therapy usually indicated

Concurrent infections are common in DKA; use of broad-spectrum, parenteral antibiotics usually indicated

Additional therapy may be needed, depending on nature of concurrent disorders

Patient Monitoring

Blood glucose measurement every 1 to 2 hours initially; adjust insulin therapy and begin dextrose infusion when decreases below 250 mg/dL (14 mmol/L)

Hydration status, respiration, pulse every 2 to 4 hours; adjust fluids accordingly

Serum electrolyte and total venous CO_2 concentrations every 4 to 8 hours; adjust fluid and bicarbonate therapy accordingly

Urine output, glycosuria, urine and plasma ketones every 4 to 8 hours; adjust fluid therapy accordingly

Body weight, packed cell volume, temperature, and blood pressure every 6 to 8 hours

Additional monitoring, depending on concurrent disease

DKA, Diabetic ketoacidosis; *IM,* intramuscular; *IV,* intravenous; *SC,* subcutaneous.

is approximately the same as the dosage of regular crystalline insulin being administered at the time the switch in insulin is made with subsequent adjustments in the dosage based on the animal's response to the insulin.

TREATMENT OF SICK DOGS AND CATS WITH DIABETIC KETOACIDOSIS

Intensive therapy is called for if the dog or cat has systemic signs of illness (e.g., lethargy, anorexia, and/or vomiting); physical examination reveals dehydration, depression, weakness, or a combination of these; or metabolic acidosis is severe (i.e., total venous CO_2 or arterial bicarbonate concentration less than 12 mEq/L). The five goals of treatment of a severely ill diabetic dog or cat with ketoacidosis are (1) to restore water and electrolyte losses; (2) to provide adequate amounts of insulin to suppress lipolysis, ketogenesis, and hepatic gluconeogenesis; (3) to correct acidosis; (4) to identify the factors precipitating the present illness; and (5) to provide a carbohydrate substrate (i.e., dextrose) when necessary to allow continued administration of insulin without causing hypoglycemia (Box 8-6). Proper therapy does not mean forcing a return to a normal state as rapidly as possible. Because osmotic and biochemical problems can arise as a result of overly aggressive therapy as well as from the disease itself, rapid changes in various vital parameters can be as harmful as, or more harmful than, no change. If all abnormal parameters can be slowly returned toward normal over a period of 24 to 48 hours, therapy is more likely to be successful.

Fluid Therapy

Fig. 8-17 shows a flowchart for fluid therapy.

Composition and Rate of Administration

Initiation of appropriate fluid therapy should be the first step in the treatment of DKA, and in most cases it should precede the initiation of insulin therapy by 2 hours or longer to minimize the development of complications affiliated with insulin administration (see Monitoring and Complications of Therapy). Replacement of fluid deficiencies and maintenance of normal fluid balance are critical to ensure adequate cardiac output, blood pressure, and blood flow to all tissues. Improvement of renal blood flow is especially critical. In addition to the general beneficial aspects of fluid therapy in any dehydrated animal, fluid therapy can correct the deficiency in total body sodium and potassium, dampen the potassium-lowering effect of insulin treatment, and lower the blood glucose concentration in diabetics, even in the absence of insulin administration (see Fig. 8-10). Fluids enhance glucose excretion by increasing glomerular filtration and urine flow, and they decrease secretion of the diabetogenic hormones

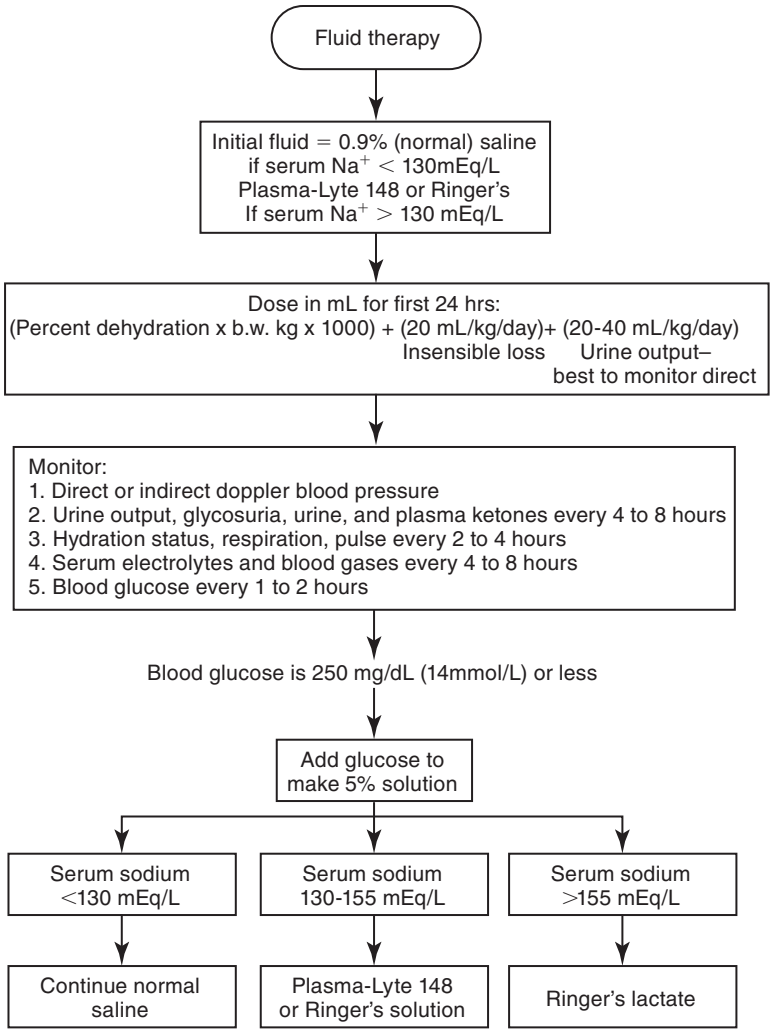

FIGURE 8-17 Intravenous (IV) fluid treatment plans for the dog or cat in diabetic ketoacidosis (DKA).

that stimulate hyperglycemia. The gradual decline in blood glucose combined with replacement of sodium for glucose in the ECF helps minimize the intracellular shift of water caused by a rapid decrease in ECF osmolality, thereby preventing cerebral edema (see Central Nervous System Signs [Cerebral Edema] under Monitoring and Complications of Therapy). Unfortunately, fluid therapy alone does not suppress ketogenesis (Foster and McGarry, 1983; Lebovitz, 1995). For this reason, insulin is always required to resolve the ketoacidotic state.

The type of parenteral fluid initially used depends on the animal's electrolyte status, blood glucose concentration, and osmolality. With rare exceptions, all dogs and cats with DKA have significant deficits in total body sodium, regardless of the measured serum concentration (see Serum Sodium Concentration earlier). Ringer's solution or Plasma-Lyte 148 (Baxter Healthcare Corp.) can be used for mild hyponatremia (serum sodium concentration of more than 130 mEq/L) and 0.9% (physiologic) saline solution for more severe hyponatremia (serum sodium concentration of less than 130 mEq/L) with appropriate potassium supplementation (see Fig. 8-17). Alternative isotonic crystalloid solutions that could be used include lactated Ringer's solution and Normosol-R (Abbott Laboratories). Each of these solutions has a slightly different electrolyte composition; none contain as much sodium as 0.9% saline (Table 8-3). Lactated Ringer's solution contains lactate, and Plasma-Lyte 148 and Normosol-R contain acetate. Lactate and acetate are metabolized to bicarbonate. A theoretical contraindication for the use of crystalloid solutions that contain lactate centers on the increase in serum lactate concentration that could occur with use of these fluids. Lactate is metabolized in the liver in a similar manner as ketones, and hyperketonemia could reduce hepatic lactate metabolism. As such, administration of fluids containing lactate could increase lactate concentrations in the circulation and, because lactate is a negatively charged ion, promote further sodium and potassium loss in the urine as lactate is excreted (Macintire, 1995). However, in our experience, use of lactated Ringer's solution has not had a recognizable deleterious impact on development of complications or resolution of DKA in dogs and cats. Lactated Ringer's solution can be used in lieu of 0.9% saline to minimize the chloride load in animals that develop hyperchloremic acidosis during treatment of DKA.

Most dogs and cats with severe DKA usually are sodium depleted and therefore not suffering from dramatic hyperosmolality. Hypotonic fluids (e.g., 0.45% saline) are rarely indicated in dogs and cats with DKA, even when severe hyperosmolality is present. Hypotonic fluids do not provide adequate amounts of sodium to correct the sodium deficiency, restore normal fluid balance, or stabilize blood pressure. Rapid administration of hypotonic fluids can also cause a rapid decrease in the osmolality of

TABLE 8-3 **ELECTROLYTE COMPOSITION OF COMMERCIALLY AVAILABLE FLUIDS**

FLUID	NA^+ (mEq/L)	CL^- (mEq/L)	K^+ (mEq/L)	GLUCOSE (g/L)	BUFFER* (mEq/L)	OSMOLARITY (mOsm/L)
0.9% saline†	154	154	0	0	0	308
0.45% saline†	77	77	0	0	0	154
Ringer's solution†	147	156	4	0	0	310
Lactated Ringer's solution†	130	109	4	0	28 (L)	272
Plasma-Lyte 148†	140	98	5	0	27 (A)	295
Normosol-R‡	140	98	**5**	**0**	27 (A)	296
Normosol-M‡	40	40	13	0	16 (A)	112
Plasma-Lyte 56†	40	40	13	0	16 (A)	110
5% dextrose in water†	0	0	0	50	0	252

*Buffers used: *A,* acetate; *L,* lactate.
†Baxter Healthcare Corp., Deerfield, IL.
‡Abbott Laboratories, Chicago, IL.

ECF, which may result in cerebral edema, deterioration in mentation, and eventually coma (see Monitoring and Complications of Therapy). Hyperosmolality is best treated with isotonic fluids and the judicious administration of insulin.

The initial volume and rate of fluid administration are determined by assessing the degree of shock, the dehydration deficit, the animal's maintenance requirements, plasma protein concentration, and presence or absence of cardiac disease. Fluid administration should be directed at gradually replacing hydration deficits over 24 hours while also supplying maintenance fluid needs and matching ongoing losses. Rapid replacement of fluids is rarely indicated unless the dog or cat is in shock. Once out of this critical phase, fluid replacement should be decreased in an effort to correct the fluid imbalance in a slow but steady manner. As a general rule of thumb, a fluid rate of 1.5 to 2 times maintenance (i.e., 60 to 100 ml/kg/24 hr) is typically chosen initially with subsequent adjustments based on frequent assessment of hydration status, urine output, severity of azotemia, and persistence of vomiting and diarrhea.

Monitoring Fluid Therapy

The rate of fluid administration and its effects on the animal must be monitored. Overzealous fluid therapy can lead to overhydration, pulmonary edema, and other "third-space" fluid loss with potentially serious consequences. Inadequate fluid administration can result in prolonged tissue underperfusion, hypoxia, continuing pancreatitis (if present), persistent prerenal azotemia, and the potential for development of primary kidney failure. Evaluation of fluid therapy should include subjective and objective assessments. Subjectively, the animal's alertness, heart rate, mucous membrane moisture, capillary refill time, pulse pressure, and skin turgor should be monitored and frequent pulmonary and cardiac auscultation performed. Objectively, serial evaluation of direct arterial or indirect Doppler blood pressure measurements, central venous pressure (CVP), urine output, body weight, and serum osmolality should be considered or completed.

Accurate assessment of urine output is extremely important in the sick ketoacidotic dog or cat, especially if azotemia is present. Diabetes-induced glomerular microangiopathy and/or the hemodynamic effects of ketoacidosis, concurrent necrotizing pancreatitis, or prolonged severe dehydration can lead to oliguric or anuric renal failure. Failure to produce urine within several hours of initiating fluid therapy is an alarming sign, and one that demands rapid recognition and an aggressive course of action. If urine production is in doubt, an indwelling urinary catheter should be secured in the bladder and attached to a closed collection system. Palpation of the bladder is not an accurate method for assessing urine output. A minimum of 1.0 to 2.0 mL of urine per kilogram of body weight per hour should be produced following the initial phase of fluid therapy. If urine production is minimal, the patency of the urinary catheter should be checked, the adequacy of fluid therapy evaluated (e.g., CVP, arterial blood pressure, subjective signs of excessive or inadequate fluids), and then attempts should be made to induce or increase the volume of urine produced with diuretics, mannitol, and/or dopamine.

Frequent assessment (ideally every 4 to 8 hours initially) of serum electrolytes and total venous CO_2 or arterial blood gases should be done and adjustments in fluid type and supplements made accordingly. Changes in serum electrolyte concentrations and blood gases are common and unpredictable during the initial 24 hours of treatment and the type of fluid (e.g., 0.9% saline, Plasma-Lyte 148, lactated Ringer's solution) and presence and amount of supplements (e.g., potassium, bicarbonate) in the fluids typically need to be adjusted several times during this period of time.

Potassium Supplementation

Fig. 8-18 shows a flow chart of potassium therapy.

Most dogs and cats with DKA have a net deficit of total body potassium due primarily to the marked urinary losses caused by the osmotic diuresis of glycosuria and ketonuria. Most dogs and cats with DKA initially have either normal or decreased serum potassium concentrations (see Fig. 8-12). During therapy for DKA, the serum potassium concentration decreases because of rehydration (dilution), insulin-mediated cellular uptake of potassium (with glucose), continued urinary losses, and correction of acidemia (translocation of potassium into the ICF compartment). Dogs and cats with hypokalemia require aggressive potassium replacement therapy to replace deficits and to prevent worsening, life-threatening hypokalemia after initiation of insulin therapy. The exception to potassium supplementation of fluids is hyperkalemia associated with oliguric kidney failure. Potassium supplementation should

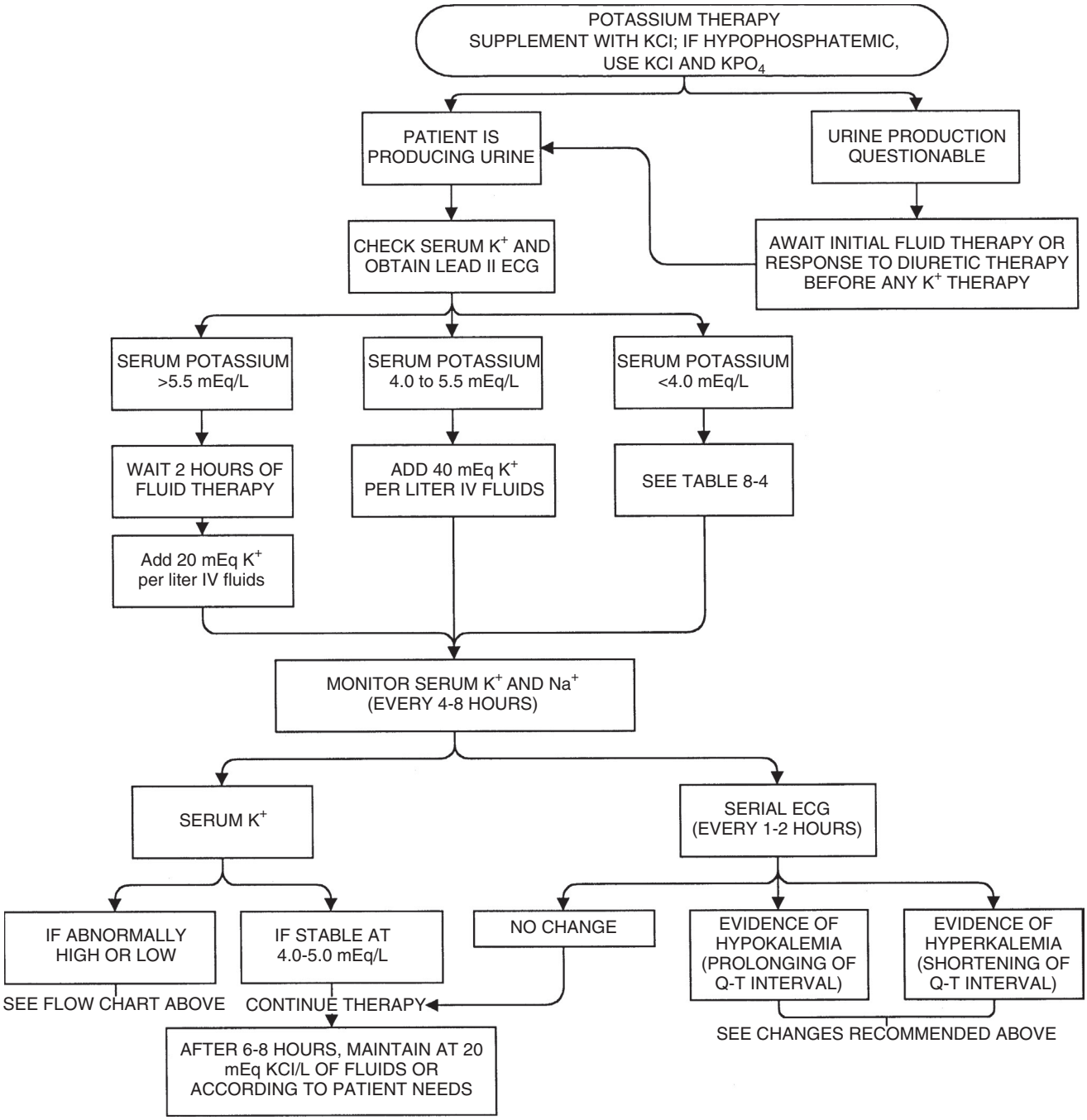

FIGURE 8-18 Potassium therapy in the management of diabetic ketoacidosis (DKA).

initially be withheld in these dogs and cats until glomerular filtration is restored, urine production increases, and hyperkalemia is resolving.

Ideally the amount of potassium required should be based on actual measurement of the serum potassium concentration (Table 8-4). If an accurate measurement of serum potassium is not available, potassium should be added to the liter of fluids to bring the potassium concentration to 40 mEq per liter. For example, 0.9% saline solution does not contain potassium, and Ringer's solution contains 4 mEq of potassium per liter; thus these fluids should be supplemented with 40 mEq and 36 mEq of potassium, respectively. Subsequent adjustments in potassium supplementation should be based on measurement of serum potassium, preferably every 4 to 8 hours until the dog or cat is stable and serum electrolytes are in the reference range.

Phosphate Supplementation

Serum phosphorus concentrations can be decreased, normal, or increased, depending on the duration of illness and kidney function. Most dogs and cats with DKA have either normal or decreased serum phosphorus concentrations on pretreatment testing. Within 24 hours of initiating treatment for DKA, serum phosphorus concentration can decline to severe levels (i.e., < 1 mg/dL) as a result of the dilutional effects of fluid therapy, the intracellular shift of phosphorus following the initiation of insulin therapy, and continuing kidney and gastrointestinal loss

TABLE 8-4 GUIDELINES FOR POTASSIUM SUPPLEMENTATION IN INTRAVENOUS FLUIDS

	TYPICAL GUIDELINES	GUIDELINES FOR DIABETIC KETOACIDOSIS
SERUM K^+ (mEq/L)	K^+ SUPPLEMENT/LITER OF FLUIDS	K^+ SUPPLEMENT/LITER OF FLUIDS
> 5.0	Wait	Wait
4.0-5.5	10	20 to 30
3.5-4.0	20	30 to 40
3.0-3.5	30	40 to 50
2.5-3.0	40	50 to 60
2.0-2.5	60	60 to 80
< 2.0	80	80

Total hourly potassium administration should not exceed 0.5 mEq/kg body weight.

(Willard et al, 1987). Hypophosphatemia affects primarily the hematologic and neuromuscular systems in dogs and cats (see Calcium and Phosphorus earlier in the chapter; Forrester and Moreland, 1989). Hemolytic anemia is the most common problem and can be life threatening if not recognized and treated. Severe hypophosphatemia may be clinically silent in many animals.

Phosphate therapy is indicated if clinical signs or hemolysis are identified or if the serum phosphorus concentration decreases to less than 1.5 mg/dL. Phosphate is supplemented by IV infusion. Potassium and sodium phosphate solutions contain 3 mmol of phosphate and either 4.4 mEq of potassium or 4 mEq of sodium per milliliter. The recommended dosage for phosphate supplementation is 0.01 to 0.03 mmol of phosphate per kilogram of body weight per hour, preferably administered in calcium-free IV fluids (e.g., 0.9% sodium chloride) (Willard, 1987). In dogs and cats with severe hypophosphatemia, the dosage may need to be increased to 0.03 to 0.12 mmol/kg/hr (Nichols and Crenshaw, 1995). Because the dose of phosphate necessary to replete an animal and the animal's response to therapy cannot be predicted, it is important to initially monitor the serum phosphorus concentration every 8 to 12 hours and adjust the phosphate infusion accordingly. Adverse effects from overzealous phosphate administration include iatrogenic hypocalcemia and its associated neuromuscular signs, hypernatremia, hypotension, and metastatic calcification (Forrester and Moreland, 1989). Serum total or preferably ionized calcium concentration should be measured at the same time as serum phosphorus concentration and the rate of phosphate infusion decreased if hypocalcemia is identified. Phosphorus supplementation is not indicated in dogs and cats with hypercalcemia, hyperphosphatemia, oliguria, or suspected tissue necrosis. If kidney function is in question, phosphorus supplementation should not be done until the status of kidney function and serum phosphorus concentration are known.

The routine supplementation of IV fluids with phosphorus during the initial 24 to 48 hours of treatment to prevent the development of severe hypophosphatemia, especially if the pretreatment serum phosphorus concentration is low, is controversial and varies with the experiences of the veterinarian queried. Routine phosphate supplementation is seldom recommended in treating DKA in humans, in part because several studies have failed to identify any apparent clinical benefit from phosphate administration, and overzealous phosphate administration may cause hypocalcemia with tetany (Becker et al, 1983; Fisher and Kitabchi, 1983; Masharani and Karam, 2001). The use of low-dose insulin treatment regimens, as described in the Insulin Therapy section, helps reduce the intracellular shift of phosphate, and the frequent monitoring of serum phosphorus concentrations during therapy ensures early recognition of worrisome changes in the serum phosphorus concentration. Arguments for routine phosphate administration, especially if the pretreatment phosphorus concentration is low, center on concerns with hemolytic anemia and the desire to avoid this serious complication. Studies documenting the effect, if any, of prophylactic phosphate supplementation on the prevalence of hemolytic anemia have not been reported in dogs or cats with DKA. If the decision is made to prophylactically administer phosphate, it can be administered separately using the dosages discussed earlier or can be included as a component of potassium replacement in the fluids. When the latter approach is used, 5 to 10 mEq of the potassium supplement added to the liter of fluids should be potassium phosphate and the remainder of the potassium supplemented as potassium chloride. The serum phosphorus concentration should be monitored every 8 to 12 hours and the phosphate supplement adjusted accordingly.

Magnesium Supplementation

Hypomagnesemia is common in dogs and cats with DKA, and it often worsens during the initial treatment of DKA but resolves without treatment as the DKA resolves (Norris et al, 1999a). Clinical signs of hypomagnesemia do not usually occur until the serum total and ionized magnesium concentration is less than 1.0 and 0.4 mg/dL, respectively, and even at these low levels, many dogs and cats remain asymptomatic (see Magnesium under Completing the Data Base). What impact, if any, hypomagnesemia has on morbidity and response to treatment of DKA is not clear. To date there are no clinical studies that have yielded guidelines for magnesium replacement in dogs and cats; currently it is determined empirically. We do not routinely treat hypomagnesemia in dogs or cats with DKA unless problems with persistent lethargy, anorexia, weakness, or refractory hypokalemia or hypocalcemia are encountered after 24 to 48 hours of fluid and insulin therapy and another cause for the problem cannot be identified.

Parenteral solutions of magnesium sulfate (8.12 mEq of magnesium per gram) and magnesium chloride (9.25 mEq of magnesium per gram) salts are available. The IV doses for rapid and slow magnesium replacement are 0.5 to 1 mEq/kg/day and 0.3 to 0.5 mEq/kg/day, respectively, administered by constant-rate infusion in 5% dextrose in water or 0.9% sodium chloride (Dhupa and Shaffran, 1995; Hansen, 2000). Kidney function must be assessed before the administration of magnesium, and the magnesium dose must be reduced by 50% to 75% in azotemic animals. The administration of magnesium to animals being treated with digitalis cardioglycosides may cause serious conduction disturbances. Magnesium is incompatible with solutions containing sodium bicarbonate or calcium. Serum total or preferably ionized magnesium, calcium, and potassium concentrations should be monitored every 8 to 12 hours and adjustments in the rate of magnesium infusion made accordingly. The goal of therapy is the resolution of clinical signs or refractory hypokalemia or hypocalcemia. The parenteral administration of magnesium sulfate may cause significant hypocalcemia such that calcium infusion may be necessary. Other adverse effects of magnesium therapy include hypotension, atrioventricular and bundle-branch blocks, and in

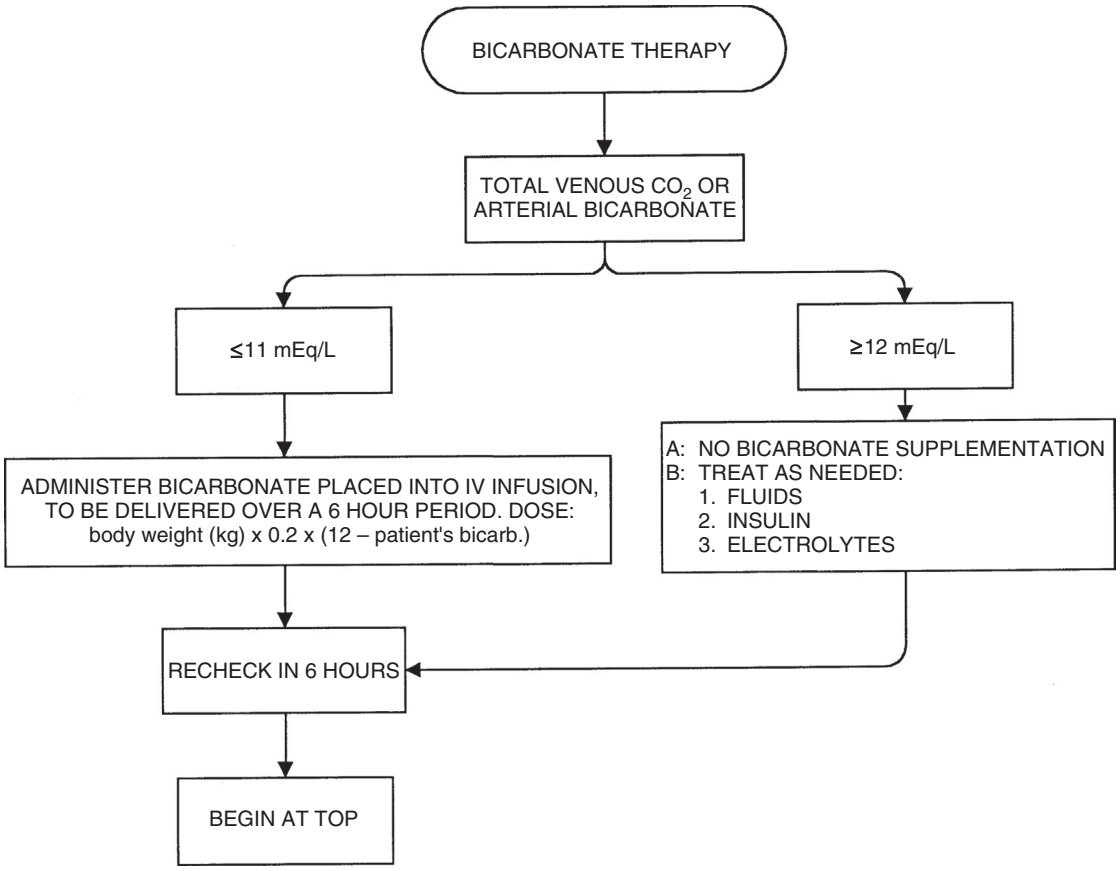

FIGURE 8-19 Bicarbonate treatment protocol for the management of diabetic ketoacidosis (DKA).

the event of overdose, respiratory depression and cardiac arrest. Overdoses are treated with IV calcium gluconate.

Bicarbonate Therapy

Fig. 8-19 shows a flow chart of bicarbonate therapy.

In humans with DKA, sodium bicarbonate treatment is reserved for patients with arterial pH of 7.0 or less and only with careful monitoring to prevent overcorrection. The primary concerns with sodium bicarbonate treatment are the potentially harmful consequences with overly aggressive bicarbonate administration, including exacerbation of hypokalemia from a rapid shift of potassium into cells, tissue anoxia from reduced dissociation of oxygen from hemoglobin when acidosis is rapidly reversed, and an exaggerated decrease in the cerebrospinal fluid (CSF) pH with resultant worsening of CNS function (Hale et al, 1984; Hood and Tannen, 1994; Kitabchi et al, 2001). The clinical presentation of the dog or cat, in conjunction with the plasma bicarbonate or total venous CO_2 concentration, should be used to determine the need for bicarbonate therapy. Bicarbonate supplementation is not recommended when plasma bicarbonate (or total venous CO_2) is 12 mEq/L or greater, especially if the animal is alert. An alert dog or cat probably has a normal or nearly normal pH in the CSF. The acidosis in these animals is corrected through insulin and fluid therapy. Improvement in renal perfusion enhances the urinary loss of ketoacid, and insulin therapy dramatically diminishes the production of ketoacid. Acetoacetate and β-hydroxybutyrate are also metabolically usable anions, and 1 mEq of bicarbonate is generated from each 1 mEq of ketoacid metabolized.

When the plasma bicarbonate concentration is 11 mEq/L or less (total venous CO_2 < 12 mEq/L), bicarbonate therapy should be initiated. Many of these animals have severe depression that may be a result of concurrent severe CNS acidosis. These can be difficult dogs and cats to treat, and the only safe therapeutic protocol involves correcting the metabolic acidosis slowly in the peripheral circulation via IV fluid supplementation, thereby avoiding major alterations in the pH of the CSF. As such, only a portion of the bicarbonate deficit is given initially over a 6-hour period of time.

The bicarbonate deficit (i.e., the milliequivalents of bicarbonate initially needed to correct acidosis to the critical level of 12 mEq/L over a period of 6 hours) is calculated as:

$$\text{mEq bicarbonate} = \text{body weight (kg)} \times 0.4 \times (12 - \text{animal's bicarbonate}) \times 0.5$$

or if the serum bicarbonate is not known:

$$\text{mEq bicarbonate} = \text{body weight (kg)} \times 2$$

The difference between the animal's serum bicarbonate concentration and the critical value of 12 mEq/L represents the treatable base deficit in DKA. If the animal's serum bicarbonate concentration is not known, the number 10 should be used for the treatable base deficit. The factor 0.4 corrects for the ECF space in which bicarbonate is distributed (40% of body weight). The factor 0.5 provides one-half of the required dose of bicarbonate in the IV infusion. In this manner, a conservative dose is given over a 6-hour period. Bicarbonate should not be given by bolus infusion (Ryder, 1984). After 6 hours of therapy, the acid-base status should be reevaluated and a new dosage calculated. Once the plasma bicarbonate level is greater than 12 mEq/L, further bicarbonate supplementation is not needed.

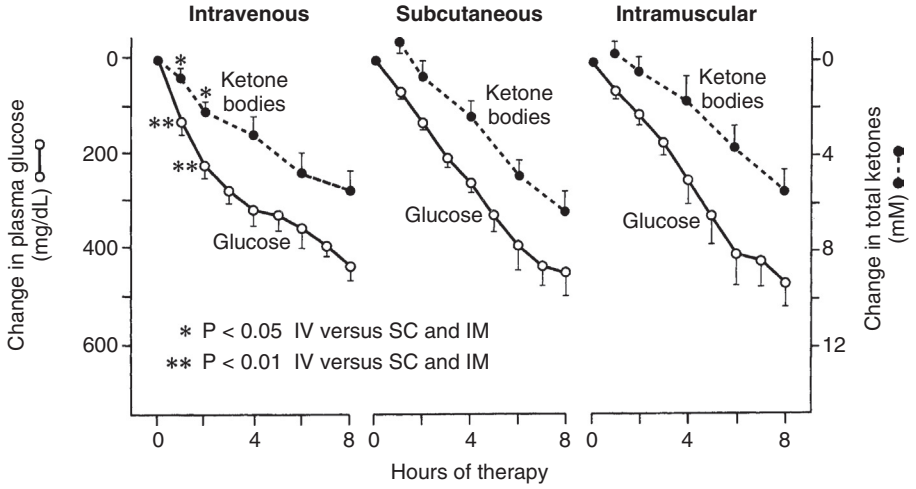

FIGURE 8-20 Effect of route of insulin therapy on reduction in plasma glucose and ketone concentrations in humans with diabetic ketoacidosis (DKA). Intravenous *(IV)* insulin was associated with a more rapid decline (initial 0 to 2 hours) in plasma glucose and ketone levels. Thereafter, no differences were noted between any of these groups. (Redrawn from Fisher JN, et al.: Diabetic ketoacidosis: low-dose insulin therapy by various routes, *N Engl J Med* 297:238-241, 1977. In DeFronzo RA, et al.: Diabetic ketoacidosis: a combined metabolic-nephrologic approach to therapy, *Diabetes Rev* 2:223, 1994; used with permission.) *IM,* Intramuscular; *SC,* subcutaneous.

Insulin Therapy

Insulin therapy is critical for the resolution of ketoacidosis. Insulin inhibits lipolysis and the mobilization of FFAs from triglycerides stored in adipose tissue, thereby decreasing the substrate necessary for ketone production; shifts hepatic metabolism from fat oxidation and ketogenesis to fat synthesis; suppresses hepatic gluconeogenesis; and promotes glucose and ketone metabolism by tissues (Hood and Tannen, 1994; DeFronzo et al, 1994). The net effect is decreased blood and urine glucose and ketone concentrations, decreased osmotic diuresis and electrolyte losses, and correction of metabolic acidosis. Overzealous insulin treatment can cause severe hypokalemia, hypophosphatemia, and hypoglycemia during the first 24 hours of treatment; these problems can be minimized by appropriate fluid therapy, frequent monitoring of serum electrolytes and blood glucose concentrations, and delaying the start of insulin treatment and modifying the initial insulin treatment protocol as indicated.

Initiating appropriate fluid therapy should always be the first step in the treatment of DKA. Delaying insulin therapy allows the benefits of fluid therapy to begin to be realized before the glucose, potassium, and phosphorus-lowering effects of insulin therapy commence. The question is how long to delay insulin therapy. We typically delay insulin therapy for a minimum of 2 hours after initiation of fluid therapy. Additional delays and decisions on the initial dosage of insulin administered are based on serum electrolyte results. If the serum potassium concentration is within the normal range after 2 hours of fluid therapy, insulin treatment should commence as described in the subsequent paragraphs. If hypokalemia persists, insulin therapy can be delayed an additional 2 hours to allow fluid therapy to replenish potassium, the initial insulin dose can be reduced to dampen the intracellular shift of potassium and phosphorus, or both can be done. The more severe the hypokalemia, the more inclined we are to delay insulin therapy and reduce the initial insulin dose. However, in our opinion, insulin therapy should be started within 4 hours of initiating fluid therapy.

Insulin therapy may not be as effective if a concurrent insulin-antagonistic disease is present, and it may be necessary to eliminate the disease while the animal is still ill to improve insulin effectiveness and resolve the ketoacidosis (e.g., a bitch in diestrus). Regardless, insulin therapy is still indicated. The amount of insulin needed by an individual animal is difficult to predict. Therefore, an insulin preparation with a rapid onset of action and a brief duration of effect is ideal for making rapid adjustments in the dose and frequency of administration to meet the needs of that particular dog or cat. Rapid-acting regular crystalline insulin meets these criteria and is recommended for the treatment of DKA (Nelson et al, 1990). Rapid-acting insulin analogs (e.g., insulin lispro and insulin aspart) are also effective for treating DKA in humans, dogs, and presumably cats (Kitabchi et al, 2008; Sears et al, 2012).

Insulin protocols for the treatment of DKA include the hourly intramuscular (IM) technique (Chastain and Nichols, 1981), the constant low-dose IV infusion technique (Macintire, 1993; Claus et al, 2010), and the intermittent IM then subcutaneous (SC) technique (Feldman, 1980). All three routes (IV, IM, and SC) of insulin administration are effective in decreasing plasma glucose and ketone concentrations (Fig. 8-20). Arguments abound regarding the most appropriate route for initial insulin administration, arguments that are primarily based on personal experiences and preferences. Successful management of DKA does *not* depend on route of insulin administration. Rather, it depends on proper treatment of each disorder associated with DKA (see Box 8-6). All three protocols are effective.

Hourly Intramuscular Insulin Technique

Dogs and cats with severe DKA should receive an initial regular insulin loading dose of 0.1 to 0.2 U/kg followed by 0.1 U/kg every 1 to 2 hours thereafter (Fig. 8-21). The insulin dose can be reduced by 25% to 50% for the first two to three injections if hypokalemia is a concern. The insulin should be administered into the muscles of the rear legs to ensure that the injections are IM and do not go into fat or SC tissue where insulin absorption may be impaired in the dehydrated dog or cat. Diluting regular insulin 1:10 with sterile saline or special diluents available from the insulin manufacturer and using 0.3 mL U100 insulin syringes are helpful when small doses of insulin are required. By means of this insulin treatment regimen, the serum insulin concentration is typically increased to and maintained at approximately 100 μU/mL (700 pmol/L) (Fig. 8-22), which is an insulin concentration

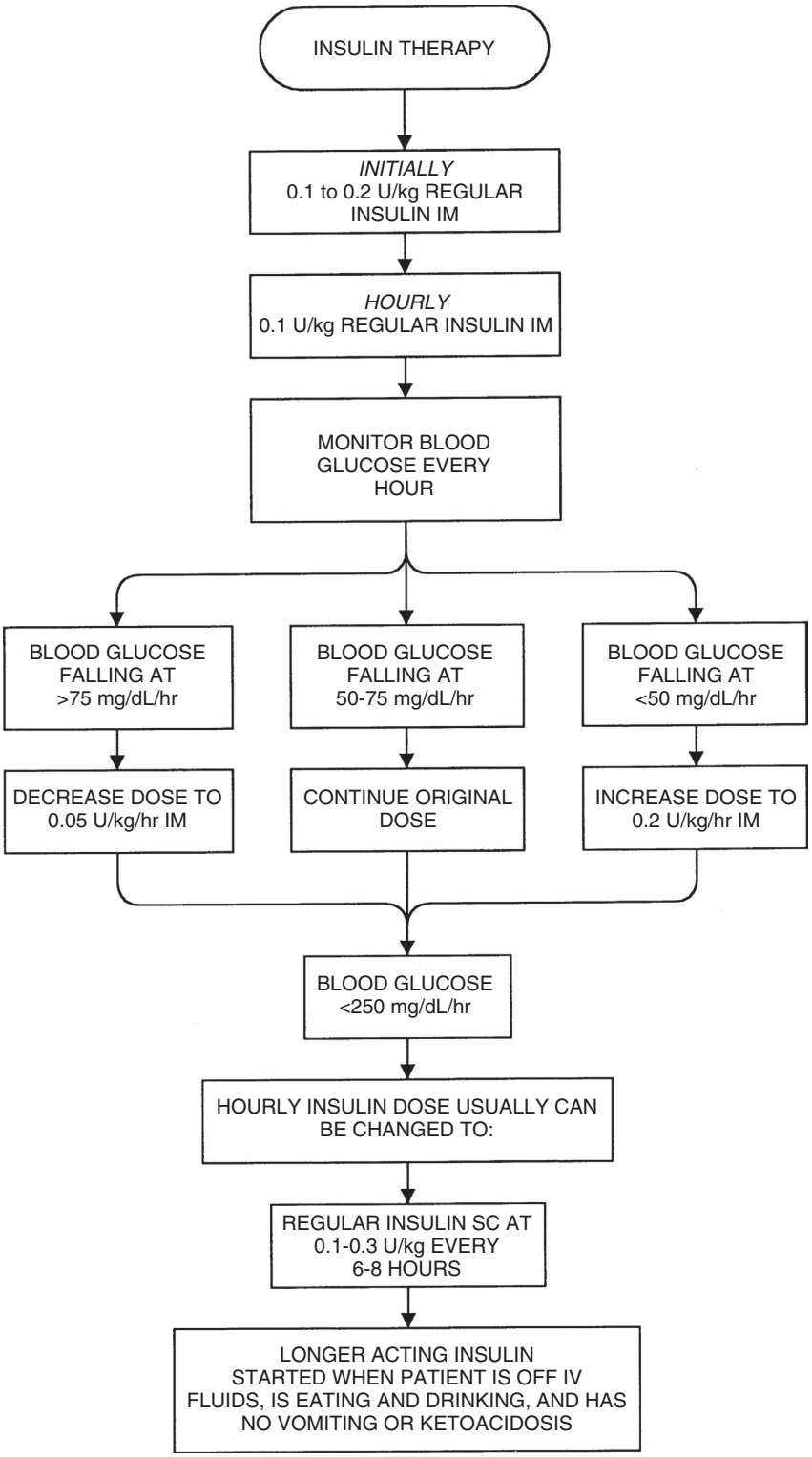

FIGURE 8-21 Hourly intramuscular (IM) insulin treatment protocol for the management of diabetic ketoacidosis (DKA). Similar principles for adjusting insulin therapy based on changes in the blood glucose concentration are used with the constant low-dose intravenous (IV) insulin infusion technique. *SC,* Subcutaneous.

that inhibits lipolysis, gluconeogenesis, and glycogenolysis and promotes utilization of glucose and ketones by tissues (Kitabchi et al, 2008).

The blood glucose concentration should initially be measured every hour using a point-of-care chemistry analyzer or portable blood glucose monitoring device and the insulin dosage adjusted accordingly (see Fig. 8-21). The goal of initial insulin therapy is to *slowly* lower the blood glucose concentration to the range of 200 to 250 mg/dL (11 to 14 mmol/L), preferably over a 6- to 10-hour time period. An hourly decline of 50 mg/dL (2.8 mmol/L) in the blood glucose concentration is ideal (Wagner et al, 1999). This provides a steady moderate decline, avoiding large shifts in osmolality.

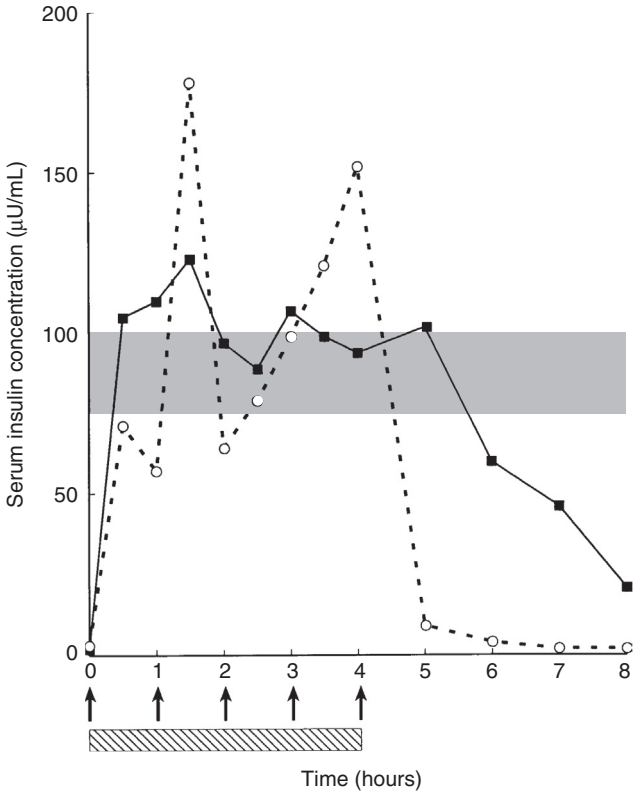

FIGURE 8-22 Mean serum insulin concentration in eight dogs with diabetic ketoacidosis (DKA) prior to and after the administration of regular crystalline insulin, 0.2 U/kg of body weight intramuscular (IM) (time 0) and then 0.1 U/kg IM hourly thereafter *(solid line),* and in six dogs with DKA prior to and after continuous intravenous (IV) infusion of regular crystalline insulin *(dashed line),* using a pediatric drip set. Insulin treatment was discontinued after the fourth hour in both groups of dogs. ↑, IM insulin administration; *hatched area,* IV insulin infusion; *shaded area,* ideal serum insulin concentration for treatment of DKA.

A declining blood glucose concentration also ensures that lipolysis and the supply of FFAs for ketone production have been effectively turned off. Glucose concentrations, however, decrease much more rapidly than ketone levels (Barrett and DeFronzo, 1984; Yeates and Blaufuss, 1990). In general, hyperglycemia is corrected within 12 hours, but ketosis often takes 48 to 72 hours to resolve.

Once the initial hourly insulin therapy brings the blood glucose concentration near 250 mg/dL (14 mmol/L), hourly administration of regular insulin should be discontinued and regular insulin given every 4 to 6 hours IM or, if hydration status is good, every 6 to 8 hours SC. The initial dose is usually 0.1 to 0.3 U/kg, with subsequent adjustments based on blood glucose concentrations. In addition, at this point, the IV infusion solution should have enough 50% dextrose added to create a 5% dextrose solution (100 mL of 50% dextrose added to each liter of fluids). The blood glucose concentration should be maintained between 150 and 300 mg/dL (8 to 17 mmol/L) until the dog or cat is stable and eating. Usually a 5% dextrose solution is adequate in maintaining the desired blood glucose concentration. If the blood glucose concentration dips below 150 mg/dL or increases above 300 mg/dL, the insulin dose can be decreased or increased accordingly. Dextrose helps minimize problems with hypoglycemia and allows insulin to be administered on schedule. Delaying the administration of insulin delays correction of the ketoacidotic state.

Marshall, et al., (2013) recently evaluated the efficacy of IM glargine with or without concurrent SC glargine administration in fifteen cats with DKA, adapting the protocol using regular insulin described earlier. All of the cats were initially administered 1 to 2 U of glargine IM, and for twelve cats 1 to 3 U of glargine SC. This was followed by intermittent IM glargine at intervals of 2 hours or more (range, 2 to 22 hours) and 1 to 3 U of glargine SC every 12 hours. Complications included hypoglycemia, hypokalemia, and hypophosphatemia. All fifteen cats survived and were discharged a median of 4 days after initiating treatment. The authors conclude that glargine may provide an alternative to regular insulin for the treatment of DKA in cats. Additional studies evaluating the safety and efficacy of glargine for treating DKA are needed before we would consider using basal insulin for the treatment of DKA.

Constant Low-Dose Intravenous Insulin Infusion Technique

Constant IV infusion of regular crystalline insulin is also effective in decreasing blood glucose concentrations. The decision to use the hourly IM technique versus constant IV insulin infusion is based primarily on clinician preference and availability of technical support and infusion pumps. To prepare the infusion, regular crystalline insulin (2.2 U/kg for dogs; 1.1 U/kg for cats) is added to 250 mL of 0.9% saline and initially administered at a rate of 10 mL/hr in a line separate from that used for fluid therapy (Church, 1983; Macintire, 1993). This provides an insulin infusion of 0.05 (cat) and 0.1 (dog) U/kg/hr, an infusion rate that has been shown to produce plasma insulin concentrations between 100 and 200 uU/mL (700 to 1400 pmol/L) in dogs (Macintire, 1993). Because insulin adheres to glass and plastic surfaces, approximately 50 mL of the insulin-containing fluid should be run through the drip set before it is administered to the animal. The rate of insulin infusion can be reduced for the initial 2 to 3 hours if hypokalemia is a concern. Two separate catheters are recommended for treatment: a peripheral catheter for insulin administration and a central catheter for fluid administration and blood sampling. An infusion or syringe pump should be used to ensure a constant rate of insulin infusion. Insulin infusions using pediatric drip sets may not provide a constant insulin infusion rate, especially if frequent monitoring of fluid administration is not possible (see Fig. 8-22). The goal of therapy is identical to that described for the hourly IM technique—to provide a continuous source of insulin at a dosage that causes a gradual decline in the blood glucose concentration. This goal is best attained with use of infusion or syringe pumps.

Adjustments in the infusion rate or the concentration of the insulin in the infusion (increased or decreased) are based on hourly measurements of blood glucose concentration; an hourly decline of 50 mg/dL (2.8 mmol/L) in the blood glucose concentration is ideal (Wagner et al, 1999). Once the blood glucose concentration approaches 250 mg/dL (14 mmol/L), the insulin infusion can be discontinued and regular insulin given every 4 to 6 hours IM or, if hydration status is good, every 6 to 8 hours SC, as discussed for the hourly IM protocol. Alternatively, the insulin infusion can be continued (at a decreased rate or decreased insulin concentration in the infusion to prevent hypoglycemia) until the insulin preparation is exchanged for a longer-acting product. Dextrose should be added to the IV fluids once the blood glucose concentration approaches 250 mg/dL, as discussed in the Hourly Intramuscular Insulin Technique section.

Claus, et al., (2010) recently compared the efficacy of three regular insulin doses (1.1 U/kg/d, 2.2 U/kg/d, and an escalating dosage from 1.1 to 2.2 U/kg during the course of the cat's stay) given by continuous IV infusion in 29 critically ill diabetic cats. There was no significant difference between groups regarding time required to reach a blood glucose of 250 mg/dL (14 mmol/L),

change in serum potassium or phosphorus concentrations relative to baseline, length of time for resolution of ketonuria, or length of hospital stay. Sears, et al., (2012) evaluated the efficacy of the short-acting insulin analog lispro (Humalog, Eli Lilly) for the treatment of DKA using an IV constant rate infusion technique. Treatment with IV constant rate infusion of lispro was safe and as effective as treatment with regular crystalline insulin. Use of lispro insulin is a viable option for treating DKA, especially if the production of regular crystalline insulin is discontinued in the future.

Intermittent Intramuscular/Subcutaneous Insulin Technique

An intermittent IM followed by intermittent SC insulin technique has been described (Feldman, 1980). Although this technique was used successfully by us for years, it has been replaced with the hourly IM and constant IV insulin infusion techniques. The intermittent IM followed by intermittent SC insulin technique is less labor-intensive than the other techniques for insulin administration, but the decrease in blood glucose can be rapid and the risk of hypoglycemia is greater. The initial regular crystalline insulin dose is 0.25 U/kg, administered intramuscularly. Subsequent IM injections are repeated every 4 hours. Usually, insulin is administered intramuscularly only once or twice. Once the animal is rehydrated, the insulin is administered subcutaneously rather than intramuscularly every 6 to 8 hours. SC administration is not recommended initially because of problems with insulin absorption from SC sites of deposition in a dehydrated dog or cat. The dosage of IM or SC insulin is adjusted according to blood glucose concentrations, which initially should be measured hourly beginning with the first IM injection. An hourly decline of 50 mg/dL in the blood glucose concentration is ideal (Wagner et al, 1999). Subsequent insulin dosages should be decreased by 25% to 50% if this goal is exceeded. Dextrose should be added to the IV fluids once the blood glucose concentration approaches 250 mg/dL (14 mmol/L), as discussed in the Hourly Intramuscular Insulin Technique section.

Initiating Longer-Acting Insulin Therapy

Longer-acting insulin (e.g., Lente, protamine zinc insulin [PZI], glargine) are administered once the dog or cat is stable, eating, maintaining fluid balance without any IV infusions, and no longer acidotic, azotemic, or electrolyte-deficient. The initial dose of the longer-acting insulin is similar to the regular insulin dose being used just before switching to the longer-acting insulin. Subsequent adjustments in the longer-acting insulin dose should be based on clinical response and measurement of blood glucose concentrations, as described in Chapters 6 and 7.

Concurrent Illness

Therapy for DKA frequently involves the management of concurrent, often serious illness. Common concurrent illness in the dog and cat with DKA include pancreatitis, bacterial infection, congestive heart failure, chronic kidney disease, hepatobiliary disease, and insulin-antagonistic disorders, most notably hyperadrenocorticism (dog), hyperthyroidism (cat), and diestrus (intact female dog) (Bruskiewicz et al, 1997; Hume et al, 2006); It may be necessary in such animals to modify the therapy for DKA (e.g., fluid therapy with concurrent heart failure) or implement additional therapy (e.g., antibiotics), depending on the nature of the concurrent illness. Insulin therapy, however, should not be delayed or discontinued. Resolution of ketoacidosis can only be achieved through insulin therapy. If nothing is to be given per os, insulin therapy should be continued and the blood glucose concentration maintained with IV dextrose infusions. If concurrent insulin-antagonistic disease is present, it may be necessary to treat the disease while the animal is still ill to improve the effectiveness of insulin and resolve the ketoacidosis (e.g., ovariohysterectomy in diestrual bitch).

Pancreatitis

Pancreatitis, acute or chronic, should always be assumed to be present in the dog or cat with DKA until proven otherwise. The diagnosis of pancreatitis should be based on a combination of presence of appropriate clinical signs; physical examination findings; abnormalities on the CBC, serum biochemistry panel, and urinalysis; results of serum pancreatic lipase immunoreactivity (see Pancreatic Enzymes earlier); radiographic evidence of a loss of detail in the right cranial abdomen accompanied by gas-filled duodenal ileus; and ultrasonographic evidence of enlargement of the pancreas and a hypoechoic to mixed echogenic pattern with or without mild to severe blockage of the bile duct (see Fig. 8-15). The presence of pancreatitis impacts fluid therapy and nutritional support during hospitalization, the duration of hospitalization, dietary recommendations, response to insulin treatment, the probability for recurrence of ketonuria and ketoacidosis following discharge from the hospital, and survival. Acute severe necrotizing pancreatitis is a common cause of death during the initial days of treatment of DKA, and the inability to prevent recurring bouts of chronic pancreatitis is one reason owners eventually elect euthanasia of their pet (Goossens et al, 1998). Avoidance of recurrent bouts of pancreatitis is critical to the long-term survival of the diabetic dog and cat. In the dog, this is primarily accomplished through appropriate dietary therapy. To date, inciting factors for development of pancreatitis in the cat have been poorly characterized, and the impact of diet, if any, on preventing recurrence of pancreatitis has yet to be clarified.

Bacterial Infections

The immunosuppressive effects of diabetes mellitus, in conjunction with the increased blood glucose concentration in body fluids, predisposes diabetic dogs and cats to bacterial infections (McMahon and Bistrian, 1995; Joshi et al, 1999). Urinary tract infections are most common, followed by infections of the oral cavity, skin, and pulmonary systems (Hess et al, 2000; Peikes et al, 2001). Life-threatening sepsis may develop in debilitated diabetics, those with severe concurrent illness (e.g., necrotizing pancreatitis), and those in which aseptic technique is not strictly followed during diagnostic and therapeutic procedures (e.g., placement of indwelling urinary or venous catheters). The clinician should always suspect infection in the DKA dog or cat. Urine cultures should be completed in all dogs and cats with DKA. Culture of blood and other fluids and tissues is usually dictated by the clinical signs and findings on the physical examination, routine blood tests, and diagnostic imaging. Whenever possible, the choice of antibiotic therapy should be based on results of culture and sensitivity testing.

Kidney Disease

Chronic and less commonly acute kidney disease may occur concurrently in dogs and cats with DKA. Abnormal kidney function may result from the deleterious effects of the diabetic state (i.e., diabetic nephropathy) or may be an independent problem that has developed in conjunction with diabetes in the geriatric dog or cat. Close monitoring of urine output and changes in BUN and serum creatinine concentration in response to fluid therapy are warranted whenever azotemia is identified in the dog or cat with

newly diagnosed DKA. See the sections Urinalysis and Urine Culture, Blood Urea Nitrogen and Creatinine, and Monitoring Fluid Therapy for information on kidney function and DKA.

Hormonal Disorders Causing Insulin Resistance

Insulin resistance accompanies many of the concurrent disorders present in dogs and cats with DKA. The severity of insulin resistance is quite variable and depends on the underlying cause (see Table 6-11). Fortunately, most disorders cause mild insulin resistance; that is, the dog or cat remains responsive to insulin therapy even at the low insulin dosages often employed during the initial 24 to 72 hours of therapy, and ketoacidosis progressively resolves. Two major exceptions are diestrus-induced insulin resistance in the intact bitch and hyperadrenocorticism. Although acromegaly also causes severe insulin resistance in the cat, ketonuria is an infrequent finding and systemic illness from DKA is uncommon, despite an inability to establish any semblance of glycemic control with massive doses of insulin. Seemingly, insulin is able to inhibit lipolysis and the supply of FFAs for ketone production but unable to control hepatic glucose secretion and/or stimulate tissue glucose utilization to control hyperglycemia in these cats.

Diestrus. Increased progesterone secretion during the diestrual phase of the estrus cycle in the bitch directly antagonizes insulin action and stimulates growth hormone secretion which, in turn, causes severe insulin resistance and the potential for life-threatening DKA. Diestrus-induced insulin resistance can be difficult if not impossible to override, despite the administration of massive doses of regular crystalline insulin. As a consequence, the metabolic derangements associated with DKA progressively worsen—ultimately resulting in death of the bitch.

Intact bitches in DKA should always be assumed to be in diestrus and should be assumed to have a pyometra, regardless of owner statements regarding estrus activity or the lack thereof. Once initial therapy for DKA is initiated, abdominal ultrasound scans or radiographs should be evaluated for pyometra and a blood progesterone concentration should be determined. A blood progesterone concentration greater than 2 ng/mL is diagnostic for ovarian luteal activity and supports the diagnosis of diestrus. The bitch should undergo ovariohysterectomy as soon as safely possible. Timing of surgery depends on the severity of clinical signs. Severely ill bitches with DKA should be stabilized as best as possible with IV fluids, regular crystalline insulin, and if indicated, parenteral antibiotics for 6 to 24 hours prior to performing surgery. We rarely wait more than 24 hours from the time of diagnosis of pyometra or diestrus to ovariohysterectomy. Insulin resistance usually begins to resolve within a week of ovariohysterectomy. In some bitches, insulin-requiring diabetes mellitus may even resolve (see Chapter 6, Other Specific Types and Diabetic Remission).

Diestrus-induced insulin resistance and its effect on responsiveness of DKA to insulin therapy are not commonly encountered in cats, because essentially all female diabetic cats have been spayed at the time diabetes is diagnosed and progesterone does not stimulate growth hormone secretion in the cat (Peterson, 1987). Progesterone can cause insulin resistance, but the insulin resistance that develops during diestrus in the queen rarely causes significant problems, presumably because the insulin resistance is not severe and the increase in plasma progesterone is transient. In contrast, insulin resistance caused by chronic progesterone excess, as occurs with exogenous progestagen administration or a progesterone-secreting adrenocortical tumor, can cause diabetes mellitus and a clinical syndrome that mimics feline hyperadrenocorticism (Boord and Griffin, 1999; Rossmeisl et al, 2000; see Chapter 11).

Exogenous Glucocorticoids. Insulin resistance induced by exogenous glucocorticoid administration can antagonize treatment of DKA. In general, glucocorticoids should not be given to dogs and cats with DKA and should be discontinued in previously undiagnosed diabetic ketoacidotic dogs and cats. This includes oral, ocular, aural, and skin preparations. The exceptions are those situations in which glucocorticoids are necessary to control life-threatening disorders (e.g., immune-mediated disease). In these situations, the lowest dosage of glucocorticoid needed to control the disorder should be administered and alternatives to glucocorticoids (e.g., azathioprine or cyclosporine) should be sought. In addition, the clinician should be willing to compensate for the insulin-antagonistic effects of glucocorticoids by administering larger dosages of insulin than are typically required to control DKA.

Naturally-Acquired Hyperadrenocorticism. Hyperadrenocorticism is a well-recognized disorder in diabetic dogs and cats and is occasionally suspected in dogs and cats with newly diagnosed DK and DKA and insulin-treated dogs and cats with persistent ketonuria. For relatively healthy dogs and cats with DK, appropriate diagnostic tests should be undertaken and appropriate treatment initiated once the diagnosis of hyperadrenocorticism is confirmed (see Chapters 10 and 11). Despite its impaired efficacy, insulin should continue to be administered to inhibit lipolysis, suppress ketone production, and prevent deterioration of the ketoacidotic state. Ketosis typically resolves once hyperadrenocorticism is controlled.

Establishing a diagnosis of hyperadrenocorticism is more problematic in the ill ketoacidotic dog or cat, in part because of concerns regarding accuracy of results when the diagnostic tests used to diagnose hyperadrenocorticism are performed in dogs and cats with severe illness (Kaplan et al, 1995). Ideally, testing for hyperadrenocorticism should be postponed until DKA has resolved and the dog or cat is stable in the home environment. We rely on results of the urine cortisol-to-creatinine ratio, low dose dexamethasone suppression test, and ultrasonographic examination of the adrenal glands to help confirm the diagnosis of hyperadrenocorticism. Interpretation of results of the low dose dexamethasone suppression test and especially the urine cortisol-to-creatinine ratio should be done with care because of the increased potential for false positive test results in sick dogs and cats. Ideally, treatment for hyperadrenocorticism should not be initiated until the DKA has resolved with fluid and insulin therapy and the dog or cat is stable and eating.

Monitoring and Complications of Therapy

Complications induced by treatment of DKA are common and usually result from overly aggressive therapy, inadequate animal monitoring, and failure to reevaluate biochemical parameters in a timely manner (Box 8-7). DKA is a complex disorder that carries a high mortality rate if improperly managed. To minimize the occurrence of therapeutic complications and improve the chances of successful response to therapy, all abnormal parameters should be *slowly* returned toward normal (i.e., over a period of 24 to 48 hours), the physical and mental status of the animal must be evaluated frequently (at least three to four times daily), and fluid therapy, urine production, urine and plasma ketones, serum electrolytes, and blood gases every 4 to 8 hours. During the initial 24 hours, blood glucose concentrations should be measured every 1 to 2 hours. Fluid, insulin, and bicarbonate therapy typically require modification three or four times during the initial 24 hours of therapy. A CBC and serum biochemistry panel that

BOX 8-7 Common Complications Caused by Treatment of Diabetic Ketoacidosis in Dogs and Cats

- Hypoglycemia from excessive use of insulin or inadequate administration of glucose
- Hypokalemia from inadequate potassium supplementation
- Hypophosphatemia and hemolytic anemia from inadequate phosphorus supplementation
- Hypernatremia from excessive administration of physiologic saline or inadequate fluid intake
- Persistent oliguria from inadequate or inappropriately slow administration of fluids
- Persistent hypotension from inadequate or inappropriately slow administration of fluids
- Cerebral edema and neurologic signs from too rapid decrease in blood glucose and/or osmolality
- Paradoxical cerebral acidosis and neurologic signs from too rapid administration of bicarbonate

includes plasma proteins, creatinine, calcium, phosphorus, and magnesium should be evaluated every 24 hours until the dog or cat is stabilized and eating. Failure to recognize changes in the status of DKA and to respond accordingly invariably leads to potentially serious complications. The more common complications are discussed below.

Hypoglycemia

Hypoglycemia is a common problem during the initial days of treatment, especially when the dog or cat is anorectic and unable to ingest a dietary source of glucose to counter the glucose-lowering effects of insulin. The goal of initial insulin therapy, regardless of how the insulin is administered, is to *slowly* lower the blood glucose concentration to the range of 200 to 250 mg/dL (11 to 14 mmol/L), preferably over an 8- to 10-hour time period. Unfortunately, this goal can be quite difficult to attain, and the blood glucose concentration may drop precipitously. To avoid hypoglycemia, it is imperative that the blood glucose concentration initially be measured every hour using a point-of-care chemistry analyzer, or a portable blood glucose monitoring device, or a continuous glucose monitoring system (see Chapter 6, Fig. 6-23). Whenever the blood glucose concentration approaches 250 mg/dL, 50% dextrose should be added to the IV infusion solution to create a 5% dextrose solution. If hypoglycemia occurs (i.e., blood glucose less than 80 mg/dL; 4.5 mmol/L) or the dog or cat is symptomatic for hypoglycemia, 0.25 to 0.50 gm/kg body weight of 50% dextrose should be administered IV as needed until the 5% dextrose solution is able to maintain the blood glucose above 80 mg/dL. Insulin therapy should also be modified and, if necessary, discontinued but only for a few hours. Discontinuing insulin therapy interferes with resolution of the ketoacidosis.

Severe Hypokalemia

Dogs and cats with DKA are at risk for development of severe hypokalemia (< 2.0 mEq/L) during the initial 48 hours of therapy for reasons that are discussed in the Potassium Supplementation section earlier in the chapter. The most common clinical sign of hypokalemia is generalized skeletal muscle weakness. In cats, ventriflexion of the neck, forelimb hypermetria, and a broad-based hind limb stance may be observed. Cardiac consequences of hypokalemia include decreased myocardial contractility, decreased cardiac output, and disturbances in cardiac rhythm. Other metabolic effects of hypokalemia include hypokalemic nephropathy, which is characterized by chronic tubulointerstitial nephritis, impaired kidney function, and azotemia and manifested clinically as polyuria, polydipsia, and impaired urine concentrating capability; hypokalemic polymyopathy, which is characterized by increased serum creatine kinase activity and electromyographic abnormalities; and paralytic ileus, manifested clinically as abdominal distention, anorexia, vomiting, and constipation (DiBartola and de Morais, 2012). Hypokalemic nephropathy and polymyopathy are most notable in cats. Cats seem more susceptible to the deleterious effects of hypokalemia than dogs. In dogs, signs may not be evident until the serum potassium concentration is less than 2.5 mEq/L, whereas in cats signs can be seen with serum potassium concentrations between 3 and 3.5 mEq/L. Clinical signs of hypokalemia can be mistakenly ascribed to other commonly encountered concurrent disorders (e.g., pancreatitis) and hypokalemia overlooked as a possible cause. Initial aggressive potassium replacement therapy, frequent monitoring of serum electrolytes, and subsequent adjustments in potassium replacement therapy are necessary to identify and prevent hypokalemia.

Central Nervous System Signs (Cerebral Edema)

Cerebral edema may result from excessive free water accumulation in the intravascular space during therapy for DKA. This typically results from a rapid decrease in the blood glucose concentration or after infusion of large quantities of hypotonic solutions (e.g., 0.45% saline). With insulin deficiency, the movement of glucose from the ECF to the ICF compartment is impaired. Glucose accumulation in the ECF causes a significant increase in ECF osmolality. A rapid increase in ECF glucose can result in cellular dehydration as water moves from the ICF to the ECF compartment in response to the increase in ECF osmolality. Neurologic signs develop as a consequence of neuronal dehydration in the CNS. Neurons in the CNS produce osmotically active substances including lactate, sorbitol, myoinositol, and idiogenic osmoles to compensate for the increasing osmolality of the ECF and prevent cellular dehydration. These intracellular substances can cause water to diffuse into the cell if the osmolality within the cell exceeds that within the ECF space. Idiogenic osmols within the neurons of a severely hyperglycemic animal is not associated with an osmotic gradient because of the equilibrium between the hyperosmotic ECF space (induced by glucose) and the hyperosmotic intracellular space (induced by idiogenic osmols). However, with aggressive fluid therapy and exogenous insulin administration, rapid reduction in blood glucose concentration and improved renal perfusion may cause a rapid reduction in ECF osmolality. A relative excess in free water accumulates in the ECF space. This water can then diffuse into the idiogenic osmol-induced hyperosmotic brain cells. A rapid decline in blood glucose concentration can thus result in cerebral edema and worsening CNS function. For these reasons, the veterinarian must be aware of the CNS status of the animal prior to initiation of therapy. If the animal becomes depressed or obtunded during treatment, it may be the result of the relatively rapidly decreasing blood glucose concentration leading to cerebral edema.

Mannitol is the most effective treatment for cerebral edema. Dexamethasone is usually recommended, but its efficacy has not been reported in diabetic dogs and cats. Passive hyperventilation to lower carbon dioxide pressure and diminish cerebral blood flow has also been recommended. Prophylactically avoiding cerebral edema through slow but progressive improvement in blood glucose concentration, serum electrolytes, and metabolic acidosis is the key.

Hemolytic Anemia

Life-threatening hemolytic anemia may develop during the initial 72 hours of therapy as a consequence of hypophosphatemia (see Phosphate Supplementation earlier in this chapter) (Willard et al, 1987; Adams et al, 1993; Bruskiewicz et al, 1997). The mechanism of hypophosphatemia-induced hemolysis is not known, but hemolysis may occur secondary to depletion of erythrocyte ATP, which is necessary for maintenance of cell membrane integrity; malfunction of the sodium-potassium pump secondary to erythrocyte ATP depletion and subsequent osmotic lysis; or alterations in red blood cell membrane lipids (Shilo et al, 1985; Adams et al, 1993).

Hypophosphatemia-induced hemolytic anemia can be serious, with hematocrits less than 15% reported in dogs and cats (Willard et al, 1987; Adams et al, 1993). Additional findings on a CBC include spherocytes, Heinz bodies, and hemoglobinemia. Treatment involves the IV administration of phosphate, and, if necessary, blood. Prevention of hypophosphatemia is the key to avoiding hemolytic anemia. Frequent monitoring of serum phosphorus concentration during the initial 24 to 48 hours of therapy for DKA and supplementation of the IV fluids with potassium or sodium phosphate when hypophosphatemia is identified is the cornerstone of prevention.

Severe Hypernatremia and Hyperchloremia

Occasionally, animals with DKA develop severe hypernatremia and hyperchloremia (see Fig. 8-12) as a result of water deprivation (i.e., inadequate fluid intake) in conjunction with urinary loss of large amounts of water in excess of electrolytes. Loss of water in excess of electrolytes creates hypertonic dehydration, a state of dehydration with few of the expected signs of severe fluid depletion (Edwards et al, 1983). Worsening hypernatremia, in combination with hyperglycemia, causes severe hyperosmolality (> 400 mOsm/kg) and CNS dysfunction. The initial critical signs of hypernatremia include irritability, weakness, and ataxia, but as the hypernatremia worsens, stupor progresses to coma and seizures. The progression and severity of these signs depend on the rate of onset, degree, and duration of hypernatremia. Therapy should be designed to replace fluid deficits, match continuing fluid losses, and decrease those losses when possible. (See Complications of the Modified Water Deprivation Test: Hypertonic Dehydration and Hypernatremia in Chapter 1 for details on the treatment of hypernatremic, hypertonic dehydration.)

It is important to consider factors that can result in artifactual changes in serum sodium concentrations. Severe lipemia can appear to *raise* the serum sodium concentration because lipemia displaces sodium into the non-lipemic volume of serum, making a normal serum sodium concentration appear increased. Hyperglycemia can also alter the serum sodium concentration. For each 100 mg/dL increment of serum glucose above the normal range, the serum sodium concentration *decreases* approximately 1.6 mEq/L (DiBartola, 2012).

PROGNOSIS

DKA remains one of the most difficult metabolic therapeutic challenges in veterinary medicine. One must remain aware of all the complicating factors in treatment and remember that fluid therapy, insulin, and potassium supplementation are the cornerstones of successful management. Added to these factors are close supervision and monitoring of the animal, without which failure rates are high, and identification and treatment of concurrent disease that is invariably present. Reported in-hospital mortality rates for DKA include 29% of 21 dogs (Macintire, 1993), 30% of 127 dogs (Hume et al, 2006), and 26% of 42 cats (Bruskiewicz et al, 1997), primarily as a result of severe concurrent illness. During the past decade in our hospital, the mortality rate has decreased to approximately 5%, and death has usually been attributed to underlying medical disorders (e.g., pancreatitis) that precipitated the DKA, client financial constraints, or both rather than to the metabolic complications of ketoacidosis (Claus et al, 2010). It is worth reiterating that a careful search should always be made, both at the time of initial history and physical examination and during therapy, for underlying problems that might have precipitated the episode of DKA or developed during treatment of DKA. In particular, pneumonia, sepsis, pancreatitis, and hormonal diseases causing insulin resistance are often silent at the time of presentation. Despite all precautions and diligent therapy, a fatal outcome cannot be avoided in some cases. Nevertheless, with logical therapy and careful monitoring, the goal of therapy for DKA (i.e., achieving a healthy diabetic dog or cat) is attainable. Diabetic remission is also possible in cats following resolution of DKA, especially in cats with concurrent pancreatic disease or cats being treated with glucocorticoids at the time DKA is diagnosed (Sieber-Ruckstuhl et al, 2008; Marshall et al, 2013).

HYPEROSMOLAR HYPERGLYCEMIC STATE

Diabetic hyperosmolar hyperglycemic state has historically been referred to by many terms, including *hyperosmolar non-ketotic syndrome, hyperosmolar coma, hyperglycemic hyperosmolar syndrome,* and *non-ketotic hyperosmolar syndrome.* Hyperosmolar hyperglycemic state (HHS) is the nomenclature recommended by the American Diabetes Association to emphasize the varying alterations in sensorium less than coma that are usually present in humans and that HHS may occur with mild ketosis and acidosis (Nugent, 2005). HHS is an uncommon complication of diabetes mellitus in the dog and cat. This syndrome is characterized by severe hyperglycemia (blood glucose concentration > 600 mg/dL; 34 mmol/L), hyperosmolality (> 350 mOsm/kg), and dehydration in the absence of significant ketosis. Progressively worsening lethargy ultimately leads to obtundation and coma as hyperosmolality becomes more severe. Concurrent disorders (e.g., kidney failure, congestive heart failure, infection, pulmonary disease and pancreatitis) are common, contribute to the progression of this syndrome, and negatively impact the prognosis. HHS is a diagnostic and therapeutic challenge that is associated with a high fatality rate (Koenig et al, 2004).

Pathogenesis

The pathogenesis of HHS is similar to that of DKA—a partial or relative insulin deficiency reduces glucose utilization by muscle, fat, and the liver while at the same time inducing hyperglucagonemia and increasing hepatic glucose output. Concurrent infection, inflammation, and organ system failure promote insulin resistance and secretion of counterregulatory hormones (e.g., catecholamines, cortisol) that exacerbate hyperglycemia. One theory for the lack of ketosis with HHS is the existence of a small population of functional beta-cells that are capable of secreting insulin, albeit in insufficient amounts to prevent hyperglycemia. However, the presence of small amounts of insulin is believed to prevent the development of ketosis by inhibiting lipolysis (see Role of Insulin Deficiency). Therefore, even though a low insulin-to-glucagon ratio promotes ketogenesis in the liver, the limited availability of precursor FFAs from the periphery restricts the rate at which

ketones are formed (Ennis et al, 1994). Hepatic resistance to glucagon may also play a role in the lack of ketosis with HHS (Yen et al, 1980; Azain et al, 1985).

If a dog or cat is unable to maintain adequate fluid intake because of an associated acute or chronic illness (e.g., pancreatitis, gastroenteritis) or has suffered excessive fluid loss (e.g., diuretics for concurrent congestive heart failure), marked dehydration results. As plasma volume contracts, glomerular filtration is impaired, limiting renal glucose excretion and contributing markedly to the rise in blood glucose. The measured serum sodium concentration is usually decreased or within the reference range, but the "corrected" serum sodium concentration is typically in the reference range or increased and is contributing to the increase in plasma osmolality (see Serum Sodium Concentration earlier). As plasma osmolality increases, water is drawn out of cerebral neurons, resulting in mental obtundation and further impairment of water intake. A vicious cycle of worsening hyperosmolality, obtundation, inadequate fluid intake, dehydration, and prerenal azotemia ensues, ultimately resulting in coma and death.

The hyperglycemia of HHS (600 to 1600 mg/dL; 34 to 90 mmol/L) tends to be more severe than the hyperglycemia of DKA (300 to 600 mg/dL; 17 to 34 mmol/L). The increase in blood glucose concentration in HHS is, as in DKA, the result of increased production of glucose by the liver coupled with its diminished use by tissues. However, two additional factors in HHS allow the hyperglycemia to become more severe. First, impaired urine output in HHS diminishes excretion of glucose in urine (Foster and McGarry, 1989). Second, low or undetectable concentrations of ketoacid in the plasma and urine in HHS removes an important and early contributor to clinical signs. As a consequence, the hyperglycemia of HHS progresses for a longer period of time, and it is not until signs of severe hyperosmolality (i.e., lethargy, obtundation) or signs related to concurrent problems become evident to the owner that veterinary care is sought.

Some dogs and cats with HHS are acidotic despite low or undetectable concentrations of ketoacid in the plasma or urine. One cause for this disparity in expected versus real results is the fact that β-hydroxybutyrate (one of two major ketoacids) is not assayed by commonly used urine and plasma reagent strips or tablets (see Establishing the Diagnosis of Diabetic Ketosis and Ketoacidosis). Another cause for acidosis in non-ketotic diabetics is lactic acidosis. Lactic acid is the end product of anaerobic metabolism of glucose. The principal sources of this acid are erythrocytes (which lack the enzymes for aerobic oxidation), skeletal muscle, skin, and brain. Lactic acid is removed via hepatic, and to some degree renal, uptake with conversion first to pyruvate and eventually back to glucose, a process that requires oxygen. Lactic acidosis occurs when excess lactic acid accumulates in the blood. This can be the result of overproduction (tissue hypoxia), deficient removal (hepatic failure), or both (circulatory collapse). Like humans, dogs and cats with lactic acidosis are usually severely ill, with problems such as sepsis, hemorrhage, anemia, pulmonary disease, liver disease, and kidney failure.

Clinical Findings

Clinical Signs

The onset of HHS may be insidious, and it may be preceded for days or weeks by the classic signs of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss). Progressive weakness, anorexia, and lethargy develop, usually in conjunction with a reduction in water intake. Additional clinical signs depend on the underlying precipitating disorder(s). Physical examination often reveals the presence of profound dehydration. These pets are typically lethargic, extremely depressed, or actually comatose. There is a direct relationship between the severity of the hyperosmolality and the severity of neurologic signs. Hypothermia and slow capillary refill time are common. Kussmaul respirations are absent unless severe metabolic (lactic) acidosis is present.

Laboratory Findings

Severe hyperglycemia is present, with blood glucose concentrations ranging from 600 to as high as 1600 mg/dL (34 to 90 mmol/L). Severe prerenal or renal azotemia is a common finding. These animals typically have depleted body potassium stores, despite the fact that serum potassium concentrations can be high, normal, or low. Serum sodium concentrations are also variable and may be low, normal, or elevated despite total body sodium depletion. Because glucose osmotically shifts water into the extracellular space, sodium is diluted and the measured value may be falsely decreased. The measured sodium value should be corrected to a sodium value that accounts for hyperglycemia by using the formula in Serum Sodium Concentration earlier in the chapter. The formula reflects that the measured serum sodium value is decreased by approximately 1.6 mEq for every 100 mg/dL increase in glucose above 100 (Nugent, 2005). A mild hyponatremia or a normal serum sodium concentration usually suggests moderate dehydration. Hypernatremia despite hyperglycemia suggests significant water loss has occurred and severe volume contraction and dehydration are present.

Hyperosmolality is a consistent finding in HHS and can exceed 400 mOsm/kg, especially in dogs and cats with hypernatremia and severe hyperglycemia. Plasma osmolality may be measured by determination of its freezing point with an osmometer or calculated using the formula given in Serum Osmolality earlier in the chapter.

Mild to moderate ketosis may occur with HHS in diabetic humans. HHS and DKA are two disorders believed to represent different points along a spectrum of emergencies caused by poorly-controlled diabetes (Kitabchi et al, 2006). Ketosis is usually absent in dogs and cats with HHS, although trace ketonuria may occur. Ketoacidosis is not a part of HHS but metabolic acidosis may be identified (usually in the form of lactic acidosis) owing to underlying disorders commonly affiliated with HHS in dogs and cats. Lactic acidosis depresses plasma bicarbonate concentrations and the arterial pH. An anion gap is present (see Anion Gap earlier in the chapter). Other causes of "anion gap" metabolic acidosis should be excluded (see Box 8-4). The diagnosis of lactic acidosis can be confirmed by measuring plasma lactate concentration.

Therapy

The goals of therapy for HHS are similar to DKA—that is, to correct severe dehydration and restore electrolyte losses, to provide adequate amounts of insulin to normalize intermediary metabolism, to correct the hyperosmolar state, and to identify and treat precipitating factors. Restoring intravascular volume and lost electrolytes using isotonic fluids has the highest priority. Osmolality is returned to normal by lowering the blood glucose concentration and by replacing water deficits. Initially, fluid therapy is used to lower the blood glucose concentration; insulin should not be administered until intravascular volume is restored, electrolyte derangements improved, and blood pressure stabilized. Careful and frequent monitoring of the dog's or cat's clinical and laboratory response to therapy is essential.

Fluid therapy is of paramount importance in treating HHS and is the primary mode of therapy for the initial 4 to 6 hours or longer. Derangements in total body water, sodium and potassium, hyperglycemia, and hyperosmolality are usually severe, in part

because the lack of ketoacidosis and associated systemic signs of illness allows HHS to develop for a longer period of time before veterinary care is sought. Despite the severe hyperosmolality, the initial fluid of choice is isotonic (0.9%) saline with appropriate potassium supplementation. Isotonic saline will correct dehydration and improve blood flow to tissues, stabilize blood pressure, improve GFR and promote glycosuria, decrease blood glucose concentration, and replace sodium for glucose in the ECF space. The net effect is a slow reduction in ECF hyperosmolality, thereby minimizing development of cerebral edema. The initial goal of fluid therapy is correction of dehydration deficits. Half of the estimated dehydration deficit plus maintenance requirements should be replaced in the first 12 hours and the remainder in the next 12 to 24 hours.

The principles of potassium and phosphorus supplementation are similar to those discussed for DKA (see Potassium Supplementation and Phosphate Supplementation earlier in the chapter). Many dogs and cats with HHS are also in kidney failure (often oliguric) and may have hyperkalemia, hyperphosphatemia, and/or impaired ability to excrete a potassium load. As such, potassium and phosphorus supplementation should be based on measurement of serum concentrations and awareness of the status of kidney function and urine production. Usually, initial therapy consists of 20 mEq/L of potassium replacement (as potassium chloride) into the infusion fluids. Subsequent adjustments are based on measurements of serum electrolytes, which should be done frequently to quickly identify problems in serum electrolyte concentrations, should they arise.

Insulin therapy should be delayed (typically 4 to 6 hours or longer) until the positive benefits of fluid therapy are documented (i.e., correction of dehydration, stabilization of blood pressure, and improvement in urine production, hyperglycemia, hyperosmolality, and derangements in serum electrolyte concentrations). The need for insulin treatment is not as critical with HHS as with DKA; this is in part because ketone production and its metabolic consequences are minimal to nonexistent with HHS. Metabolic acidosis, if identified in HHS, is more likely caused by lactic acidosis, which can be improved with fluid therapy. In addition, insulin can cause a rapid decrease in the blood glucose concentration and ECF osmolality—changes that promote cerebral edema (see Central Nervous System Signs [Cerebral Edema]). The techniques for insulin administration are similar to those discussed for DKA (see Insulin Therapy). However, the insulin dosage used for the hourly IM technique or the insulin infusion rate used for the constant low-dose insulin infusion technique should be decreased by 50% initially to dampen the decrease in the blood glucose concentration and avoid a rapid decrease in ECF osmolality. Subsequent adjustments in the amount of insulin being administered are based on the rate of decline in the blood glucose concentration. The goal is a decrease of 50 mg/dL/hour (2.8 mmol/L/hour), although the rate of decrease is hard to predict or control, in part because of differences in insulin sensitivity between animals. Once the blood glucose concentration is less than 250 mg/dL (14 mmol/L), dextrose should be added to the IV fluids to make a 5% dextrose solution.

Monitoring urine output, blood pressure, blood glucose, serum electrolytes, creatinine, BUN, and urine glucose is imperative. As with ketoacidosis, the clinician must attempt to correct the hyperosmolality, hyperglycemia, and dehydration steadily (not precipitously) while stimulating diuresis to improve azotemia. These animals are critically ill and require close supervision.

The prognosis for recovery is guarded to poor. In a retrospective study of 17 diabetic cats with HHS, 65% did not survive the initial hospitalization, with most dying or being euthanized within 10 hours of presentation (Koenig et al, 2004). The long-term survival rate was low (12%). The most common concurrent disease affiliated with death or euthanasia in our animals with HHS is kidney failure.

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