

67 Chapter 67 Diabetic Ketoacidosis

Rebecka S. Hess, DVM, DACVIM

67.1 KEY POINTS

- Diabetic ketoacidosis (DKA) is a severe form of complicated diabetes mellitus that requires emergency care.
- Acidosis and electrolyte abnormalities can be life threatening.
- Fluid therapy and correction of electrolyte abnormalities are the two most important components of therapy.
- Concurrent disease increases the risk for DKA and must be addressed as part of the diagnostic and therapeutic plan.
- Bicarbonate therapy usually is not needed and its use is controversial.
- About 70% of treated dogs and cats are discharged from the hospital after 5 to 6 days of hospitalization.
- The degree of base deficit is associated with outcome in dogs with DKA. Additionally, dogs that have concurrent hyperadrenocorticism are less likely to be discharged from the hospital.

67.2 INTRODUCTION

Diabetic ketoacidosis (DKA) is a severe form of complicated diabetes mellitus that requires emergency care. Ketones are synthesized from fatty acids as a substitute form of energy, because glucose is not transported into the cells. Excess ketoacids result in acidosis and severe electrolyte abnormalities, which can be life threatening.

67.3 PATHOPHYSIOLOGY

Ketone bodies are synthesized as an alternative source of energy when intracellular glucose concentration can not meet metabolic demands. Ketone bodies are synthesized from acetyl-coenzyme A (acetyl-CoA) which is a product of mitochondrial β -oxidation of fatty acids. This adenosine triphosphate (ATP)-dependent catabolism of fatty acids is associated with breakdown of two carbon fragments at a time and results in formation of acetyl-CoA. Synthesis of acetyl-CoA is facilitated by a decreased insulin concentration and increased glucagon concentration. The anabolic effects of insulin include conversion of glucose to glycogen, storage of amino acids as protein, and storage of fatty acids in adipose tissue. Similarly, the catabolic effects of glucagon include glycogenolysis, proteolysis, and lipolysis. Therefore a low insulin concentration and elevated glucagon concentration contribute to decreased mobilization of fatty acids into adipose tissue and increased lipolysis, resulting in elevated acetyl-CoA concentration. In nondiabetics acetyl-CoA and pyruvate enter the citric acid cycle to form ATP. However, in diabetics, glucose does not enter the cells in adequate amounts, and production of pyruvate by glycolysis is decreased. The activity of the citric acid cycle is therefore diminished, resulting in decreased utilization of acetyl-CoA. The net effect of increased production and decreased utilization of acetyl-CoA is an increase in the concentration of acetyl-CoA, which is the precursor of ketone body synthesis.¹

The three ketone bodies synthesized from acetyl-CoA are β -hydroxybutyrate, acetoacetate, and acetone. Acetyl-CoA is converted to acetoacetate by two metabolic pathways, and acetoacetate is then metabolized to β -

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hydroxybutyrate or acetone. One of the pathways of acetoacetate synthesis involves condensation of two acetyl-CoA units and the other utilizes three units of acetyl-CoA. Ketone bodies are synthesized in the liver.¹

Acetoacetate and β -hydroxybutyrate are anions of moderately strong acids. Therefore accumulation of these ketone bodies results in ketotic acidosis. Metabolic acidosis may be worsened by vomiting, dehydration, and renal hypoperfusion.¹ Metabolic acidosis and the electrolyte abnormalities that ensue are important determinants in the outcome of patients with DKA.²

One of the beliefs regarding the pathophysiology of DKA had been that individuals that develop DKA have zero or undetectable endogenous insulin. However, in a study that included seven dogs with DKA, five had detectable endogenous serum insulin concentrations, and two of these dogs had endogenous serum insulin concentration within the normal range.³ Therefore it is possible that other factors, such as an elevated glucagon concentration (or less likely cortisol or catecholamines), contribute to DKA. Glucagon concentration may be elevated as a result of concurrent disease.

67.4 RISK FACTORS

The median age of dogs with DKA is 8 years (range 8 months to 16 years).² The mean age of cats with DKA is 9 years (range 2 to 16 years).⁴ Breed or sex has not been shown to increase the risk of DKA in dogs or cats.^{2,4,5}

Concurrent disease has been documented in about 70% of dogs with DKA and 90% of cats with DKA. The most common concurrent diseases noted in dogs with DKA are acute pancreatitis, bacterial urinary tract infection, and hyperadrenocorticism.² The most common concurrent diseases noted in cats with DKA are hepatic lipidosis, chronic renal failure, acute pancreatitis, bacterial or viral infections, and neoplasia.⁴ It is possible that concurrent disease results in an elevated glucagon concentration and increased risk of DKA. The role of cortisol and catecholamines remains to be elucidated.

Most dogs and cats with DKA are newly diagnosed diabetics. It is possible that insulin treatment reduces the risk of DKA in dogs and cats.^{2,4}

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67.5 CLINICAL SIGNS AND PHYSICAL EXAMINATION FINDINGS

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Clinical signs and physical examination findings may be attributed to chronic unmanaged diabetes mellitus, concurrent disease, and the acute onset of DKA. The most common clinical signs in dogs or cats with DKA are polyuria and polydipsia, lethargy, inappetence or anorexia, vomiting, and weight loss.^{2,4} Common abnormalities noted on physical examination of dogs with DKA are subjectively overweight or underweight body condition, dehydration, cranial organomegaly, abdominal pain, cardiac murmur, mental dullness, dermatologic abnormalities, dyspnea, coughing, abnormal lung sounds, and cataracts.² Common abnormalities noted in cats with DKA are subjectively underweight body condition, dehydration, icterus, and hepatomegaly.⁴

67.6 CLINICAL PATHOLOGY

Approximately 50% of dogs with DKA have a nonregenerative anemia (which is not associated with hypophosphatemia), left shift neutrophilia, or thrombocytosis.² Anemia and left shift neutrophilia are also common

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features of feline DKA.⁴ These cats also have significantly more red blood cell Heinz body formation than do normal cats, and the degree of Heinz body formation is correlated with plasma β -hydroxybutyrate concentration.⁶

Persistent hyperglycemia is apparent in all dogs and cats diagnosed with DKA, unless they receive insulin.² Alkaline phosphatase activity is elevated in almost all dogs with DKA.² Alanine aminotransferase activity, aspartate aminotransferase activity, and cholesterol concentration are increased in about half of the dogs with DKA.² Elevations in alanine aminotransferase activity and cholesterol concentration are also commonly observed in cats with DKA.⁴ Azotemia is reported more commonly in cats than in dogs with DKA.^{2,4}

Electrolyte abnormalities are common in both dogs and cats with DKA.^{2,4} Initially, an animal with DKA may appear to have extracellular hyperkalemia due to dehydration, decreased renal excretion, hypoinsulinemia, decreased insulin function, hyperglycemia, and acidemia (leading to movement of hydrogen ions into the cells and potassium ions out to maintain cellular electronegativity). However, with rehydration, potassium ions are lost from the extracellular fluid and a true hypokalemia from depletion of total body potassium stores becomes apparent. Hypokalemia may be exacerbated by binding of potassium to ketoacids, vomiting, inappetence, and anorexia, and osmotic diuresis. Insulin therapy may worsen extracellular hypokalemia as insulin shifts potassium into cells.⁷ The most important clinical manifestation of hypokalemia in DKA is profound muscle weakness, which may result in respiratory paralysis in extreme cases.

An apparent hypophosphatemia often develops when phosphate shifts from the intracellular space to the extracellular space as a result of hyperglycemia, acidosis, and hypoinsulinemia. Dehydration and decreased phosphorus excretion by the kidneys also contributes to this finding. Osmotic diuresis or fluid therapy along with insulin therapy causes extracellular phosphate depletion, leading to whole body phosphate depletion.⁷

Hypophosphatemia related to DKA has been associated with hemolysis (in a cat) and seizures (in a dog).⁸ Additional clinical signs that may develop because of hypophosphatemia include weakness, myocardial depression, and arrhythmias.

Decreased plasma ionized magnesium (iMg) concentration has been documented in four of seven cats with DKA, and may be due to increased urinary excretion of magnesium.⁹ The clinical significance of hypomagnesemia in cats is unknown. The clinical consequence of hypomagnesemia in humans with diabetes includes insulin resistance, hypertension, hyperlipidemia, and increased platelet aggregation. Dogs with DKA usually do not have low iMg concentrations at the time of initial examination.^{2,10} In one study of 78 dogs with uncomplicated diabetes mellitus, 32 dogs with DKA, and 22 control dogs, plasma iMg concentration at the time of initial examination was significantly higher in dogs with DKA than in dogs with uncomplicated diabetes mellitus and control dogs.¹⁰ Hyponatremia, hypochloremia, and decreased ionized calcium concentration have also been documented in about 50% of dogs with DKA. Low sodium concentration may be secondary to the hyperglycemia, leading to a 1 mEq/L decrease in sodium concentration for every 62 mg/dl increase in glucose concentration in humans, and is often referred to as *pseudohyponatremia*. Venous pH is less than 7.35 in all dogs and cats with DKA. Lactate concentration is elevated in about one third of dogs with DKA and is not correlated with degree of acidosis.²

Urinalysis is usually indicative of glucosuria. Proteinuria or ketonuria may also be apparent. Ketonuria may not be detected because the nitroprusside reagent in the urine dipstick reacts with acetoacetate and not with β -hydroxybutyrate, which is the dominant ketone body in DKA. Measurement of serum β -hydroxybutyrate is more sensitive than measurement of urine ketones.¹¹ On urinalysis, the number of white blood cells per high-power field is usually five or fewer, although 20% of dogs with DKA have aerobic bacterial growth on culture of urine

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obtained by cystocentesis.² This is likely a result of immunosuppression of diabetics and decreased ability to mobilize white blood cells to the site of infection.

Results of additional clinicopathologic or imaging tests such as urine culture, abdominal ultrasonography, thoracic radiographs, adrenal or thyroid axis testing, pancreatic lipase immunoreactivity, liver function tests, or liver biopsy depend on concurrent disorders.

67.7 DIFFERENTIAL DIAGNOSIS

Differential diagnoses for ketosis include DKA, acute pancreatitis, starvation, low-carbohydrate diet, persistent hypoglycemia, persistent fever, or pregnancy. Differential diagnoses for a primary metabolic acidosis include DKA, renal failure, lactic acidosis, toxin exposure, severe tissue destruction, severe diarrhea, and chronic vomiting.

67.8 TREATMENT

Administration and careful monitoring of intravenous (IV) fluid therapy is the most important component of treatment (see [Chapters 64](#) and [65](#), Daily Intravenous Fluid Therapy and Shock Fluids and Fluid Challenge, respectively). Any commercially available isotonic crystalloid solution may be used. The use of 0.9% saline has been advocated because of its relatively high sodium concentration⁷; however, it may be contraindicated in hyperosmolar diabetics. Additionally, 0.9% saline may contribute further to the acidosis because of the high chloride concentration and lack of a buffer. Lactate (contained in lactated Ringer's solution) and acetate (contained in Plasma-Lyte and Normosol-R) are converted to bicarbonate and may contribute to management of acidosis. Another advantage of these buffer-containing crystalloids is that they contain some potassium, which may blunt the acute decline in potassium concentration that the animal could suffer with initiation of fluid and insulin treatment. As long as the patient is monitored carefully, particularly in regard to hydration, mental status, and electrolyte concentrations, any of the above crystalloids can be used for management. Fluid therapy may contribute to a decrease in blood glucose concentration by improving renal perfusion and decreasing the concentration of counter regulatory hormones, most importantly glucagon.¹²

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Correction and monitoring of electrolyte abnormalities is the second most important component of therapy. Electrolyte supplementation must be monitored frequently, because frequent adjustments may be required. An animal that appears hyperkalemic at the time of initial examination may become hypokalemic shortly after fluid therapy has begun. Hypokalemia can be treated by administering potassium as an IV constant rate infusion (CRI) at a rate that should generally not exceed 0.5 mEq/kg/hr ([Table 67-1](#)). If higher dosages are required, continuous electrocardiographic monitoring should be performed simultaneously.

Hypophosphatemia is corrected with an IV CRI of potassium phosphate (solution contains 4.4 mEq/ml of potassium and 3 mM/ml of phosphate) at a rate of 0.03 to 0.12 mM/kg/hr. Serum potassium concentration must be taken into account when giving potassium phosphate for correction of hypophosphatemia. A magnesium sulfate solution (containing 4 mEq/ml) given intravenously as a CRI of 1 mEq/kg q24h has been used successfully for correction of hypomagnesemia (range 0.5 to 1 mEq/kg q24h). Toxicity from erroneously administered intravenously magnesium has been reported in one diabetic cat and one dog with acute renal disease.¹³ Signs of magnesium toxicity in these animals included vomiting, weakness, generalized flaccid muscle tone, mental dullness, bradycardia, respiratory depression, and hypotension.¹³ Care must be taken to administer intravenous magnesium only to patients that have documented decreased iMg concentrations. As the hyperglycemia resolves, the sodium concentration is expected to appear higher secondary to the decrease in osmolality and subsequent

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movement of free water from the intravascular space. If the hyponatremia and hypochloremia persist, they are corrected by administering a 0.9% saline solution.

Table 67-1 Potassium Supplementation in Hypokalemic Animals*

Serum Potassium Concentration (mmol/L)	Potassium (mEq) Added to 250-ml Fluid Bag
1.6–2	20
2.1–2.5	15
2.6–3	10
3.1–3.5	7

Hyperglycemia is corrected with insulin therapy. Although several new rapid-acting products are being used successfully in humans with DKA, their use in dogs and cats has not yet been investigated. Therefore regular insulin is recommended (Humulin R, Novolin R). Regular insulin is administered as an intravenous CRI ([Table 67-2](#))¹⁴ or intramuscularly.¹⁵ When intravenous regular insulin is administered as a CRI, blood glucose is measured every 2 hours. When insulin is administered intramuscularly, it is given every hour, and blood glucose is measured every hour. The initial dose of intramuscular therapy is 0.2 U/kg regular insulin, followed by 0.1 U/kg regular insulin IM 1 hour later. Treatment with IM regular insulin is continued with 0.05 U/kg/hr, 0.1 U/kg/hr, or 0.2 U/kg/hr if blood glucose drops more by than 75 mg/dl/hr, by between 50 and 75 mg/dl/hr, or by less than 50 mg/dl/hr, respectively.⁷

Acidosis is usually corrected with intravenous fluid administration and insulin therapy alone.^{2,4,12} Bicarbonate administration for correction of acidosis in humans with DKA is controversial.^{12,16-18} The American Diabetes Association recommends bicarbonate supplementation only in patients with DKA in which arterial pH remains less than 7.0 after 1 hour of fluid therapy.¹⁶ Risks associated with bicarbonate treatment in humans with DKA include exacerbation of hypokalemia, increased hepatic production of ketones, paradoxical cerebrospinal fluid acidosis, cerebral edema, and worsening intracellular acidosis due to increased production of carbon dioxide (also known as paradoxical cerebral acidosis).^{12,17,18} Bicarbonate treatment is not needed in most dogs and cats with DKA.^{2,4} However, a recent retrospective study of 127 dogs with DKA reported that the degree of acidosis was associated with poor outcome.² The same study reported that intravenous sodium bicarbonate therapy was also associated with poor outcome.² It is not known if bicarbonate therapy in itself, or the severe degree of acidosis that prompted such therapy, was the cause of poor outcome in dogs treated with bicarbonate.

One bicarbonate treatment protocol is to administer sodium bicarbonate at $\frac{1}{2}$ to $\frac{1}{3}$ of $(0.3 \times \text{body weight} \times \text{negative base excess})$ over a 20-minute interval every hour, while monitoring venous pH every hour. However, there are no studies to support this or any other bicarbonate treatment protocol in dogs and cats with DKA. The American Diabetes Association recommends treating pediatric patients with DKA who maintain a pH of less than 7.0 after 1 hour of fluid therapy with 2 mEq/kg sodium bicarbonate added to 0.9% sodium chloride, in a solution that does not exceed 155 mEq/L of sodium, over 1 hour.¹⁶ The pH is monitored every hour and treatment is repeated until pH is 7.0 or greater.¹⁶

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Table 67-2 Administration of IV Insulin in Patients With DKA*

Blood Glucose Concentration (mg/dl)	Fluid Composition	Rate of Administration (ml/hr)
>250	0.9% NaCl	10
200 to 250	0.45% NaCl + 2.5% dextrose	7
150 to 200	0.45% NaCl + 2.5% dextrose	5
100 to 150	0.45% NaCl + 5% dextrose	5
<100	0.45% NaCl + 5% dextrose	Stop fluid administration

DKA, Diabetic ketoacidosis; *IV*, intravenous; *NaCl*, sodium chloride.

Concurrent disease is believed to contribute to DKA. Therefore identification and treatment of concurrent disease are indicated. It is possible that the latter decreases glucagon secretion and contributes to improved diabetic regulation and resolution of DKA.

* Not to exceed 0.5 mEq/kg/hr without electrocardiographic monitoring.

* 2.2 U/kg of regular crystalline insulin added to 250 ml of 0.9 % NaCl solution. The administration set must be flushed with 50 ml of the mixture before administering the solution to the animal.

67.9 OUTCOME

Most dogs and cats (70%) treated for DKA survive to discharge from the hospital.^{2,4} Median hospitalization time for dogs and cats with DKA is 6 and 5 days, respectively.^{2,4} At least 7% of dogs and up to 40% of cats experience recurring episodes of DKA.^{2,4} Dogs with coexisting hyperadrenocorticism are less likely to be discharged from the hospital, and the degree of base deficit in dogs is associated with outcome.²

67.10 SUGGESTED FURTHER READING*

KA Bruskiwicz, RW Nelson, EC Feldman, et al.: Diabetic ketosis and ketoacidosis in cats: 42 cases (1980-1995). *J Am Vet Med Assoc.* **211**, 1997, 188, *A detailed retrospective study of cats with DKA.*

DZ Hume, KJ Drobatz, RS Hess: Outcome of dogs with diabetic ketoacidosis: 127 dogs (1993-2003). *J Vet Intern Med.* **20**, 2006, 547, *A detailed retrospective study of dogs with DKA.*

DK McIntire: Treatment of diabetic ketoacidosis in dogs by continuous low-dose intravenous infusion of insulin. *J Am Vet Med Assoc.* **202**, 1993, 1266, *The first report of DKA treatment by way of an IV CRI of insulin in dogs, which has remained the gold standard since its publication.*

SE Parsons, KJ Drobatz, SV Lamb, et al.: Endogenous serum insulin concentration in dogs with diabetic ketoacidosis. *J Vet Emerg Crit Care.* **12**, 2002, 147, *A study documenting that endogenous insulin concentrations are detectable in most dogs with DKA and occasionally normal in some dogs with DKA.*

* See the CD-ROM for a complete list of references

68 Chapter 68 Hyperglycemic Hyperosmolar Syndrome

Amie Koenig, DVM, DACVIM, DACVECC

68.1 KEY POINTS

- Hyperglycemic hyperosmolar syndrome (HHS) is a form of diabetic crisis marked by severe hyperglycemia (>600 mg/dl) and hyperosmolality with no or minimal urine ketones.
- Absence or resistance to insulin and increases in diabetogenic hormone levels stimulate glycogenolysis, and gluconeogenesis, hyperglycemia, osmotic diuresis, and dehydration result.
- Reduction of glomerular filtration rate (GFR) is essential to attain the severe, progressive hyperglycemia associated with HHS.
- Renal failure and congestive heart failure are common concurrent diseases. These likely contribute to HHS via effects on reduction of GFR.
- The most important goals of therapy are to replace fluid deficits and then slowly decrease the glucose concentration, thereby avoiding rapid intracranial shifts in osmolality and preventing cerebral edema. Fluid therapy will start to reduce blood glucose levels via dilution and by increasing GFR and subsequent urinary glucose excretion.
- Prognosis for HHS patients is poor, primarily as a result of concurrent disease.

68.2 INTRODUCTION

Nonketotic HHS is an uncommon form of diabetic crisis marked by severe hyperglycemia (>600 mg/dl), minimal or absent urine ketones, and serum osmolality more than 350 mOsm/kg.¹ Other names for this syndrome include *hyperosmolar hyperglycemic nonketotic state* and *hyperosmolar nonketotic coma*. These terms have been replaced by *hyperglycemic hyperosmolar syndrome* in human medicine to better reflect the variable degrees of ketosis and inconsistent incidence of coma that occur with this syndrome.^{2,3} Coma appears to be an uncommon form of this syndrome in animals.

Hyperglycemic Hyperosmolar Syndrome (HHS) is an infrequent, albeit well documented, complication of diabetes mellitus.⁴⁻⁷ The incidence in human diabetics has been estimated to represent less than 1% of all human diabetic hospital admissions.^{3,8,9} In comparison, HHS accounted for 6.4% of total emergency room visits by diabetic cats in one retrospective study.⁴ The incidence in dogs is unknown.

This chapter will review the pathogenesis, clinical findings, diagnostic evaluation, and treatment of HHS.

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68.3 PATHOGENESIS

Pathogenesis of HHS involves hormonal alterations, reduction of glomerular filtration rate (GFR), and contributions from concurrent disease.

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68.3.1 Hormonal Alterations

HHS begins with a relative or absolute lack of insulin coupled with increases in circulating levels of counterregulatory hormones including glucagon, epinephrine, cortisol, and growth hormone. These counterregulatory hormones are elevated in response to an additional stressor, such as concurrent disease. Epinephrine and glucagon inhibit insulin-mediated glucose uptake in muscle and stimulate hepatic glycogenolysis and gluconeogenesis, increasing circulating glucose concentration. Cortisol and growth hormone inhibit insulin activity and potentiate the effects of glucagon and epinephrine on hepatic glycogenolysis and gluconeogenesis. In conjunction with insulin deficiency, increases in the diabetogenic hormones increase protein catabolism, which in turn impairs insulin activity in muscle and provides amino acids for hepatic gluconeogenesis.¹⁰ Pathogenesis of HHS is very similar to that of diabetic ketoacidosis, except that in HHS it is believed that small amounts of insulin and hepatic glucagon resistance inhibit lipolysis, thereby preventing ketosis^{3,11,12} and instead promoting HHS. Lower levels of growth hormone have also been documented in patients with HHS.^{12,13}

Hyperglycemia is the primary result of these hormonal alterations. It promotes osmotic diuresis, and osmotic diuresis increases the magnitude of the hyperglycemia, thus leading to a vicious circle of progressive dehydration and hyperosmolality. Neurologic signs are thought to develop secondary to cerebral dehydration induced by the severe hyperosmolality. In humans, elevated blood urea nitrogen (BUN) levels, acidemia, elevated sodium concentration and osmolality, but not glucose concentration, are correlated with the severity of neurologic signs.¹⁴

68.3.2 Reduction of Glomerular Filtration Rate

Osmotic diuresis, additional losses such as via vomiting, and decreased water intake contribute to progressive dehydration, hypovolemia, and ultimately a reduction in the GFR as the syndrome progresses. Severe hyperglycemia can occur only in the presence of reduced GFR, because there is no maximum rate of glucose loss via the kidney.^{15,16} That is, all glucose that enters the kidney in excess of the renal threshold will be excreted in the urine. An inverse correlation exists between GFR and serum glucose in diabetic humans.¹⁵ Reductions in GFR increase the magnitude of hyperglycemia, which exacerbates glucosuria and osmotic diuresis. Human HHS survivors have also shown a reduced thirst response to rising vasopressin levels, which may also contribute to dehydration¹⁷ and decreased GFR.

68.3.3 Influence of Concurrent Disease

Concurrent disease is important for initiating the hormonal changes associated with HHS and can also be important for exacerbating hyperglycemia. Diseases that are thought to predispose previously stable diabetics to a diabetic crisis include renal failure, congestive heart failure (CHF), infection, neoplasia, and other endocrinopathies,^{1,18} although any disease can occur. Pancreatitis and hepatic disease seemed to be uncommon concurrent diseases in cats with HHS.⁴

Renal failure and CHF also exacerbate the hyperglycemia associated with HHS because of their effects on GFR. Decreased GFR is inherent to renal failure. Inability to concentrate urine provides another source for obligatory diuresis. Myocardial failure, diuretic use, and third spacing of fluids associated with CHF may decrease GFR.

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Cardiac medications such as β -blockers and diuretics are also known to alter carbohydrate metabolism, thus predisposing to diabetic crisis.³

68.4 HISTORY AND CLINICAL SIGNS

Animals diagnosed with HHS may be previously diagnosed diabetics receiving insulin or may be newly diagnosed at the time HHS is recognized. The most common client complaints are fairly nonspecific and include decreased appetite, lethargy, vomiting, and weakness. Owners may report polyuria, polydipsia, and polyphagia consistent with diabetes, although these clinical signs may have gone unrecognized. History may also reveal recent onset of neurologic signs including circling, pacing, mentation changes, or seizure. Weight loss is an inconsistent finding.

68.5 PHYSICAL EXAMINATION

Vital parameters (temperature, pulse, and respiration) and body weight vary considerably with severity of the syndrome and presence and chronicity of comorbid diseases. Hypothermia is not uncommon as the syndrome progresses. Dehydration, marked by decreased skin turgor, dry or tacky mucous membranes, sunken eyes, and possibly prolonged capillary refill time, are common findings on physical examination. Mentation changes are also common. Most animals are reported as being depressed, but severely affected patients may be obtunded, stuporous, or comatose. Additional neurologic abnormalities including weakness or ataxia, abnormal pupillary light reflexes or other cranial nerve abnormalities, twitching, or seizure activity may be noted. Plantigrade stance, especially in cats, may be present subsequent to unregulated diabetes mellitus.

Other findings in patients with HHS are dependent on coexisting diseases. Animals should be examined closely for signs of heart disease which may include any of the following: heart murmur, gallop, bradycardia, tachycardia or other arrhythmias, dull lung sounds, crackles, increased respiratory rate and effort, pallor, prolonged capillary refill time, and decreased blood pressure. Increased respiratory rate and effort may suggest cardiac failure but could also be secondary to infection, hyperosmolality, acidosis, asthma, or neoplasia. Animals with renal failure may have kidneys of abnormal size, oral ulceration, and pallor from anemia and may smell of uremia.

68.6 DIAGNOSTIC CRITERIA

The standard criteria for diagnosis of HHS in veterinary medicine are a serum glucose concentration greater than 600 mg/dl, absence of urine ketones, and serum osmolality greater than 350 mOsm/kg.¹ In humans, the criteria for diagnosis of HHS require a serum glucose greater than 600 mg/dl, arterial pH over 7.3, serum bicarbonate greater than 15 mmol/L, effective serum osmolality greater than 320 mOsm/kg, and anion gap less than 12 mmol/L. In addition, humans with HHS may have small quantities of urine and serum ketones, measured by the nitroprusside method.^{2,3}

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Glucose concentrations can reach 1600 mg/dl in severely affected animals.¹ Blood glucose concentration may exceed the readable range on patient-side analyzers. Clinical suspicion for HHS should remain high in this situation and additional diagnostic methods should be instituted to better define the severity of hyperglycemia, state of diabetes, and presence of coexisting diseases. Measuring glucose is also vital to rule out hypoglycemia as a cause of neurologic signs.

Osmolality measured by freezing point depression is not a commonly available patient-side test. Estimated serum osmolality can be calculated using the following formula¹⁹:

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$$\text{Serum osm}_{(\text{calc})} = 2(\text{Na}^+ + \text{K}^+) + (\text{BUN} \div 2.8) + (\text{glucose} \div 18)$$

BUN and glucose are measured in mg/dl.

Because BUN equilibrates readily across cell membranes and effects of potassium on osmolality are small, calculating effective osmolality may be a better estimate¹⁹:

$$\text{Effective osm} = 2(\text{Na}^+) + (\text{glucose} \div 18)$$

BUN and glucose measured in mg/dl.

Normal serum osmolality is 290 to 310 mOsm/kg. Neurologic signs have been documented in animals when osmolality exceeds 340 mOsm/kg²⁰ ([Box 68-1](#)).

Urine ketones can be assessed quickly using urine dipsticks. If urine is not available, serum ketones may be assessed by placing a few drops of serum on urine dipsticks.

68.6.1 Additional Diagnostic Evaluation

Additional diagnostic parameters, including serum chemistry analysis (with precise glucose measurement), complete blood count, urinalysis, urine culture, and (venous) blood gas, should be pursued in patients with confirmed or suspected HHS. Blood cell count abnormalities are varied and nonspecific. The packed cell volume and total solids level may be high secondary to dehydration. Chemistry abnormalities are dependent on degree of dehydration and presence of underlying disease. The most common biochemical abnormalities in cats with HHS include azotemia, hyperphosphatemia, elevated aspartate transaminase, acidosis, elevated lactate concentration, and hypochloremia.⁴ Azotemia may be prerenal or renal in origin.

68.6.1.1 Box 68-1 Important Calculations

Dehydration deficit:

$$\text{Fluid deficit (ml)} = \text{body wt (kg)} \times \% \text{ dehydration (as decimal)} \times 1000 \text{ (ml/L)}$$

Osmolality:

$$\text{Serum osm}_{(\text{calc})} = 2(\text{Na}^+ + \text{K}^+) + (\text{BUN} \div 2.8) + (\text{glucose} \div 18)$$

Effective osmolality:

$$\text{Effective osm} = 2(\text{Na}^+) + (\text{glucose} \div 18)$$

Corrected sodium:

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$$\text{Na}_{(\text{corr})}^{+} = \text{Na}_{(\text{measured})}^{+} + 1.6([\text{measured glucose} \\ - \text{normal glucose}] \div 100)$$

BUN, Blood urea nitrogen; *K*⁺, potassium; *Na*⁺, sodium; *osm*, osmolality. BUN and glucose measured in mg/dl.

Venous blood gas analysis should be used to assess the degree of acidemia. It is not possible to differentiate HHS from DKA in cats based on the degree of metabolic acidosis.⁴ In HHS, metabolic acidosis is caused by accumulation of uremic acids and lactic acid, rather than ketones. Lactic acidosis is an indicator of poor tissue perfusion secondary to dehydration and hypovolemia.

Serum electrolytes should be monitored to help in choosing fluid therapy and to calculate the osmolality. Sodium concentration is the prime determinate of serum osmolality. In HHS, the true magnitude of sodium concentration will be masked by the hyperglycemia. Measured serum sodium is reduced by hyperglycemia-induced osmotic pull of water into the vasculature.²¹

Sodium level should be expected to rise as glucose levels return to normal. Calculating the corrected serum sodium value can give a better indication of severity of free water loss (see [Box 68-1](#)). For every 100 mg/dl increase in glucose above normal, the measured serum sodium decreases by 1.6 mEq/dl.²¹ A corrected serum sodium level can be calculated using the following formula:

$$\text{Na}_{(\text{corr})}^{+} = \text{Na}_{(\text{measured})}^{+} + 1.6([\text{measured glucose} \\ - \text{normal glucose}] \div 100)$$

Animals in diabetic crisis are classically expected to have low total body potassium concentrations,¹ although cats with HHS tend to have a normal serum potassium concentration.⁴ Potassium losses are expected via diuresis, vomiting, and decreased intake; increases in potassium may occur secondary to acidosis, severe hyperosmolality,²² insulin deficiency, and poor renal perfusion. Potassium levels are expected to decrease as acidosis improves and with insulin-induced cotransport of glucose and potassium into cells.

A thorough search for underlying disease should be undertaken in all patients with HHS. Additional diagnostic techniques including thoracic and abdominal radiographs, abdominal ultrasonography, echocardiogram, retroviral testing (cats), and endocrine testing (especially thyroid hormone levels in cats) may be indicated based on historical or physical findings or results of preliminary diagnostic results.

68.7 TREATMENT

Goals of therapy for patients with HHS include replacing the fluid deficit, slowly reducing serum glucose levels, addressing electrolyte abnormalities, and treating concurrent disease.²

To prevent exacerbation of neurologic signs, it is important not to lower the serum glucose or sodium too rapidly. Hyperosmolality induces formation of osmotically active idiogenic osmoles in the brain. These idiogenic osmoles protect against cerebral dehydration by preventing movement of water from the brain into the hyperosmolar blood.

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Because idiogenic osmoles are eliminated slowly, rapid reduction of serum osmolality establishes an osmotic gradient across the blood-brain barrier, leading to cerebral edema and neurologic signs.²³

The first goal of therapy is to replace dehydration deficits slowly using an isotonic crystalloid solution. Initially, 0.9% sodium chloride solution is the fluid of choice, because it will both address the fluid deficits and replace glucose with sodium in the extracellular space, thus preventing a rapid shift in osmolality. Hyponatremia should be corrected slowly with a decrease of no more than 1 mEq/L/hr.²⁴

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The fluid therapy plan should include dehydration deficit, ongoing losses and maintenance fluid needs (see [Box 68-1](#)). Fluid deficit (in ml) should be calculated by multiplying body wt (kg) × % dehydration (expressed as decimal) × 1000 (ml/L). On its own, fluid therapy will start to reduce blood glucose levels via dilution and by increasing GFR and subsequent urinary glucose excretion.²⁵ Ideally, the dehydration deficit should be replaced over 24 hours. Treating a patient with HHS and concurrent CHF presents a dilemma. Even maintenance amounts of parenteral fluids could be detrimental, so rehydration must be done more slowly and with care. Forced enteral fluid supplementation, as via a nasoesophageal tube, may be a viable option to aid in rehydration of some patients with CHF that are not vomiting.

Insulin should not be given until the hypovolemia and dehydration have improved. Unlike in DKA where insulin therapy is vital because of its role in reducing ketogenesis, insulin therapy is not as critical for resolution of HHS, because much of the syndrome can be improved just by correcting fluid deficit. Mechanics of insulin therapy for HHS are similar to those used in DKA, with protocol changes designed to lower the glucose levels more slowly. Using regular insulin as part of either intramuscular or intravenous protocols, at dosages 50% of those used for DKA, should prevent rapid decline in serum glucose.¹ Insulin therapy should be instituted after a minimum of 4 to 6 hours of fluid therapy and only if the potassium is at least 3.5 mmol/L. Intravenous constant rate infusion of 0.025 to 0.05 U/kg/hr can be made by adding 0.5 U/kg (cat) to 1 U/kg (dog) regular insulin to 250 ml 0.9% sodium chloride; the resulting solution should be started at 10 ml/hr via a dedicated intravenous line. For the intramuscular protocol, 0.1 U/kg of regular insulin should be given, followed by 0.05 U/kg q1-2h until the glucose is less than 300 mg/dl, then q4-6h. With both protocols, the goal is to decrease the glucose levels by no more than 50 to 75 mg/dl/hr.^{2,26} If the glucose is dropping too rapidly, the insulin dosage should be decreased by 25% to 50%. If the glucose is less than 250 to 300 mg/dl, 5% dextrose should be added to the fluids. Regular insulin should be continued until the animal is eating. Once the animal is eating and drinking, long-acting insulin therapy, dietary management, and monitoring should be started as for a standard diabetic. Vigilant therapy and careful monitoring of concurrent diseases are essential.

68.8 MONITORING

Glucose should initially be measured every 1 to 2 hours, and ketones should be checked daily. Serial neurologic examinations should be performed to monitor for signs of cerebral edema. Potassium, phosphorus, and magnesium levels should be monitored at least once daily and supplemented in fluids as needed. Electrocardiogram, blood pressure, and central venous pressure may be helpful in monitoring patients with HHS. Multilumen central venous catheters will facilitate glucose and central venous pressure monitoring and administration of multiple infusions.

68.9 PROGNOSIS

The mortality rate for patients with HHS is high because of the severity of the syndrome as well as presence of concurrent disease. In humans, the mortality rate is consistently 15% to 17% of HHS admissions, and many

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outcome predictors have been identified.^{14,27-29} There are no clear predictors of survival from HHS for animals. In one feline study, in-hospital mortality was 64.7% and long-term (>2 month) survival was only 12%.⁴ Outcome was not predicted by presence of neurologic signs, serum glucose concentration, measured serum sodium concentration, corrected serum sodium concentration, or total and effective serum osmolality. Long-term survivors had curable concurrent diseases.

68.10 SUGGESTED FURTHER READING*

SP DiBartola: In *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, St Louis, *Excellent review of electrolytes and acid-base physiology*.

EC Feldman, RW Nelson: In *Canine and feline endocrinology and reproduction*. ed 3, 2004, Saunders, St Louis, *The most comprehensive reference on small animal endocrinology. Excellent review of pathophysiology, clinical characteristics, and management of all forms of diabetes*.

A Koenig, K Drobotz, AB Beale, L King: Hyperglycemic, hyperosmolar syndrome in feline diabetics 17 cases (1995-2001). *JVECC*. **14**(1), 2004, 30–40, *A retrospective study evaluating clinical and laboratory findings and outcome in HHS cats*.

* See the CD-ROM for a complete list of references