Advances in Managing Diabetic Ketoacidosis
Patty Lathan, VMD, DACVIM
Mississippi State University
Mississippi State, MS

Pathophysiology
Diabetic ketoacidosis is a life-threatening complication of diabetes mellitus, characterized by hyperglycemia, ketoacidosis and electrolyte abnormalities. Ketosis is likely the result of both relative insulin deficiency and glucagon excess. In a non-diabetic animal, insulin decreases lipolysis via inhibition of hormone-sensitive lipase. In the absence of insulin and under the influence of hormone-sensitive lipase, triglycerides stored in adipose tissue are broken down into free fatty acids (FFAs), which are released into circulation and then converted into triglycerides and ketone bodies by the liver. In an uncomplicated diabetic, most of the excess FFAs are converted to triglycerides. However, in patients with DKA, concurrent disease processes are thought to increase the concentration of the counterregulatory hormones, including glucagon, cortisol, and epinephrine. Glucagon inhibits storage of triglycerides in the liver, and stimulates the conversion of FFAs to the ketone body acetoacetic acid (ACA). Acetoacetic acid can then be converted to acetone and betahydroxybutyric acid (BHB). Thus, it is likely the combination of relative insulin deficiency and excess glucagon production that results in ketosis. Cortisol and epinephrine also contribute to ketogenesis by stimulation of hormone-sensitive lipase. In addition, these three counterregulatory hormones increase hyperglycemia via glycolysis and gluconeogenesis.

BHB and ACA are both relatively strong acids, and dissociate into hydrogen ions and ketoanions at physiologic pH. (Acetone does not dissociate, but is excreted by the lungs.) This results in a high anion gap metabolic acidosis. Glucosuria and excretion of ketoanions (in combination with cations such as sodium and potassium) lead to significant fluid losses through the kidney, which contributes to hypovolemia, lactic acidosis, and exacerbation of the metabolic acidosis. Anorexia and vomiting, caused by stimulation of the chemoreceptor trigger zone by ketonemia and hyperglycemia, also contribute to the dehydration, hypovolemia, and lactic acidosis.

In patients with DKA, hyponatremia is common due to dilution (hyperglycemia causes fluid to shift to intravascular space, diluting the sodium) and loss through the urine with ketoanions. Whole-body potassium depletion occurs through several mechanisms, including osmotic diuresis, hypovolemia-induced hyperaldosteronism, and loss through vomiting. Even if the serum potassium concentration is within reference range at initial presentation, it usually decreases following rehydration, increased diuresis, and treatment with insulin therapy, which shifts potassium intracellularly.

Signalment, history, and clinical signs
Diabetes mellitus is newly diagnosed in 50-60% of cats and 65% of dogs that present with DKA. The signalment for DKA is typically the same as that for diabetes mellitus. Historical findings often include signs of previously uncomplicated DM, including PU/PD, polyphagia, and weight loss, with a more recent onset of lethargy, inappetance, and vomiting. Additional signs may occur due to concurrent disease, which is present in approximately 70% of dogs and 90% of cats with DKA. The most common concurrent conditions found in dogs are acute pancreatitis, bacterial urinary tract infection, and hyperadrenocorticism. In cats, hepatic lipidosis, cholangiohepatitis, pancreatitis, chronic renal failure, urinary tract infection, and neoplasia have been documented concurrent disorders.

Physical examination almost always reveals dehydration, lethargy, and depression. Cranial organomegaly is also common, as are mental dullness (particularly in cats) and cataracts (in dogs). Other signs, such as abdominal pain, dyspnea, coughing, and abnormal lung sounds, may be present due to concurrent disease.

Diagnostic findings
Hyperglycemia, glucosuria, ketonuria or ketoacidosis, and acidemia confirm the diagnosis of DKA. Urine ketone test strips can be used to identify ketones in the urine or in plasma, which is useful when a urine sample is not available. However, these test strips utilize a methodology that detects ACA and acetone, but not BHB. Since more ACA is converted to BHB in the presence of acidemia, BHB is thought to be present in higher quantities in more acidic patients. Given that the urine test strips don’t measure BHB, they likely underestimate the degree of ketosis in the more acidic patients. However, the measurement of BHB using a point of care ketonemeter has been shown to correlate with results of a reference laboratory. A recent study (Tommaso et al, 2009) demonstrated that, in dogs, blood BHB is a more accurate predictor of DKA than is the use of urine ketone sticks on urine. Additionally, results suggest that patients with a BHB concentration >3.5 mmol/L are at a high risk of developing DKA, whereas dogs with a concentration <2.8 mmol/L are at low risk. Thus, in diabetic dogs hospitalized for other reasons, measurement of BHB might help identify those patients at risk for DKA.

The minimum data base recommended for a patient with DKA is a serum biochemistry (including electrolytes), CBC, blood gas (or at least a tCO2 on the serum chemistry), urinalysis, and urine culture. Additional diagnostics are indicated based on physical
examination and history, and to help identify and characterize concurrent disease. These may include abdominal and thoracic imaging, quantitative fPLI/cPLI, and T4 (cats only!).

Anemia is present in about half the dogs with DKA, and is generally normochromic/normocytic. Cats also tend to be anemic, and have an increased amount of Heinz body formation, relative to normal cats. A left-shifted neutrophilia is common in both species.

As with DM, the ALP is increased in most dogs with DKA, and ALT, AST, and cholesterol are increased in many. In cats, ALT and cholesterol are also frequently increased. Azotemia occurs more often in cats than in dogs, and may be pre-renal or renal in origin.

Electrolyte abnormalities are common in both dogs and cats with DKA. Hypokalemia is common, but the potassium concentration may be normal at presentation due to acidosis and lack of insulin. Close monitoring is necessary during therapy, however, as treatment with insulin and resolution of acidemia reveal whole body depletion. Profound muscle weakness may occur without adequate supplementation. Phosphorus concentration may be normal, decreased, or increased at presentation. Insulin therapy will drive it into the cell, often resulting in hypophosphatemia, which can cause hemolysis. Hyponatremia occurs in approximately 50% of dogs with DKA, and is due to dilution and loss in the urine. A decreased ionized magnesium concentration is reported in cats with DKA, but the clinical significance is unclear at this time. Conversely, dogs with DKA do not typically have decreased ionized magnesium concentrations.

Urinalysis will reveal glucosuria and ketonuria, and potentially an active sediment. However, due to the immunosuppression and impaired neutrophil chemotaxis caused by DM, an infection may be present despite inactive sediment. Thus, urine culture should be performed in every patient with DKA.

**Treatment**

The goals of treatment of DKA are:

1. Correction of dehydration, electrolyte abnormalities, and acidosis
2. Administration of insulin and dextrose
3. Treatment of the underlying cause

**Fluid therapy**

The cornerstone of treatment for DKA is intravenous fluid therapy. In addition to treating dehydration and hypovolemia, fluids dilute out ketones and glucose, improve renal perfusion, and increase renal filtration and excretion of ketones and glucose. Thus, fluids alone will help decrease ketone and glucose concentrations, while correcting acidemia.

Although a jugular catheter is preferred for continued maintenance of these patients (particularly while administering dextrose), a peripheral catheter is often placed for initial fluid stabilization. A crystalloid fluid (0.9% NaCl or Plasmalyte) should be given for several hours prior to initiating insulin therapy. This helps prevent a rapid decrease in BG caused by simultaneous rehydration and insulin administration, and also allows for correction of electrolyte abnormalities prior to insulin therapy. The fluid rate depends upon dehydration, ongoing losses, and other problems (such as cardiac disease). Dehydration is typically corrected over 12-24 hours.

Hypokalemia may result in muscle weakness, which can be profound in some patients. K supplementation should be provided based on K concentration (almost never exceeding 0.5 mEq/kg/hr). Correction of acidemia with fluid therapy will drive some K intracellularly, resulting in a lower K concentration even prior to insulin therapy, which will drive more K intracellularly. So getting ahead of the hypokalemia prior to insulin therapy will help prevent more severe hypokalemia associated with insulin therapy.

<table>
<thead>
<tr>
<th>Serum K+ concentration (mmol/L)</th>
<th>Potassium (mEq) added to 250 mL fluid bag</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1-3.5</td>
<td>7</td>
</tr>
<tr>
<td>2.6-3.0</td>
<td>10</td>
</tr>
<tr>
<td>2.1-2.5</td>
<td>15</td>
</tr>
<tr>
<td>1.6-2</td>
<td>20</td>
</tr>
</tbody>
</table>

*Potassium supplementation not to exceed 0.5 mEq/kg/hr*

Hyponatremia is treated with 0.9% NaCl. Care should be taken not to increase it >0.5 mEq/kg/hr, to avoid cerebral myelinolysis. Hypophosphatemia is often present prior to and/or following initiation of insulin therapy, and may lead to hemolysis. Most authors recommend supplementation when P< 1.5 mg/dL, at a rate of 0.01 – 0.03 mmol/kg/hr in calcium-free fluids. However, I start supplementing when P is 1.5-2 mg/dL, initially at a rate of 0.01 mmol/kg/hr. Potassium phosphate contains 4.4 mEq/mL of K and 3 mmol/mL of phosphate. Make sure to take this added K into account when calculating the amount of KCl added to fluids.

In hypomagnesemic cats, magnesium sulfate can be administered at 1 mEq/kg IV over 24 hours.

Bicarbonate therapy to correct acidosis is not usually needed, and has been shown to increase ketone levels in people with DKA. Fluid therapy alone helps reverse acidosis through increased renal blood flow, resulting in renal excretion of acid and regeneration of bicarbonate. Additionally, insulin-induced metabolism of ketoacids results in regeneration of bicarbonate. Potential risks associated with bicarbonate therapy include paradoxical cerebral acidosis and metabolic alkalosis. Bicarbonate therapy is very controversial in humans with DKA, and a recent review article found insufficient evidence for its use, even in patients with pH<6.9 (Chua et al, 2011).
If the clinician chooses to use bicarbonate (possibly when the pH is <7.0), one possible protocol is to add 1/3 – 1/2 of the calculated bicarbonate dose (below) to fluids and give over 4-6 hours. A blood gas should be rechecked following therapy.

Bicarbonate dose (mEq) = body weight (kg) x 0.4 x (12 - patient’s HCO3–)

Initially, electrolytes and phosphorus concentrations should be monitored 2-4 times per day. I often check K concentration following the first few hours of fluid administration (prior to insulin therapy).

**Insulin therapy**

In addition to decreasing the BG concentration, insulin administration inhibits ketone formation and promotes metabolism of ketones to bicarbonate. By stimulating cellular uptake of glucose, it also inhibits additional glucagon release.

Ideally, insulin therapy will decrease the BG slowly, by approximately 50-75 mg/dL/hr, to avoid rapid decreases in serum osmolality. When BG falls below 250 mg/dL, dextrose is added to the IV fluids so that insulin administration can continue while avoiding hypoglycemia (which would also stimulate glucagon release).

The most common treatment protocols involve administration of regular insulin as a constant rate infusion or as hourly intramuscular injections. For the constant rate infusion, 2.2U/kg of regular insulin is added to a 250 mL bag of 0.9% NaCl. The first 50 mL of the solution is run through the IV line to saturate non-specific binding sites in the plastic tubing. The CRI is begun at 10 mL/hr (approximately 0.1 U/kg of R insulin), and BG monitored q2h. Insulin CRI rate and IV fluid composition are adjusted based on BG.

<table>
<thead>
<tr>
<th>BG (mg/dL)</th>
<th>IV fluids</th>
<th>Insulin rate (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;250</td>
<td>0.9% saline</td>
<td>10</td>
</tr>
<tr>
<td>200-250</td>
<td>0.9% saline + 2.5% dextrose</td>
<td>7</td>
</tr>
<tr>
<td>150-200</td>
<td>0.9% saline + 2.5% dextrose</td>
<td>5</td>
</tr>
<tr>
<td>100-150</td>
<td>0.9% saline + 5% dextrose</td>
<td>5</td>
</tr>
<tr>
<td>&lt;100</td>
<td>0.9% saline + 5% dextrose</td>
<td>Stop fluid administration</td>
</tr>
</tbody>
</table>

For the intermittent IM protocol, 0.2 U/kg of R insulin is given initially, followed by 0.1 U/kg, 1 hour later. BG is checked hourly, and 0.1 U/kg is given IM every hour until BG<250 mg/dL. If the BG is decreasing by more than 75 mg/dL/hr, insulin dose should be halved. When the BG hits 250 mg/dL, injection frequency can be decreased to q4-6h IM or SC (if rehydrated). Dextrose should be added to the fluids when the BG is <250 mg/dL. Note that the use of a jugular catheter for administration of dextrose-containing fluids, and for blood sampling, is ideal in these patients.

Once the patient is eating consistently and no longer ketotic, dextrose is discontinued and the patient is switched to a twice daily insulin (usually NPH or porcine lente insulin for dogs, and glargine or PZI for cats). The first injection may be given when the patient is mildly hyperglycemic (>250 mg/dL).

Recently, DKA treatment using newer insulin analogs has been reported. Lispro is a rapidly acting insulin that was shown to be safe and effective when used as a CRI in dogs (Sears et al, 2012). Glargine insulin has the same pharmacokinetic and pharmacodynamic properties as regular insulin when given IV or IM. A protocol using a combination of IM and SC injections of glargine led to resolution of DKA in 15 cats (Marshall et al, 2013).

**Prognosis**

Based on a recent study, approximately 70% of dogs treated for DKA survive to discharge, with a median hospitalization time of 6 days (Hume et al, 2006). Patients with concurrent hyperadrenocorticism and with more severe metabolic acidosis were less likely to survive.

At least 7% had recurring episodes of DKA.

The survival rate in cats is also approximately 70%. Cats that present with DKA are as likely as other cats with DM to achieve diabetic remission.

**References**


