**Introduction**

Diabetic ketoacidosis (DKA) is a life-threatening condition, and requires aggressive treatment. This lecture will review its pathogenesis and key diagnostic steps, and then outline a logical approach for effective patient management.

**Pathophysiology of Diabetic Ketoacidosis**

The fundamental trigger for DKA is a relative or absolute lack of insulin. Although most patients are totally insulin deficient (e.g., a dog with untreated diabetes mellitus [DM]), some are receiving exogenous insulin when the condition arises. Patients with relative insulin deficiency usually have a concurrent disorder, such as an infection, which counteracts the effect of exogenous insulin, or they are receiving drugs such as glucocorticoids that cause insulin resistance.

If a healthy animal is fasted for several hours, the body enters starvation mode and insulin secretion drops. It does not stop completely and these minimal amounts play an important role as a brake on the release of stored energy. Also, as insulin secretion slows, pancreatic α cells secrete progressively more glucagon. This hormone promotes hepatic gluconeogenesis and the release of stored energy from fat (lipolysis). Stored triglycerides are broken down into free fatty acids and glycerol. The glycerol can be converted to glucose, and the fatty acids are converted by the liver into ketones (i.e., β-hydroxybutyrate, acetoacetate and acetate). Ketones can be used to generate energy via the Kreb’s cycle and can be used very efficiently by the brain, the heart, and other tissues when food is unavailable.

In a diabetic animal, lipolysis moves at an accelerated rate. The absolute lack of insulin lets glucagon secretion continue unchecked, and this hormone drives the mobilization of fat from stores. Consequently, a dog or cat with DKA may produce ketones at twenty times the rate seen in simple starvation. As ketone production also results in the generation of protons, the patient becomes progressively acidotic.

Additional metabolic derangements predictably occur in animals with DKA, and worsen the clinical picture. Profound hyperglycemia results in a marked osmotic diuresis and involuntary water loss. Initially, this can be mitigated by increased water intake, but as the patient’s condition worsens, it becomes progressively dehydrated. This results in lactic acid production and exacerbation of acidemia. Patients with DKA also have deranged potassium homeostasis, with decreased intake and loss from the gastrointestinal and urinary systems. Total body potassium stores are generally very low, although serum potassium concentrations are variable and are a very poor reflection of true potassium status. There is strong evidence to suggest that high concentrations of circulating free fatty acids cause pancreatitis, and it is likely that many patients with DKA have some degree of acinar injury. Concurrent pancreatitis will cause abdominal pain and vomiting, and worsen other ongoing metabolic derangements.

**Diagnosis**

Three simple criteria are needed to establish a diagnosis of DKA, namely, hyperglycemia, ketonemia/ketonuria, and metabolic acidosis. It is important to remember that many diabetic dogs and cats are ketotic at the time of diagnosis, but are still eating, drinking, and stable. These can be managed on an outpatient basis, although exogenous insulin therapy must be started promptly.

**Physical Examination**

A thorough examination is necessary to assess hydration status and identify any important concurrent disease(s). Most patients are at least 8 percent dehydrated, so do not be tentative in making this assessment. As many patients have pancreatitis, it is important to identify and score their pain level, so that this is addressed. Concurrent cardiac disease will impact fluid therapy decisions, so a murmur or a gallop should be noted. Severe dental and dermatologic disease may cause insulin resistance, and will need to be addressed when the patient is more stable.

**Laboratory Findings**

A CBC provides useful information about inflammatory diseases, concurrent anemia, and early evidence of DIC. A stress leukogram is expected, and some dogs (more often than cats) have a substantial neutrophilia. Mild toxic changes and a small increase in band forms may be noted, but a degenerative left shift is not typical. Cats may
develop a hemolytic anemia secondary to Heinz body formation. This can be severe and transfusion may be necessary. It is important that a blood smear is examined so that signs of oxidative damage are noted promptly.

Blood glucose (BG) concentrations are substantially elevated, but rarely exceed 600 mg/dl. Values approaching 1,000 mg/dl are more often associated with a condition called hyperosmolar non-ketotic diabetes mellitus (HONK-DM), also called hyperosmolar hyperglycemic syndrome. These patients are minimally ketonuric, and usually have severe underlying renal or cardiac disease. It is important to recognize the HONK-DM patient, as these cases are often more sensitive to insulin therapy and the prognosis is generally worse.

BUN and creatinine are often increased, due to dehydration. As urine specific gravity is impacted by glucosuria, it is very difficult to assess renal function in these patients. Severe azotemia (BUN > 100 mg/dl or creat > 5 mg/dl) is rarely noted in patients with DKA but are routinely seen in patients with HONK-DM. Severe azotemia may indicate preexisting renal disease or pyelonephritis.

Most dogs with uncontrolled diabetes show some changes in liver enzyme activities. Alkaline phosphatase (ALP) activity is routinely increased and does not necessarily indicate hyperadrenocorticism. If the alanine aminotransferase (ALT) is > 2x upper end of the normal range this should be rechecked in 24 hours. Some degree of hepatic lipidosis is expected in cats with DKA. ALP activity is often increased and is an early marker for this disorder. Depending on the duration of anorexia, some degree of hyperbilirubinemia may be noted.

Cholesterol concentrations are usually increased in both dogs and cats with DKA. Icterus is not routinely noted in dogs but may be a consequence of extra-hepatic bile duct obstruction secondary to pancreatitis. Substantial icterus in a cat with DKA suggests hepatic lipidosis or hemolysis, secondary to Heinz body formation.

Serum sodium concentrations are generally subnormal, due to the dilutional effect of the hyperglycemia. Serum potassium concentrations are often within or slightly above the reference range, despite potentially severe total body depletion. Serum levels are elevated by the lack of insulin (which carries potassium in to cells), metabolic acidosis, and poor renal perfusion. As soon as circulating volume is restored, the serum potassium will drop. This process is hastened by insulin administration, and aggressive supplementation is necessary in every patient. I start to supplement potassium in generous amounts (details provided later) as soon as potassium is within the normal range. If a patient presents with hypokalemia, this must be addressed before insulin is given. Phosphate is often increased initially due to poor renal perfusion. However, phosphate follows potassium in DKA cases, and life-threatening hemolysis can occur as the levels drop. If serum phosphorus concentrations cannot be easily tracked, it is best to assume that phosphorus is following potassium. Magnesium concentrations at presentation are variable, but are likely to move down during fluid therapy.

The urine will contain a substantial amount of glucose. This affects specific gravity, which is usually > 1.020 despite the severe polyuria. Ketones will be present, but the regular dipsticks only identify acetoacetate and acetone; β-hydroxybutyrate is not recognized. Adding a few drops of hydrogen peroxide will convert this to acetoacetate and permit detection. A urine culture should be performed on all patients, even if the sediment appears inactive. If the urine is at all suspicious for a UTI, antibiotics should be administered while culture is pending.

DKA patients are predictably acidicemic, and the severity of acidosis may provide some prognostic information. There are several reasons for the acidosis, but generation of ketoacids is the primary influence. Because unmeasured anions (ketones, lactate) are present in serum, this is a high anion-gap metabolic acidosis. This is characterized by a low bicarbonate or TCO₂ and low serum chloride concentration. In human medicine, serum ketones are routinely measured, but this is not commonly done in veterinary patients. The machines available measure β-hydroxybutyrate, so may identify patients with negative urine dipstick results.

**Additional Diagnostics**

Serum amylase or lipase activities are an unreliable way to detect pancreatitis. Newer tests (Spec cPL® and fPLI®) can accurately identify pancreatic-specific lipase, and have been shown to be both sensitive and specific. In-house test kits are now available for dogs and cats; a negative result essentially rules out pancreatitis. Ultrasonography may not be necessary in every case, but can provide useful information about renal status, hepatic architecture, and the condition of the pancreas. Also, any concurrent abdominal disorders may be identified. A baseline lateral thoracic film is appropriate in any patient with clinical findings suggestive of cardiac disease (murmur, gallop,
irregular rhythm). A 3-view study should be considered in a patient with a fever or abnormal auscultation, as aspiration pneumonia may be present. In our clinic, we routinely collect baseline coagulation profiles. In many instances, the results are within normal limits. However, baseline data let us identify trends and intervene proactively. The most common finding is an increase in d-dimer levels, probably due to pancreatitis.

**Therapeutic Plan**

A DKA patient can appear a little overwhelming at presentation, so I focus on four treatment goals:

- Restore circulating volume and correcting dehydration
- Anticipate and address electrolyte disorders
- Turn off ketosis
- Identify and address concurrent disorders (e.g., urinary tract infection, pancreatitis)

**Restore Circulating Volume and Correct Dehydration**

This is done in the standard fashion: an estimate is made of total fluid losses and this number is then divided by the number of hours in which the loss is to be replaced. I usually aim to replace that loss within 12 hours, but will move more cautiously in patients with cardiac disease or other issues that may impact fluid tolerance. I would stress, however, that an aggressive rehydration plan is my default approach, as concurrent issues such as pancreatitis require prompt reestablishment of effective circulating volume. If the patient is severely dehydrated and has evidence of ineffective circulating volume (tachycardia, cold feet, etc.), a fluid bolus is administered immediately; this volume is then subtracted from the total loss before the hourly replacement rate is calculated. A typical bolus would be 20 ml/kg for a dog or 15 ml/kg for a cat, given over 15 minutes. This can be repeated if necessary.

Due to substantial polyuria, it takes a robust amount of fluids to simply “stand still,” so calculation of maintenance needs must be generous. I use a nonlinear formula \((\text{kg}^{0.75} \times 130)\) to calculate daily maintenance volumes, but am aware that it may not meet some patients’ needs.

Many clinicians start with 0.9 percent NaCl, but any of the replacement fluids (i.e., those with a sodium concentration similar to plasma) are appropriate. I usually reach for 0.9 percent NaCl as this is compatible with all the fluid additives I routinely use in these patients and I do not have to worry about incompatibilities. LRS contains calcium and cannot be infused through the same vein as potassium phosphate, but Normosol-R is calcium free.

As a general guideline, IV fluids should be administered for about 6 hours before insulin is started. This will improve renal perfusion and is likely to decrease BG by up to 100 mg/dl. Insulin should not be withheld until fluid deficits are restored. Standard monitoring should include respiratory rate every hour (to identify fluid overload). Central venous pressure, renal status, and urine output should be measured in critical patients.

**Anticipate and Address Electrolyte Disorders**

Major electrolyte derangements occur due to rapid shifts in potassium and phosphorus. Failure to specifically consider electrolyte needs is a common cause of poor outcomes in patients with DKA.

Some patients present with hypokalemia; this must be addressed aggressively before insulin is administered. Ideally, potassium chloride should be administered as a constant rate infusion (CRI), close to K-max (0.5 mEq/kg/hr). If given through a peripheral vein, KCl must be diluted 1:10 with sterile water. Alternatively, KCl can be added to the IV fluid bag, although a separate CRI is often less complicated. If potassium is at the lower end of the reference range at admission, KCl should be added to the initial IV fluids (30–40 mEq/L).

Check the serum potassium concentrations after 2–3 hours of fluid therapy and adjust appropriately. Potassium should be checked again immediately before starting insulin, as this will drive those levels down precipitously. Hopefully, levels are within the reference range at this point. Most of the bedside electrolyte machines do not measure phosphorous levels, but it is safe to presume that phosphorus is going to follow potassium. It is important to add phosphate before the level gets too low; there are complex formulas for calculating phosphate doses, but it is easiest to just provide 50 percent of the potassium supplement as KPO₄ and 50 percent as KCl. Remember that the volumes will not be equal, as KPO₄ has more mEq of K⁺ in each ml.

**Turn Off Ketosis**

The only way to turn off ketosis is by giving of insulin. I plan to start insulin about 6 hours after admission; by this
time, I have (hopefully) made substantial headway with the dehydration and have a handle on potassium status. Patients will not substantially improve until insulin is given so this should not be delayed. Although some publications describe IM insulin protocols for DKA patients, the IV plans are much easier. The only equipment needed is a BG monitor and some kind of syringe pump or low-volume IV pump.

The dose of regular (R) insulin for dogs is 0.1 unit/kg/hour, or 2.4 units/kg/day. Opinions differ for cats; some clinicians use the same dose as for dogs, while others recommend 0.05 U/kg/hr (1.2 U/kg/day). Draw up the total daily dose and add this to a 250 ml bag of 0.9 percent NaCl. Insulin will adhere to the plastic tubing, so slowly run 50 mls through the line before attaching it to the patient. Replace this bag every 24 hours. No matter how large or small, every patient starts at 10 mls/hour of insulin. This insulin CRI is then adjusted based on two-hourly BG measurements. When BG is below 250 mg/dl, the concurrent fluid is switched to a fluid containing dextrose, so that insulin can be continued. This is administered at a rate appropriate to meet the patients fluid therapy needs.

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Insulin CRI rate</th>
<th>Concurrent fluid therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 250 mg/dl</td>
<td>10 ml/hr</td>
<td>0.9% NaCl</td>
</tr>
<tr>
<td>200–250 mg/dl</td>
<td>7</td>
<td>0.45% NaCl with 2.5% dextrose</td>
</tr>
<tr>
<td>150–200 mg/dl</td>
<td>5</td>
<td>0.45% NaCl with 2.5% dextrose</td>
</tr>
<tr>
<td>100–150 mg/dl</td>
<td>5</td>
<td>0.45% NaCl with 5% dextrose</td>
</tr>
<tr>
<td>&lt; 100 mg/dl</td>
<td>OFF</td>
<td>0.45% NaCl with 5% dextrose</td>
</tr>
</tbody>
</table>

The regular insulin CRI is continued until ketones are clearing and the patient is able to eat. In some patients, ketonuria worsens initially as β-hydroxybutyrate is metabolized to acetoacetate. However, most patients are ketone negative within 72 hours. Premature withdrawal of the insulin CRI may lead to renewal of ketone generation. Similarly, it is essential to get calories into the patient promptly, as anorexia perpetuates the starvation response. If necessary, an NE or esophagostomy tube should be placed for enteral nutrition.

Cats should be started on a long-acting insulin such as insulin glargine or protamine zinc insulin; appropriate choices for dogs would be lente (Vetsulin®) or NPH insulin. Refer to the AAHA guidelines on the management of diabetes mellitus for information on dosing etc.

**Identify and Address Concurrent Disorders**
Urinary tract infection should be treated appropriately. Patients with evidence of pancreatitis need pain relief; opioids are the best choice. Anti-emetics (such as maropitant +/- metoclopramide) and gastric acid inhibitors (such as pantoprazole or famotidine) may improve patient comfort and hasten the return of appetite.

If acute pancreatitis is present, I will consider the use of low molecular weight heparin, but there is little evidence to support this plan and some concerns exist about the pro-inflammatory properties of heparin. Bicarbonate therapy should be avoided as the acidosis associated with DKA will resolve quickly with appropriate therapy.

**Summary**
DKA requires prompt intervention and is fatal if untreated. Although treatment requires a logical, careful, and systemic approach, it is fairly straightforward. Most patients will do well and merit a favorable prognosis.

**Recommended Reading**
