Managing severe DKA in dogs and cats

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Diabetic ketoacidosis (DKA) is characterized by hyperglycemia, ketonemia, and high anion-gap metabolic acidosis. It occurs because of an absolute or relative insulin deficiency **and** a concurrent increase in counter regulatory hormones (catecholamines, cortisol, glucagon, growth hormone). In other words, it occurs because a patient with diabetes mellitus (DM) develops a concurrent illness or injury that causes an increase in circulating amounts of hormones that interfere with normal insulin function and glucose metabolism.

DKA is most common in previously undiagnosed diabetic dogs and cats. The most reasons for a diabetic patient to develop DKA are an underlying infection, inflammatory disease, or insulin-resistant hormonal disorder. It can also be seen in patients who have missed or incorrectly dosed insulin therapy. Hospital-acquired DKA in known diabetic patients is due to inadequate insulin therapy. This can be the result of incorrect dosing or administration of insulin, insufficient monitoring, or incorrect interpretation of the patient's blood glucose.

Initial emergency treatment

The degree of initial resuscitation required will vary with the severity of dehydration, hypovolemia, and acidosis. The "healthy" ketotic pet should get the same work-up as a non-ketotic diabetic patient, and can generally be managed conservatively. The remainder of the discussion will focus on the critically ill DKA patient.

At presentation the critically ill patient should have IV access established with the largest reasonable IV catheter, blood collected for subsequent analysis (CBC, serum chemistry, venous blood gas [serum tCO_2 will suffice if blood gasses are not available], serum or plasma ketone measurement, lactate, and electrolytes including ionized calcium and magnesium if available), urine collected for subsequent urinalysis and culture, and immediate initiation of volume resuscitation. Resuscitative efforts should not be delayed for blood or urine sample collection in patients with cardiovascular instability. ECG and blood pressure monitoring should be initiated early in the resuscitation process. As soon as feasible a secondary IV catheter should be placed for adjunctive medication administration during fluid resuscitation.

There are 7 mainstays of management in the DKA patient

1. Restore and defend the intravascular volume
2. Restore perfusion and defend the mean arterial pressure (MAP)
3. Treat abdominal pain, nausea, vomiting
4. Administer insulin to reduce hyperglycemia and acidosis
5. Anticipate and manage electrolyte derangements
6. Monitor attentively
7. Treat the co-morbid condition(s)

Restoration of the intravascular volume should ideally be accomplished within 1-2 hours of presentation. Careful monitoring, frequent reassessment, and administration of additional fluid to keep up with the large ongoing losses is then necessary to maintain the intravascular volume. Correcting the intracellular dehydration will take hours to days depending on the degree of the patient's dehydration, hyperosmolar state, and your ability to keep up with ongoing losses. See the treatment notes below for more discussion on restoring and maintaining the intravascular volume.

The initial fluid for resuscitation should be an isotonic crystalloid, with preference given to the balanced isotonic solutions. Plasmalyte A, Normosol R, Lactated Ringer's, and 0.9% saline are all reasonable choices. Older references (human and veterinary) have recommended 0.9% saline as the fluid choice. The reasoning was the higher sodium content could help to treat the low sodium often observed in DKA patients. However it may not be beneficial to treat the hyponatremia early and aggressively (discussed below), and the high chloride concentration may be harmful. If available, a balanced isotonic solution (Plasmalyte A or 148, Normosol R, Lactated Ringer's) is preferred.

Restoration of perfusion and the mean arterial pressure occurs simultaneously with restoration and management of the intravascular volume. In most patients restoring and maintaining intravascular volume will be all that is necessary to restore adequate perfusion. In patients with severe metabolic

acidosis vasopressor support may be necessary. The most common indication for vasopressors in DKA dogs and cats is failure to adequately respond to fluid therapy. As a general guideline, if you have been attempting volume resuscitation for an hour and have not achieved a minimum MAP of 65mmHg AND a patient who appears to be normally perfused (see perfusion parameters below), vasopressor support is indicated. If you have administered a 'shock dose' of fluids (60cc/kg [cats] or 90cc/kg [dogs] of crystalloid fluid in 1 hour or less) without adequate response vasopressors should be initiated sooner than the 1 hour mark. Likewise, patients in extremis [comatose or stuporous without a palpable pulse and who are expected to arrest within seconds to minutes) may need vasopressor support within minutes of initiating fluid therapy.

Treating pain, nausea, and vomiting should occur as soon as IV fluid therapy has started. These interventions should be early and aggressive. Comfortable patients are easier to resuscitate, and controlling vomiting will reduce volume losses, electrolyte disturbances, and risk of aspiration pneumonia.

Nausea should be treated using IV drugs. Maropitant 1mg/kg, ondansetron 0.7-1mg/kg IV, or metoclopramide 0.5mg/kg IV are all reasonable choices. Multiple agents may eventually be necessary to achieve patient comfort.

Nasogastric tubes are very useful for decompressing the stomach, reducing nausea and vomiting induced by stretching of the gastric wall, and reducing the risk of aspiration pneumonia. Placement is usually delayed until the patient is volume resuscitated. However patients with gastric distension severe enough to inhibit adequate venous return may need to be decompressed in order to become adequately resuscitated. Similarly, patients who are profusely vomiting or regurgitating may need to have a nasogastric tube placed earlier in resuscitation to reduce the risk of aspiration pneumonia and improve patient comfort. Patients who are sick enough to require nasogastric tube placement during resuscitation typically will allow placement without sedation if adequate topical analgesia and IV pain medications are applied. A small amount of 2% lidocaine instilled into the nostrils (bilaterally) and allowed to sit for 7-10 minutes is usually adequate.

Pain should be treated with pure-mu opioid drugs (fentanyl, morphine, hydromorphone, methadone, oxymorphone, etc). These drugs will be effective, can be reversed if necessary (very rare), and most importantly will NOT worsen the patient's shock when used appropriately. In critically ill animals use the 'start low and go slow' technique is safe and effective, and allows you to safely ramp up to the level of analgesia necessary for the patient. This technique can be used in any patient population:

- Choose a dose at the low-end of the dose range. For patient with severely compromised circulation, consider a 50% dose reduction as the starting dose (but be certain to continue to administer doses until pain is appropriately controlled).
- Administer the chosen starting dose IV, and set a timer for 7-10 minutes (the time to peak onset of most pure-mu opioids when given IV)
- Re-assess the patient's pain, and administer additional analgesia at 50% of the starting dose.
- Set a timer for 7-10 minutes, and repeat this process using 50% of the starting dose, until pain is controlled

Avoid using buprenorphine and butorphanol. Both of these drugs are inferior to the pure-mu opioids for pain relief, they will inhibit the better pain relievers from working fully for many hours should the buprenorphine/butorphanol prove inadequate, and are not easily reversed with naloxne. Use pure mu opioid drugs for painful patients with cardiovascular compromise.

Insulin therapy should begin once the intravascular volume has been restored. Realistically this means starting insulin therapy within 2-3 hours of initiating IV fluid therapy. The practice of delaying insulin therapy for several hours prolongs duration of hospitalization and prolongs the time to resolution of hyperglycemia, ketonemia, and hyperosmolality **without** reducing the rate of complications (including hypokalemia).

Insulin therapy should reduce the blood glucose approximately 50-75mg/dL per hour. Overzealous correction of hyperglycemia will result in more severe electrolyte derangements and rapid shifts in osmolality than a more controlled approach. The total amount of insulin a patient will require to achieve this rate of decrease varies widely from patient to patient. There are several published insulin administration protocols (a summary of the published protocols is available at www.eccvetmed.com under the tools and reference section) however it is important to remember that these are starting points, and

therapy has to be titrated to the individual patient. The goal is a controlled decrease in the blood glucose then maintenance of the blood glucose in the 100-250mg/dL range.

Once reaching the maintenance phase, dextrose is supplemented parenterally to allow insulin therapy to continue, which allows resolution of ketoacidosis. This is very important: ongoing insulin therapy is necessary to resolve ketoacidosis! Don't decrease or stop the insulin. Supplement with parenteral dextrose to allow insulin therapy to continue!

Insulin does much more than just lower the blood glucose - it plays a vital role in correcting the deranged physiology that is perpetuating the DKA state. Insulin administration:

- inhibits lipolysis and mobilization of fats in adipose tissue which decreases the substrate necessary for ketone production
- shifts the hepatic metabolism from fat oxidation to fat synthesis
- suppresses gluconeogenesis
- promotes glucose metabolism in the tissues
- promotes ketone metabolism in the tissues

As the patient progresses through hospitalization and blood glucose begins to normalize continue to supplement glucose and insulin until the patient is eating well - this will provide substrate for ongoing insulin, glucose and ketone metabolism. Without ongoing insulin administration the patient will return to a state of lipolysis, fatty acid mobilization, ketone production, and rising glucose, perpetuating the cycle of DKA rather than resolving it. Once the patient is eating reliably (or tolerating enteral nutrition reliably) IV dextrose supplementation can be decreased and eventually withdrawn.

Electrolyte derangements are expected during management of DKA. They should be anticipated, prevented when possible, and addressed early when they occur. Hypokalemia is the most-discussed electrolyte abnormality. Anticipate that all DKA patients will need potassium supplementation during the course of treatment. Patients with a normal potassium at presentation should be volume resuscitated, rechecked, and then have potassium supplemented in their ongoing IV fluids. Patients with low serum potassium at presentation may need to have potassium supplemented during resuscitation (my practice is to start a potassium infusion during resuscitation if the potassium is less than 3.0mEq/L).

The Sliding Scale of Scott is commonly used to guide potassium supplementation (this is the table seen in all the textbooks) as it is a quick and easy reference to use. The recommended rate of potassium supplementation is 0.1-0.5mEq/kg/h - it is best to confirm that the patient is getting the desired amount of potassium any time the fluid rate is adjusted up or down, and at the start of each shift. Use caution when supplementing at rates above 0.5mEq/kg/h. Patients will continue to lose potassium due to vomiting, diarrhea, and osmotic diuresis, and insulin therapy will cause extracellular potassium to be take into the cells further lowering the extracellular potassium concentration. Ongoing supplementation and close monitoring is necessary.

Phosphate can be high, low, or normal in DKA patients initially. Within 24 hours of initiating insulin therapy it will usually decrease, sometimes severely. The human literature suggests there is no benefit to pre-emptive supplementation with phosphate, rather it should be supplemented if/when it becomes low. This has not been studied in veterinary medicine and the choice to initiate supplementation early, or to treat when necessary usually depends on the clinician's preferences. Phosphate needs to be supplemented when the serum concentration is less than 1.5mg/dL. At concentrations less than 1mg/dL a severe hemolytic anemia (sometimes requiring transfusion) can occur. Phosphate is supplemented IV at a rate of approximately 0.01-0.03mmol phos/kg/h. In patients with severe hypophosphatemia this rate may need to be up to 0.12mmol/kg/h of phosphate. Phosphate comes in preparation as potassium phosphate (4.4mEq K and 3mmol phos per mL) or sodium phosphate (4mEq sodium and 3mmol phos per mL). Because the timing and amount of phosphate supplementation required cannot be predicted the serum phosphate should be measured every 8-12 hours in the first 1-2 days, then once daily. Overzealous administration of phosphate can cause clinical hypocalcemia, therefore it is recommended to measure the calcium (preferably the ionized calcium) along with the phosphorus during phosphorus supplementation. Signs of over-supplementation with phosphate include ionized hypocalcemia and its associated neuromuscular complications, hypernatremia, neuromuscular weakness, hypotension, and metastatic calcification.

Hypomagnesemia is common in dogs and cats with DKA, and will worsen with initial treatment. Literature suggests this will spontaneously resolve in most patients as DKA resolves. Clinical signs usually do not develop until the total Mg is less than 1.0, or ionized Mg less than 0.4mg/dL, and some

may not be clinical even at these low levels. There are no veterinary studies to date (and limited human data) to provide guidance for when to supplement, or the effect of hypomagnesemia on morbidity and mortality. Magnesium is available for parenteral supplementation as magnesium sulfate and magnesium chloride. For rapid repletion of Mg supplement patients at 0.5-1mEq/kg/d. For slower repletion use 0.3-0.5mEq/kg/d. Both of these doses should be delivered as a CRI, and the dose should be reduced by half for azotemic animals. The (preferably ionized) Mg, Ca, and potassium concentrations should be monitored every 8-12 hours in animals receiving magnesium infusions.

The use of bicarbonate in both human and veterinary patients with DKA is controversial. In the human literature bicarbonate therapy is reserved for patients with blood pH less than 7.0, and veterinarians generally follow this guideline as well. Ketoacidosis is not technically a bicarbonate-deficient acidosis - the ketones will be metabolized to bicarbonate once insulin therapy is initiated, and indeed as ketonemia resolves a rebound metabolic alkalosis is typically observed. Bicarbonate therapy can be considered if the measured pH is less than 7.0 or the serum bicarbonate is <12mEq/L *after volume resuscitation.*

When used, bicarbonate is supplemented by giving a portion of the bicarbonate deficit in IV fluids over about 6 hours. The amount given is calculated to improve the bicarbonate to 12mEq/L NOT back to a normal bicarbonate. This amount is calculated:

mEq bicarbonate = BW_{kg} x 0.4 x (12-measured bicarbonate) x 0.5

Bicarbonate should NOT be given as a bolus dose. It should be administered in saline or D5W over 6 hours.

Hyponatremia is common in patients with DKA. It is due to a combination of GI losses, losses due to osmotic diuresis, and dilution due to a hyperosmolar state (from hyperglycemia). This will usually resolve spontaneously as the DKA resolves - sodium supplementation is generally not necessary beyond what is in IV fluids used for resuscitation and maintenance. The safe rate of sodium correction is about 10mEq/L per 24 hour period. Patients with serum sodium 135mEq/L or greater at presentation have a low risk of sodium-related complications provided hypernatremia does not develop. Patients with serum sodium <135mEq/L will need sodium monitored more closely with careful attention paid to rate of sodium increase. The lower the sodium is the greater the risk of sodium-associated complications. Be aware once IV fluid resuscitation begins, renal blood flow will be restored and osmotic diuresis will resume. Although patients do lose some sodium during an osmotic diuresis, water is lost in significant excess of sodium (and other electrolytes). This can result in a very rapid rise in the serum sodium. Additionally, very rapid reduction in the blood glucose (and therefore rapid reduction of serum osmolality) can induce a water diuresis, similarly resulting in a rapid rise in the serum sodium. Monitoring of urine output (either by urinary catheter or other measures such as weighing the patient, litter boxes/bedding, or just noticing an increase in the degree of polyuria) is vital, and polyuria should trigger close attention to both the serum sodium concentration and patient volume status.

Careful, attentive monitoring is necessary for patients with DKA. A tool such as Kirby's Rule of 20 or similar guides to patient monitoring should be closely followed in these critically ill patients. Briefly, these patients will be dehydrated, and the sicker patients hypovolemic at presentation. In the first hours to days of treatment these patients have huge ongoing losses that must be identified and maintained. IV fluids need to be provided at a rate to provide maintenance fluids, correct dehydration, and make up for ongoing losses. These ongoing losses will be from osmotic diuresis (estimate urine output), from the GI tract (measure fluid effluent from nasogastric suction, estimate volumes of vomit and diarrhea), and respiratory losses (these patients have a higher respiratory rate due to acidosis). Serial monitoring of body weight is considered one of the better ways to track patients with losses from multiple body systems. One Kg is equal in weight to 1L of fluid, so a loss of 0.3kg suggests a loss of 300mL of fluid. Remember that as dehydration is corrected an equal amount of body weight should be gained (a 5kg cat who was 10% dehydrated should gain 0.5kg as that volume is replaced). Do not confuse this with volume excess. Although it is labor intensive, my preference is to weigh these patients every 4-6 hours in the initial phases of treatment to ensure we are keeping up with volume losses.

In the resuscitation and early maintenance phase, continuous blood pressure and ECG monitoring, as well as frequent (q15-30 minute) assessment of temperature, heart rate, respiratory rate, mucus membrane color and capillary refill time, pulse quality, etc should occur. Expect significant

fluctuations over the first 24-36 hours and monitor frequently to intervene before crises occur. As the patient stabilizes time between assessments can be extended.

At a bare minimum the electrolytes (sodium, potassium, chloride, calcium (ionized preferred), and phosphate; ideally magnesium as well (ionized preferred), a venous blood gas, and the PCV should be measured every 12 hours. In very sick patients this should occur every 4-6 hours, with the frequency decreased out as patient condition improves.

Blood glucose measurement will need to occur every 1-4 hours depending on the protocol used and severity of illness. Interstitial continuous glucose monitors are now widely available. While these have been cumbersome to use in the past requiring frequent calibration and concurrent capillary glucose measurements, a new device, the FreeStyle Libre from Abbott has been used in dogs and cats with good success. This device consists of a sensor pod that is very lightweight and is attached to the patient (even small cats and dogs), and a reader that captures the current glucose when held over the sensor pod. The pod needs to be in place for 1 hour before it will provide a reading, and once in place will provide readings for 14 days. It provides a numeric result when the blood glucose is between 35-650mg/dL. These devices are well-tolerated by dogs and cats, have been well-received by both ICU staff and pet owners, and greatly reduce the amount of labor (and 'pokes' for the patient) necessary for management of diabetic patients. They are available at the pharmacy counter in most US pharmacies. More information about the system is available at https://www.freestylelibre.us/index.html

Monitoring serum ketones with a quantitative ketone meter is now generally accessible in veterinary medicine. These monitors measure beta-hydroxybutyrate and are considered the most reliable method of monitoring ketones in patients with DKA. The color change urine strips detect acetoacetate and acetone but not beta-hydroxybutyrate. They can be useful for screening for ketones but may miss a significant ketonuria (or ketonemia) since they do not detect beta-hydroxybutyrate. They generally are not helpful for serial monitoring of ketone levels due to the imprecise nature of the color-change test and need for very large changes in serum concentration to detect a degree of change on the test. Serial ketone measurement with a ketone meter can be helpful in management of some cases but is not considered a core test for serial monitoring at this time.

Treatment of concurrent illness is necessary to resolve DKA, prevent it's recurrence, and to achieve long-term control of diabetes. Commonly reported concurrent illnesses in veterinary patients include pancreatitis, bacterial infections (particular urinary tract, but elsewhere also), congestive heart failure, chronic kidney disease, hepatobiliary disease, and other endocrine diseases. Concurrent endocrine disorders are of particular importance as they are usually insulin-antagonistic. The most common are hyperadrenocorticism (dogs), hyperthyroidism (cats), and diestrus (intact females). Management of any concurrent disease should occur simultaneous with management of DKA, and should NOT delay insulin administration.

As patients improve interventions and monitoring should be slowly scaled back. Insulin and dextrose supplementation should be tapered according the protocol being used. Once patients are eating reliably dextrose supplementation can be discontinued and long-acting insulin therapy initiated. Once long-acting insulin therapy is started intensive glucose monitoring needs to be stopped. There is no point in getting a glucose curve at this time - the patient's counter regulatory hormones are still deranged from the recent critical illness and attempts to 'regulate' the patient at this juncture will result in over-treatment and subsequent hypoglycemic events when the patient's health is improved. Instead, pick a starting dose of insulin, initiate therapy, monitor for clinical signs of hypoglycemia, and get the patient discharged. The glucose curve should occur in 2-3 weeks.

The choice of what long-term insulin to use should ideally be made in conjunction with the doctor who will provide long-term management. For cats, there is evidence that glargine insulin as the first insulin they are exposed to may increase the rate of spontaneous remission of DM. The initial long-term insulin for cats should be glargine unless there is a very specific reason to choose something else. The starting dose for most cats is 1U per cat SQ q12 hours. Very small cats and cats that are relatively insulin sensitive may need to go down to 1/2 U per dose. For dogs, NPH is the typical first line choice as it is relatively inexpensive compared to other insulins, and readily available. The starting dose of NPH insulin in dogs is 0.25-0.5U/kg SQ q12h. Finally, insulin is a twice daily (ideally q12h) drug. There is no rational physiologic basis for starting with once daily dosing 'to get the body used to it.' There are very rare cats and even fewer dogs that are truly very well controlled on once daily insulin. For all other patients, their disease will be much better controlled with twice daily dosing. The standard is to begin with twice daily

dosing and *only* accept once daily dosing in animals who failed twice daily dosing AND have near-perfect glucose curves with once daily dosing. The starting point is twice daily dosing.

At discharge owners should be given information regarding at home monitoring, follow-up recommendations, and signs that indicate return for emergency care are necessary. Ideally the owner will schedule the follow-up appointment before or at the time of discharge so that it is clear to everyone when follow-up care will occur. The discharge appointment should include instruction on how to handle and administer insulin. If the discharge is not occurring at the time insulin is due, the owner can use a vial of sterile saline to practice rocking or rolling the 'insulin,' drawing it out of the vial, and administering the injection SQ. Some owners find it beneficial to come into the hospital at the time the pet is due for insulin injections (toward the end of hospitalization) and administer the injection themselves in order to have a chance to practice before discharge. Having the owner give the SQ injection in a monitored environment for the first time is extremely important to help them get past the fear of injecting the pet and sets them up for success at home.

Other instructions should include what to feed, how often to feed, monitoring for signs of hypoglycemia, monitoring for signs DM is not well controlled (PU/PD, weight loss, etc), and routine monitoring of urine glucose and ketones at home. The urine glucose should always be positive, and ketones negative in diabetic dogs and cats. If the pet was started on a continuous glucose monitor in hospital and will continue with it at home, instructions regarding when to check the glucose and what to do with particular values should be included in the take-home instructions. Finally, an information sheet about DM in dogs or cats (as appropriate) should be provided to the owner if one has not already been provided (I prefer to provide this on the day of diagnosis rather than at discharge). There are several good client handouts available through ACVIM.org, VIN, and in association with textbooks such as Ettinger's Textbook of Veterinary Internal Medicine.