Diabetic ketoacidosis in cats and dogs

Diabetic ketoacidosis, a complication of diabetes mellitus, is an important differential for acute collapse in dogs and cats. In this article, Poppy Gant BVSc MRCVS, final-year emergency and critical care resident at the Royal Veterinary College, aims to review the pathophysiology, diagnostics and main aspects of treatment, with particular reference to what can initially be achieved in general practice

PATHOPHYSIOLOGY

Diabetes mellitus occurs either secondary to absolute insulin deficiency and/or relative insulin receptor resistance due to down regulation or dysfunction. As a result, glucose cannot be transported into cells for production of adenosine triphosphate (ATP), leading to hyperglycaemia and glucosuria.

Ketone body production itself is a normal attempt of the body to provide an alternative energy source for cells in the absence of glucose. Figure 1 shows how fat stores are mobilised and fatty acids then oxidised by the liver to form ketones which can be transported to extra hepatic tissues. Increased gluconeogenesis in the liver also depletes intermediates of the citric acid cycle and diverts acetyl-CoA to ketone body production.

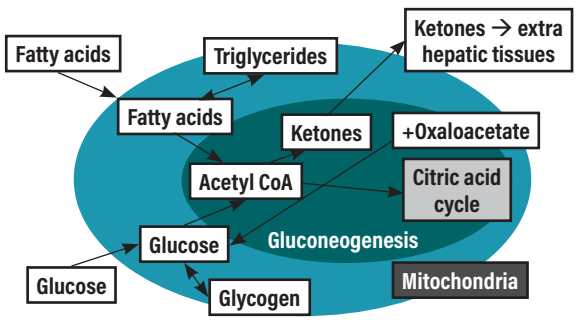

Figure 1: Ketone production in the liver.

Ketones are 'volatile acids', which means that they fully dissociate in the body to form hydrogen ions and respective anions. Bicarbonate is initially used to buffer these hydrogen ions but when ketones are produced beyond the capacity of extra hepatic tissues to utilise them, an acidaemia results. This acidaemia can contribute to the non-specific signs associated with diabetic ketoacidosis (DKA), including lethargy, anorexia, vomiting, dehydration and eventual collapse. Both glucose and ketones are also osmotically active, leading to polyuria and polydipsia and subsequent dehydration, with risk of hypovolaemia.

This process most commonly develops in undiagnosed or newly diagnosed diabetics that are not receiving adequate insulin. However, all diabetic patients are at risk, especially if they have or develop comorbidities. The vast majority of patients with DKA (reportedly 70% of dogs and 90% of cats) have a concurrent disease process (Cooper et al, 2015; Hume et al, 2006). This leads to an increase in 'stress' hormones (eg. glucagon and cortisol) which counteract the effects of insulin and results in further ketone production. Identifying an underlying 'trigger' for the development of DKA is therefore a vital part of the diagnostic plan. Figure 2 gives some of the most common concurrent diseases seen in DKA patients.

Dogs:	Cats:
Acute pancreatitis **Urinary tract infections** **Hyperadrenocorticism**	**Hepatic lipidosis** **Chronic renal disease** **Acute pancreatitis** **Infections** **Neoplasia**

Figure 2: Common concurrent diseases.

TRIAGE OF THE DKA PATIENT

Initial assessment of the collapsed patient should focus on the major body systems to determine whether emergency treatment (eg. fluid therapy, oxygen) is needed.

Neurological assessment

Obtundation to comatose state may be secondary to:

- Dehydration and/or progression to hypovolaemic shock;
- Maldistributive shock secondary to underlying disease; and
- Hyperosmolality.

Abnormal mentation on presentation has been associated with a poor outcome in DKA patients.

Cardiovascular assessment

Assessment of extravascular (dehydration) and intravascular (hypovolaemia) volume depletion:

- Extravascular – including skin tent, tacky mucous membranes, sunken eyes;
- Intravascular – including altered mentation, Pulse quality, heart rate; and
- Also note evidence of concurrent heart disease (eg. abnormal rhythm or murmur) which may affect fluid administration.

Respiratory

Abnormal respiratory rate and effort or thoracic auscultation:

- Tachypnoea/hyperpnoea may be seen as a compensatory response to metabolic acidosis but consider aspiration pneumonia (particular in patients with a history of vomiting and regurgitation) or other pulmonary pathology as a comorbidity.

Once an initial triage has been performed and the patient deemed to be stable, a complete physical examination and further diagnostic tests can be performed. These should take into consideration the most common comorbidities seen in veterinary patients (Figure 2).

Diagnosis

The history and initial physical examination of patients with DKA is likely to be fairly non-specific. The only clinical finding seen more often in cats with DKA compared to non-acidaemia diabetic cats is hypothermia. Fortunately, there are several diagnostic options available to confirm (or at least increase the suspicion of) DKA.

USEFUL POINT OF CARE TESTING FOR DIAGNOSIS OF DKA

Blood gas analysis with or without electrolyte analysis

Figure 3, eg. veterinary specific options include IDEXX bench top VetStat®with blood gas cartridge or Woodley's portable EPOC® blood analysis:

- Identify an acidaemia associated with a metabolic acidosis.
- Identify an increased anion gap (see below).

Figure 3: Venous blood gas results from a cat with DKA showing a metabolic acidosis with a high anion gap (Radiometer Blood Gas Analyser).

Point of care glucose analysis

eg. Alphatrak® 2 glucometer (Figure 4):

- Identify hyperglycaemia.
- Not all point of care glucometers are veterinary specific. This can result in lower blood glucose readings owing to species differences in the distribution of glucose in the plasma and red blood cells.

Figure 4: Alphatrak 2 glucometer.

Point of care ketone analysis

eg. Freestyle Optium Neo (Figure 5):

- Identifies serum ketonaemia – specifically levels of beta-hydroxybutyrate (b-OHB) which is the prominent ketone generated in DKA.

Point of care analysers

Have been shown to be highly correlated with laboratory

Figure 5: Freestyle Optium Neo H ketometer.

methods (Weingart, Lotz, & Kohn, 2012b; FK Zeugswetter & Rebuzzi, 2012) 217 sets of data (venous blood gas analysis and β-hydroxybutyrate measurements.

Semi-quantitative nitroprusside reagent test strips (Figure 6):

- Identify glucosuria and/or ketonuria.
- Plasma can also be used on urine test strips (see below).
- Only measure acetoacetate, levels of which don't increase as much as b-OHB in patients with DKA.

Figure 6: Nitroprusside reagent urine (or plasma) test strips:

Only practices with the ability to run blood gas analysis will be able to truly diagnose DKA. Where this is not available, some studies have tried to investigate the degree of ketonaemia or ketonuria that is consistently associated with acidaemia. Dogs with ketones >3.8mmol/L and cats with ketones >2.4-2.5mmol/L are more likely to have DKA. Values less than this, particularly if <1-2mmol/L suggest although the patient may be ketotic, it is unlikely the primary cause of systemic illness (Weingart et al, 2012; Zeugswetter et al, 2010).

In practices without a ketometer, although the urine nitroprusside reagent strips only test for acetoacetate, several studies have shown that using heparinised plasma on urine semi-quantitative test strips can improve the sensitivity of ketone detection. In this way, use of heparinised plasma on urine reagent strips can therefore still act as a good 'rule out' for DKA (Zeugswetter, Handl, Iben, & Schwendenwein, 2010b).

Semi quantitative ketone reading	Sensitivity (%)	Specificity (%)
Plasma - '+'	100	67
Plasma - '++'	100	88
Urine - '+'	88	95
Urine – '++'	73	100

'+' = equivalent to >1.5mmol/L
'++' = equivalent to >4mmol/L

NB: high sensitivity means cats with DKA are likely to be detected (ie. 100% = all detected), whereas high specificity means cats are likely to be truly DKA, rather than just ketotic.

CALCULATION OF THE 'ANION GAP'

Calculation of the anion gap could be helpful if there is no access to a ketometer and urine cannot be sampled. However, it requires bicarbonate which may not be routinely measured. Figure 7 shows how to calculate the anion gap. The anion gap is typically 12-24mEq/L in dogs and 13-27mEq/L in cats. The anion gap can also be increased in other disease processes. However, a normal (or only mildly increased) lactate and creatinine and low risk of toxin exposure makes a diagnosis of diabetic ketosis much more likely.

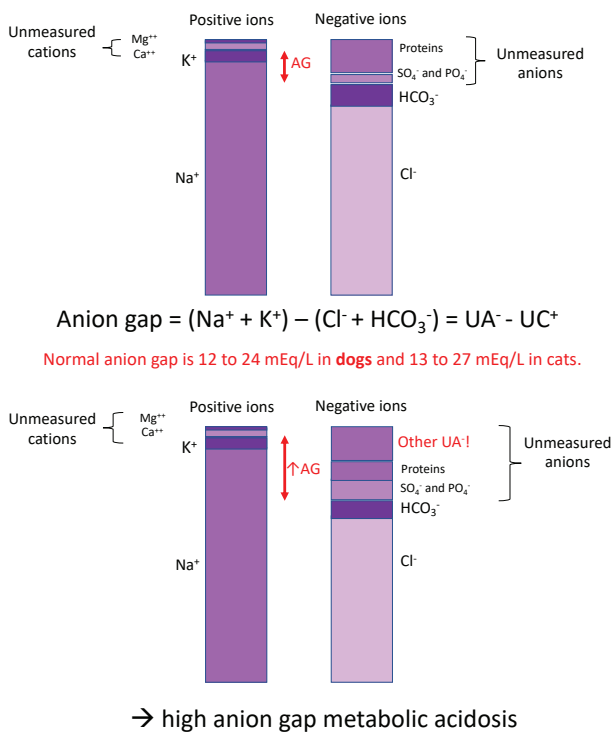

Figure 7: Calculation of the anion gap and representation of a high anion gap.

Extended minimum database

Given the high prevalence of concurrent disease, an extended minimum database for all patients should ideally include complete blood count, serum biochemistry with electrolytes (ideally with pancreatic lipase serology), urinalysis and culture and thoracic and abdominal imaging.

Additional points

- Dogs with suspected DKA should not undergo testing for hyperadrenocorticism at the time of emergency presentation, as this is highly likely to result in a false positive result due to being systemically unwell.
- Cats, in particular, are at risk of hepatic lipidosis and can often be affected by cholangiohepatitis. If liver enzymes are elevated then ultrasonographic evaluation and possibly aspiration of the liver and biliary system may be indicated.

Urinalysis

- Urine-specific gravity is usually low secondary to osmotic diuresis but concurrent renal disease is also possible, particularly in cats.
- Cytology: Diabetic patients often have problems mobilising white blood cells to sites of infection and therefore, may have an inactive urine sediment, even with infections. A urine culture is therefore always recommended. Empirical antimicrobials may be started where there is a concern for a urinary tract infection.

Outline treatment plan

Every patient presenting for DKA will be subtly different and require a tailored treatment plan. Those with severe acidaemia, electrolyte abnormalities, known comorbidities or previously poorly controlled diabetes, should be considered for transfer to a specialist centre once initial assessment and stabilisation has been performed. However, the guidelines below address the key points that should be considered for the initial stabilisation and ongoing management of DKA patients.

Considerations for initial stabilisation

1. Fluid resuscitation
2. Correction of electrolyte and acid base abnormalities

Fluid resuscitation

If physical examination is compatible with shock, an element of hypovolaemia is likely. Administration of judicious fluid boluses (eg. 10ml/kg over 15 minutes) while monitoring for improvement in perfusion parameters can therefore be started following intravenous catheter placement. Failure of perfusion parameters to improve after 20-30ml/kg should prompt assessment for additional causes of shock. Cats are more at risk of volume overload compared to dogs and greater care should be taken with repeated fluid boluses.

A note on sodium, glucose and osmolality

- Sodium levels can quickly change in response to fluid therapy and insulin. Patients experiencing sodium changes >0.5mEq/h are at risk of complications associated with transcellular fluids shifts eg. demyelineation or cerebral oedema.
- Patients with DKA have a variety of reasons to have abnormal sodium concentrations which can impact on fluid therapy decision making:
- Hyperglycaemia can result in increasesed water retention in the intravascular space and therefore a pseudohyponatraemia via dilution.

- Fluid therapy alone can rapidly decrease blood-glucose concentrations and this has led to the common recommendation to only start insulin therapy after fluid resuscitation to avoid rapid changes in sodium.
- However, one study in dogs failed to show an increase in complications when starting insulin within six hours of presentation. Ketosis will only resolve with Insulin therapy and delaying treatment further is unlikely to be beneficial.
- Patients may also be hypernatraemia due to concurrent cardiac or renal disease which prevents adequate sodium excretion. Patients may also experience dramatic solute free water loss through the urinary or respiratory tracts.
- Sodium chloride (NaCl 0.9%) has traditionally been the recommended fluid choice in these patients because the higher sodium content was thought to reduce fluid shifts and therefore the risk of cerebral oedema. However, it is also acidfying and recent research in people has suggested that the use of buffered crystalloids with lower sodium concentrations (eg. compound sodium lactate) are not associated with a greater risk of cerebral oedema.
- Rarely, some patients will require a personalised intravenous fluid therapy bag, made up to contain a set sodium concentration to avoid rapid changes in osmolality. Seek specialist advice for patients with marked, or persistent sodium derangements or those who have already experienced rapid changes.

TREATMENT OF OTHER ELECTROLYTE ABNORMALITIES AND METABOLIC ACIDOSIS

Potassium

Almost all patients will be total-body potassium depleted but this can be masked by dehydration and acidosis. Therefore, regardless of the baseline potassium, immediate supplementation is likely indicated (usually above the ordinary recommended rates found in formularies and occasionally even above the 'safe' 0.5mEq/kg/h). This is because insulin therapy will worsen hypokalaemia by shifting potassium intracellularly and there will likely be ongoing renal losses (osmotic diuresis and coexistent hypomagnesaemia) and gastrointestinal losses (vomiting and diarrhoea or malabsorption syndromes).

Phosphorous

Phosphorous is no longer empirically supplemented in people with DKA but cats in particularly are at risk of haemolytic anaemia secondary to hypophosphataemia. In cats this can occur if phosphorous levels decrease or if the concentration drops rapidly (dogs are slightly more resistant). Ideally phosphorous levels should be measured and supplemented as required. However, if monitoring is not available, and particularly if there is any indication of a haemolytic anaemia on daily monitoring, a constant rate infusion can be started.

Magnesium

Measurement of ionised magnesium levels is not readily available. However, if there is a concern for hypomagnesaemia (particularly a hypokalaemia not responding to aggressive potassium supplementation), then empirical treatment (eg. 0.4mmol/kg/day) can be started.

Bicarbonate therapy

Bicarbonate therapy is rarely necessary as the acidosis usually improves rapidly with fluid therapy alone. Guidelines from people suggest administering bicarbonate only if the patients' pH remains <6.9mmol/L after one hour of fluid therapy. However, this is based on little evidence. Risks include cerebral oedema, exacerbation of hypokalemia, increased ketogenesis and paradoxical cerebral acidosis (increased carbon dioxide production in animals that are not adequately ventilating). However, in animals with a severe acidaemia that is compromising normal physiology, the amount to administer can be calculated as follows:

- NaHCO3 (mEq) = (desired HCO3 - patient HCO3) x 0.3 x body weight (kg); and
- Give one third of the total dose intravenously over one hour and then reassess (1mEq = 1ml).

Considerations for ongoing therapy include:

- Maintenance fluid therapy plan;
- Insulin therapy;
- Nutrition;
- Antimicrobials; and
- Monitoring.

Maintenance fluid plan

It is not uncommon to have DKA patients to require very high fluid rates. This should be carefully calculated and regularly reassessed to ensure that excess losses are being replaced but also that there is no risk of volume overload.

Ongoing rates can be calculated as:

- Ongoing maintenance requirements + correction of dehydration + ongoing losses;
- Estimated level of dehydration = deficit (ml) = body weight x % dehydration x 10; and
- Ongoing losses will likely be high with ongoing osmotic diuresis and renal medullary wash out. Weighing patients every four to six hours can help to monitor for changes in hydration.

Insulin therapy

There are now many suggested protocols for the type, route and dose of insulin to be administered to patients with DKA. These can easily be found in textbooks or associated articles (see reference list). However, there is no conclusive evidence that any particular protocol is superior, and the most important thing is that patients are receiving some insulin in order to reverse the ketosis.

The main considerations are:

- Short-acting insulins are the generally the preference for management of DKA as they can be titrated to effect. However, changes in the availability of neutral/soluble insulin has prompted research into other analogues eg. Lispro and Aspart. These have been shown to be safe in cats and dogs (Malerba et al, 2019; Sears et al, 2012; Walsh et al, 2016);
- Historically, cats received lower rates of infusion infusions compared to dogs. However, studies have since shown that using the same dose as dogs is safe and potentially

associated with better outcomes (Claus et al, 2010);
- Other studies have focused on developing less time-consuming protocols or those that reduce cost for owners by utilising a maintenance insulin during the acute treatment for DKA. For example, subcutaneous and intramuscular glargine or intermittent subcutaneous glargine and neutral insulin (Marshall et al, 2013; Gallagher et al, 2015) bicarbonate, hyperglycemia, ketonemia, and appetite, as well as duration of hospitalisation were recorded. Both of these protocols have been shown to be effective.

Nutrition

- Although it is rarely possible to institute feeding immediately, anorexia of more than three days in dogs and any duration in cats should prompt consideration for assisted enteral feeding. Parenteral feeding may also be required depending on other comorbidities.
- Easily placed feeding tube options in dogs and cats include naso-oesophageal or nasogastric tube and oesophagostomy tube. Nasal tubes are more likely to be used initially as they do not require general aesthesia to place.
- If assisted nutrition is required, this can be started at a fraction of the patient's resting energy requirement (RER) depending on the period of anorexia and any concurrent gastrointestinal disease. If tolerated, then this can then be increased to 100% RER over roughly 72 hours.
- Diet options suitable for this small tube size include Royal Canin convalescence powder or the convenient Royal Canin low fat liquid for dogs. Ideally patients can then be transferred onto a veterinary prescription diet for diabetes. This is particularly important in cats where it can help to aid diabetic remission.

Antimicrobials

Diabetic patients do not have normal immune systems. Although urine and any other appropriate samples based on minimum database assessment should ideally be taken first, empirical antimicrobial therapy can be considered in the presence of:

- Left shift neutrophilia
- Pyrexia
- Severe respiratory signs
- Documented sepsis on cytology

Broad spectrum first line antimicrobials (eg. amoxicillin clavulanate) are likely appropriate pending culture and sensitivity results but consider any recent antimicrobials usage that may result in an abnormal sensitivity profile.

Monitoring in hospital

- Ongoing monitoring of blood glucose, particularly whilst on insulin infusions, is important to detect hypoglycaemia. Electrolyte are also likely to change, and assessment every four to six hours may be required initially.
- The impact of recurrent sampling and the development of anaemia, particularly in cats, should be carefully considered.
- A jugular catheter is incredibly useful for blood sampling, as well as providing multiple ports for several different infusions (for example, compound sodium lactate fluid cannot be administered with phosphate). However, if this cannot be placed, then marginal ear vein sampling using a 25G needle can be performed. The medial saphenous vein in cats is also a good site for intravenous catheter placement if both cephalic veins have been used.
- Subcutaneous glucose monitoring systems are also available and are clinically accurate in patients with DKA – although accuracy is better in well hydrated patients (Reineke et al, 2010)

Figure 8: Free Style Libre glucose-monitoring system in place on a cat with DKA.

Figure 9: Free Style Libre glucose-monitoring system.

Prognosis

Reportedly most dogs and cats with DKA (70%) survive to discharge. However, the median hospitalization times can be six and five days respectively. Owners also need to be aware that at least 7% of dogs and up to 40% of cats experience recurring episodes of DKA (in spite of this, cats with DKA are just as likely to achieve remission if they survive to discharge). Management of DKA can therefore be costly and owners should be appropriately informed of this prior to starting treatment.

Post-hospital management

As with any recently diagnosed diabetic, do not try to determine the ideal insulin dose in hospital. Start at the low end of the dose range and then discuss options with the owner for at home or in hospital assessment of control. Options at this time include:

- At home subcutaneous glucose monitoring systems or at home glucose curve using point of care device. Spot check' glucose tests are only useful if hypoglycaemia is suspected – not for assessing overall control of diabetes;
- In-hospital glucose curve;
- Serum fructosamine; and
- Monitoring of glucosuria: advise to seek veterinary attention if urine is repeatedly negative which may indicate impending ketosis.

In summary, the diagnosis and treatment of cats and dogs with DKA can present many difficulties for the general practitioner, whether that be issues with diagnostic availability, ensuring adequate monitoring or even having insulin or supplements in stock. However, an understanding of the different diagnostic options available and the priorities for initial triage and treatment mean the vast majority of these cases can be stabilised and then further tailored advice can be sought for ongoing treatment.

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READER QUESTIONS AND ANSWERS

1. WHAT PERCENTAGE OF CATS WITH DKA ARE REPORTED TO HAVE A CONCURRENT DISEASE?

A. 10%
B. 30%
C. 50%
D. 90%

2. WHICH IS THE PREDOMINANT KETONE IN PATIENTS WITH DKA?

A. Beta-hydroxybutyrate
B. Acetoacetone
C. Acetone

3. WHAT IS THE MAXIMUM RATE AT WHICH SODIUM CONCENTRATIONS SHOULD CHANGE AFTER STARTING TREATMENT FOR DKA?

A. 0.5mEq per hour
B. 5mEq per hour
C. 10mEq per hour
D. 15mEq per hour

4. WHAT PERCENTAGE OF CATS HAVE BEEN REPORTED TO HAVE REPEATED EPISODES OF DKA?

A. 10%
B. 20%
C. 40%
D. 60%

5. WHICH INTRAVENOUS FLUID SUPPLEMENT SHOULD BE GIVEN ROUTINELY TO DKA PATIENTS?

A. Bicarbonate
B. Potassium
C. Phosphorous
D. Magnesium

ANSWERS: 1:D; 2:A; 3:A; 4:C; 5:B.