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Endocrinology Case Challenges Mini Series

Session Two: Diabetes

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Part 2: Diabetes

Introduction

Diabetes mellitus (DM) arises from an absolute or relative lack of insulin. In dogs the most commonly recognised form of DM involves a complete lack of insulin, associated with irreversible loss of beta cells. In most cats insulin is still being produced by pancreatic beta cells at the time of diagnosis but this insulin is either inadequate and/or being antagonised by other disease processes present. The most commonly recognised consequence DM is hyperglycaemia, leading to glucosuria, osmotic diuresis and PU/PD. In addition to this, the lack of insulin leads to ineffective utilisation of glucose, putting animals into a catabolic state with breakdown of muscles and fat, weight loss and an increase in appetite in an attempt to keep up with this catabolism.

Diagnosis

Presentation

The majority of patients diagnosed with DM are bright animals that are well in themselves with an increase in appetite and no gastrointestinal signs. Energy levels are typically normal although a slight decrease in energy can be noted. The commonest presenting complaints that may be given by the owner or noted on examination are polyuria/polydipsia, weight loss and polyphagia, as noted above. In addition to muscle wasting, hepatomegaly may be noted on physical examination. Diabetic cataracts or signs of neuropathy (see below) may also be noted although these are typically absent early in the disease. Careful history/examination are required to make sure that no other features are present as this should lead clinicians to either reconsider their diagnosis or to look for comorbidities that may explain additional signs.

Routine Biochemistry

A routine serum biochemistry typically has changes indicative of DM. In addition to hyperglycaemia (see below) elevations in liver enzymes, particularly AlkP, are often present. Cholesterol may also be elevated. A mild hyponatraemia is common and hypokalaemia may also be seen in association with diuresis.

Blood Glucose

Hyperglycaemia is a hallmark feature of DM in cats and dogs. In people fasted blood glucose (BG) that is within the upper part of the reference range can indicate DM but in cats and dogs, where overt clinical signs are typically present at diagnosis, then BG is usually high enough to be associated with glucosuira and PU/PD. In dogs this corresponds to a blood glucose >10mmol/L and in cats blood glucose >16mmol/L is required to cause these signs. Although this feature is consistently present in dogs and cats with DM it is important to realise that the presence of hyperglycaemia does not necessarily indicate that DM is present. This is particularly true in cats where “stress hyperglycaemia” associated with veterinary interventions can cause marked hyperglycaemia (>20mmol/L) which may last several hours. As such a single BG measurement in a cat can be considered suggestive, but not diagnostic, for DM. Repeated measurements over several hours/days, combined with compatible clinical signs and a lack of other causes is far more suggestive.

Urinalysis

As noted above, DM in cats/dogs is typically associated with PU/PD and glucosuria and this can readily be detected on a urine dipstick. Glucosuria is the inevitable consequence of a BG>10mmol/L in a dog or >16mmol/L in a cat and it may occur with lower BG if there is proximal renal tubular dysfunction. As such, glucosuria and hyperglycaemia is indicative of hyperglycaemia that has lasted at least an hour or two and is further supportive of DM but may occasionally be seen with sustained stress hyperglycaemia.

Ketones are often formed in DM prior to treatment (see below) but are not typically formed in stress hyperglycaemia. The presence of glucosuria and ketonuria is therefore more specific for DM. As noted below, the presence of ketones does not necessarily indicate ketoacidosis so should not cause alarm in its own right.

Fructosamine

Serum fructosamine is a measurement of glycosylated serum proteins (mainly albumin). The amount of glycosylation that takes place is a direct result of the concentration of glucose in the serum and it equilibrates over about 1 week, meaning that Fructosamine can be used to infer the “average” blood glucose over that time and eliminating influences such as stress hyperglycaemia. It is generally reliable for the diagnosis of DM but cannot be used to detect very early cases, where the BG has not been high enough for long enough, or in cases where there is increase albumin turnover, such as protein losing nephropathy or hyperthyroidism.

Treatment

Treatment aims

The treatment of DM in cats and dogs has fundamentally different goals in many instances. In dogs DM is a permanent state and so the aim of treatment should be to minimise clinical signs (PU/PD, polyphagia, weight loss) and minimise the risk of complications (see below) while avoiding unnecessary side effects.

In cats DM can be a temporary state, with many cats entering diabetic remission when the balance between their insulin production and antagonism improves. Diabetic remission is considered most likely to be achieved within the first 6 months of diagnosis and it is thought that more aggressive lowering of blood glucose, to rest the pancreas and eliminate any self-perpetuating insulin antagonism that was caused by hyperglycaemia. In light of this a more aggressive approach to treatment is typically adopted with the hope of achieving remission.

Insulin choice in dogs

There is currently only 1 licensed insulin product for dogs in the UK, which is a porcine insulin in a 70% crystalline zinc and 30% amorphous mixture (Caninsulin™). With the mix of insulins in this preparation, it typically has 2 peaks in action, at 4 hours and 11 hours after administration. Although licensed for once daily dosing, in many dogs this proves to be inadequate and so twice daily administration is typically advised. I typically start with a dose in the range of 0.3-0.5mg/kg BID, spacing doses as close to 12 hours apart as practical for the owners. If there is a need to adjust the insulin dose based on monitoring then steps should be made in the range of 10-25% of the previous dose.

Dietary choice in dogs

As for any dog, it is important that dogs with DM receive a balanced complete diet. This should be divided into 2 feeds per day, given at approximately the same time as the insulin administered. I typically advise that the food is given first and that insulin is given as soon as the dog eats. Prescription diabetic diets are available that are higher in fibre and lower in carbohydrates, in order to minimise post-prandial hyperglycaemia, but in the majority of dogs these are not required to meet the treatment goals outlined above. They should be considered in cases where significant post-prandial hyperglycaemia occurs and makes control of DM more challenging.

Insulin choice in cats

Caninsulin™ is licensed for use in cats but there is an additional product based on human insulin in a protamine-zinc salt (ProZinc™). This is a longer acting insulin and therefore is associated with smaller peaks/troughs compared to Caninsulin™ which is thought to make it beneficial for achieving remission. I typically advise starting at a dose of 1iu/cat for cats <4kg and 2iu/cat for larger cats, both given SC BID. As this is a long acting insulin and cats typically graze, I do not give owners specific instructions about the timing of insulin relative to feeding but it is important that insulin dosing is still given at 12 hour intervals and that it is only given to cats that are eating. Other longer acting human insulin products (glargine/detemir) have been studies in cats with promising results but their use is off label and the evidence supporting their use in based on small studies, making it difficult to draw conclusions.

Dietary choice in cats

In cats diet I thought to play an important role in achieving remission as the wrong diet can cause large post-prandial hyperglycaemia spikes or promote excessive insulin secretion, leading to beta cell exhaustion. The ideal diet is low in carbohydrates and also in amino acids which may promote insulin secretion. Numerous prescription diets are available tailored for this purpose. Generally, canned diets are considered superior to dry diets as dry diets inherently have a higher carbohydrate content. Of note, one study found good results when comparing canned kitten food (which is high protein, low carbohydrate) to some of the prescription diets available and so this can be considered as a cheaper alternative if prescription diets are cost-prohibitive.

Exercise

The role of exercise in the treatment of DM is often overlooked but this can have huge impact on BG concentrations. As such it is important that animals with DM receive exercise but also that it is regular so that there is not fluctuation in DM control associated with fluctuation in exercise. In addition, exercise is associated with an increase in muscle mass, countering the muscle wasting form the underlying disease, and an increase in musculature and decrease in fat is also associated with improved insulin sensitivity.

Monitoring

Clinical signs

As noted above, the principle aim of DM treatment in dogs is to control the clinical signs. As such monitoring them objectively is an important part of assessing treatment success. Good control of DM should be associated with an increase in energy levels, increase in weight and decrease in PU/PD and these factors should be regularly monitored throughout treatment.

Spot Blood glucose

If DM is characterised by hyperglycaemia then it makes sense to monitor BG as a way of assessing its treatment Unfortunately, this is not as straightforward as it should be as BG will vary throughout the day and is often high for brief periods of the day in a well controlled diabetic. Additionally, the manner in which BG varies is not predictable, depending on the insulin kinetics in an individual dog, its dietary intake and a number of other factors. This means that a single BG measurement reveals very little about whther a patient is well controlled, overdosed, underdosed or has a problem with the choice of insulin/diet. As such, it is not generally recommended to measure single BG reading for assessment of DM control.

Glucose curves

A glucose curve assesses BG measurements and fluctuations over the course of a day in order to give a truer representation of how successful BG control is and where any problems may occur. It is generally made by measuring BG every 2 hours for a 10-12 hour period starting at 1 insulin dose and finishing shortly before the next. Curves can be measured in a clinic but this creates an artificial environment with more stress, potentially differing dietary intake, differing timing and different exercise, limiting their utility but providing a broad overview of how a given dose of insulin is working.

Curves can also be measured at home by training owners to measure BG. This avoids the problems of the clinic environment but places emphasis on the owners, which may or may not be appropriate depending on their nature. Home BG curves reduce, but do not eliminate patient stress and studies indicate that even in a home environment there can be quite a lot of variability in the curves obtained from a given animal from day to day.

More recently flash blood glucose monitoring systems have become widely available and affordable. One of these (Freestyle Libre™) has recently been validated for use in dogs. These involve placing a sensor into an area of shaved skin on a dog's neck. The sensor is stuck in place but it can then measure interstitial glucose (which is closely related to BG) every few minutes for up to 2 weeks without having to perform any further intervention, making them ideally suited to collected data for more natural BG curves. The devices have also been used in cats but it is more challenging to stick the device to cat skin and the measurements have not been fully validated in this species yet.

Urinalysis

As noted above, hyperglycaemia is a normal finding for periods of the day in most diabetic animals. As such, glucosuria is also a normal finding making urine poorly suited as a monitoring tool. If owners are keen to monitor urine then I provide guidance stating that the absence of glucosuria for 2 consecutive days should raise concern as this may indicate that BG is too low. Similarly he development or worsening of ketones should raise concerns as it may indicate poor control and a tendency towards ketoacidosis.

Fructosamine

Subject to the limitations noted above, fructosamine is well suited to monitoring DM control in dogs, when combined with clinical signs as the minutiae of BG fluctuations are less important as noted above. It can also provide useful insight in cats regarding the overall level of DM control but it cannot provide information about the severity of BG fluctuations over the course of the day. With an appropriate diet and long acting insulin the significant BG fluctuations are not to be expected and so many cats monitored with clinical signs and Fructosamine can go into diabetic remission but Fructosamine will not identify if there are any significant fluctuations so problems that could be addressed may be missed if using this without occasional BG curves as well.

Considerations for poor response

With appropriate insulin, diet, lifestyle and monitoring, most diabetic animals can achieve good clinical response and a proportion of cats will go into remission but this is not always the case. If animals appear to be responding poorly to insulin then several possibilities exist and these should be investigated in a systematic fashion.

One of the commonest issues and simplest to fix is problems with the animal not receiving what has been prescribed. This may be due to compliance issues if the owners do not understand or are not able to administer the insulin or it may be because the insulin has been improperly handled/stored and it has consequently denatured. A review with the owner and a change of insulin bottle is often all that is required to address this.

The next thing to consider is that the combination of diet/insulin that the patient is receiving is resulting in suboptimal glucose control, either due to excessive post-prandial peaks or inappropriate duration of insulin in the patient. This is best investigated through blood glucose curves to better understand how these interactions are effecting the patient.

Finally, insulin resistance can be caused by almost any disease, making animals less responsive to insulin than anticipated. If an animal is receiving a dose of insulin in excess of 1iu/kg with minimal signs of response then causes of insulin resistance should be sought. This should fist involve consideration of common diabetic comorbidities as outlined below but then potentially expanded to consider any other disease that the patient may have.

Comorbidities

There are numerous other conditions that may occur in conjunction with DM, either as a cause or a consequence. These should be considered at the time of diagnosis but also reviewed at a later stage if there are any clinical signs that outlast the DM coming under control, are not attributable to DM or if DM proves challenging to regulate.

Urinary tract infections

DM is associated with glucosuria, polyuria and an element of immune dysfunction, all of which predispose animals to urinary tract infections. These may not be associated with lower urinary tract signs (pollakiuria) or active sediment (haematuria/pyuria). Nonetheless they can progress to pyelonephritis or be a source of insulin resistance so they should be looked for by urine culture and appropriately treated if identified.

Pancreatitis

Pancreatitis can be a cause of DM, associated with beta cell loss, a cause of insulin resistance, due to severe inflammation, and a result of DM, contributing to difficulty controlling it. Although it is sometimes recommended to screen diabetics for pancreatitis, I do not recommend this practice in the absence of clinical signs as there is no evidence to suggest that specific dietary modification or other treatment is beneficial in such a setting. It is often worth looking for pancreatitis (eg by measuring lipases or an ultrasound) if insulin resistance or inappetance are present, although the appropriate response to finding it is uncertain.

Hyperadrenocorticsm

HAC is a potential cause of DM or insulin resistance in cats and dogs. In dogs it is tempting to screen every case of DM for HAC as they have PU/PD, polyphagia, hepatomegaly, muscle wasting, increases in AlkP and cholesterol etc. It is important to note that all of the above are directly attributable to DM and so I only advise screening for HAC if there are signs not attributable to DM (eg dermatologic changes) or if insulin resistance is suspected after starting treatment.

Acromegaly

Recent studies screening cats for acromegaly have indicated that it may be present in up to 25% of cats in the UK with DM. In many this seems to have very few attributable signs but in a proportion it can cause clinical signs of organomegaly, weight gain, thick set features and marked insulin resistance. Diagnosis is typically based on measurement of IGF1 and this should be done after starting insulin therapy as false negatives may occur if animals have insufficient insulin at the time of measurement. Treatment of acromegaly is challenging as options available include radiotherapy or hypophysectomy, which have limited availability, or the drug paseriotide, which has only been used in limited numbers at great expense. Many cases of acromegaly are manged by increasing insulin doses massively, often to >20iu, but this carries a marked risk of hypoglycaemia as insulin resistance can vary on a daily basis.

Dioestrus

Dioestrus in intact bitches is associated with insulin resistance and so it is recommended that dogs with diabetes are neutered to prevent this fluctuation. In a small number of intact bitches they can develop “dieoestrus diabetes” which is associated with relatively normal insulin concentration but marked resistance, more akin to feline diabetes. Many of these dogs will go into remission with prompt neutering and tight glycaemic control.

Complications

Hypoglycaemia

Hypoglycaemia is one of the most concerning potential complications of diabetes as it is iatrogenic (caused by excessive insulin administration) and can be fatal in minutes. As such it is always best to err towards under-dosing when giving insulin and so owners are always advised if in doubt about the wellness of their pet or if insulin has been given, to not give more.

Hypoglycaemia is uncommon if animals are given doses of insulin <1iu/kg but will occasionally occur even at these doses. If is important to make sure that owners are aware of the signs (lethargy, tremors, seizures etc) and that they know to give a glucose source and seek immediate attention if concerned.

Samogyi Effect

The samogyi effect is a specific effect where patients are given an insulin dose leading to hypoglycaemia but there is a robust physiologic response to counter this, resulting in hyperglycaemia. In some cases this can cause challenging to diagnose insulin resistance as the hypoglycemic episode may last less than an hour but the insulin resistnace that follow may last for days. If the response to this is higher insulin dosing then the problem gets worse. It can be recognised through BG curves but measurements every 15 minutes may be required, potentially for several days and so this is often impractical unless a continuous monitor is used. Alternatively, if suspected, then insulin dose can be restored to more conventional levels (0.5-1iu/kg) to see if a better response is seen compared to the higher dose where no response was seen.

Cataracts

Owners of diabetic dogs should be warned that cataracts are an inevitable consequence that seems to occur, irrespective of DM control. They will lead to blindness and in some instances a severe uveitis. Prior to the development of uveitis they can be successfully treated though surgery but if delayed then vision may be permanently lost and if the uveitis is not recognised/treated it may be associated with ocular pain. Diabetic cataracts do not occur in cats.

Diabetic neuropathy

Diabetes in cats may be associated with a neuropathy, typically characterised by a low gait and sinking of the hocks. There is some limited evidence to suggest that oral methylcobalamin may be helpful in the treatment of this condition if it is identified.

Diabetic Ketoacidosis (DKA)

Introduction

Diabetic Ketoacidosis (DKA) is a potentially life threatening complication of diabetes mellitus (DM) that is commonly encountered in small animal practice. It is a true emergency that necessitates prompt recognition and aggressive treatment/monitoring to maximise patient outcome yet even when this is provided, reported survival rates for dogs and cats are only in the region of 70%.

Pathophysiology

As noted above, DM arises from an absolute or relative lack of insulin. The most commonly recognised consequence of this is hyperglycaemia, leading to glucosuria, osmotic diuresis and PU/PD. Despite the hyperglycaemia, cellular utilisation of glucose is decreased in patients with DM and so ketones are synthesized as an alternative energy source.

Ketones are produced from Acetyl-CoA - a product of lipolysis, which is also increased by insulin deficiency. Ordinarily, Acetyl-CoA enters the krebs cycle together with pyruvate but the lack of cellular glucose utilisation leads to decreased pyruvate and hence increased build-up of Acteyl-CoA. This, in turn can be converted into 3 different ketone bodies – acetone, acetoacetate and β-hydroxybutyrate. Acetoacetate and β-hydroxybutyrate are strong acids that lead to the development of a metabolic acidosis.

Following development of acidosis, the osmotic diuresis caused by glucosuria continues but the compensatory polydipsia does not, leading to rapid onset hypovolaemia and potentially hyperosmolarity. Acidosis and a lack of insulin lead to movement of potassium from the intracellular space to the extracellular space, where it is then lost in the urine due to the massive diuresis, compounded by any anorexia and vomiting. Phosphorus and magnesium are also lost by similar mechanisms.

Diagnosis and Investigation

Cats and dogs with DM are usually bright and alert with polyphagia and minimal gastrointestinal signs whereas patients with DKA are typically obtunded with signs of cardiovascular collapse, anorexia, vomiting and/or diarrhoea.

As the name implies, diagnosis of DKA is based on demonstrating DM, ketosis and acidosis. Most cats and dogs with DKA have not previously been diagnosed with DM but this can readily be recognised from a compatible history of PU/PD, polyphagia and weight loss and the presence of hyperglycaemia/glucosuria.

Ketones can be detected in the blood or urine. Urine dipsticks detect acetoacetate and so they may only be weakly positive in animals with severe ketosis as β-hydroxybutyrate is the dominant ketone body formed. Dipsticks can also be used to test for the presence of ketones in plasma, with greater sensitivity compared to their use on urine. β-hydroxybutyrate can also be directly measured using portable hand held devices or on serum samples sent to an appropriate laboratory. Alternatively a raised anion gap in a diabetic, acidotic patient with no known toxin ingestion and normal lactate is strong supportive evidence for the presence of ketones. It is important to note that ketosis is not the same as DKA. Ketones may be present in cats or dogs for a variety of reasons, including stable but untreated DM, pancreatitis, low carbohydrate diet, hypoglycaemia, fever and pregnancy.

The presence of a metabolic acidosis should be confirmed through blood gas analysis, identifying a pH<7.35 together with low HCO_3^-/BE. Total CO_2 can be used as an indicator of a metabolic acidosis if blood gas analysis is not available.

A rarer condition, related to DKA, is hyperglycaemic hyperosmolar state where similar clinical signs develop due to poorly regulated diabetes and the loss of water but in this condition sufficient insulin is present to prevent lipolysis/ketosis and so ketones cannot be detected. The condition can be recognised by the presence of severe hyperglycaemia (BG>30mmol/L), often coupled with normal sodium concentrations to result in a serum osmolarity >320mOsm in an obtunded patient without ketosis.

Additional findings commonly reported in cats and dogs with DKA include a non-regenerative anaemia, left shifted neutrophilia, thrombocytosis (dogs) and Heinz body formation (cats). Most dogs have AlkP elevations. Many cats and dogs have elevations in ALT, AST and cholesterol and some cats are azotaemic. AS detailed above and below, disturbances in acid-base, sodium, potassium, phosphorus and magnesium are common but dynamic and require frequent reassessment during treatment.

Approximately 70% of dogs and 90% of cats with DKA have a disease other than DM identified at the time of diagnosis. In many cases it is thought that this comorbidity leads to production of counter-regulatory hormones (glucagon, adrenaline, growth hormone, cortisol) and this is the trigger that leads to decompensation of DM into DKA. It is important that these comorbidities are identified so that they can be appropriately addressed. Common comorbidities identified include urinary tract infections, pancreatitis, hyperadrenocorticism (or steroid administration) and neoplasia. Investigation should therefore include assays to investigate for such comorbidities.

Urine culture should be performed on all patients with DKA as urinary tract infections are common but pyuria is rare (likely due to an impaired immune system) and so sediment alone cannot be relied on. Adrenal axis testing should probably be delayed until several weeks after a DKA crisis as false positives for hyperadrenocorticism may occur otherwise. Thoracic and abdominal imaging is indicated to evaluate the major organ systems and to screen for neoplasia. Pancreatitis can be screened for through imaging and cPLI or fPLI testing. Use of semi-quantitative in-house tests is discouraged in this setting as in the author's experience many mild PLI elevations can be seen in such patients and these likely represent secondary pancreatic inflammation rather than primary disease.

Treatment

Fluid Therapy

Although it is tempting to start insulin therapy immediately following a diagnosis of DKA, this is to be discouraged as patients are often hypovolaemic/dehydrated and administration of insulin is likely to worsen this by moving glucose from the extracellular space to the intracellular space, drawing water with it. Instead, immediate fluid therapy should be initiated with insulin therapy initiated 4-12 hours later, once the patient is more stable.

The aims of fluid therapy are to correct hypovolaemia, dehydration, acid-base and electrolyte disturbances. Patients often appear hyponatraemic on initial bloodwork but this is typically a "pseudohyponatraemia" because the total plasma osmolarity is a function of sodium, glucose and urea. As noted above, patients typically have a normal or elevated plasma osmolarity and so it is likely more rational to use a buffered, low sodium isotonic fluid such as Hartmann's solution. The choice of isotonic crystalloid is controversial as human patients with DKA have a better neurologic outcome when using 0.9% NaCl but no such data exists in veterinary literature. It is likely that any isotonic crystalloid fluid will suffice.

If the patient is assessed to be hypovolaemic (hypotensive, tachycardic, prolonged CRT, weak pulses) then fluid boluses can be given initially (15-20ml/kg over 15 minutes, repeated to effect). Thereafter, fluid therapy should aim to correct dehydration over the next 6-12 hours and replace ongoing losses. When calculating fluid rates, it is important to remember that ongoing maintenance requirements are likely to be high due to osmotic diuresis and should likely be estimated at ~5ml/kg/hr over the first 12 hours then reassessed.

Insulin Therapy

Following initial stabilisation with fluid therapy, it is likely that substantial reductions in blood glucose concentration and the degree of acidosis will have already occurred, in addition to significant electrolyte changes. At this stage, insulin therapy should be initiated. While various protocols using various insulins have been described for the treatment of DKA in cats and dogs, most of these protocols should be considered experimental and regular insulin is still considered the treatment of choice. This can be given either intramuscularly or intravenously. Subcutaneous administration of insulin is not appropriate for initial treatment of DKA.

Intramuscular therapy involves an initial injection of 0.2IU/kg regular insulin, followed by 0.1IU/kg every hour. Blood glucose should be rechecked at each injection and if the glucose has dropped by more than 4mmol/L in the past hour the insulin dose should be reduced to 0.05IU/kg. If the glucose reduction is less than 2mmol/L in the past hour, insulin may be increased upto 0.2IU/kg. This shou;ld be continued with the same glucose supplementation and endpoints as described for intravenous administration below.

Intravenous insulin therapy involves the injection of 2.2IU/kg regular insulin into 250ml of 0.9% saline. Lower doses were previously recommended in cats but recent data suggests that this is unnecessary. Once the insulin has been mixed in saline, it should be run through an administration set with the first 50ml discarded as insulin will initially bind to the plastic tubing. Thereafter, it should be administered as per the table below, with blood glucose measurement and rate adjustment every 2 hours.

Blood Glucose (mmol/L)	Insulin CRI rate (ml/hr)	Glucose (dextrose) concentration in maintenance fluids
>14	10	None
11-14	7	2.5%
8-11	5	2.5%
5.5-8	3	5%
<5.5	STOP	5%

It is important to note from the above protocol that reduction of blood glucose is not the principle aim of insulin therapy. Whilst this reduction is important, it is secondary to the other major action of insulin in this situation, namely to reduce ketone formation and allow ketone utilisation in the Krebs cycle, reducing the metabolic acidosis. To this end, glucose is aggressively supplemented when it approaches the normal range to allow safe continuation of insulin therapy. Additionally, rapid glucose reductions (<4mmol/L/hr) are not desirable as the rapid change in serum osmolarity can have significant neurologic effects.

Regular insulin therapy should be continued until acidosis resolves, ketonaemia/ketonuria are reduced and the patient starts to eat. At that point normal subcutaneous medium/long acting insulin regimens can be started. If a period exists following resolution of ketoacidosis but before the patient starts to eat, regular insulin can be given every 4-6 hours subcutaneously to maintain blood glucose concentrations below 14mmol/L and prevent the recurrence of ketoacidosis.

Potassium

As noted above, patients with DKA often have marked depletion in total body potassium stores and fluid therapy/insulin therapy can exacerbate this by increasing urinary loss and causing intracellular potassium shifts. It is therefore important that electrolytes are monitored on a regular basis, preferably every 6-8 hours, so that these changes can be detected and corrected.

Correction of potassium should be in the form of intravenous potassium chloride, administered through the maintenance fluid or a separate line (but should always be dilutes in an isotonic fluid to prevent severe local irritation or potential overdose). Often very aggressive supplementation is required to keep up with the ongoing loss from the extracellular space but the total rate of potassium administration should not exceed 0.5mmol/kg/hr unless continuous ECG monitoring is used. Suggested starting rates are shown in the table below but these should be adjusted, depending on individual patient response.

Serum potassium concentration (mmol/L)	Potassium (mmol or mEq) per litre of fluids	Maximum safe administration rate (ml/kg/hr)
<2	80	6
2.1-2.5	60	8
2.6-3	40	12
3.1-3.5	30	18
3.6-4	20	25
4.1-5	10	50
>5	None	-

Magnesium

Hypomagnesaemia is a reported complication of DKA/insulin therapy which is rarely seen but is a potential cause of refractory hypokalaemia. Ideally magnesium concentrations should be checked daily during therapy and certainly checked if hypokalaemia is persistent despite aggressive supplementation. If required, mangensium can be supplemented using intravenous magnesium sulphate at a rate of 0.5-1mmol/kg/day.

Phosphorus

Serum phosphorus concentrations can be markedly reduced in DKA/insulin therapy and at very low levels this can be associated with neurologic signs (mainly dogs) of haemolysis (mainly cats). Phosphorus should be checked on a daily basis and if concentrations approach 1.0 mmol/L or lower then supplementation should be commenced using Potassium Phosphate. This supplement is incompatible with calcium containing fluids (such as Hartmanns solution) and must be given in 0.9% saline. The infusion rate should be 0.03-0.12 mmol phosphate/kg/hr. It is important to remember that this also contains potassium and so if used, the amount of potassium chloride added to the fluids must be accordingly reduced so that the total potassium administered to the patient remains correct.

Additional considerations

From the treatments outlined above, it is clear that patients often end up receiving several fluids/infusions concurrently and require regular blood sampling. The author favours the use of triple-lumen jugular catheters in this situation as it allows greater patient mobility, administration of several infusions with minimal tangling of lines and regular sampling without repeated venepuncture. Depending on the circumstances, these can be placed at presentation with minimal sedation or with sedation following initial fluid stabilisation through a peripheral catheter.

As noted above, urinary tract infections are common in patients with DKA but are difficult to detect on sediment examination. For this reason I advocate starting broad spectrum antibiotics (eg amoxicillin-clavulonate) immediately after diagnostics have been performed whilst waiting for urine culture results. If the culture result is negative then antibiotics should be discontinued immediately or the choice of antibiotic revised based on positive culture/sensitivity results.

Another common comorbidity associated with DKA is pancreatitis and due consideration should be given to analgesia for these patients, which are often obtunded and difficult to accurately assess for pain.

Gastrointestinal signs and anorexia are common in these patients and this can be in association with gastric hyperacidity, decreased intestinal motility and central nausea. For these reasons, anti-emetics (eg maropitant 1mg.kg SC SID), pro-kinetics (eg metoclopramide 1-2mg/kg/day IV CRI) and antacids (eg omeprazole 1mg/kg IV SID) are often indicated in these patients. If anorexia continues beyond the initial 48 hours of therapy then consideration should be given to a feeding tube (naso-oesophageal or oesophageal). Enteral nutrition through a feeding tube will improve intestinal healing and motility and potentially allow faster transition to a subcutaneous long acting insulin protocol.