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Hot Topics in Canine Medicine Mini Series

Session One: Difficult Diabetics

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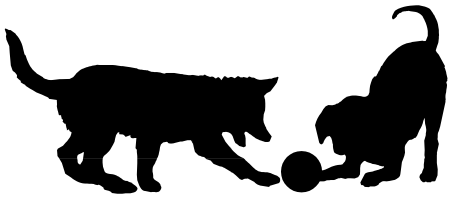

Hot Topics In Canine Medicine

Session 1: Difficult diabetics

Diabetes mellitus is a common canine endocrinopathy. In some cases, diabetic stability can prove elusive. In this session, we will cover one of the most serious complications of diabetes mellitus- diabetic ketoacidosis. We will discuss the diagnosis of DKA and the emergency management of this challenging condition. In addition, we will look at common causes leading to diabetic instability and a practical approach to stabilising some of the more difficult diabetic dogs in practice.

- How to diagnose diabetic ketoacidosis
- Emergency management of diabetic ketoacidosis
- Understand the multiple factors that can affect diabetic stability
- How to monitor the diabetic dog
- Understand the limitations of glucose curves

Investigating the Difficult Diabetic

The most important thing to consider in the first instance is whether the animal requires further investigation. If the animal is clinically well with stable body weight and water intake is not excessive then further investigation may not be warranted. It is not essential for blood glucose to be within the reference range or below the renal threshold for glucose at *all* times during the day. In fact, overtight control may be associated with greater short-term risks to the patient! Do not expect diabetic stability to be achieved in just a week or two in a newly diagnosed diabetic! It usually takes somewhere between 2 and 4 months to stabilise a diabetic animal. False expectations (by either the owner or the vet) can lead to overzealous and premature investigations in these cases. Fructosamine measurement can be used to assess glycaemic control over the preceding 1-2 weeks rather than necessitating the need for multiple glucose curves in many patients.

Most diabetics can be controlled relatively easily using a combination of insulin therapy and dietary manipulation. Twice daily injections are associated with better glycaemic control in both cats and dogs. Starting doses of 0.25 IU/kg lente insulin twice daily are commonly used. Most dogs and cats can be stabilised with insulin doses around or <1.0 IU/kg per injection. Oral hypoglycaemic agents such as sulphonylureas or metformin are sometimes used in diabetics, however most diabetics are truly insulin deficient and as such any treatment other than exogenous administration of insulin is unlikely to be effective. Oral agents are not recommended in dogs but can be used in cats when owners decline insulin therapy or in uncomplicated cases once initial glucose toxicity has resolved with insulin therapy.

Difficult diabetics usually fall into one of the following categories:

- Poor owner compliance leading to instability
- Transient diabetics (uncommon in dogs)
- Animals with very high requirements for insulin (>1.5 units/kg for those receiving twice daily injections, or >2units/kg for once daily injections)
- Somogyi overswing- periods of hypoglycaemia followed by rebound hyperglycaemia. Periods of apparent insulin resistance may also follow an overswing in these cases making them difficult to diagnose.

Initial Checklist for the difficult diabetic:

- Is insulin being stored appropriately?
- Is insulin being administered properly?
- Does the animal have a consistent routine of injections, feeding and exercise?
- Does the animal have a concurrent disease that may be affecting diabetic control?
- Is the animal unstable despite insulin doses >1.5 IU/kg per injection?

Not all unstable diabetic dogs have hyperadrenocorticism! An ACTH stim test is not an appropriate first step in an unstable diabetic dog; in fact, false positives are quite likely in such cases leading to an incorrect diagnosis of HAC in these cases. Urinary tract infections are a much more likely reason for instability and should be investigated early (by performing urine culture) in any unstable patient even if urine sediment is inactive. Common factors leading to diabetic instability are outlined below:

Owner Factors:

A regular routine is essential to achieve optimal control of diabetes mellitus. If the owner is not able to adhere to a strict regime of feeding, injecting and regular exercise then it will ultimately lead to suboptimal diabetic control.

Owner factors Checklist:

- Observe client drawing up and administering the insulin to ensure correct technique
- Check feeding regime and exercise routine
- Are any additional medications being administered that may antagonise insulin (e.g. topical or oral steroids)?

Technique of Insulin administration: Common mistakes in newly diagnosed diabetics include inclusion of large air bubbles in the syringe leading to inaccurate dosing with insulin and injection into hair rather than into subcutaneous site. Where possible, observe the client drawing up and administering the insulin. It is also worth checking whether any other carers are involved in administering insulin as their technique should also be checked.

Timing of Injections: Injections should be given at roughly the same time every day for most consistent results. Marked variation in the time of administration of insulin will obviously affect glycaemic control. Where possible encourage the client to keep a diary showing injection times and feeding times.

Feeding and exercise regime: Diet should be standardised on a daily basis and fed at set times. Feeding titbits or offering various types of food will significantly affect diabetic stability and should be avoided. In dogs, feeding a high fibre diet (such as Chappie) is usually beneficial as it improves glycaemic control by promoting weight loss. High fibre diets should not be used in underweight dogs! In cats high protein, low carbohydrate diets (e.g. Hills m/d) are most likely to lead to optimal control as cats use proteins for gluconeogenesis.

Insulin Factors:

Failure to store or administer insulin correctly will certainly affect diabetic stability. All of the following points should be considered prior to performing more costly and time-consuming investigations.

Insulin Factors Checklist:

- Check expiry date
- Ensure the bottle has not been frozen or stored close to the freezer cabinet
- Ensure owner is not shaking the bottle prior to use, instead insulin should be gently inverted to mix the contents.
- Check for skin fibrosis at injection site which may lead to poor absorption
- Are correct syringes being used?
- Is dose appropriate?
- Are dose adjustments being made by the client?

Insulin storage:
Insulin is a protein, which can be denatured by exposure to extremes of temperature or violent shaking. Insulin efficacy cannot be guaranteed beyond the expiry date. If there are any concerns regarding storage of the bottle, then it should be discarded and a fresh bottle used.

Insulin absorption:
Poor absorption from subcutaneous sites may result in instability. The site at which insulin is injected should be rotated as repeated injections can lead to low-grade inflammation and fibrosis leading to poor absorption of insulin. Certain types of insulin (PZI) may be poorly absorbed and changing to an alternative type such as lente should be considered in such cases.

Insulin syringes:
The syringe type **MUST** match the insulin preparation being used (i.e. Caninsulin is supplied as 40 IU/ml and so 40 IU/ml syringes MUST be used). It is common for incorrect syringes to be supplied as owners may obtain syringes from multiple surgeries/branches and this will result in incorrect dosing of insulin. In the case of clients mistakenly using 40IU/ml syringes rather than 100 IU/ml syringes this will lead to a significant overdose with potential for hypoglycaemic crisis!

Insulin Dose:
Wait several days following any adjustment in dose of insulin before assessing its effect as it can take some time for equilibrium to be reached. More frequent monitoring may lead to further unnecessary dose adjustments and risk of overswing. Owners should NOT be encouraged to adjust the dose of insulin unless veterinary advice has been sought especially if adjustments are being based solely on results of urine dipsticks. When dosage changes are considered appropriate then only small increments or decrements should be used (unless hypoglycaemia has been confirmed, in which case larger reductions in dose would be appropriate).
Most cats and dogs can be stabilised with 1 IU/kg of insulin per injection. Insulin resistance is likely when requirements exceed 2 IU/kg per injection.

Endogenous Factors:

When owner and insulin factors leading to diabetic instability have been ruled out, endogenous factors must then be considered. Presence of various concurrent diseases can lead to a much greater requirement for insulin and lead to instability.

Endogenous Factors Checklist:
- Is the animal overweight?
- Is the animal neutered (female dogs only)?
- Has a UTI been ruled out?
- Has pancreatitis been ruled out?
- Any other concurrent illnesses e.g. liver disease, skin disease, gingivitis etc
- Does the animal have any signs suggestive of a concurrent endocrine disorder (e.g. HAC, hypothyroidism)?
- Could animal be in diabetic remission?
- Any current drug therapies, which may be affecting glycaemic control (e.g. steroids, progestogens)?
- Insulin antibodies?

Obesity:
Obesity leads to reduced insulin receptor sites and reduced responsiveness to insulin through the action of leptin. Leptin is a hormone secreted from adipose tissue; levels are therefore expected to rise as body fat increases. Leptin decreases the sensitivity of muscle cells and hepatocytes to insulin.

Dioestrus:
Endogenous progesterone and exogenous progestogens antagonise the effects of insulin through production of growth hormone, which enters the systemic circulation in dogs. All diabetic bitches should be neutered as not only can this significantly improve diabetic control but also it may in fact lead to diabetic remission if the animal was a newly diagnosed diabetic. Entire female dogs may have **markedly** increased requirements for insulin following oestrus! The proportion of entire female diabetic dogs has decreased over the last two decades.

Urinary Tract Infection (UTI):
Bacterial UTIs are very common in diabetics as a result of glycosuria. Diabetics have reduced neutrophil function and may not be able to mount a typical inflammatory response in the face of infection, so UTI should NOT be ruled out on the basis of a single inactive sediment.

A urine sample (collected by cystocentesis to avoid contamination) should be submitted for culture and sensitivity even in the absence of inflammatory cells on deposit exam.

Pancreatitis:
Pancreatitis is likely to lead to very variable insulin requirements and it can be difficult to manage both the underlying pancreatitis and the effects on glycaemic control. Evidence of pancreatitis has been reported in up to 40% of dogs with diabetes yet pancreatitis is likely to remain very under diagnosed in both cats and dogs. Uncontrolled diabetes mellitus predisposes the patient to pancreatitis while pancreatitis may also cause sufficient pancreatic damage to lead to diabetes mellitus. Repeated bouts of pancreatitis will lead to poor control in the diabetic patient and may even be associated with development of diabetic ketoacidosis (DKA).
Specific pancreatic lipase (specPL) is is currently the most sensitive and specific blood test for pancreatitis but occasional false negatives can occur. Amylase and lipase are of limited use in the dog. It is worth testing for pancreatitis, using specPL, in any difficult diabetic even if the animal does not appear to be demonstrating 'classical' signs of pancreatitis.

Other illnesses:
Diabetes reduces resistance to infection by impairing phagocytosis and microcirculation. Gingivitis and the presence of bacterial infections in other areas (such as skin disease) can affect diabetic stability by stimulating secretion of cortisol and glucagons which antagonise the effects of insulin. Attention should be paid to oral hygiene.

Concurrent Endocrine Diseases:
Testing for concurrent endocrine diseases should only be considered in animals showing signs strongly suspicious of the suspected disorder (e.g. symmetrical alopecia in HAC). Not every unstable diabetic dog has hyperadrenocorticism! However inappropriate testing is further complicated by the fact that false positives are likely when an ACTH stim test is performed in an unstable diabetic dog! This can lead to an incorrect diagnosis and unnecessary treatment.
Thyroid dysfunction can affect glycaemic control in both cats and dogs. In such cases, TT4 may be falsely suppressed so concurrent measurement of free T4 (by equilibrium dialysis) may be of use as this parameter is less affected by non-thyroidal illness.

Diabetic Remission:
Diabetic remission is unlikely to occur in dogs unless brought on by recent oestrus activity (and the animal is subsequently neutered).

Drug Therapies:
Cortisol antagonises the effects of insulin. Use of steroids (including topical preparations!) is to be avoided in any diabetic animal as it will significantly increase the animal's insulin requirements and complicate monitoring (water intake can no longer be used for monitoring in such patients). Synthetic progestogens (e.g. megoestrol acetate) have similar adverse effects on diabetic control and should not be used.

Insulin antibodies:
Canine and porcine insulins (e.g. Caninsulin) are identical. Bovine insulin is antigenic in diabetic dogs and will stimulate production of antibodies however; it remains uncommon for animals to develop insulin antibodies to a level that significantly affects glycaemic control. However, if insulin antibodies are suspected to be contributing to instability then a change in insulin type may be beneficial.

Blood Glucose Curves

Blood glucose curves can be used to identify glucose nadir and evaluate the duration of action of insulin in the individual. Somogyi overswing can also be identified but may not occur every day despite the same dose of insulin being administered! A flatline response suggests insulin resistance. Causes of insulin resistance have been discussed and include drugs, insulin antibodies, concurrent disease including endocrine disease and kidney disease, pancreatitis and obesity
The effects of stress can have a profound impact on glucose curves in cats, which can make results meaningless; effects of stress can be reduced by sampling from peripheral veins or training clients to perform curves at home.
Results of curves can vary widely from day to day so results should be taken in context and interpreted along with clinical data (including demeanour, water intake etc), and fructosamine results.

Daily fluctuations in glucose curves are to be expected, so trends are much more important that individual results!

Aims:
- Maintain blood glucose between 5-15mmol/l
- Control PUPD
- Maintain stable body weight
- Avoid ketonuria

Curves allow us to determine the following information
- Is current insulin dose effective?
- Time at which peak insulin activity occurs (nadir)
- Duration of insulin activity
- Fluctuations over time

Somogyi Overswing:
If excessive doses of insulin are being administered, then hypoglycaemic episodes may occur. Rapid decreases in blood glucose leads to secretion of antagonistic hormones (cortisol, glucagon and adrenaline) which then results in rebound hyperglycaemia (often >20mmol/l). Somogyi is more likely to occur in animals receiving once daily insulin therapy but can occur in patients receiving twice daily treatment when there is prolonged duration of activity. Fructosamine levels may be low or low normal reflecting hypoglycaemia but unfortunately can also be increased as a result of the rebound hyperglycaemia induced by excessive insulin administration!

Recommendations based on Glucose Curve Results

Blood Glucose Concentration (mmol/l)	Recommendations
Pre-insulin <15mmol in cats	With-hold insulin & check for diabetic remission
Pre-insulin <10mmol/l in dogs	Reduce dose by 10%
Nadir < 3mmol/l	Reduce dose by 50%
Nadir 3-5mmol/l	Reduce dose by 10% in dogs Reduce dose by 1 unit in cats
Nadir 6-9mmol/l	Maintain current dose
Nadir >9mmol/l	Increase dose by 10% in dogs Increase dose by 1 unit in cats

Emergency Management of Diabetic Ketoacidosis

Introduction:

Diabetes mellitus is a common endocrinopathy in dogs and cats which results from relative or absolute insulin deficiency.

Insulin deficiency (absolute):

1. Immune-mediated destruction of ß-cells of pancreas
2. Pancreatitis

Insulin insensitivity (relative):

1. Obesity
2. Antagonism by steroids, growth hormone, progestagens

When diabetes mellitus is uncontrolled, insulin deficiency leads to deranged hepatic lipid metabolism resulting in non-esterified fatty aciods being converted to acetyl coenzyme A, rather than triglycerides. Acetyl co-enzyme A then accumulates in the liver and ultimately is converted to ketone bodies. Build up of ketone bodies progresses to metabolic acidosis, dehydration and diabetic ketoacidosis (DKA).

DKA can be precipitated by factors such as insufficient insulin therapy, bacterial infections and drugs that affect insulin action. Concurrent disease or steroid administration is identified in over 70% of cases presenting with DKA. Common concurrent disorders found in dogs with DKA include urinary tract infections, hyperadrenocorticism, cardiac failure, renal failure and drug therapies (steroids or progestagens).

Diabetic ketoacidosis due to:

- Marked insulin deficiency (+/- glucagon excess)
- Overproduction of glucose
- Decreased peripheral utilisation of glucose
- Hyperglycaemia ⇨exceeds renal threshold ⇨ osmotic diuresis ⇨ polyuria ⇨ polydipsia
- Mobilisation of fat and protein stores
- Increased delivery of fatty acids to liver ⇨ ketone production
- Buffering capacity exceeded ⇨ ketoacidosis

In the vast majority of cases DKA occurs in animals that have been previously diagnosed with diabetes mellitus

Ketone Bodies:

- ß-hydroxybutyrate
- Acetone
- Acetoacetate

Clinical findings:

- Sick animal
- Dehydration (due to osmotic diuresis and vomiting/diarrhoea)
- Tachycardia
- Jaundice?
- Depressed demeanour
- Vomiting/diarrhoea/anorexia

Clinicopathological findings:

- Hyperglycaemia
- Glycosuria
- Ketonuria/ketonaemia
- Metabolic acidosis
- Increased anion gap
- Often azotaemic
- Electrolyte abnormalities
- Neutrophilia +/- left shift

- Mild anaemia
- Hyperosmolar

Serum osmolality is correlated with mental status. Most DKA patients are hyperosmolar due to severe hyperglycaemia although this may not be readily detectable due to concurrent hyponatraemia. Hyperosmolarity will generally resolve with fluid therapy.

Treatment Objectives:

- Correct dehydration
- Correct acidosis
- Restore euglycaemia (slowly!)
- Remove underlying causes

Dehydration can be severe and results from the osmotic diuresis which occurs due to glycosuria and ketonuria. In addition, most DKA patients will present with vomiting (and diarrhoea) which leads to further fluid losses. A marked metabolic acidosis is often present due to acidic ketone bodies. Usually there is a high anion gap which reflects the presence of ketoacid anions and loss of bicarbonate due to acidosis. In addition, in the presence of significant dehydration lactic acidosis will also develop and contribute to increased anion gap. Specific treatment for acidosis is rarely required but should be considered if initial blood ph <7.1 or bicarbonate is less than 12mmol/l (in which case sodium bicarbonate administration may be required). In the vast majority of cases acidosis will resolve following appropriate fluid therapy and insulin administration. Fluid therapy improved tissue perfusion and oxygenation, while insulin therapy switches off ketone production. The use of bicarbonate can have significant adverse effects in DKA patients including worsening hypokalaemia and hypophosphataemia.

Therapy:

- Fluids (0.9% NaCl)
- Insulin (Regular)
- Potassium supplementation
- Treat concurrent illness

DKA Emergency Management Protocol

1. Place large bore catheter for IV fluids (consider jugular line for sampling)
2. Take bloods for PCV/TS, BUN, glucose, venous blood gas analysis (incl electrolytes), CBC, basic chemistries & plasma ketones (and specPL).
3. Estimate/calculate osmolality: [1.86 x (Na +K) +glu + BUN + 9]
    - 290-310mOsm/l is ref range for osmolality in dogs
4. Obtain urine sample (cysto) for glu/ketones/SG.
    - Save sample for culture (boric acid container)
5. Estimate fluid deficit (% dehydration x BWt (kg) x 1000) + (60ml/kg/day)
6. Start IV fluids
    - Isotonic crystalloid (0.9% NaCl)
    - Replace 50% of fluid deficit in first 4-6 hours (longer if hyperosmolar)

- Replace remaining 50% over following 18-20hours
- Animals presenting in shock may need higher fluid rates
- IVFT will lower blood glucose by improving GFR

7. Supplement potassium (see table below)
    - Total body potassium deficit always present even if serum potassium is initially within range
8. Initiate insulin therapy- only regular insulin is appropriate for stabilization of DKA (2 options available). Insulin should be administered until ketosis has resolved, even if this means that glucose has to be supplemented to prevent hypoglycaemia. Generally insulin therapy should be delayed until fluid therapy has been initiated as insulin can promote fluid movement into cells which can lead to vascular collapse.

Low dose intermittent intramuscular regime

- 0.2 iu/kg **regular** insulin *intramuscularly*
- Measure blood glucose hourly
- Administer 0.1 iu/kg **regular** insulin *i/m* hourly until blood glucose drops to 10-15mmol/l
- Change IV fluids to 2.5-5% dextrose to keep blood glucose between 10-15mmol/l (Can add glucose to 0.9% NaCl)
- Measure blood glucose every 2-4 hours
- Start *subcutaneous* **regular** insulin (0.25-0.5iu/kg) every 6 hours
- Start **lente** insulin *subcutaneously* once the animal is eating and no longer vomiting.

OR

Insulin CRI

- Add 2.2 iu/kg of **regular** insulin to 250mls of 0.9% NaCl in dogs
- Discard first 50mls (not into the patient!!) as insulin adheres to plastic
- Administer insulin CRI via separate IV line or piggy back with IVFT
- Administer insulin CRI at 5-10ml/hr depending on patient size and glucose result (see below)
- Adjust dose as necessary (approx 25-50%) based on subsequent glucose results
- Add glucose (2.5-5%) to IVFT once blood glucose <15mmol/l but **continue with insulin.** (Adding 50mls of 50% glucose to 1000mls of 0.9% NaCl = 2.5% solution)

The table below outlines the fluid rates and fluid type which may be needed to stabilize DKA when using an insulin CRI.

If Glucose is.... mmol/l	Fluids	Insulin CRI rate (ml/hr)
>15mmol/l	0.9% NaCl	10
12-15mmol/l	0.9% NaCL + 2.5% glucose	7
9-12mmol/l	0.9% NaCl + 2.5% glucose	5
6-9mmol/l	0.9% NaCl +5.0% glucose	5
<6mmol/l	**0.9% NaCl + 5% glucose**	**Stop CRI**

Blood glucose should be monitored q1-2hrs with both methods. Aim for a slow but steady reduction in blood glucose.

9. Supplement phosphate as required (0.03mmol/kg/hr). Phosphate supplementation is generally only recommended if hypophosphataemia is confirmed and if phosphate levels can readily be measured throughout the period of supplementation.

10. Switch to s/c regular insulin q6hrs once eating and vomiting has resolved

Ancillary therapy:

1. Antimicrobials (many have UTIs)
2. Gut protectants (ranitidine/famotidine/omeprazole) if concurrent conditions
3. Anti-emetics (maropitant, metoclopramide)
4. Identify and treat concurrent illness (e.g. UTI, pancreatitis)
5. Bicarbonate only considered if pH<7.1 and unresponsive to fluid therapy
6. Magnesium- hypomagnesaemia can lead to hypokalaemia which is unresponsive to supplementation. In such cases magnesium should be supplemented (0.75-1MEq/kg/24hrs)

Monitoring:

1. Check electrolytes every 6-8hours initially and adjust potassium as required
2. Check phosphate levels every 6-8hours (not required for first 12hrs)
3. Check blood glucose q2-4hrs until stabilized

Potassium Supplementation:

Serum Potassium (mmol/l)	Amount of potassium (mmol) to be added to 1 litre of fluids @ maintenance rates
>3.5	20
3.0-3.5	30
2.5-3.0	40
2.0-2.5	50
<2.0	60

N.B. The above recommendations are for maintenance fluid rates. If *twice* maintenance fluids are being administered the amount of potassium added should be *halved.* If a smaller bag of fluids is being used (500mls) then the amount of potassium added should be *halved.*

Rates of potassium administration *must not* exceed K_{max} = 0.5mmol/kg/hr

Top Tips for DKAs!

- If finances are very tight and owners cannot afford repeat electrolyte measurement, add 40mmol KCl to each litre of fluids at **maintenance** rates. (NB K_{max})
- If you do not have facilities to measure phosphate assume that hypophosphataemia is present if the animal is becoming progressively more anaemic or the serum is haemolysed. Hypophosphataemia usually occurs 12-24hrs after initiation of insulin.
- An easy way to determine the amount of potassium and phosphate to be added to intravenous fluids is to calculate amount of potassium required (see table above) then supplement *half* as potassium chloride and *half* as potassium phosphate.
- If finances are severely restricted, some animals will improve using regular (neutral) insulin injected subcutaneously every 6 hours. However, insulin will not be absorbed from s/c tissues in a dehydrated animal so you must rehydrate the animal first!
- Urine ketones during initial treatment may become more positive as ß-hydoxybutyrate is converted to acetoacetate (as ketodiastix do not detect ß-hydoxybutyrate).
- If urine cannot be obtained, test plasma for ketones using ketodiastix.
- ALL diabetic animals require insulin EVERY day to prevent ketoacidosis developing. If a diabetic animal is vomiting or anorexic it is usually safe to advise clients to administer HALF the usual insulin dose. Obviously the underlying cause for the vomiting or anorexia should be dealt with promptly.
- Remember frequent blood sampling can lead to anaemia in smaller patients- take minimum amounts of blood for tests required. Use of the Alphatrak glucometer allows an accurate glucose measurement to be obtained using a very small sample of blood.
- Remember the dose for regular (neutral) insulin is considerably lower than that of lente insulins

N.B. Ketonuria does not always equate to ketoacidosis. A bright animal with ketonuria can be managed far less intensively than a sick dog with ketonuria.