Diabetic Ketoacidosis (DKA)

**CLINICAL SIGNS**
- Vomiting
- Diarrhea
- PU/PD
- Anorexia
- Weight loss
- +/- Cachexia
- Dull- obtunded

**DIAGNOSTICS**
- PCV/TSP
- Electrolytes + blood gas
- Biochemistry
- Urinalysis
- +/- Diagnostic imaging

**HISTORY**
- Typically middle-aged dogs, median of 8 years of age [range 8 months to 16 years]
- In cats, also typically middle aged, with a median of 9 years of age [range 2-16 years]
- Concurrent disease has been documented in about 70% of dogs and 90% of cats with DKA
- Commonly diagnosed concurrent diseases in dogs with DKA include: acute pancreatitis, bacterial urinary tract infection and hyperadrenocorticism
- Commonly diagnosed concurrent diseases in cats with DKA include: hepatic lipidosis, chronic renal failure, acute pancreatitis, bacterial or viral infections, and neoplasia

**PATHOPHYSIOLOGY**

Diabetic ketoacidosis [DKA] is an acute pathological process that is characterised by increased blood glucose, ketone bodies, and subsequent metabolic acidosis. These metabolic derangements occur due to decreased appropriate insulin activity with concurrent increased glucagon, epinephrine, cortisol and growth hormone.

In healthy animals, insulin produced by the pancreatic beta cells promotes glucose uptake, glycogen synthesis, lipid and protein anabolism and storage, while inhibiting glycogenolysis, gluconeogenesis, lipolysis, ketogenesis and proteolysis. Conversely, glucagon produced by pancreatic alpha cells promotes glycogenolysis, gluconeogenesis, lipolysis and ketogenesis while inhibiting glycogen synthesis.

An absolute or relative lack of insulin production alone or in combination with a loss or inactivity of insulin receptors results in decreased glucose utilization and subsequent accumulation of glucose in serum [hyperglycemia]. Lack of insulin activity allows glucagon driven hepatic gluconeogenesis and glycolysis to continue uncontrolled, which further exacerbates the hyperglycemia.

A decreased insulin:glucagon ratio also causes an alteration in hepatic lipid metabolism. Low glucose availability causes a decrease in hepatic fatty acid synthesis via glycolysis and the citric acid cycle. This leads to rapid mobilisation of fat from adipose tissue, where adipocytes undergo lipolysis to release non-esterified fatty acids into circulation. Further alteration in hepatic lipid metabolism promotes non-esterified fatty acid conversion to acetyl-coenzyme A [acetyl-CoA] rather than being incorporated into triglycerides. Decreased pyruvate production by glycolysis and decreased activity of the citric acid cycle results in subsequent decreased utilization of acetyl-CoA. As a result, there is an accumulation of acetyl-CoA in the liver. Acetyl-CoA is the precursor for the synthesis of ketone bodies, including acetoacetate, beta-hydroxybutyrate and acetone. Ketone production that
exceeds the body’s energy requirements and buffering capacity, results in ketoacidosis.

Stress hormones [cortisol, epinephrine, and growth hormone] play an important role in the pathogenesis of DKA by promoting lypolysis, muscle glycogenolysis and protein breakdown at the level of the myocyte, increasing the level of circulating amino acids available for hepatic gluconeogenesis in the absence of insulin activity. Concurrent disease may promote increased concentrations of these stress hormones.

When hyperglycaemia exceeds the renal threshold for glucose resorption [10-12 mmol/L (dogs), and up to 16mmol/L (cats)], this results in osmotic diuresis and compensatory polydipsia/polyuria. The accumulation of ketones and lactic acid in the blood, combined with electrolyte and water loss to urine results in severe dehydration, hypovolemia, metabolic acidosis and shock. Ketonemia stimulates the chemoreceptor trigger zone in the brain causing nausea, anorexia and vomiting, which further contributes to electrolyte loss, metabolic acidosis, and dehydration. Eventually, the severe dehydration may result in hyperviscosity, thromboembolism, severe metabolic acidosis, renal failure and death.

**DIAGNOSTICS**

**PCV/TSP, CBC**
- Common findings in both dogs and cats include: non-regenerative anemia, neutrophilia with a left shift
- May see thrombocytosis in dogs
- May see Heinz body formation in cats which is correlated with plasma beta-hydroxybutyrate concentration

**Electrolytes and blood gas**
- Accumulation of ketone bodies overwhelm the buffering capabilities of the body, resulting in increased hydrogen ions and decreased bicarbonate and subsequent metabolic acidosis and increased anion gap \([Na+K]-(HCO3+Cl)\]
- Dehydration, hypovolaemia and lactic acid build up may contribute to the acid-base derangements
- Potassium:
  - Most DKA patients are hypokalemic due to potassium binding to ketoacids, vomiting, anorexia, and osmotic diuresis, however, it may be masked initially due to potassium shifting from the intracellular to the intravascular space as a result of metabolic acidosis, insulin deficiency and serum hypertonicity. Hyperkalaemia may also develop secondary to acute kidney injury.
  - Fluids and insulin therapy may exacerbate hypokalemia due to kaliuresis and intracellular movement of potassium, respectively
- Phosphorus:
  - Decreased total body phosphorous occurs due to phosphorus shifting from the intracellular to the extracellular space, and may be further depleted due to osmotic diuresis
  - Some patients may have normal or increased phosphorus levels due to dehydration or decreased excretion in later stages of DKA
  - Fluid resuscitation in combination with insulin therapy may cause rapid declines in phosphorus
  - Hypophosphatemia in DKA patients has been associated with haemolysis (reported in a cat) and seizures (reported in a dog). Additional clinical signs seen include weakness, myocardial depression and arrhythmias
Magnesium
- Decreased magnesium concentration has been reported in cats, however the clinical significance of this is unknown. It may be due to increased urinary excretion of magnesium, though is also likely related to intracellular movement in the presence of insulin therapy.
- Hypomagnesemia leads to cardiac arrhythmias, ileus and reduced renal absorption of electrolytes, and other co-transport of electrolytes intracellularly.

Sodium:
- Hyponatremia may be due to fluid shifts as a result of hyperglycemia [pseudohyponatremia], increased free water and its retention, including total body sodium loss from natriuresis from glucosuria induced osmotic diuresis.
- As hyperglycemia resolves, sodium concentrations may increase secondary to a decrease in osmolality and movement of free water from the intravascular space.

Other electrolyte derangements that have been reported in canine DKA patients include hypochloremia and decreased ionized calcium, usually because GIT losses and diuresis.

Biochemistry
- Persistent hyperglycemia is due to excessive hepatic production of glucose and decreased utilization due to a relative or absolute lack of insulin.
- Increased liver enzymes may be due to diabetic hepatopathy. This is due secondary to fatty liver syndrome, hypovolaemia, poor hepatic blood flow and subsequent hepatocellular damage.
- Serum alkaline phosphatase may further increase with the presence of concurrent pancreatitis and secondary cholestasis.
- Cholesterol and triglyceride concentrations may be elevated secondary to derangements of lipid metabolism as a result of decreased levels of insulin.

Blood Ketones
- Blood ketones should be evaluated wherever possible. False negatives are uncommon, compared with urine ketone measurement.

Urinalysis
- Glucosuria, proteinuria, ketonuria are seen.
- Osmotic diuresis and chronic hypokalaemia may contribute to low USG and may not signify renal insufficiency.
- Urea and creatinine may be normal or elevated due to dehydration or underlying renal insufficiency or failure.
- Ketonuria may not be detected because nitroprusside reagent in the urine dipstick detects only acetoacetate and not beta-hydroxybutyrate, which is the dominant ketone body in DKA.
- May see evidence of infection due to diabetic immunosuppression and decreased ability to mobilize white blood cells to the site of infection.

Diagnostic imaging
- Diagnostic imaging may be helpful in diagnosing concurrent disease in DKA patients, if present, including pancreatitis, hepatic disease and neoplasia.
TREATMENT

INITIAL MANAGEMENT

FIRST 24H:

Fluid resuscitation:
- Fluid therapy alone [without concurrent insulin therapy] significantly decreases blood glucose concentration in dogs with DKA
- Balanced replacement crystalloids are recommended: Hartmanns or Plasmalyte 148 (C1)
  - Maintenance rates
  - Dehydration deficit: % dehydration x kg x 10 = fluid deficit [mL] to replace over 24hr (Give half over the first 6 hours and the other half over the next 18 h)
  - Estimate ongoing loss: vomiting, diarrhea, and osmotic diuresis secondary to hyperglycemia
  - The osmotic diuresis is often under-estimated

Correction of electrolyte derangements:
- Supplement potassium [KCl], phosphate [KPO₄], and magnesium [MgCl₂] based on results of previous blood tests (C1)
- Phosphate: administer half the amount of potassium supplementation required as KCl and the other half as KPO₄ if hypophosphatemia on presentation, or after 6-12h of treatment (C2)
- Magnesium: if low or if hypokalaemia/ hypocalcaemia are refractory to treatment (C2)
  - 0.75-1 mEq/kg/day (0.35-0.5mmol/kg/day) as CRI for 24h
  - 0.3-0.5 mEq/kg/day (0.15-0.25mmol/kg/day) for additional 2-5 days

Correction of acidosis:
- Intravenous fluids and insulin therapy are usually sufficient to correct any underlying acidemia
- The use of sodium bicarbonate therapy is not needed in most dogs and cats with DKA and may be associated with a poor outcome (C3)

Supportive care:
- Antibiotics: Ampicillin 22mg/kg IV q8h if infection is suspected (UTI, GIT bacterial translocation) (C2)
- Antiemetics
  - Maropitant: 1mg/kg IV q24h (C1)
  - Metoclopramide: 0.2-0.5mg/kg PO, SC, IV q6-8hr or 1-2mg/kg/day IV as CRI (C2)
- Analgesia [especially if concurrent pancreatitis and abdominal pain]
  - Methadone: 0.2-0.5mg/kg IM or SC q4-6h initially (C1)
  - Fentanyl CRI: 1-5 ug/kg/hr (C2)
  - Buprenorphine: 0.005-0.02 mg/kg IM, IV, SC q6-8h (C2)

Insulin therapy:
- Delay initiation of insulin therapy at the onset of fluid therapy as may decrease blood glucose and electrolyte concentrations too rapidly, causing harmful osmotic shifts (C1)
- Initiate insulin therapy only once patient has been resuscitated with fluids [average 6 hours] (C1)
- Regular insulin is used most commonly in DKA patients, and can be given as a CRI or intramuscularly
- Blood glucose concentration should be measured every 2 hours if insulin therapy given as a CRI, or every

Guidelines:
- Class 1 (C1) – Definitely perform (good evidence)
- Class 2 (C2) – Consider performing (some evidence)
- Class 3 (C3) – Do not perform (unsound evidence and/or deleterious)
hour if given IM (C1)

- Phosphorus supplementation: measure after 24h. If <30mg/L add 10mmol/L of KPO4 [1 vial] and monitor q12h until eating (C2)
- Long acting insulin is started when the patient is eating and drinking and maintaining hydration (C2)

**Constant rate infusion protocol - Actrapid (regular insulin) CRI [Canine and Feline]**

- Add 2.2 U/kg [Dog] or 1.1 U/kg [cat] regular insulin [Actrapid] to a 500ml bag of saline or Hartmans. Mix well then run approximately 50ml through tubing to discard [as insulin binds to plastic].

**Do not flush this IV line as patient will receive a bolus of insulin!**

<table>
<thead>
<tr>
<th>Glucose concentration mmol/L</th>
<th>Maintenance fluid type</th>
<th>Insulin CRI [2.2-4.4 U/kg insulin in 500ml bag of saline] ml/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 14</td>
<td>Hartmanns + KCl</td>
<td>10 or higher if not reducing</td>
</tr>
<tr>
<td>10-14</td>
<td>Hartmanns + KCl + 2.5% dextrose</td>
<td>7</td>
</tr>
<tr>
<td>8-10</td>
<td>Hartmanns + KCl + 2.5% dextrose</td>
<td>5</td>
</tr>
<tr>
<td>6-8</td>
<td>Hartmanns + KCl + 2.5% dextrose</td>
<td>5</td>
</tr>
<tr>
<td>&lt;6</td>
<td>Hartmanns + KCl + 2.5% dextrose</td>
<td>Stop insulin</td>
</tr>
</tbody>
</table>

Aim to decrease glucose at 2-3 mmol/L/hr. Any faster may cause detrimental changes in osmolality

**Intramuscular protocol - Actrapid (regular insulin) IM [Canine and Feline]**

- Can use intramuscular protocol of patient is more stable or if blood glucose has been dropped to <14mmol/L on the CRI protocol and the patient is well hydrated
- Initial dose regular insulin 0.2U/kg IM, followed by regular insulin 0.1U/kg IM 1 hour later
- Monitor blood glucose levels every hour for the first 4-6 hours
- Insulin doses are then given q1h based on degree of drop in blood glucose per hour, as described below
- Once blood glucose has dropped to below 6mmol/L, stop IM insulin and repeat blood glucose in 1 hour to determine subsequent doses

<table>
<thead>
<tr>
<th>Glucose drop/ hr</th>
<th>Insulin IM U/kg</th>
<th>Blood glucose [mmol/L]</th>
<th>Maintenance fluid type</th>
<th>Insulin IM U/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3.5mmol/L</td>
<td>0.05</td>
<td>10-14</td>
<td>Hartmanns + KCl + 2.5% dextrose</td>
<td>0.2</td>
</tr>
<tr>
<td>2.5-3.5 mmol/L</td>
<td>0.1</td>
<td>8-10</td>
<td>Hartmanns + KCl + 2.5% dextrose</td>
<td>0.1</td>
</tr>
<tr>
<td>&lt;2.5mmol/L</td>
<td>0.2</td>
<td>6-8</td>
<td>Hartmanns + KCl + 2.5% dextrose</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;6</td>
<td>Hartmanns + KCl + 2.5% dextrose</td>
<td>Don’t give insulin, repeat BG in 1h</td>
</tr>
</tbody>
</table>

**ONGOING MANAGEMENT**

>24H:

**Transition to home maintenance therapy:**

- **DOG:** Caninsulin 0.25 IU/kg SC BID with food once eating (will need BG curve and revision)
- **CAT:** Glargine 0.25 IU/kg SC BID with food once eating initially (will need BG curve and revision)
- Monitor blood glucose for 12h prior to discharge

Guidelines:

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- **Class 2 (C2) – Consider performing (some evidence)**
- **Class 3 (C3) – Do not perform (unsound evidence and/or deleterious)**
Follow up blood glucose curve at regular clinic in 3-7 days following discharge.

MEDICATIONS TO BE DISPENSED
- DOG: Caninsulin 0.25-0.5 U/kg SC BID with food
- CAT: Glargine 0.25-0.5 IU/kg SC BID with food

COSTS AND HOSPITALISATION
- Hospitalisation time to expect: $3000-6000
- Costs whilst hospitalized: 4-6 days

PROGNOSIS AND RISK FACTORS
- Prognosis is good with 70% of dogs and cats treated surviving to discharge
- Median time in hospital for dogs and cats is typically 6 and 5 days, respectively
- 7% of dogs and up to 40% of cats may experience recurrence of episodes of DKA
- Dogs with concurrent hyperadrenocorticism are less likely to be discharged from hospital

REFERENCES

*Use of any of this material is not for retail or public disclosure. It is intended for personal use and knowledge only

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