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Understanding Diabetic Ketoacidosis

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Diabetic ketoacidosis (DKA) is a complication of unregulated diabetes mellitus (DM) that produces marked hyperglycemia, profound metabolic acidosis, and hyperketonemia in severely affected patients. DKA is often discussed as a condition that is separate from uncomplicated diabetes mellitus but, in fact, diabetes mellitus is a spectrum of disorders that ranges from non-ketotic hyperosmolar diabetes mellitus on one end to diabetic ketoacidosis on the other end. It is important to remember that most complicated diabetics have another medical problem. Thus, management of DKA must be performed in the context of any concurrent disorder.

DKA can be precipitated by factors such as inadequate insulin therapy, physiologic stress, drugs that affect insulin production or action, bacterial infection, and decreased fluid intake. Concurrent illness is common in animals with DKA. In one study, about half of cats with DKA had azotemia on admission; azotemia was moderate to severe in 20% of those cats. Other concurrent disorders found in that same group of cats included: inflammatory bowel disease, asthma, pancreatitis, hyperthyroidism, urinary tract infection, neoplasm, and corticosteroid therapy. In dogs, concurrent disorders include: urinary tract infection, neoplasia, pneumonia, pyometra, prostatitis, renal failure, hyperadrenocorticism, heart failure, and drug therapy (corticosteroids or progestins), among others.

Patient Factors

Signalment: There is no characteristic or specific signalment for animals with DM or those likely to develop complicated DM.

• Gender. Middle-aged and older female dogs have an increased risk for the development of diabetes mellitus when compared to males. In addition, 80% of dogs with DKA were female in one study of DKA. It is generally accepted that male cats develop DM more frequently than females, although this is not supported by all studies.

• Age. Although dogs of any age can develop DKA, most dogs diagnosed with DKA are older than 7 yrs. of age. Most cats with DKA are 6 years or older.

• Breed predisposition. DKA is more likely to be diagnosed in those dog breeds that have a high incidence of DM, such as miniature and toy poodles, miniature schnauzers, beagles, and Cairn Terriers. Among cats, an Australian study reported an increase in the frequency of DM in the Burmese breed. There is no data to suggest that any breed is more likely than another to develop ketoacidosis.

Presenting Complaint: DKA is associated with non-specific signs. Severely affected animals may present in shock or comatose without any supporting history. Careful questioning of the owner may elicit a history of signs more typical of diabetes mellitus.

• Polydipsia and polyuria are the most frequently reported complaints in dogs and cats with DKA.

• Other common complaints include:

   Lethargy and weakness
   Anorexia
Vomiting 
Weight loss 
Signs of abdominal pain

• Neurologic impairment ranging from depressed mentation to coma.

• Other historical considerations/predisposition. Precipitating factors, such as the recent administration of glucocorticoid drugs or the presence of concurrent illness, are identified in over 70% of cases. Identification and correction of contributing factors is essential for a favorable clinical outcome.

**Physical Examination Findings:**

• Dehydration (mild to severe)

• Abnormal body temperature (hyper- or hypothermia)

• Abdominal pain

• Jaundice

• Tachycardia, diminished femoral pulses, prolonged capillary refill time, and cool extremities due to cardiovascular collapse and shock occur in severely hypovolemic patients.

• Neurological abnormalities range from mild (depressed mentation, quiet demeanor) to severe (stupor, coma).

• Other common findings are those also detected in animals with uncomplicated DM and include weight loss, muscle wasting, hepatomegaly, cataracts (dogs), and dermatological abnormalities.

• Abnormal physical exam findings caused by concurrent illness may also be detected.

• Acetone odor –The “fruity” odor of acetone is detected on the breath of some animals with DKA.

**Laboratory Findings:**

• Hyperglycemia (100% of patients) - hyperglycemia may be severe (>500 mg/dl).

• Glucosuria (100% of patients) - occurs when the blood glucose exceeds renal threshold for glucose (about 200 mg/dl in dogs and 220 mg/dl in cats).

• Ketonemia and ketonuria – are detected in essentially 100% of patients. Rarely, ketones are undetectable due to a laboratory error.

• Metabolic acidosis – Although the severity of acidosis varies, a decrease in blood pH and in bicarbonate concentration occurs in all patients with DKA due to ketoacid production.

• Increased anion gap: The anion gap increases in parallel to the production of ketoacid anions. The normal range for the anion gap is 12 – 24 mEq/L.

• Hyperosmolarity: The markedly elevated serum glucose increases the effective serum osmolarity (normal range (280 – 295 mOsm/L) in dogs and cats with DKA. Most animals with DKA also have an increase in total serum osmolarity.

• Azotemia: Pre-renal azotemia from dehydration is found in most animals with DKA. Patients with concurrent renal insufficiency may be severely azotemic from pre-renal and renal causes.

• Electrolyte abnormalities: Hyponatremia, hypochloremia, and hypokalemia are common in patients with DKA. Hypophosphotemia and hypomagnesemia may also be present, but usually develop after insulin therapy.

• Hyperlipidemia: Dogs and cats with DKA may have elevations in serum lipid and triglyceride concentrations.
Pyuria, hematuria, proteinuria and bacteriuria are found when a urinary infection precipitates DKA.

Mild anemia is common in dogs and cats with DKA

Leukocytosis (+ a left shift) occurs when infection is present.

Treatment:
The emergency management of DKA requires that life-threatening problems be identified and treated quickly. Typical problems associated with DKA are dehydration, hyperglycemia, electrolyte abnormalities, acid/base imbalance, and hyperosmolarity. These will be addressed in turn below.

DEHYDRATION

Dehydration results from:

1. Osmotic diuresis: sodium and glucose act as an osmolytes in urine.
2. Protracted vomiting and diarrhea
3. Decreased fluid intake due to weakness, lethargy, and anorexia

Treatment:

Intravenous crystalloid fluids are preferred:

- The fluid of choice is physiologic saline (0.9% sodium chloride) solution. The initial rate of fluid administration depends on the patient’s hydration status.

Hypovolemic shock – The shock dose of fluid (90 ml/kg/hr for dogs; 50 ml/kg/hr for cats) is used for volume resuscitation of animals with hypovolemic shock. A recommended approach is to infuse a portion (e.g. 25 - 50%) of the total estimated shock volume as a bolus and re-evaluate the patient’s need for additional fluid. Rapid administration of large fluid volumes is contraindicated when DKA precipitated by cardiac failure.

Moderate to severe dehydration – Saline fluid should be administered at an hourly rate that provides maintenance fluid requirements (2 - 4 ml/kg/hr), replaces contemporary fluid losses, and will replace the estimated fluid deficit over 6-12 hrs.

Rehydration improves:

Electrolyte disturbances - Rehydration with isotonic saline and potassium supplementation helps to replenish body stores of sodium and potassium. Without sufficient potassium supplementation, isotonic saline may lower serum potassium concentrations via a dilution effect. Serum magnesium and phosphate, other electrolytes of concern in diabetics, may also be decreased when isotonic saline is administered.

Acid/base status - Most animals with complicated DM (especially those with DKA) have metabolic acidosis. Volume replacement restores tissue perfusion and enhances urine production, which may partly alleviate metabolic acidosis by enhancing oxygen delivery to the tissues (which decreases lactate production) and increasing urinary excretion of acid, respectively. Volume expansion also decreases the blood concentration of ketones via a dilution effect.

Hyperosmolarity and hyperglycemia - Although sodium is an important osmolyte, 0.9% saline is hypotonic when administered to hyperosmolar diabetics. Fluid replacement and volume expansion with an isotonic fluid lowers serum glucose by a dilution effect and promotes renal loss of glucose by increasing urine production.

HYPERGLYCEMIA

Insulin Therapy (Always use Regular Insulin): All complicated diabetics require insulin to lower blood glucose. Only regular insulin is appropriate for emergency management of DKA.

Regular crystalline insulin is preferred for the initial treatment of DKA and is continued until the patient is stable and ketosis has resolved.
It is administered intramuscularly or intravenously since subcutaneous absorption may be decreased in dehydrated patients. Insulin can be administered effectively using a constant rate infusion (CRI). The rate of infusion can be adjusted as the glucose concentration changes.

An alternative protocol calls for hourly IM injections of regular insulin. Insulin is given IM at an initial dose of 0.2 to 0.25 U/kg and followed by 0.1 U/kg IM hourly.

Therapy should be tailored to reach a target for blood glucose of 250 - 300 mg/dL in 12 hrs.

The administration of insulin can be delayed until vascular volume is restored in some cases.

Insulin enhances fluid and electrolyte movement into cells, which could precipitate vascular collapse.

Volume expansion will lower serum glucose concentrations by a dilution effect and urinary excretion.

Increased urine production will enhance renal glucose loss and lower BG.

The goals of insulin treatment are to lower blood glucose and to halt ketone production. Insulin administration should continue until ketosis has resolved, even if this means that glucose supplementation must be given to maintain euglycemia.

**Constant Rate Infusion (CRI) of regular insulin**

1. Add a total dose of 2.2 U/kg of regular insulin to 250 ml of 0.9% NaCl fluid.
2. "Run out" and discard 50 ml of the insulin solution. This procedure allows insulin, which binds to plastic, to saturate the infusion tubing.
3. The insulin solution is infused at an initial rate of 10 ml/hr. (An infusion pump is recommended.)
4. The infusion should be continued until ketosis has resolved.
5. When the blood glucose falls to 250 – 300 mg/dl, the insulin infusion rate is decreased by 25 – 50% and a glucose-containing fluid (2.5 – 5% dextrose) is infused to prevent hypoglycemia. If the blood glucose is < 100 mg/dl, the insulin infusion is temporarily stopped.

**Hourly IM administration of regular insulin**

1. The initial dose is 0.2 to 0.25 U/kg IM
2. Follow-up doses of 0.1 to 0.2 U/kg IM are given hourly
3. Regular insulin administration is continued until the patient’s ketosis is resolved.
4. When the blood glucose falls to 250 – 300 mg/dl the hourly dose is decreased by 25 – 50% and a glucose-containing fluid (2.5 – 5% dextrose) is infused to prevent hypoglycemia. If the blood glucose is < 100 mg/dl, the insulin administration is temporarily stopped.

Regardless of the protocol chosen, blood glucose measurements are performed q 1-2 hours in the initial stages of treatment. Glucose should remain around 250 mg/dL while the patient is being stabilized.

**Intermediate- and long-acting insulin preparations**

1. The administration of depot insulin preparations (e.g. NPH) is delayed until the patient is stable and eating, and ketone production is stopped.

**Rationale for glucose supplementation.**

Insulin treatment lowers blood glucose sooner than it reverses ketosis.

An intravenous infusion of 2.5% or 5% glucose is used to prevent hypoglycemia (maintain blood glucose >250 mg/dL).
The insulin dose is decreased by 25 –50% as the glucose concentration falls.

If hypoglycemia occurs, insulin is discontinued only long enough to allow the blood glucose to rise above 150 – 200 mg/dL.

**ELECTROLYTE DISTURBANCES**

**Potassium**

The most common electrolyte disturbance associated with DKA is hypokalemia, which may be detected at the time of presentation or may develop during treatment. Body stores of potassium are depleted even if the blood concentration of potassium is normal. Insulin treatment can precipitate or worsen hypokalemia by driving potassium into cells. Fluid treatment can exacerbate hypokalemia via a dilution effect on serum potassium. Potassium supplementation should not exceed 0.5 mEq/kg/hr IV and is contraindicated in animals with hyperkalemia or acute renal failure.

The amount of KCl added to fluids is adjusted relative to the serum potassium concentration.

If serum [K+] is:

- > 3.5 - add 20 mEq KCl per liter
- 3.0 – 3.5 - add 30 mEq KCl per liter
- 2.5 – 3.0 - add 40 mEq KCl per liter
- 2.0 – 2.5 – add 60 mEq KCl per liter
- < 2.0 – add 80 mEq KCl per liter

**Sodium**

Sodium deficits are addressed by the use of 0.9% NaCl for fluid and volume resuscitation. Generally, no additional sodium supplementation is required. Very severe hyponatremia (less than 120 mEq/L) may require hypertonic saline-containing fluids, but these will not be discussed here.

**Phosphorous. • • • • •**

Routine phosphorous supplementation to prevent hypophosphotemia is controversial.

Supplementation and is indicated when phosphorous is < 2.0 mg/dL. (normal range 2.7 – 6.8 mg/dL).

Severe hypophosphotemia (1.0 mg/dL) may lead to hemolysis and neuromuscular signs.

Phosphorous is given at a dose of 0.01 – 0.03 mmol/kg/hr IV for 6 hours.

Phosphorous is commercially supplied as potassium phosphate ( K2PO4), which contains 3.0 mmol phosphate and 4.4 mEq potassium per ml of solution.

Serum phosphorous concentrations should be maintained > 2.0 mg/dL. Oversupplementation should be avoided. Phosphate supplementation can produce hypocalcemia in some circumstances.

Phosphorous supplementation should not be attempted if serum concentrations cannot be monitored during treatment. Aggressive phosphate supplementation is contraindicated in patients with renal failure.

Phosphate solutions are incompatible with many intravenous fluid solutions and drugs, but are reported to be compatible with 0.9% saline solution.

**Magnesium. • • • •**

Severe hypomagnesemia (total magnesium <1.2 mg/dL) is an indication for magnesium supplementation.
Dose: 0.75 – 1.0 mEq Mg2+ /kg/day in D5W, given as an IV infusion.

Magnesium chloride (9.25 mEq Mg2+/gm) and magnesium sulfate (8.13 mEq Mg2+/gm) are available commercially as 50% solutions. These solutions are diluted (maximum concentration 20%) in D5W for IV administration.

Magnesium solutions are incompatible with many intravenous fluid solutions and drugs.

**ACID/BASE IMBALANCE**

The acid/base abnormality most frequently associated with DKA is marked metabolic acidosis, which develops by several mechanisms and usually causes an elevation in the anion gap. The most important cause is the generation of acidic ketones (beta hydroxybutyrate and acetoacetic acid). Ketones are the product of unregulated lipolysis occurring in adipose tissue. The non-esterified fatty acids that are released can be used as a fuel substitute by most tissues, including the liver. Without insulin (and with increased glucagon), FFA conversion to triglycerides in the liver is markedly impaired and the FFA are instead converted to fatty acyl-CoAs (acyl-CoA derivatives of the FFA), which are oxidized to acetyl-CoA and then converted to ketone bodies, rather than oxidized to CO2. Essentially the FFA metabolism of the liver is reset, both by the relative lack of insulin and the relative increase of glucagon and other counter-regulatory hormones, to favor ketone production over FA oxidation. Other mechanisms for acidosis is include lactic acid overproduction, impaired tissue perfusion from dehydration and shock, and reduced renal excretion of H+. Mixed disturbances are possible if neurologic compromise leads to depressed respiration (respiratory acidosis) or loss of gastric contents potentiates metabolic alkalosis.

Specific therapy for metabolic acidosis is rarely indicated in complicated DM unless the blood pH is < 7.1. Studies in human subjects with complicated DM have not demonstrated a beneficial effect of bicarbonate treatment on clinical outcome. Other studies have demonstrated that there is not a correlation between the blood pH and neurologic status or mortality in people with DKA. If therapy is warranted, bicarbonate therapy (as sodium bicarbonate) is the therapy of choice. In most patients treated with fluids and insulin, acidosis will usually improve without the need for bicarbonate. Fluid replacement increases blood volume, improves tissue perfusion and oxygenation, and resuscitation and insulin therapy inhibits ketogenesis and promotes the replenishment of endogenous bicarbonate. Bicarbonate use is associated with potential detrimental effects. It can worsen hypokalemia and hypophosphotemia, contribute to the development of cerebral edema, promote tissue hypoxia (due to increased hemoglobin affinity for oxygen), precipitate hypernatremia and fluid overload, and produce paradoxical CSF acidosis.

**Bicarbonate replacement. • • •**

Bicarbonate therapy is rarely needed to correct acidosis in DKA.

Used only for life-threatening acidosis (pH < 7.0) and when blood pH can be monitored.

Low Dose: 0.1 x base deficit x weight (kg) = amount (ml). Give IV slowly over 2 hours.

Anion gap (AG) is the mathematical difference between the measured cations (sodium and potassium) and the measured anions (chloride and bicarbonate) and represents unmeasured anions (e.g. sulfates, phosphates, and serum proteins). The normal anion gap in is 12 – 24 mEq/L. The AG increases in DKA because the concentration of unmeasured anions in the blood is increased by the anions of ketoacids and also because the concentration of bicarbonate (a measured anion) is decreased by acidosis.

**DKA AND HYPEROSMOLALITY**

Plasma hyperosmolality represents a free water deficit. Under normal physiologic conditions, sodium is the main determinant of serum osmolarity. In DM, glucose contributes substantially to hyperosmolality, while sodium concentrations are usually normal or even decreased. Hyperosmolality quickly approaches lethal levels (>400 mOsm/L) when marked hyperglycemia and hypernatremia are present.

A distinction must be drawn between measured and effective osmolarity. Measured osmolarity is of greater magnitude than effective osmolarity because it includes osmoles (e.g. urea) that freely permeate all body compartments but do not influence fluid shifts. Effective osmolarity measures only osmoles that draw fluid from one compartment, these include sodium, potassium, and glucose. Serum effective osmolarity is closely correlated with mental status and the degree of obtundation in human diabetics; coma ensues when the effective osmolarity exceeds 340
mOsm/L. Most dogs and cats with DKA have an increase in total serum osmolarity and an increase in the anion gap. Thus, the calculated serum osmolarity can differ greatly from the measured osmolarity in patients with DKA. The effective osmolarity is not readily measured but is estimated from the glucose and electrolyte concentrations.

Estimating osmolarity:

Total Osmolality: 2(Na + K) + (GLUCOSE/18) + BUN/2.8 = osmolarity (mOsm/L)

Effective osmolarity: 2(Na) + GLUCOSE/20 = effective osmolarity (mOsm/L)

TREATMENT CONTRAINDICATIONS

Steroidal drugs – Glucocorticoids and progestins are contraindicated in dogs and cats with DKA, unless there is a compelling reason for their use.

Oral hypoglycemic drugs – Oral hypoglycemic drugs (for example, the sulfonylurea class of drugs) have no role in the treatment of DKA.

Depot insulin preparations - Regular insulin is the preferred insulin for its better short-term control of glucose and its short duration of action. Insulin preparations with slow release and prolonged action (e.g. NPH or lente insulins) have no role in emergency treatment of DKA.