DKA in the ER

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Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS) are life-threatening complications of diabetes mellitus (DM). Although a distinction is made in the definitions of the two syndromes, there is much commonality between them.

DKA is a syndrome of hyperglycemia, metabolic acidosis, ketosis, and variable degrees of volume depletion. DKA is the result of an absolute or relative deficiency in insulin, usually with an abundance of stress or counter regulatory hormones (glucagon, catecholamines, cortisol, and growth hormones). DKA may be precipitated by lack of insulin (before diagnosis, noncompliance, product expiration or heat inactivation), dietary mismanagement, or physical stressors - infection (urinary tract infections, pneumonia, etc.), endocrine (hyperadrenocorticism, diestrus, acromegaly, etc) or inflammatory (pancreatitis, inflammatory bowel, surgery, neoplasia, etc) conditions. Increased glucose production and impaired peripheral glucose utilization leads to hyperglycemia, hyperosmolality, glucosuria and osmotic diuresis with fluid and electrolyte depletion. Inability of tissues to utilize glucose causes unfettered lipolysis (triglycerides broken down into glycerol and free fatty acids) with subsequent production of ketone bodies, as cells oxidize free fatty acids for energy, resulting in the formation of ketone bodies. The latter contribute to the osmotic diuresis and produce the acidosis.

HISTORY AND PHYSICAL EXAM FINDINGS

Clients are likely to recognize signs mirroring those of DM (polyuria, polydipsia, weight loss), as well as those of ketosis (vomiting, anorexia, lethargy, etc.). Physical exam findings of DKA reflect the underlying metabolic derangements of dehydration / intravascular volume deficits (delayed skin turgor, dry mucous membranes, sunken eyes, tachycardia, delayed capillary refill time, weak pulses, altered mentation, hypothermia), ketosis (ketotic fetor or fruity odor of acetone), and metabolic acidosis (Kussmaul respiration) and possibly those of the precipitating factors (fever, etc.). In addition, abdominal pain, hepatomegaly, cataracts (dogs) and plantigrade stance (cats), may be observed. Volume depletion and dehydration tends to be less profound in DKA than in HHS, presumably because the acidosis of DKA precipitates clinical deterioration sooner. Deep and rapid “Kussmaul” respirations are an attempt to compensate for metabolic acidosis. An unexplained feature of DKA is abdominal pain, but this typically resolves with correction of the acidosis.

LABORATORY FEATURES

Biochemically, DKA is defined at the triad of metabolic acidosis, ketosis and hyperglycemia. The severity of DKA is typically defined by the degree of metabolic acidosis, which is characterized by a low pH, low serum bicarbonate, elevated anion gap (AG = Na + K – Cl + HCO3), raised ketone levels, and a compensatory hypocapnia.

Ketone measurements should be made initially in patients with hyperglycemia to confirm the diagnosis. False negatives can occur with urinary dipstick ketone measurements, but is less likely when utilizing handheld, point-of-care blood ketone monitors. In patients with DKA, three ketone bodies are present and in chemical equilibrium: acetoacetate, acetone and β-hydroxybutyrate, but only acetoacetate (strongly reactive) and acetone (weakly reactive) are measured by the nitroprusside assay, found on urine multisticks. As acidosis progresses, the equilibrium shifts in favor if β-hydroxybutyrate (measured by some point-of-care blood ketone monitors; Abbott Precision Xtra results have been validated for veterinary use). As the acidosis improves with therapy, this dynamic equilibrium shifts in favor of acetoacetate, and ketone concentrations may *appear* to worsen. As such, there is little value in *serial* monitoring of

ketonuria or ketonemia with urine multisticks. Of note, sulfhydryl-containing drugs can react with nitroprusside reagent, resulting in false-positive results for ketones.

Glucose levels typically range between 300 and 600 mg/dl, but may be lower in well-hydrated patients whose preserved glomerular filtration facilitates glucose clearance, or higher with greater degrees of dehydration / intravascular volume deficits. Loss of free water, because of osmotic diuresis, may lead to hyperosmolarity and hemoconcentration.

The osmotic effects of glucose translocate water from the intracellular to the extracellular space, producing hyponatremia in most patients. Measured sodium concentration typically declines 1.6 to 2.4 mEq/L for each 100 mg/dl increase in glucose. Artifactual decreases in sodium concentration may be seen in DKA when triglycerides contribute substantially to plasma volume, referred to as pseudohyponatremia.

Most patients with DKA have normal or elevated serum potassium values, despite total body deficits, because acidosis, insulin deficiency and the osmotically induced flow of water out of cells shifts potassium from the intracellular to the extracellular compartment. With appropriate volume expansion, insulin therapy, and correction of the acidosis, potassium values plummet. Total body depletion of phosphorus and magnesium are extremely common, while calcium depletion may also be present.

Serum BUN and creatinine are commonly elevated by intravascular volume deficit-induced decreases in glomerular filtration rate (GFR). Amylase and lipase values may be elevated for the same reasons. Elevations in ALT and cholesterol are common. Leukocytosis may occur in the absence of infection.

Ancillary diagnostics (abdominal ultrasound, thoracic radiographs, urine culture, Spec cPl / fPl, FeLV/FIV tests) may be necessary to evaluate for comorbidities, and should be tailored to the individual patient. Urine cultures are advised, regardless of sediment examination findings.

TREATMENT

The most important aspects of DKA therapy are adequate fluid replacement, insulin administration, close monitoring of biochemical parameters, and diligent record keeping. Prompt restoration of intravascular volume should occur with infusions of glucose-free, isotonic crystalloid (Plasmalyte®, Normosol-R®, etc.) in patients with evidence of hypoperfusion. Despite traditional teachings, the author does not recommend the use of 0.9% NaCl, reasoning discussed below. In patients with DKA and hypotension refractory to repletion of volume, one should consider bleeding (gastrointestinal), sepsis, or third spacing (pancreatitis, etc.). Following initial resuscitation, the aim should be to restore the remaining volume deficit (dehydration) within 24 hours - exact fluid rate is determined by level of dehydration, maintenance fluid requirement and ongoing losses. Fluid choice and rate are determined by admitting parameters, with subsequent changes guided by serial physical examinations, urine output and frequent electrolyte measurements.

Insulin therapy is *essential* to reverse the metabolic derangements (lipolysis, ketogenesis, and hyperglycemia). This is equally true for euglycemic DKA (eDKA) patients, despite their normal blood glucose values. In the absence of hypokalemia or hypophosphatemia, short-acting insulin is routinely started within 1-4 hours of starting fluid replacement. Regular insulin is administered by intermittent intramuscular injections or by an insulin infusion, with the latter being titrated by infusion pump for accurate delivery.

Rate of regular insulin infusion: canine = 1-2 units/kg/day felines = 1 unit/kg/day

The author starts at lower rates, especially in cats, to avoid unintended, precipitous drops in glucose levels. The initial goal should be to reduce plasma glucose by 35 to 75 mg/dl/hr, with a goal of maintaining serum glucose levels between 180 to 250 mg/dl. Initially, blood glucose measurements should occur at 1- to 2- hour intervals to guide rate of insulin and fluid administration. Alternatively, newer subcutaneous interstitial glucose monitoring devices are available. Failure of glucose to decline significantly within 2-3 hours should prompt an increase in insulin rate. As glucose levels stabilize over the first 12-24 hours, intervals between laboratory sampling become longer. Lipolysis is controlled *before* glycemic control is achieved, spurring metabolism of the ketone bodies. Insulin infusions should be continued until the ketoacidosis resolves even if supplemental glucose must be used to prevent hypoglycemia. In the author's experience, the latter is rarely necessary. Published data describes combined subcutaneous and intramuscular glargine injections to treat feline DKA cases, but the value of this over regular insulin protocols is rightfully questioned.

Clearance of ketoacids, and the metabolic acidosis that they cause, can be simply tracked by a rise in the serum bicarbonate and a fall in the anion gap (signifying metabolism of the ketone bodies). The latter, is the single best indicator of successful therapy. While the serum bicarbonate may also be used, this may be less reliable if isotonic saline is used for fluid replacement, as this produces a hyperchloremic acidosis. This can keep the bicarbonate from rising, despite a resolving ketoacidosis. In this situation, the *pattern* of the acidosis is changing from a high anion gap acidosis to a nonanion gap (hyperchloremic) acidosis. The metabolic acidosis rarely, if ever, requires specific therapy and corrects with volume expansion and insulin therapy. Even with severe academia (pH <7.0), there is no proven advantage to using bicarbonate therapy.

Some advocate delaying conversion to long-acting insulin until after ketonuria resolves (occurs after resolution of the acidosis), but in most patients this unnecessarily prolongs hospital stay and cost of care. Instead, once the patient is eating well (generally occurs as anion gap resolves) the transition may be scheduled. It is advised to continue the insulin infusion for 2-4 hours after the first dose of long-acting insulin, to avoid a "rebound" hyperglycemia.

Arrhythmias induced by acid-base and electrolyte disturbances are a major preventable cause of morbidity in DKA. Therefore, after adequate urine flow is established, potassium should be administered to most DKA patients. Potassium supplementation should occur at a rate roughly 10-20 mEq/L higher than standard KCl supplementation recommendations. Refractory hypokalemia should prompt the clinician to rule out hypomagnesemia. Hypophosphatemia may decreased 2,3-diphosphoglyceric acid (2,3-DPG) levels, muscle strength, and ATP levels (cause for hemolysis). However, while routine in veterinary medicine to provide prophylactic phosphate supplementation (incompatible with calcium-containing solutions), this has yet to be shown in humans to improve outcome. Risks of phosphate therapy include acute hypocalcemia and tissue deposition of calcium-phosphate complexes, occasionally inducing acute renal failure. Hypoglycemia, a common complication of aggressive DKA therapy, may be prevented through vigilant monitoring.

Successful resolution of the ketoacidosis, also requires successful treatment of comorbidities. This may prove challenging, as the requirements may be diametrically opposed to those necessary for treatment of the hyperglycemic syndrome.

The complications of the treatment itself must also be addressed and may include hypokalemia, hypophosphatemia, sustained hyperglycemia, hypoglycemia, iatrogenic hyperchloremic metabolic acidosis, fluid overload and cerebral edema.

Avoiding rapid decreases in blood glucose levels, and therefore osmolality, may help limit onset of cerebral edema (altered mentation, seizures, etc.). While cerebral edema was once thought to be caused by abrupt alterations in osmolality, in the face of slowly declining levels of idiogenic osmoles, other theories (cerebral ischemia /hypoxia, etc.) have surfaced. Nevertheless, a patient's seizures are not attributed to hypoglycemia, administration of mannitol (0.5-1.0 g/kg) intravenously, over 20-30 minutes, should be considered to limit cerebral edema.

HYPEROSMOLAR HYPERGLYCEMIC SYNDROME

HHS is a disorder of glucose metabolism in which plasma osmolality is dramatically elevated (often > 350 mOsm/L) by profound increases in plasma glucose concentration (typically > 540 mg/dl, often > 1000 mg/L). The main differentiation of HHS, compared to DKA, is not only the presence of at least some insulin (sufficient to prevent ketone formation, but insufficient to prevent hyperglycemia) and more variable levels of counter-regulatory hormones, but also commonly the presence of renal dysfunction. Renal dysfunction (decreased GFR) and impaired renal tubular function result in less capacity to deal with high solute and osmotic loads (compensatory glucosuria is overwhelmed). Despite the development of marked depletion of total body water, the osmotic effects of high blood glucose levels help maintain intravascular volume. Although the intravascular volume is usually better preserved in HHS than in DKA, it is usually at the expense of the intracellular compartment. This, together with impaired water intake (due to age, underling disease, etc), results in profound dehydration. This effect is responsible for the primary clinical expression of HHS – life-threatening impairment of the neurologic function. Unlike DKA, where the accumulating ketones stimulate ventilation, HHS patients are often minimally symptomatic initially and maintain near-normal acid-base status for long periods of time. It is not until profound volume depletion limits organ function, that these patients present for medical attention.

Laboratory features of HHS are similar to those of DKA, but differ somewhat in degree, such that serum glucose values are higher (producing the marked hyperosmolarity that characterizes this disorder), serum sodium levels may be normal, markers for renal dysfunction are worse, while the ketoacidosis is absent or minimal (metabolic acidosis is absent or not as severe, anion gap is normal, ketonemia/ketonuria absent or minimal).

Since the osmotic effect of glucose is required to maintain intravascular volume, insulin administration before restoring circulating volume with isotone crystalloid can cause sudden and profound hypotension by producing a rapid shift of glucose and water into cells. Total body deficits of potassium and phosphorus are as common in HHS as in DKA, although at presentation potassium and phosphorus levels are usually normal or even modestly elevated.

Correction of HHS must be cautious, as abrupt reversal of serum hyperosmolarity may produce intracellular water intoxication manifested by dysphoria and seizures. Despite differences in pathophysiology, the treatment of HHS is similar to that of DKA – initial restoration of circulating volume with isotonic crystalloid, followed by complete fluid replacement over 36-72hours (slightly more prolonged). Insulin therapy should be initiated only after circulating volume has been repleted (as evidenced by stable blood pressure, adequate urine output and possibly reduction in heart rate). Insulin administration and free water repletion should be guided by serial electrolyte and glucose measurements.

REFERENCES

Available upon request