Management of Diabetic Ketoacidosis in the Emergency Department

Naomi Fogel, MD, Donald Zimmerman, MD

Diabetic ketoacidosis (DKA) is a potentially fatal complication of diabetes mellitus (DM). It results from insulin deficiency and from an associated increase in the counterregulatory hormones glucagon, cortisol, growth hormone, and catecholamines. Diabetic ketoacidosis is characterized by hyperglycemia and by increased lipolysis and fatty acid oxidation. These pathophysiologic changes lead to metabolic acidosis, severe fluid and electrolyte imbalances, and dehydration.

Epidemiology

Up to 67% of DKA patients have previously undiagnosed type 1 DM and are presenting with DKA.1 Diabetic ketoacidosis at onset of diabetes is more common in children from families of lower socioeconomic status, in young children, and in those children who do not have a first-degree relative with type 1 DM.1 Approximately 1% to 10% of patients with known type 1 diabetes develop DKA each year.1 The risk of DKA is increased in children with poor metabolic control or in those with previous episodes of DKA, in adolescent girls, in children with psychiatric disorders (including eating disorders), and in those with lower socioeconomic status or lack of health insurance.2-4 Diabetic ketoacidosis is also more common in children on insulin pump therapy, as only short-acting insulin is used in pumps. Because of the use of short-acting insulin in insulin pumps, any interruption of insulin
delivery will quickly lead to insulin deficiency. Diabetic ketoacidosis accounts for approximately 65% of hospital admissions for patients with diabetes younger than 19 years.1

**PATHOPHYSIOLOGY**

An absolute or relative insulin deficiency, along with increased counterregulatory hormones, is the basis for DKA. Absolute insulin deficiency occurs in new-onset type 1 DM or in previously diagnosed patients who omit insulin doses, either intentionally or accidentally. Relative insulin deficiency occurs due to increased counterregulatory hormones in response to stress from trauma, infection, or other systemic illness.

Low serum insulin and elevated counterregulatory hormones result in increased glucose production by the liver and kidney and impaired peripheral glucose utilization. Increased glucose production and decreased glucose utilization lead to hyperglycemia and hyperosmolality. At the same time, increased lipolysis and ketogenesis cause ketonemia and metabolic acidosis. The hyperglycemia, when it exceeds the renal threshold of approximately 180 mg/dL, in combination with the ketonemia, leads to osmotic diuresis, dehydration, and loss of electrolytes. As the glomerular filtration rate decreases due to increasing dehydration, glucose and ketone clearance is impaired, thus worsening the hyperglycemia and acidosis. These metabolic changes further stimulate stress hormone production, resulting in increased insulin resistance and worsening hyperglycemia and hyperketonemia.

**LABORATORY FINDINGS**

The laboratory tests diagnostic for DKA include hyperglycemia (serum glucose >250 mg/dL), acidosis (venous pH <7.3, or serum bicarbonate ≤ 15 mEq/L) and ketonemia/ketonuria. There is an increased anion gap in DKA, due to the ketoacids, β-hydroxybutyrate, and acetoacetate. Other significant laboratory values include an increased leukocyte count with left shift, which occurs in response to stress hormones (catecholamines and glucocorticoids) and is not necessarily an indication of infection. Blood gases may show hypocarbia due to a partial respiratory compensation for acidosis. The effective osmolality of the extracellular fluid compartment is high in DKA, often in the range of 300 to 350 mOsm/L.2 The effective osmolality is calculated using the equation (2 [Na + K] + glucose). This calculation may serve as a useful way to monitor resolution of DKA and to guide fluid and electrolyte therapy.

**MANAGEMENT OF DKA**

**Initial Stabilization**

The basic approach in DKA aims to restore circulatory volume, treat insulin deficiency and slow ketone production, and to resolve electrolyte abnormalities. Immediate actions to take upon suspicion of DKA include the following:

- Weigh the patient and determine body surface area.
- Assess degree of dehydration.
- Assess level of consciousness.
- Obtain vascular access with 2 catheters.
- Obtain blood for laboratory tests: venous blood gas, serum glucose, electrolytes including calcium and phosphorus, blood urea nitrogen (BUN), creatinine, and complete blood count.
- Obtain a urine sample for urinalysis.
- Place on cardiac monitor to assess T waves for signs of hypokalemia or hyperkalemia.
- Provide airway management support as needed.

Further management guidelines, largely based on the 2004 consensus statement by the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society, are discussed below.2
Fluids
Fluid administration should begin before the administration of insulin. Patients with DKA are generally thought to be approximately 7% to 10% dehydrated at presentation. This may be an overestimate, as studies have shown that attempts to estimate dehydration in DKA based on clinical signs are not accurate. Dehydration itself adds to the acidosis through lactic acid production and decreased renal clearance of acids. It also contributes to the hyperglycemia by decreasing the renal clearance of glucose. In fact, much of the initial decrease in serum glucose after treatment is initiated is related to rehydration and an increased glomerular filtration rate.

An initial fluid bolus should be given immediately with an isotonic solution at a volume of 10 to 20 mL/kg for 1 to 2 hours, depending on circulatory status. Subsequent fluids should be calculated to replace the fluid deficit evenly for 48 hours, at a rate of 1.5 to 2 times the maintenance rate. Shock with hemodynamic changes is rare in DKA, but if present, it should be treated accordingly to restore peripheral circulation. The current guidelines recommend fluid replacement with a solution equal to or greater than 0.45% saline. Using hypotonic solutions with a large amount of free water may lead to rapid changes in osmolality due to intracellular fluid shifts. There is concern that using hypotonic fluids may increase the risk of cerebral edema (CE), though this has not been definitively proven.

Insulin
Rehydration alone improves tissue perfusion and renal function; it also improves clearance of glucose and ketones. However, insulin is absolutely necessary to suppress lipolysis and ketogenesis. The administration of insulin stops production of ketones and allows for their metabolism. This, in turn, results in the production of bicarbonate (HCO₃⁻) and improvement in acidemia.

Continuous intravenous insulin administration is the standard of care in DKA, starting at a dose of 0.1 U/kg/hr. If intravenous administration is not possible, subcutaneous or intramuscular routes may be used, but absorption will likely be impaired due to poor perfusion related to dehydration. An intravenous bolus of insulin is not necessary before initiation of continuous insulin infusion. Insulin administration should begin after the initial fluid bolus is completed so that insulin-induced reduction in extracellular osmolality does not further reduce an already tenuous circulating volume. The insulin dose should usually remain at 0.1 U/kg/hr at least until ketoacidosis has resolved, as evidenced by pH > 7.3 and HCO₃⁻ > 15 mmol/L. Exceptions to this include excessive lowering of blood glucose despite use of fluids with relatively high concentrations of dextrose (eg, 12.5% dextrose). It is generally recommended that the plasma glucose concentration decrease by 50 to 100 mg/dL every hour. To prevent a rapid drop in glucose level and possible hypoglycemia, dextrose should be added to the intravenous fluids when the plasma glucose reaches approximately 250 to 300 mg/dL. If blood glucose decreases too quickly or if levels fall too low before acidosis has resolved, the amount of glucose administered should be increased. It may be necessary to use dextrose concentrations as high as 12.5% to prevent hypoglycemia during insulin infusion. If necessary to avoid hypoglycemia, the rate of fluid administration may subsequently be increased.

The insulin infusion rate should generally not be decreased until acidosis is resolved. Once the bicarbonate level approaches normal, the insulin infusion may be decreased in increments of 0.02 U/kg/hr to maintain plasma glucose between 100 and 200 mg/dL.

Sodium
The measured serum sodium level is generally low in DKA, due to the osmotic effects of glucose. The high effective osmolality of the extracellular fluid compartment and restriction of glucose to the extracellular space result in a shift of water from the intracellular to the extracellular fluid compartment. This causes a decrease in the measured serum sodium concentration.

During DKA therapy, it is important to monitor the corrected sodium value, which should remain relatively stable. A commonly used correction factor is 1.6 mmol/L decrease in serum sodium concentration per 100 mg/dL (5.6 mmol/L) increase in blood glucose concentration above normal. The sodium level can therefore be corrected by using the formula: corrected Na = measured Na + [0.016 × (glucose − 100)]. As the plasma glucose decreases with insulin and fluid therapy, the measured sodium value should increase in accordance with the above formula. If the measured serum sodium level does not rise, or declines further with therapy, this may be a predictor of CE.

Potassium
Diabetic ketoacidosis is characterized by total body potassium depletion due to hypertonicity, insulin deficiency, and intracellular buffering of...
hydrogen ions. At presentation, serum potassium levels may be normal, increased (due to poor renal function and acidosis), or decreased (due to urinary losses). Insulin administration will drive potassium back into the cells and decrease serum levels. Unless the initial potassium value is elevated (above 5.5 mEq/L), potassium should be added to the intravenous fluids at the same time that insulin therapy is started. It should be administered at a concentration of 40 mEq/L, generally half in the form of potassium acetate and half as potassium phosphate, both to correct the phosphate deficit and to limit the amount of chloride given.

**Phosphate**

Phosphate is lost in DKA due to osmotic diuresis, due to phosphate buffering of accumulated acid caused by depletion of intracellular phosphate. As insulin drives phosphate into the cells, there is a further drop in plasma phosphate levels. The clinical consequences of this are unclear and unproven. Theoretical possibilities include phosphate's shifting the oxygen-hemoglobin dissociation curve to the right by increasing production of erythrocyte 2,3-diphosphoglycerate and the role of phosphate in contributing to adequate energy production in respiratory muscles. Most emergency physicians, intensivists, and endocrinologists recommend phosphate therapy as potassium phosphate in intravenous fluids. The caveat in the use of phosphate is the possibility that circulating calcium levels will be excessively lowered; thus, periodic measurement of calcium and phosphorus is advised.

**Bicarbonate**

The indications for bicarbonate therapy in DKA are unclear, and under most circumstances, there are actually compelling arguments against it. Controlled trials have shown no clinical benefit from the administration of bicarbonate. In fact, the use of bicarbonate in children with DKA has been associated with an increased risk of CE. Bicarbonate administration may cause a paradoxical central nervous system (CNS) acidosis. It combines with hydrogen ions and then dissociates to CO₂ and H₂O. Though bicarbonate does not freely diffuse into the cerebrospinal fluid, CO₂ does diffuse into the cerebrospinal fluid increasing the concentration of carbonic acid. Consequently, the use of bicarbonate may worsen acidosis in the CNS, whereas serum acidosis improves. Furthermore, rapid correction of acidosis may cause hypokalemia and may increase the sodium load, thereby increasing hypertonicity. It may also increase hepatic ketone production.

There are some patients who may benefit from bicarbonate therapy. These are patients with severe acidemia (arterial pH <6.9), in whom the acidosis adversely affects cardiac function, and patients with severe hyperkalemia and electrocardiogram changes.

**CONTINUED MANAGEMENT AND MONITORING**

Children with signs of severe DKA (shock, mental status changes) or children who are at increased risk for CE (children younger than 2 years, those with an initial pH less than 7.0) should be transferred to a pediatric intensive care unit. Vital signs, intake and output, and capillary blood glucose should be monitored hourly. Venous blood gases, electrolytes, serum glucose, and urine ketone measurements should be repeated every 2 to 4 hours. A flow sheet is helpful to track response to therapy and to allow for adjustments based on biochemical and clinical patterns. Neurologic status should be monitored hourly, specifically looking for signs or symptoms of CE.

**COMPLICATIONS**

The mortality rate for DKA has been reported to range between 0.15% to 0.31% in population-based studies. Cerebral edema is a leading cause of morbidity and mortality in DKA. Other causes of morbidity and mortality are hypokalemia, hyperkalemia, hypophosphatemia, hypoglycemia, other CNS complications, sepsis, venous thrombosis, and pulmonary edema.

**Cerebral Edema**

Cerebral edema occurs in 0.46% to 0.87% of DKA cases, according to population-based studies. It carries a mortality rate of 40% to 90% and accounts for approximately 50% to 80% of all diabetes-related deaths. Up to 35% of survivors of CE have lasting morbidity. Cerebral edema is more common in children with severe DKA, new-onset type 1 DM, younger age, and longer duration of symptoms. It may occur at any time in the course of DKA. Most commonly, symptoms begin 4 to 12 hours after treatment begins, but CE can occur before treatment even commences or at any other time during the course of treatment. Some studies have shown that all
patients with DKA have some degree of CE, though it is generally subclinical.\textsuperscript{18-20} Children who exhibit signs of CE usually do so early enough to allow intervention.\textsuperscript{1} Initial computed tomographic (CT) scans are often reported as normal, so the diagnosis must be made based on clinical parameters. Signs of CE include mental status changes, headache, gradual decrease in level of consciousness, decrease in oxygen saturation, inappropriate slowing of heart rate, and increase in blood pressure.\textsuperscript{5}

Treatment of CE should begin as soon as it is suspected. Fluid administration should be reduced. Mannitol has not been shown to have any definite effects, beneficial or harmful, in retrospective studies,\textsuperscript{21} but in case reports, it has demonstrated possible benefit.\textsuperscript{2} Mannitol should therefore be available at the bedside during DKA therapy and should be administered at a dose of 0.25 to 1 g/kg over 20 minutes in patients with signs of CE. It may be repeated after 2 hours if there is no response. Hypertonic saline may also be used. Intubation may be necessary, but hyperventilation should be avoided because it has been associated with poor outcomes.\textsuperscript{21} Once treatment for CE has started, a CT scan of the head should be obtained. The purpose of the scan is to rule out other causes of neurologic deterioration (thrombosis or hemorrhage) rather than to specifically rule in CE, as CT scans may be normal.

Despite many studies, there is no consensus as to the mechanism of CE in DKA, and it remains poorly understood. The traditional theory implicates the rate and volume of fluid administration. This theory states that during the development of DKA, the chronic hyperosmolarity causes cerebral cells to store intracellular “idiogenic” osmoles (taurine and myo-inositol) to equalize the osmolality and thus avoid losing water. As the plasma glucose concentration declines with therapy, the cytosolic osmolality in the brain becomes comparatively high and pulls water into the cells by osmosis. This leads to swelling of the cells and CE. Based on this theory, the conventional accepted protocol (as reflected in the guidelines above) is to utilize cautious hydration.

Many researchers have attempted to validate this theory, mostly with retrospective studies of risk factors related to fluid administration. Some of the proposed risk factors and related evidence are as follows:

- There has been little evidence to associate the volume of intravenous fluids, the sodium content of intravenous fluids, or the rate of change in serum glucose, with an increased risk for CE.\textsuperscript{6,7,22,23} A large study of 6977 children with DKA that matched 61 cases of CE with 6 controls each found no association between CE and rates of fluid, insulin, and sodium administration.\textsuperscript{5}
- Failure of the measured serum sodium level to increase, and/or a fall in the calculated sodium level, during therapy is thought to increase the risk for CE.\textsuperscript{6,8-11}
- Bicarbonate therapy has been found to be associated with an increased risk of CE.\textsuperscript{6}
- CE is associated with higher serum BUN concentrations at presentation.\textsuperscript{6}
- One study showed an association between increased acidosis and development of CE.\textsuperscript{24}
- Two studies have associated CE with greater hypocapnia at presentation, after adjusting for degree of acidosis.\textsuperscript{6,7}

Many of the above studies are difficult to interpret due to their retrospective nature, lack of controls, and the presence of other confounding variables.\textsuperscript{8} Furthermore, most of the proposed risk factors are conditions that indicate a more critically ill patient. Consequently, an increased risk of CE may be related to being sicker at presentation.

Another theory for the development of CE is the vasogenic theory, which suggests that this occurs as a response to vasoconstriction and ischemia from dehydration. Some of the validated risk factors, such as hypocapnia and increased BUN concentration, are known to decrease perfusion to the brain and therefore support this theory.\textsuperscript{6} A study that used magnetic resonance imaging with diffusion and perfusion-weighted imaging demonstrated increased apparent diffusion coefficient during DKA treatment, which suggests an expanded extracellular space and vasogenic edema.\textsuperscript{20} A larger study by the same group confirmed these findings and showed that CE is related to cerebral hypoperfusion before treatment, with vasogenic edema developing during reperfusion.\textsuperscript{25}

Overall, though numerous risk factors related to both clinical and treatment variables have been suggested, no one factor can be fully implicated in the development of CE. Cerebral edema may be fundamentally related to the severe metabolic disturbances of DKA themselves, rather than other variables.\textsuperscript{5,26} Thus, emergency department physicians should focus on early recognition of ketoacidosis, prompt initiation of established treatment protocols, and careful monitoring of clinical and biochemical parameters, with the goal of avoiding morbidity and mortality.
**SUMMARY**

Diabetic ketoacidosis is a manifestation of uncontrolled DM and poses significant risks of morbidity and mortality. It must be suspected in patients with known DM who present with polyuria, polydipsia, vomiting, abdominal pain, and disturbed consciousness. Treatment with fluids, insulin infusion, and careful monitoring are described. Also discussed are diagnosis and treatment of CE complicating this condition.

**REFERENCES**