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Management of Diabetic Ketoacidosis

Elisabeth Donahey, PharmD, BCPS
Stacey Folse, PharmD, MPH, BCPS

ABSTRACT
Diabetes, a chronic medical condition, continues to increase in prevalence. One of the most severe complications of diabetes, diabetic ketoacidosis (DKA), results from insulin deficiency and is a medical emergency that is frequently encountered in the emergency department. Prompt diagnosis, assessment of key laboratory values, appropriate treatment, and close monitoring are important to the successful treatment of this complex metabolic disorder. Fluid repletion and insulin administration are mainstays of DKA treatment and serve to restore normal hemodynamic status while decreasing the metabolic acidosis. Careful monitoring of glucose concentrations, vital signs, and electrolytes is essential to prevent complications arising from the treatment of DKA. This article provides an overview of the pathophysiology, presentation, diagnosis, treatment, monitoring, and complications of DKA. **Key words:** diabetes complications, diabetic ketoacidosis, diabetes mellitus

DIABETES is a chronic condition that affects 25.8 million people (8.3%) in the United States. Of these, 7 million cases are undiagnosed. Diabetes continues to increase in prevalence, with the most recent data indicating that 1.9 million people were newly diagnosed in 2010 (Centers for Disease Control and Prevention, 2010). Two of the most serious and life-threatening complications of diabetes are diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state. This review focuses on the management of DKA.

Diabetic ketoacidosis is an acute metabolic emergency, and affected patients most commonly present with hyperglycemia, anion gap metabolic acidosis, and hyperketonemia. The majority of patients who present with DKA have Type 1 diabetes, whereas approximately one third of patients have Type 2 diabetes (Kitabchi, Umpierrez, Miles, & Fisher, 2009). The annual incidence of DKA is estimated to be between five and eight episodes per 1,000 diabetic patients and results in approximately 68,000 emergency department (ED) visits per year (Ginde, Camargo, & Pelletier, 2006; Kitabchi et al., 2001; Wilson, 2010; Charfen & Fernandez-Frackelton, 2005). The mortality rate associated with DKA is less than 5%, with the highest mortality occurring in elderly individuals and those with myocardial infarction and pneumonia (Wilson, 2010).

Author Affiliations: *Emory University Hospital; and Mercer College of Pharmacy and Health Sciences, Atlanta, GA.*

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Corresponding Author: *Stacey Folse, PharmD, MPH, BCPS, Emory University Hospital, 1364 Clifton Road, Atlanta, GA 30322 (stacey.folse@emoryhealthcare.org).*

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Therefore, an understanding of the pathophysiology and appropriate identification and treatment of this disease state is of great importance in the ED.

PATHOPHYSIOLOGY

The inciting factors for developing DKA include infection, noncompliance, previously undiagnosed diabetes, pancreatitis, myocardial infarction, stroke, and medications. Although previously undiagnosed diabetes accounts for approximately 20% of presentations, infection remains the most common precipitating event for adults (Kitabchi et al., 2001; Thewjitcharoen & Sunthornyothin, 2011). In contrast, pediatric patients have a high incidence of insulin noncompliance (unintentional or purposeful) leading to DKA (McFarlane, 2011).

Regardless of the inciting factor, the pathophysiology of DKA consists of insulin deficiency, which leads to decreased cell utilization of glucose. Insulin deficiency may be a consequence of insulin insufficiency and/or insulin resistance. Another important component is increased production of counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone. This, in conjunction with insulin deficiency, results in ketosis and accelerated glycogenolysis and gluconeogenesis, leading to hyperglycemia (Koul, 2009). Hyperglycemia causes an increase in serum osmolality, which, in combination with decreased insulin, results in osmotic diuresis. This diuresis leads to many of the electrolyte abnormalities observed in DKA, namely, sodium, potassium, calcium, magnesium, chloride, and phosphate abnormalities. Osmotic diuresis can cause hypovolemia, which can be profound and may lead to decreased perfusion of organs including the kidneys (Defronzo, Cooke, Andres, Faloona, & Davis, 1975; Kitabchi et al., 2001). Finally, decreased insulin action along with hormone alterations leads to lipolysis and free fatty acids are released. In the liver, free fatty acids are metabolized to ketone bodies. The accumulation of ketone bodies results in an anion gap metabolic acidosis characteristic of DKA.

CLINICAL PRESENTATION AND DIAGNOSIS

As previously discussed, the clinical presentation of DKA typically includes hyperglycemia (blood glucose concentration over 250 mg/dl), hyperketonemia, and acidosis (pH or lower), which are manifested in patients' presenting signs and symptoms. Patients may complain of nausea, vomiting, and abdominal pain from metabolic disturbances, which typically develop within 24 hours (Kitabchi et al., 2009; Wilson 2010). Patients may also convey a history of recent polydipsia and polyuria due to hypovolemia and osmotic diuresis (Kitabchi et al., 2009; Wilson 2010). In addition, there may be signs of hemodynamic instability displayed as hypotension and/or tachycardia due to hypovolemia. Signs and symptoms of an infection that triggered the episode, such as leukocytosis and hypothermia as a result of vasodilation, may be evident. Upon physical examination, the patient's breath may have a fruity odor, resulting from ketonemia, and Kussmaul respirations (i.e., rapid, deep sighing breaths) may be noted as result of acidosis. In addition, the patient may present with altered mental status, ranging from lethargy and confusion to coma (Kitabchi et al., 2009; Wilson 2010; Wolfsdorf, et al., 2007).

Diabetic ketoacidosis can cause multiple laboratory abnormalities. Table 1 lists common laboratory values associated with DKA. One of the hallmark laboratory abnormalities associated with DKA is an anion gap metabolic acidosis. Table 2 lists the potential causes of anion gap metabolic acidosis. The anion gap can be calculated as shown in Figure 1, with an anion gap present if the calculated value is more than 10 mEq/L (Kitabchi et al., 2001).

Apart from laboratory abnormalities, patients may or may not have a prior diagnosis of diabetes (Type 1 or Type 2) but may have risk factors for developing diabetes (i.e., family history, history of glucose intolerance,

Table 1. Common laboratory values associated with DKA

Laboratory	DKA value
Blood glucose (mg/dl)	>250
Arterial pH	≤7.30
Anion gap	>10
Serum bicarbonate (mEq/L)	≤18
Urinalysis	Ketones, glucose present
Serum creatinine	Often elevated
Serum sodium	Often elevated or normal
Serum potassium	Often elevated or normal
Serum phosphate	Often elevated or normal
White blood cell count	Mildly elevated

Note. DKA = diabetic ketoacidosis.

history of gestational diabetes, etc.). If the diagnosis of DKA is unclear, differential diagnoses should be ruled out. An important consideration in the diagnosis of suspected DKA includes infection, which should be worked up in the initial evaluation. Vital signs may not be a reliable indicator of infection, as hypotension, tachycardia, and body temperature may be confounded by DKA (Kitabchi et al., 2009). Therefore, it is essential to gather information with a focus on potential infectious causes. Two of the most common infectious causes are pneumonia and urinary tract infection; evaluation of a chest radiograph, complete blood cell count, urinalysis, and urine culture are warranted (Kitabchi et al., 2001). As listed earlier, a patient with DKA may present with abdominal pain due to metabolic disturbances; however, abdominal pain can also suggest intra-abdominal infection. If the pain does not improve within 24 hours of initiating therapy, other sources of abdominal pain should be evaluated.

Table 2. Causes of anion gap metabolic acidosis (CAT MUDPILES)

Carbon monoxide poisoning
Alcoholic ketoacidosis
Toluene toxicity
Methanol intoxication
Uremia
Diabetic ketoacidosis
Paraldehyde toxicity
Propylene glycol toxicity
Iron toxicity
Isoniazid toxicity
Lactic acidosis
Ethanol toxicity
Ethylene glycol intoxication
Salicylate toxicity

MONITORING

Careful monitoring of the DKA patient is essential for providing optimal patient care. The 2009 American Diabetes Association (ADA) consensus statement recommends monitoring blood glucose concentrations every 1–2 hours in DKA. Point-of-care glucose testing may be used, especially at the initiation of insulin infusion therapy. After initial laboratory workup, monitoring of serum electrolytes, venous pH, blood urea nitrogen, and serum creatinine should occur every 2–4 hours (Kitabchi et al., 2009). Continuous cardiac monitoring is also recommended, as changes in serum potassium concentrations may result in cardiac rhythm abnormalities. In patients with renal and/or cardiac dysfunction, urine output, mental status, vital signs, and serum osmolality should be monitored carefully during rehydration, as volume overload may occur (Kitabchi et al., 2009).

TREATMENT

Fluid Resuscitation

The first and most essential treatment of DKA is fluid resuscitation. Fluid resuscitation serves several functions, including clearance of ketones and other by-products of DKA, restoring blood flow to vital organs, and correcting electrolyte imbalances (Savage,

$$Anion\ gap = Na^{+}\left(\frac{mEq}{L}\right) - \left(Cl^{-}\left[\frac{mEq}{L}\right] + HCO_3^{-}\left[\frac{mEq}{L}\right]\right)$$

Figure 1. Formula to calculate anion gap.

2011). The type of fluid used for resuscitation may vary according to the patient's serum sodium concentration, which needs to be corrected for hyperglycemia using the formula given in Figure 2 (Katz, 1973).

Initial fluid repletion in adults includes 0.9% NaCl administered at 15–20 ml/kg/hr over the first hour, or a total of 1–1.5 L in the first hour, in the absence of cardiac dysfunction. Further choice of intravenous fluids should be based on serum sodium concentration; patients with a normal or elevated corrected serum sodium concentration may receive 0.45% NaCl, whereas patients with a lower than normal serum sodium concentration should continue to receive 0.9% NaCl. Estimated fluid deficits should be repleted over the initial 24 hours (Kitabchi et al., 2009). In either patient population, appropriate volume resuscitation may be monitored using blood pressure, heart rate, and urine output.

Conversely, pediatric patients should have their volume repleted evenly over the initial 48 hours, and if fluid boluses are needed to improve systemic perfusion at initial presentation, 0.9% NaCl or lactated Ringer's may be given at 10–20 ml/kg over 1–2 hours (Wolfsdorf et al., 2007). The initial volume repletion should not exceed 50 ml/kg over the first 4 hours (ADA, 2004). Following initial volume resuscitation, 0.9% NaCl may be replaced with 0.45% NaCl with added potassium, depending on serum sodium and potassium concentrations (Wolfsdorf et al., 2007). Pediatric DKA patients may require up to 1.5 times the usual 24-hours maintenance fluid requirements (based on weight); however, fluid repletion generally should not exceed 1.5–2 times the usual daily maintenance fluid requirements. With fluid resuscitation, decreases in serum osmolality should not exceed 3 mOsm/kg/hr. Excessive fluid repletion in pediatrics may lead to cerebral edema, a potentially fatal complication (ADA, 2004).

Initial goals of fluid resuscitation include restoration of circulating volume and increased urine output, which should be monitored continuously. Once urine output has improved from initial presentation and serum potassium concentration is known and not elevated (not greater than 5–5.2 mEq/L), resuscitation fluids should include 20–30 mEq/L of potassium (Kitabchi et al., 2009). When blood glucose concentrations reach 250 mg/dl or lower, depending on the patient's clinical status and laboratory values, 5% dextrose should be added to maintenance fluids to avoid hypoglycemia.

Insulin

Insulin is the mainstay of therapy for DKA. Administration of insulin allows cellular utilization of glucose, which decreases ketosis and blood glucose concentrations. However, because insulin also results in an intracellular shift of potassium, it is essential to obtain the patient's serum potassium concentration before administering insulin. If the serum potassium concentration is less than 3.3 mEq/L, repletion of potassium should occur prior to any insulin therapy, as insulin will serve to further decrease serum potassium concentrations (Kitabchi et al., 2001). Once the serum potassium concentration is above 3.3 mEq/L, insulin infusion therapy may be initiated.

The 2009 ADA consensus statement recommends either beginning with an insulin

$$Corrected\ Na\ (mEq) = Measured\ Na + \left(\left[\left(Measured\ blood\ glucose\ \left[\frac{mg}{dl}\right] - 100\right) \div 100\right] \times 1.6\ mEq\right)$$

Figure 2. Formula for correction of serum sodium.

bolus of 0.1 units/kg or beginning an infusion of insulin at a rate of 0.14 units/kg/hr, without a bolus in adults. Boluses are not recommended in pediatric patients (Kitabchi et al., 2009). If a bolus is used for an adult patient, it should be followed by a continuous infusion of insulin at a rate of 0.1 units/kg/hr. If the patient's blood glucose concentration does not decline by at least 10% of the original value in the first hour, a bolus of 0.14 units/kg may be given (Kitabchi et al., 2009). In pediatric patients, continuous infusion of insulin should begin 1–2 hours after initial fluid resuscitation (Wolfsdorf et al., 2007). For patients with excessive insulin sensitivity, it may be necessary to start the infusion of insulin at a lower or higher rate than recommended. In particular, the initial infusion rate for pediatric patients may need to be decreased to 0.05 units/kg/hr. Frequent injections of subcutaneous insulin may be used in place of continuous infusions, especially in mild DKA. However, continuous infusions are preferred because of faster onset, ability to titrate, and shorter half-life (Kitabchi et al., 2009; Kitabchi, Umpierrez, Fisher, Murphy, & Stentz, 2008). Blood glucose concentrations should decline by 50–75 mg/dl/hr in adults. If this does not occur, the infusion rate of insulin may be increased hourly to achieve a steady decline of blood glucose concentration. Once blood glucose concentrations fall below 200 mg/dl, it may also be appropriate to decrease the infusion of insulin to 0.02–0.05 units/kg/hr to prevent hypoglycemia.

When initial volume resuscitation has been achieved, insulin is the one treatment that will close the anion gap. Therefore, it is essential that the infusion of insulin be continued until the anion gap is closed. When blood glucose concentrations fall below 250 mg/dl, 5% dextrose should be added to maintenance fluids in order to maintain blood glucose between 150 and 200 mg/dl (Kitabchi et al., 2009). This will prevent hypoglycemia and ensure that insulin therapy can be continued while there is still an anion gap acidosis. If 5% dextrose in maintenance fluids is insufficient to prevent blood glucose concentrations from falling below 150 mg/dl, 10% or 20% dextrose concentration may be used (Wilson, 2010).

Diabetic ketoacidosis is considered to be resolved when the blood glucose concentration is less than 200 mg/dl and two of the following criteria have been met: serum bicarbonate 15 mEq/L or higher, venous pH above 7.3, or anion gap 12 mEq/L or less (Kitabchi et al., 2009). At this time, patients can be transitioned to subcutaneous insulin administration if they are tolerating a diet. Because of delayed absorption, it is important to continue the infusion of insulin for at least 1–2 hours following rapid (e.g., aspart or lispro) or short-acting (e.g., regular) subcutaneous insulin administration (Kitabchi et al., 2009). If a longer acting (e.g., detemir, glargine, or NPH) insulin formulation is chosen for subcutaneous administration, overlap time may need to be extended to 2–4 hours with careful blood glucose monitoring.

Electrolytes

Patients with DKA frequently present with normal or elevated serum potassium concentrations even in the face of overall decreased potassium stores. This is due to osmotic diuresis and transcellular fluid shifts. Potassium is also the electrolyte most likely to be rapidly affected by the treatment of DKA. Insulin will quickly facilitate intracellular movement of potassium ions, resulting in hypokalemia. Therefore, it is necessary to check potassium concentrations at presentation and every 2–4 hours thereafter and to replete them in order to keep serum potassium concentrations between 4 and 5 mEq/L (Kitabchi et al., 2009). In addition, ensuring that the patient's serum magnesium concentration is above 2 mg/dl will assist in correcting hypokalemia, as magnesium is a cofactor in cellular potassium uptake. Therefore, it assists in maintaining intracellular potassium concentrations. A low magnesium concentration that is not repleted may lead to refractory hypokalemia (Cohn, Kowey, Whelton, & Prisant, 2000).

Bicarbonate therapy may be considered in DKA patients who present with severe

acidosis (i.e., serum pH less than 6.9); bicarbonate therapy in less severe acidosis has shown no benefit (ADA, 2004; Kitabchi et al., 2009; Wolfsdorf et al., 2007). Bicarbonate therapy is also not without risks, as it may contribute to hypokalemia, central nervous system acidosis, and increased osmolality (Wolfsdorf et al., 2007). For pediatric patients with a serum pH less than 6.9, it is reasonable to consider administration of 0.5-1 mEq/kg of sodium bicarbonate over 1 hour. In adults, 100 mmol of sodium bicarbonate (two ampoules of 8.4% sodium bicarbonate) in 400 ml of sterile water at a rate of 200 ml/hr may be used (Kitabchi et al., 2009; Koul, 2009). In either population, potassium concentrations and pH should be monitored frequently (Wilson, 2010).

Phosphate, like potassium, is an intracellular ion that is affected by the transcellular fluid shifts in DKA. Therefore, patients may have overall phosphate deficits but present with normal or elevated serum phosphate concentrations. Phosphate repletion alone is usually not indicated in DKA but may be necessary if serum concentrations fall to less than 1 mg/dl during insulin therapy. If necessary, 20–30 mEq/L of potassium phosphate may be added to replacement fluids (Kitabchi et al., 2009). When phosphate is given, serum calcium should be monitored in addition to the other electrolytes listed (Wilson, 2010).

COMPLICATIONS

Some of the most common complications arising from the treatment of DKA include hypoglycemia and hypokalemia. As previously discussed, both of these complications may be prevented by careful monitoring and addition of dextrose and potassium to maintenance fluids when appropriate. Another potential complication arising from excessive fluid resuscitation is chloremic acidosis, which can aggravate concurrent ketoacidosis. Recent evidence suggests that fluid resuscitation with a balanced electrolyte solution may lead to decreased incidence of chloremic acidosis in adults with DKA (Mahler, Conrad, Wang, & Arnold, 2011). However, until additional evidence is available, initial fluid resuscitation per the 2009 ADA consensus statement should be strongly considered. If a chloremic acidosis develops, switching maintenance fluids to a formulation with a lower chloride concentration, such as a balanced electrolyte solution or lactated Ringer's, would be appropriate.

Finally, although rare, cerebral edema may occur and is more common in children than in adults. Signs and symptoms of cerebral edema are multiple and variable but may include headache, decreased mental status, seizure, respiratory decline, and hemodynamic changes. Although the cause of cerebral edema in DKA is not well defined, prevention strategies include slowing fluid replacement to minimize rapid changes in serum osmolality and targeting a slightly higher goal blood glucose concentration of 250–300 mg/dl until stabilization (Kitabchi et al., 2009). Treatment of cerebral edema in pediatric patients includes mannitol, hypertonic saline in mannitol-refractory cases, and decreased fluid administration rate (Wolfsdorf et al., 2007). Treatment recommendations for adults with cerebral edema include mannitol and mechanical ventilation if needed (Kitabchi et al., 2009).

CONCLUSION

Diabetic ketoacidosis is increasing in prevalence and may be fatal if not treated quickly and appropriately. Patients with DKA are at risk for complications due to the complexity of the disease, potential for error in fluid, electrolyte, and insulin administration, and adverse effects of treatment. A DKA protocol is helpful for organizing tasks and prioritizing treatment and may be found in the 2009 ADA consensus statement (Kitabchi et al., 2009). The emergency nurse has an important role in the monitoring and treatment of the DKA patient. Although DKA represents a complex metabolic imbalance, a systematic approach to fluid resuscitation, insulin administration, electrolyte repletion, and monitoring is

advantageous to emergency nurses in providing excellent patient care.

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