# Diabetic Ketoacidosis in the Pediatric Emergency Department

Laura Olivieri, MD[a], Rose Chasm, MD[b,c,*]

**KEYWORDS**

• Diabetic ketoacidosis • Cerebral edema • Fluid resuscitation • Insulin

**KEY POINTS**

- Despite advances in research and treatment, the incidence of pediatric-onset diabetes and diabetic ketoacidosis is increasing.
- Diabetes mellitus is one of the most common chronic pediatric illnesses and, along with diabetic ketoacidosis, is associated with significant cost and morbidity.
- DKA is a complicated metabolic state hallmarked by dehydration and electrolyte disturbances. Treatment involves proper fluid resuscitation with insulin and electrolyte replacement under constant monitoring for cerebral edema, which is the deadliest complication.
- When DKA is recognized and treated immediately, the prognosis is excellent. However, when a patient has prolonged or multiple courses of DKA or if DKA is complicated by cerebral edema, the results can be devastating.

## INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases among children and adolescents worldwide. Over the past 20 years, the incidence of type 2 diabetes (formerly known as adult-onset diabetes) has increased among children in the United States.[1] European studies have demonstrated an increased frequency of type 1 diabetes in children and adolescents.

A major complication of diabetes, diabetic ketoacidosis (DKA), is characterized by the metabolic triad of hyperglycemia, anion gap metabolic acidosis, and ketonemia that develops from an absolute or relative insulin deficiency and excess of counterregulatory hormone. DKA results in dehydration and electrolyte derangements. This

[a] Department of Emergency Medicine, University of Maryland Medical Center, 110 South Paca Street, 6th Floor, Suite 200, Baltimore, MD 21201, USA; [b] Combined Emergency Medicine/Pediatrics Residency, Department of Emergency Medicine, University of Maryland School of Medicine, 110 South Paca Street, 6th Floor, Suite 200, Baltimore, MD 21201, USA; [c] Pediatric Quality Assurance and Risk Management, University of Maryland Emergency Medicine Network, Baltimore, MD, USA
* Corresponding author. 110 South Paca Street, 6th Floor, Suite 200, Baltimore, MD 21201.
*E-mail address:* rchas001@umaryland.edu

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combination, along with the major complication of cerebral edema, is the most important cause of morbidity and mortality among children with DKA. The mainstay of therapy is rehydration with intravenous (IV) fluids, insulin, and potassium repletion, as needed. Bicarbonate therapy is rarely, if ever, indicated and can lead to complications.

## EPIDEMIOLOGY

In 2010, the Centers for Disease Control and Prevention estimated that 215,000 Americans younger than 20 years of age were diabetic.[1] Despite significant advances in diabetes management, the incidence of DKA and diabetes complications remains high, probably as a result of the alarming increase in childhood obesity and its direct link to diabetes. The incidence of DKA at the time diabetes is diagnosed varies by geographic location, ranging from 12% to 80%; approximately one-third of type 1 diabetics have DKA at the time of diagnosis.[2–5] Young children, especially those younger than 5 years of age, are at high risk for DKA. The severity of DKA is also inversely related to age,[6] placing the youngest children at the greatest risk. Other factors that increase the likelihood of DKA at the time of diagnosis of diabetes include ethnic minority status, lack of health insurance, lower body mass index, missed diagnosis at previous health care visits, delayed treatment, and preceding infection.[6] The incidence of DKA among established diabetics is 25%.[7]

Type 2 diabetes is becoming increasingly common among children as a result of obesity.[8] DKA also occurs in type 2 diabetics; 5% to 25% of type 2 diabetics present with DKA at the time of diagnosis.[3,9] In a study of type 1 and type 2 diabetics, the most common cause of DKA was insulin omission, especially in type 1 diabetics. Although less common overall, infection is more often associated with DKA in type 2 diabetics. Although acidosis tends to be more severe in type 1 diabetics, type 2 diabetics require a longer duration of insulin infusion to achieve ketone-free urine, possibly because of underlying insulin resistance.[10]

DKA is associated with significant cost and morbidity.[11] In the United States, the average cost for a hospitalization is $13,000, yielding annual hospital costs exceeding $1 billion.[12] Although the mortality rate associated with DKA is less than 1%, this imbalance accounts for most diabetes-related deaths in children,[13] most of which result from cerebral edema that progresses to brain herniation. Cerebral edema, a rare and devastating complication of DKA, is clinically apparent in 1% to 5% of patients with DKA.[2,14,15] Mortality rates ranging from 20% to 90% have been reported.[15–17] A large proportion of survivors, up to 26%, experience permanent neurologic deficits.[16] Studies have also demonstrated risks of long-term memory dysfunction in children who experienced DKA without cerebral edema.[18]

## PATHOPHYSIOLOGY

Insulin is the primary hormone of blood glucose regulation. It is responsible for increasing peripheral glucose uptake and stopping hepatic gluconeogenesis. As blood glucose levels increase, counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) play reciprocal roles with insulin in attempts to maintain glucose homeostasis. DKA results from an absolute or relative deficiency of insulin and the resulting excess of counter-regulatory hormones. Absolute insulin deficiency occurs in new-onset type 1 diabetes as a result of pancreatic β-cell failure and in established diabetes as a result of insulin omission or insulin pump failure. Relative insulin deficiency can be attributable to insulin resistance or inadequate insulin dosing to balance the increased counter-regulatory hormone levels present during infection, trauma, or other physiologic stressors. Medications such as high-dose

glucocorticoids, atypical antipsychotics,[19–21] and immunosuppressive drugs can also trigger DKA.[22,23]

Insulin deficiency leads to impaired glucose uptake and use by tissues. Counterregulatory hormone excess leads to increased glycogenolysis, gluconeogenesis, proteolysis (which creates more substrates for gluconeogenesis), and lipolysis. Lipolysis generates free fatty acids, which normally undergo β-oxidation to generate acetyl coenzyme A, an entry molecule for the citric acid cycle. In the absence of insulin, the significant lipolysis and fatty acid burden is diverted toward ketogenesis instead. The two main ketones produced are acetoacetate and β-hydroxybutyrate, which dissociate fully at physiologic pH.[24] Acetone is the least abundant product of ketogenesis but does not contribute to acidosis, as it does not dissociate to yield hydrogen ions. It is metabolized through the lung and produces the fruity breath characteristic of DKA. The ratio of β-hydroxybutyrate to acetoacetate, normally 1:1, increases to as high as 10:1 in DKA.[24] Although ketones are weak acids, their severe overproduction overwhelms the buffering capacity of the body, which leads to an anion gap metabolic acidosis. Lactic acidosis and renal dysfunction caused by prerenal azotemia and dehydration may also contribute to acidosis. Respiratory compensation for this acidosis results in the classic shallow rapid breathing (Kussmaul respirations).

Dehydration is a significant consequence of DKA and has several causes. Decreased glucose uptake and increased glucose production via glycogenolysis and gluconeogenesis lead to hyperglycemia, causing extracellular fluid and electrolyte shifts. An osmotic diuresis results when serum glucose levels increase above the renal threshold for glucose reabsorption. This causes free water, glucose, and electrolytes to be lost in urine. Ketone-induced nausea and vomiting, along with the insensible losses associated with Kussmaul respirations, compound fluid losses.

Multiple electrolyte abnormalities occur in the setting of DKA. Sodium, potassium, chloride, phosphorus, calcium, and magnesium are all affected. The most significant and imminently life-threatening electrolyte imbalance is hypokalemia. Potassium shifts out of the cells because of insulin deficiency and the exchange of hydrogen ions to compensate for acidosis. This can cause the serum potassium level to be normal or even increased, despite the total body depletion of potassium that results from osmotic diuresis, gastrointestinal losses, and volume depletion. Under these conditions, the renin-angiotensin-aldosterone system is activated, exacerbating renal potassium excretion via urine.

## CLINICAL PRESENTATION

DKA can develop quickly in patients with established diabetes, especially when it is related to insulin omission. However, when DKA acts as the first presentation of diabetes, the symptoms emerge over several days. Typical symptoms are the classic triad of polyuria, polydipsia, and weight loss with or without polyphagia. These symptoms are easy to miss in children who are wearing diapers and being fed by multiple caretakers. Abdominal pain, nausea, and vomiting are also common complaints. Dehydration and electrolyte derangements can lead to muscle pains and cramping. The abdominal pain can mimic an acute abdomen. It can also be an indication of an underlying cause, so further evaluation is warranted if the pain does not resolve with hydration and resolution of ketoacidosis.[12] Persistent candidal infections or new-onset enuresis should raise suspicion for diabetes or DKA. Late findings include changes in mental status, Kussmaul respirations, and fruity, sweet, ketotic breath. Because the presentation of DKA may vary and be subtle in children who may not

have an established diagnosis of diabetes or be able to communicate their complaints verbally, a high degree of suspicion is needed to diagnose DKA in the pediatric population.

Complaints of headache or changes in mental status are worrisome as indications of cerebral edema. Focal neurologic deficits can also be seen. Hemodynamic instability and shock are rare in children with DKA, but patients are often dehydrated to varying degrees as a result of fluid shifts, osmotic diuresis, gastrointestinal losses, and insensible losses (see section on assessing dehydration).

## DIAGNOSIS

The biochemical criteria for DKA are as follows[12,25–27]:

- Hyperglycemia with blood glucose concentration greater than 200 mg/dL (>11 mmol/L)
- Venous pH less than 7.3 or bicarbonate concentration less than 15 mmol/L
- Ketonuria and ketonemia

The severity of DKA can be categorized as follows[12,25–27]:

- Mild: venous pH less than 7.3, $HCO_3$ less than 15 mmol/L
- Moderate: venous pH less than 7.2, $HCO_3$ less than 10 mmol/L
- Severe: venous pH less than 7.1, $HCO_3$ less than 5 mmol/L

The basic initial diagnostic tests that should be obtained in all patients suspected of having DKA are listed in **Box 1**. Although hypotension is not common in

**Box 1**
**Initial diagnostic workup of all patients with DKA**

- Vital signs
- Weight
- Capillary blood glucose
- Electrocardiogram
- Serum chemistry
  - Glucose
  - Sodium
  - Potassium
  - Chloride
  - Blood urea nitrogen
  - Creatinine
  - Calcium
  - Magnesium
  - Phosphorus
- Complete blood count
- Venous blood gas
- β-Hydroxybutyrate or urine ketones (see section on ketone testing)

straightforward DKA, tachycardia is. Fever may occur in the setting of infection but is not caused by DKA inherently. Tachypnea is present in later compensatory stages of DKA. It is imperative to weigh all patients so that accurate medication and fluid doses can be calculated.

The measurement of glucose levels in capillary blood samples with bedside meters provides information immediately and is adequate for monitoring changes during treatment. Values should be obtained at least every hour during acute management.

An electrocardiogram must be obtained if potassium measurement is not available immediately, such as via point-of-care testing, as early detection of arrhythmogenic electrolyte imbalances is crucial.[28] U waves are suggestive of hypokalemia, whereas short QT intervals and peaked T waves may progress to prolonged PR intervals, widened QRS complexes, or a sine wave pattern in hyperkalemia.[29]

The complete blood count might show leukocytosis, which is not specific for infection in the setting of DKA[3] and could be related to dehydration. An infectious workup should be initiated if the patient has a history of fever or other suggestive symptoms.

Serum chemistry is obtained for both the individual electrolyte values and to perform the calculations listed in **Box 2**. The serum sodium concentration is corrected to account for the dilutional effect of the degree of hyperglycemia. The anion gap, however, is calculated using the measured serum sodium level rather than a corrected sodium level because glucose is electrically neutral and does not contribute to the anion gap. The anion gap is determined by negatively charged ions and proteins such as albumin. Therefore, in the setting of albumin deficiency, the anion gap should be corrected, assuming a normal serum albumin concentration of 4 g/dL and an expected reduction in the anion gap by 2.5 mEq/L for every 1 g/dL decrease in serum albumin. Albumin levels should be obtained if there is a concern about nephrotic syndrome or severe malnutrition but not necessarily in a previously healthy child.

### *Venous Blood Gas Analysis*

It is well established that venous and arterial pH are well correlated in DKA.[30] Consensus guidelines for management now include venous pH, rather than arterial pH, as part of the biochemical definition of DKA. This eliminates the added risk of pain, hemorrhage, fistula formation, thrombosis, and infection when obtaining a sample for analysis of arterial blood gases.[31] Although arterial blood gases used to be considered essential in the diagnosis of DKA, they have not been found to influence decision making in the emergency department when treating patients with DKA.[32] Based on various studies, the mean difference between arterial and venous pH ranges from 0.015 to 0.05, and venous pH accurately measures the degree of acidosis in adult patients with DKA.[30,32,33] Subtle differences are not likely to be clinically significant. However, it can be difficult to identify mixed acid-base disturbances, thus arterial blood gas analysis may be indicated in certain cases.[30]

**Box 2**
**Calculations using serum chemistry**

Corrected sodium = serum sodium + 1.6 × [(serum glucose in mg/dL − 100)/100]

Anion gap = serum sodium − (serum chloride + serum bicarbonate)

Anion gap corrected for albumin = anion gap − 2.5 × (4 − serum albumin in g/dL)

Consensus statements recommend measuring both bicarbonate and pH from venous blood. However, venous blood gas (VBG) analysis is not readily available in all treatment settings, requires extra blood to be drawn, and incurs extra cost. A recent comparison of pH and serum bicarbonate levels in 300 children with diagnosed DKA confirmed excellent correlation between the 2 measures.[34] In addition, the ketoacids present in DKA increase the number of unmeasured anions, resulting in an anion gap metabolic acidosis. Therefore, the anion gap and serum bicarbonate can be used to monitor DKA if VBG analysis is unavailable.

VBG electrolyte testing is a newer aspect of DKA diagnosis and monitoring that may allow the rapid assessment of essential data in a single test. Menchine and colleagues's[35] prospective observational study investigating the diagnostic accuracy of VBG electrolytes in hyperglycemic adults, including sodium, chloride, and bicarbonate, showed 97.8% sensitivity and 100% specificity in diagnosing DKA, suggesting that this method could supplant serum electrolytes in addition to VBG analysis. However, Fu and colleagues[36] showed a difference between VBG potassium and serum potassium levels ranging from 0.9 to 2.9 mmol/L, and 20% of the sample pairs had a difference greater than 0.5 mmol/L, which was the maximum clinically acceptable difference predetermined before the study by surveying 15 physicians. Given the lack of substantial data and the possible inconsistency of the VBG potassium readings, further testing is necessary before VBG can be recommended as an alternative to testing serum for electrolytes.

### *Ketone Testing*

Although β-hydroxybutyrate is the predominant ketone produced in DKA, urine and serum ketone assays typically use the nitroprusside reaction, which detects only acetone and acetoacetate and is semiquantitative using dilutions. During treatment with insulin therapy, β-hydroxybutyrate is oxidized to acetoacetate, causing β-hydroxybutyrate levels to decrease before acetoacetate levels. A ketone assay may give the false impression that the patient is not improving, when, actually, the overall quantity of ketones has decreased. Therefore, when interpreting ketone tests, both the time delay before the development of ketonemia and ketonuria must be considered in diagnosing DKA as well as the earlier clearance of β-hydroxybutyrate rather than urine ketones alone.[24,37] Furthermore, urine ketone testing is affected by hydration status and urine stagnation in the bladder, and false-positive results can be encountered if patients are taking captopril, penicillamine, *N*-acetylcysteine, mesna, dimercaprol, or isopropyl alcohol.[38] To more precisely measure ketone burden, a quantitative serum β-hydroxybutyrate test should be used.[12,24,27]

The use of β-hydroxybutyrate testing has been proposed as an end point to monitor resolution of ketosis and direct insulin infusion therapy.[27,37,39] Compared with urine ketone testing, serum β-hydroxybutyrate-guided DKA treatment has been associated with shorter intensive care unit (ICU) and hospital stays as well as decreased costs.[39] However, because serum β-hydroxybutyrate assays are not available at all institutions, the anion gap, pH, or bicarbonate can be used to direct DKA treatment.

An additional laboratory study that can benefit inpatient and especially outpatient diabetes management is hemoglobin A1C testing. Although it does not necessarily change emergency department management, it can provide valuable information regarding the chronicity and severity of hyperglycemia in all patients and overall glycemic control in established diabetics if increased, and acuity in well-controlled patients if close to normal limits.

## EMERGENCY DEPARTMENT MANAGEMENT

Current practice guidelines are based on both evidence and consensus recommendations. First and foremost, pediatric resuscitation principles should be followed. Airway, breathing, and circulation should be secured. Intravenous access must be obtained. Aspiration precautions should be taken if the patient has an altered level of consciousness. Continuous cardiac monitoring and pulse oximetry are imperative to assess for arrhythmias secondary to hyperkalemia or hypokalemia and to ensure adequate oxygenation. Frequent neurologic monitoring is also warranted. The best outcomes are achieved when children are monitored closely and continuously, with prompt attention to any changes.[40]

Additional hourly monitoring should include vital signs, neurologic checks, blood glucose, and accurate fluid intake and output. Frequent neurologic checks are particularly important in patients at greater risk for cerebral edema, such as those with new-onset diabetes, patients younger than 5 years old, and patients with greater degrees of acidosis, hypocapnia, or azotemia.[14–16] Capillary blood glucose levels should be confirmed with laboratory venous values. Initially, VBGs and chemistries should be checked every 2 hours, but depending on those initial values, may require more frequent monitoring. As previously mentioned, ketone testing should not guide treatment. The serum β-hydroxybutyrate concentration is ideal for monitoring progress; if that reading is not available, anion gap, pH, and bicarbonate can also be used as end points.

Specific aspects of DKA management are as follows[27]:

- Fluid resuscitation to rehydrate and improve tissue perfusion and glomerular filtration rate
- Correction of ketoacidosis and hyperglycemia via inhibition of lipolysis and ketogenesis with insulin
- Restoration of electrolyte balance
- Avoidance of complications, specifically cerebral edema

### *Fluids*

Intravenous fluids are administered for resuscitation and rehydration as well as to decrease the blood glucose level by improving the glomerular filtration rate and, thus, glucose and ketone clearance. Although adults tend to present with large volume deficits requiring aggressive fluid repletion, a more restrictive strategy must be used in the pediatric setting to avoid potential complications. The initial resuscitation of a pediatric patient in DKA calls for administration of an isotonic crystalloid solution as a bolus of 10 to 20 mL/kg over 1 to 2 hours. The dose can be repeated if the patient is hemodynamically unstable.[12,25–27] Children rarely present in hypovolemic shock caused by DKA alone. If a child does not respond to the initial resuscitation bolus, search for other causes of shock. To avoid increasing the risk of cerebral edema and herniation, resuscitation volumes should not exceed 40 to 50 mL/kg during the first 4 hours of treatment, unless the patient is in shock.[12,17,41]

After the initial bolus of IV fluid, the goal of rehydration is to administer the remainder of replacement fluids evenly over 24 to 48 hours with 0.45% to 0.9% saline.[25] Overzealous fluid resuscitation could lead to further complications, particularly cerebral edema,[41,42] although no data have demonstrated increased safety with rehydration over 48 hours. The rate of total fluid administration includes maintenance plus replacement of the fluid deficit based on the patient's estimated degree of dehydration (see section on degree of dehydration) and should not exceed 2 times the maintenance

volume. Fluids that were administered before arrival should be accounted for in these calculations, but urinary losses should not.

Weight-based 24-hour maintenance fluid requirements can be calculated as follows[43]:

- 100 mL/kg for the first 10 kg of body weight
- 50 mL/kg for the second 10 kg of body weight
- 20 mL/kg for each kilogram above 20 kg of body weight

Using the 4-2-1 rule, the requirements can be estimated as follows:

- 100 mL/kg/24 h = 4 mL/kg/h for the first 10 kg of body weight
- 50 mL/kg/24 h = 2 mL/kg/h for the second 10 kg of body weight
- 20 mL/kg/24 h = 1 mL/kg/h for each kilogram above 20 kg of body weight

***Fluid type***

Normal saline (0.9% NaCl) is commonly used as the replacement fluid for patients with DKA and can be switched to half normal saline (0.45% NaCl) once the corrected sodium concentration normalizes (see section on sodium). There is no evidence supporting the use of solutions with tonicity lower than 0.45% NaCl, which can lead to rapid osmolar changes and intracellular movement of fluid,[25] or colloids.

Recent evidence implicates the administration of large volumes of saline in the development of hyperchloremia with a nongap metabolic acidosis,[44,45] which increases with treatment duration and can mask the resolution of DKA if base deficit alone is being monitored as an end point for treatment. The clinical significance of hyperchloremia with acidosis is unclear, but concerns about possible deleterious effects from excessive saline administration have raised controversy with respect to fluid choice. A small blinded, randomized controlled trial failed to show any difference in time to normalization of pH and resolution of DKA between patients resuscitated using normal saline and others who received Ringer's lactate.[46] Recent literature comparing non–calcium-containing balanced crystalloid such as Plasma-Lyte (Plasma-Lyte 148 or Plasma-Lyte A, Baxter Healthcare, Deerfield, IL) with normal saline administration to patients with DKA reported lower serum chloride levels and higher bicarbonate concentrations after resuscitation in the Plasma-Lyte group, consistent with prevention of hyperchloremia and acidosis.[47] The effect of these changes on outcome and mortality rate is unknown. Chua and colleagues[48] attained similar results, that is, faster resolution of acidosis in the first 12 hours of treatment with Plasma-Lyte and stable chloride levels. They reported no difference in the rate of resolution of hyperglycemia, the duration or total dose of IV insulin administration, or length of ICU stay. Further investigation is needed to determine whether the administration of a saline solution to patients with DKA carries any clinically significant risks; there is no evidence of associated morbidity. Currently, the use of saline remains the standard of care.

***Rate of rehydration***

Because of conflicting theories on the underlying mechanism of cerebral edema in patients with DKA, arguments for both slower and faster rehydration have been put forth. If cerebral edema results from osmotic changes or vasogenic edema associated with a compromised blood-brain barrier, slower rehydration might limit edema. On the other hand, if ischemia and hypoperfusion are the major insults to the brain, then more rapid rehydration could rectify the problem sooner and prevent ischemia when intracellular fluid shifts during treatment with insulin.[15]

Unfortunately, little evidence is available to definitively guide the rapidity of fluid therapy. The large, multicenter Pediatric Emergency Care Applied Research Network (PECARN) trial is investigating the impact of the administration of 0.9% versus 0.45% normal saline at 2 rates on short-term and long-term neurologic outcome,[49] which might clarify the role and implications of fluid resuscitation.

### *Degree of dehydration*

The clinical assessment of dehydration is obfuscated by multiple factors. Although previous studies of nonacidotic children demonstrated the usefulness of multiple physical examination signs, such as reduced skin turgor, increased capillary refill time, dry tongue, and sunken eyes or fontanelle, in assessing degree of dehydration,[50,51] none of these parameters have been found to be accurate predictors of hydration status in DKA because they might not reflect only fluid losses.[50] Acidosis can make a child seem more dehydrated because of the tachypnea of Kussmaul respirations, which results in dry mucous membranes, and vasoconstriction, which leads to cooler extremities.[52,53] The ongoing lipolysis, proteolysis, and weight loss caused by insulin deficiency[50] can also make a child seem clinically more dehydrated. On the other hand, hyperosmolarity tends to preserve intravascular volume (and thus pulses, blood pressure, and urine output) until extreme volume depletion and shock occur.[53,54] Therefore, physical examination findings are often unreliable in estimating dehydration in the setting of DKA.

Historically, children were assumed to be 10% dehydrated at presentation[55] unless they were hemodynamically unstable. Because of concerns about an increased risk of cerebral edema with rapid fluid administration, it has been suggested to assume 5% to 8% dehydration.[56] More recent guidelines advise stratifying the degree of dehydration based on the severity of DKA, estimating 5% to 7% dehydration in moderate DKA and 7% to 10% dehydration in severe DKA.[27]

Multiple prospective studies based on percent loss of body weight (PLBW), calculated by the difference between initial and discharge weight as a percentage of the discharge weight, have shown that the degree of dehydration cannot be predicted clinically.[50,52–54] Using PLBW as a surrogate marker for dehydration, several groups of investigators[50,52,53] have reported median dehydration percentages of 5% to 8%.[50,52,53] Up to 70% of patients were assessed incorrectly; some were overestimated and some underestimated. Ugale and colleagues[53] showed that, although 60% of their study patients presented with severe DKA, their median dehydration was 5.4%. No significant difference was found in the measured degree of dehydration between severity groups, suggesting that patients with severe acidosis are not necessarily more dehydrated than other patients with DKA. Based on the available data, it might be excessive to estimate up to 10% dehydration in patients. Administration of maintenance fluids, based on an assumed 6% deficit, seems more reasonable.

### *The two-bag system*

Because of rapid fluctuations in fluid, electrolyte, and dextrose requirements, patients with DKA require frequent adjustments in fluid and insulin administration. The two-bag system was introduced in the 1990s[57] to facilitate these changes. This system consists of two bags of fluids with identical electrolyte content but different dextrose concentrations (0% and 10%) that are administered simultaneously into the same IV line.

The rate of fluid delivery is determined by the degree of dehydration and individual patient needs, whereas the concentration of dextrose depends on the patient's serum glucose level and its rate of decline during treatment. These factors can be manipulated independently, as different proportions of fluid from each bag are administered.

Initially, no dextrose is given; as hyperglycemia resolves with the infusion of insulin, dextrose is titrated up to control the rate of decrease in blood glucose while continuing the insulin infusion. The IV fluids can therefore be customized to meet the patient's individual glucose, fluid, and insulin needs by creating a fluid dextrose concentration that ranges between 0% and 10% to control the rate of blood glucose decline and prevent hypoglycemia.[58]

Koul[59] described a system of fluids and concentrations to be given based on different serum glucose values:

- If greater than 250 mg/dL (13.8 mmol/L), give normal saline (NS) alone
- If less than 250 mg/dL (13.8 mmol/L), give half of the rate from each bag to make 5% dextrose (D5) NS
- If less than 150 mg/dL (8.33 mmol/L), give 10% dextrose (D10) NS alone at a predetermined rate

Studies have shown multiple advantages to the two-bag system. Rather than changing an individual IV fluid bag each time the dextrose concentration needs to be adjusted during correction of hyperglycemia and acidosis, which can take more than 30 minutes, the two-bag system allows rapid transitioning of fluids when necessary, taking as little as one minute.[58] Based on the billing system in the late 1990s, the two-bag system cost approximately $500 less per DKA admission than the one-bag system, because of the reduction in the number of IV fluid bags required.[57] More recent data have shown a faster rate of bicarbonate and ketone correction with the two-bag system compared with the one-bag system[60]; the significance of this observation requires further study.

The two-bag system is superior to the single-bag system with respect to flexibility, timeliness, and cost-effectiveness. The rate and dextrose concentration of the fluids can be adjusted independently, and the dextrose concentration can be changed quickly in response to updated serum glucose levels without discarding partially used bags of fluids. Studies have not yet demonstrated clinical benefit, but the two-bag system does not increase the risk of complications from DKA[57,58] and could have clinical benefits in addition to its more practical advantages (**Table 1**).

### *Insulin*

Rehydration alone can decrease the blood glucose concentration, but insulin is required to suppress the lipolysis and ketogenesis that drive DKA. Insulin therapy is initiated after volume resuscitation has been started[27,41] and after the serum

**Table 1**
**Differential rates and dextrose concentrations made possible by the 2-bag system**

| Bag A | | Bag B | | Overall Composition and Rate of Administration |
|---|---|---|---|---|
| 100 mL/h NS | + | 0 mL/h D10 NS | = | NS at 100 mL/h |
| 90 mL/h NS | + | 10 mL/h D10 NS | = | D1 NS at 100 mL/h |
| 80 mL/h NS | + | 20 mL/h D10 NS | = | D2 NS at 100 mL/h |
| 75 mL/h NS | + | 25 mL/h D10 NS | = | D2.5 NS at 100 mL/h |
| 50 mL/h NS | + | 50 mL/h D10 NS | = | D5 NS at 100 mL/h |
| 40 mL/h NS | + | 40 mL/h D10 NS | = | D5 NS at 80 mL/h |
| 20 mL/h NS | + | 60 mL/h D10 NS | = | D7.5 NS at 80 mL/h |
| 0 mL/h NS | + | 100 mL/h D10 NS | = | D10 NS at 100 mL/h |

potassium level is known. Low-dose insulin is the standard of care. Start and maintain a low-dose regular insulin IV infusion at 0.1 units/kg/h and continue until the ketoacidosis resolves or until the anion gap closes. Although still a point of contention in the management of adults with DKA, an initial bolus of insulin is not necessary in pediatric patients[61] and may even be harmful by predisposing patients to hypoglycemia and increasing the risk of cerebral edema.[41,62] Theoretically, rapid correction of hyperglycemia may shift osmolarity and lead to cerebral complications, but the rate of glucose correction has not been shown to increase the risk of cerebral edema or brainstem herniation.[15,17]

Hyperglycemia usually resolves before the acidemia, but the insulin infusion must be continued to achieve full resolution of the ketoacidosis (pH >7.3, bicarbonate >15 mmol/L, β-hydroxybutyrate <1 mmol/L, and/or closure of the anion gap). The target serum glucose level during treatment is approximately 200 mg/dL. To avoid hypoglycemia during insulin infusion, dextrose should be added to IV fluids when the blood glucose concentration reaches 250 to 300 mg/dL (14 17 mmol/L)[25] or if the decline in the blood glucose level exceeds 100 mg/dL/h (5.6 mmol/L/h).[27] This practice is facilitated by the two-bag fluid system as described earlier. If hypoglycemia occurs on the maximum dextrose concentration of D10, then lower the insulin drip to no less than 0.05 units/kg/h,[63] as rates less than this can prevent full resolution of the ketoacidosis.

The transition from intravenous to subcutaneous insulin should occur after ketoacidosis resolves. Subcutaneous insulin is given at least 30 minutes before discontinuing the insulin infusion to allow time for absorption and prevent rebound hyperglycemia. The patient must be able to tolerate oral fluids and should begin to eat at that time.

End points used to determine the transition from intravenous to subcutaneous insulin vary, mainly because no evidence-based guidelines have been established. Using a pH of 7.3 as a signal to make the transition might be inadequate, as patients have been found to be ketotic at this pH.[37] Vanelli and colleagues[39] used normalization of the β-hydroxybutyrate concentration as the signal to change the route of administration and reported financial savings and patient benefit stemming from a shorter ICU stay.

#### *Route of administration*

Intravenous insulin is indicated for patients with type 1 diabetes and moderate to severe DKA (pH <7.2 and bicarbonate <10 mmol/L). Mild DKA (pH 7.2–7.3 and bicarbonate 10–15 mmol/L) can be treated with either subcutaneous or IV insulin, depending on the clinical situation.[26] If it is not possible to give an IV insulin infusion, insulin therapy can be given as subcutaneous or intramuscular injections of short-acting or rapid-acting insulin analogues, such as lispro or aspart. As with the IV insulin infusion, to maintain a goal blood glucose level of approximately 200 mg/dL, D5 should be added to the IV fluid when the blood glucose concentration decreases to less than 250 mg/dL (14 mmol/L) and the ketoacidosis has not resolved. Several studies have compared different dosages and schedules.[64,65] Although the data thus far seem to support the use of subcutaneous insulin as an alternative mode of DKA treatment that would not require ICU level care, further studies must be done to clarify subcutaneous insulin dosing and schedule.

### *Sodium*

The corrected sodium concentration should be calculated and monitored and should increase with treatment. A failure of the serum sodium level to increase or a decrease in the level despite treatment is associated with an increased risk of cerebral

edema.[15,66] In this situation, the sodium content of the fluid being administered may need to be increased.

### *Potassium*

As previously mentioned, despite total body potassium depletion, serum potassium levels might be normal or even increased in response to transcellular shifts resulting from insulin deficiency and acidosis. Potassium levels quickly decrease with insulin therapy; therefore, to prevent fatal arrhythmias secondary to severe hypokalemia, insulin should not be given until an initial potassium level is obtained.[12,25,26,67] If the serum potassium concentration cannot be measured immediately, an electrocardiogram should be obtained to assess for signs of hyperkalemia or hypokalemia.

Potassium needs to be replaced depending on the initial serum concentration. The level must be checked at least hourly. If the initial serum potassium level is increased, give insulin without supplemental potassium until the patient's ability to urinate is ensured. If the initial serum potassium level is normal, give potassium (40 mEq/L) with IV fluids when insulin administration is started. If the initial serum potassium level is low, replete potassium when beginning volume resuscitation and before initiating insulin. Intravenous potassium administration should not exceed a rate of 0.5 mEq/kg/h. If the serum potassium level remains low despite supplementation during insulin infusion, consider adding oral potassium supplementation or slightly decreasing the insulin infusion rate.

Potassium can be given as potassium chloride, potassium phosphate, or potassium acetate. To avoid administering excess chloride and exacerbating hyperchloremia associated with saline administration, potassium can be replenished with half potassium phosphate and half potassium chloride or acetate, as long as serum calcium levels are monitored to avoid hypocalcemia resulting from phosphate administration.[12,27]

### *Phosphate*

Like potassium, phosphate is lost with osmotic diuresis. IV fluids decrease phosphate levels, and insulin exacerbates this change by causing the intracellular movement of phosphate. Symptoms of profound hypophosphatemia emerge with decreasing intracellular concentrations of adenosine triphosphate and 2,3-diphosphoglycerate, that is, when the plasma levels decrease to less than 0.32 mmol/L. Severe hypophosphatemia can occur in the setting of prolonged fasting (>24 hours).[27] No data have demonstrated significant clinical benefits from phosphate repletion,[68] and phosphate administration can result in hypocalcemia. However, if the patient has unexplained severe muscle weakness or decreased cardiac function, phosphate administration should be considered.[27]

### *Magnesium*

Serum magnesium levels can be low in patients with DKA, but they tend to normalize with resolution of the acidosis and with oral intake. There is no evidence supporting repletion of magnesium in the management of DKA.

### *Bicarbonate*

Bicarbonate administration is not recommended or indicated in the management of DKA.[25–27] Historically, the use of bicarbonate in DKA treatment has been controversial. No pediatric studies have investigated the impact of bicarbonate on outcome. Although studies involving small numbers of adult patients have shown transient improvement in biochemical parameters, they have not reported clinical benefits or

improved outcomes.[48,69–73] Studies suggest that bicarbonate administration is associated with longer hospital stays for children,[71] paradoxic worsening of ketosis in adults,[69] and hypokalemia.[72] Not only can bicarbonate exacerbate hypokalemia and decrease tissue perfusion by decreasing oxygen delivery but it has also been strongly associated with the development of cerebral edema in children.[15,41]

The mainstay of treatment of acidosis is fluid replacement and insulin. Fluids improve tissue perfusion and increase the glomerular filtration rate, enhancing the excretion of acid, and insulin inhibits the underlying ketone production.

## COMPLICATIONS

The most common complications of DKA are hypokalemia and hypoglycemia, which occur in response to treatment, as discussed previously. Thus, blood glucose and electrolyte concentrations must be monitored frequently throughout the course of DKA management. Cerebral edema, the most feared complication, is exclusive to pediatric patients with DKA. Almost no cases have been reported in patients older than 20 years of age.

Cerebral edema is a potentially devastating complication of pediatric DKA. It occurs in up to 1.5% of cases, with a mortality rate as high as 24%.[16] Numerous factors have been implicated in the pathophysiology of DKA-related cerebral edema, but no single mechanism has been definitively proven as causative. Most investigators suspect it is caused by a combination of factors that arise before treatment, which are then exacerbated by therapy. Ischemic and cytotoxic edema secondary to acidosis decrease cerebral perfusion. Vasogenic edema that causes direct damage to cerebral vascular endothelium increases blood-brain permeability.[74] Risk factors for DKA-induced cerebral edema are listed in **Box 3**.

Typically, cerebral edema occurs within 4 to 12 hours after initiation of treatment, but its onset can be delayed up to 24 to 48 hours after initiation of treatment. It has been postulated that cerebral edema could be iatrogenic, related to fluid resuscitation, or the speed with which hyperglycemia is corrected; however, it has been well established that symptomatic cerebral edema can develop in type 1 and type 2 diabetics without aggressive treatment.[14,16,76–79] Death has been described even before initiation of DKA treatment.[79]

**Box 3**
**Risk factors for pediatric DKA-induced cerebral edema**

- New-onset diabetes[15]
- Younger age
- Longer duration of DKA symptoms
- Degree of acidosis at presentation (pH <7.1)[17,41]
- Greater hypocapnia ($P_{CO_2}$ <20 mm Hg)[15,17]
- Greater initial rate of fluid resuscitation for treatment of severe DKA (>50 mL/kg in the first 4 hours)[41]
- Administration of insulin during the first hour of fluid resuscitation[41]
- Higher blood urea nitrogen at presentation[15,75]
- Slower increase in measured serum sodium concentration during treatment of DKA[15,66]
- Bicarbonate treatment[15,73]

Regular neurologic checks along with assessment of vital signs are crucial. Mental status changes, which can range from somnolence to irritability, are worrisome, as are focal neurologic deficits. Age-inappropriate incontinence can be a sign of cerebral edema. Complaints of headache should be considered seriously. The combination of hypertension, bradycardia, and irregular respiration (Cushing triad) is a sign of increased intracranial pressure. Hypoxemia can also result from compression of the brain's respiratory center, leading to impending brain herniation.

Physicians should have a low threshold to diagnose and treat cerebral edema. When it is suspected based on clinical signs and symptoms, treatment should be initiated immediately. Treatment should never be postponed to wait for confirming computed tomography (CT) imaging; changes that indicate cerebral edema that can be seen on CT images occur late in its development. Treatment includes elevation of the head of the bed and reduction of IV fluids by one-third.[27]

Mannitol should be administered at a dose of 0.5 to 1 g/kg IV over 20 minutes. This regimen can be repeated if there is no clinical response within 30 to 120 minutes.[80,81] Mannitol decreases blood viscosity and thus improves cerebral blood flow acutely.[82] Caution with its use is warranted, however, because mannitol can induce diuresis, thereby decreasing intravascular volume and causing hypokalemia. This may result in hypotension and, subsequently, decreased cerebral blood flow.

Alternatively, 3% hypertonic saline can be given at a dosage of 5 to 10 mL/kg over 30 minutes, either instead of or along with mannitol.[83,84] Hypertonic saline lowers intracranial pressure, increases intravascular volume, and increases mean arterial pressure.

Patients might require intubation and mechanical ventilation to manage respiratory depression and avert impending respiratory failure. Patients with intracranial hypertension may be cautiously hyperventilated; however, hyperventilation to a $P_{CO_2}$ less than 22 mm Hg should be avoided, as one study found poorer neurologic outcomes in intubated patients who were aggressively hyperventilated.[75]

## DISPOSITION

Established diabetics with mild DKA who are alert and tolerating oral fluids can be treated in the emergency department and discharged, provided they have close supervision at home, possess the proper medications and supplies, have been educated about insulin administration, have the ability to monitor their blood glucose level, and have access to close follow-up.[27] Patients with new-onset diabetes must be admitted. Patients requiring IV rehydration over an extended period need to be admitted to a unit capable of hourly blood glucose measurement and frequent measurement of vital signs and neurologic checks. Patients with severe DKA should be admitted to the ICU, especially if they have had a long duration of symptoms, any hemodynamic instability, altered mental status, a high risk of cerebral edema (eg, age <5 years), low partial pressure of carbon dioxide ($P_{CO_2}$), or high BUN.[27]

## SUMMARY

Despite advances in research and treatment, the incidence of pediatric-onset diabetes and diabetic ketoacidosis is increasing. Diabetes mellitus is one of the most common chronic pediatric illnesses and, along with diabetic ketoacidosis, is associated with significant cost and morbidity. DKA is a complicated metabolic state hallmarked by dehydration and electrolyte disturbances. Treatment revolves around proper fluid resuscitation with insulin and electrolyte replacement under constant monitoring for cerebral edema, which is the deadliest complication. When DKA is

recognized and treated immediately, the prognosis is excellent. However, when a patient has prolonged or multiple courses of DKA or if DKA is complicated by cerebral edema, the results can be devastating.

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