

The Evaluation and Management of Children With Diabetic Ketoacidosis in the Emergency Department

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Key Words: diabetes mellitus, diabetic ketoacidosis, DKA

DKA episodes in children with type 2 DM are also becoming more frequent.¹⁻³

TARGET AUDIENCE

Physicians, nurse practitioners and physician assistants who evaluate and care for children, particularly those patients who are acutely ill.

Specialists including pediatricians, emergency physicians, pediatric emergency physicians, family practitioners, and endocrinologists will find this information especially useful.

LEARNING OBJECTIVES

After completion of this article, the reader will be able to:

1. Recall the epidemiology and pathophysiology of diabetes, particularly in regard to ketoacidosis.
2. Describe the clinical findings and laboratory abnormalities found in children with diabetic ketoacidosis.
3. Describe the treatment of diabetic ketoacidosis in terms of the volume and rate of infusion of intravenous fluids and glucose, the electrolyte concentrations use, and the role of insulin.

Diabetic ketoacidosis (DKA) occurs frequently in children with new onset of type 1 diabetes mellitus (DM), and may occur in patients with established type 1 DM during episodes of intercurrent illness, with omission of insulin injections or due to malfunction of diabetes care equipment. With increases in the prevalence of type 2 DM in children,

EPIDEMIOLOGY

DKA occurs in 25% to 40% of children with new-onset type 1 diabetes.^{4,5} The frequency of DKA at the time of diagnosis of diabetes is increased in very young children,⁵⁻⁷ likely as a reflection of the greater difficulty in recognizing symptoms of diabetes in this age group. Similarly, in populations with a low overall prevalence of type 1 diabetes in children, where symptoms of diabetes may be less familiar to practitioners, patients more frequently present with DKA as the initial manifestation of diabetes.⁸

In children with established diabetes, DKA occurs at a rate of approximately 1% to 8% per year.^{5,9-11} Risk factors for DKA in patients with established diabetes include lower socioeconomic status, lack of adequate health insurance, poorer diabetes control (reflected in higher HbA1c levels), and psychiatric disorders.⁹ In children, episodes of DKA after diagnosis of DM are usually due to missed insulin injections and are infrequently (31%) caused by infection or other intercurrent illnesses.¹² These data contrast with figures from adult populations where much higher frequencies of infections or other illnesses as precipitating factors for DKA have been reported.^{13,14}

Although mortality rates from childhood DKA are less than 1%, DKA is nonetheless the most frequent diabetes-related cause of death in children.^{15,16} The majority (62-87%) of these DKA-related deaths are caused by cerebral edema.^{15,16}

PATHOPHYSIOLOGY

In patients with evolving diabetes, low serum insulin concentrations lead to diminished peripheral glucose uptake and increased hepatic glucose output resulting in hyperglycemia. When the serum glucose concentration rises above approximately 180 mg/dL, exceeding the renal tubular threshold for glucose reabsorption, glucosuria results. Glucosuria leads to osmotic diuresis and compensatory polydipsia. Further declines in insulin secretion eventually result in a relative excess of counter-regulatory hormones (glucagon, cortisol, catecholamines, and growth hormone) in relation to insulin. This imbalance between insulin and counter-regulatory

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hormones stimulates ketogenesis, further increases hepatic glucose output, and stimulates catabolism of triglyceride and muscle protein to fuel hepatic production of ketones and glucose (Fig. 1). In patients with established diabetes, a similar imbalance between insulin and counter-regulatory hormones may occur when insulin injections are omitted or in the setting of infection or other illness, triggering DKA.

Continued ketone production eventually results in acidosis with an elevated anion gap. Acidosis, along with diminished splanchnic perfusion, frequently causes intestinal ileus with vomiting and abdominal pain. As the ability to compensate for osmotic diuresis by increased intake of fluids is compromised by vomiting, dehydration worsens. As dehydration worsens, tissue perfusion is eventually diminished, resulting in production of lactic acid and worsening of acidosis. Severe dehydration leads to impaired renal function and diminished capacity for clearance of glucose and ketones, increasing both hyperglycemia and acidosis. Depletion of electrolytes (sodium, potassium, chloride, phosphate, and magnesium) occurs as a result of osmotic diuresis and acidosis.

The combination of acidosis and osmotic diuresis leads to the classic symptoms of DKA, including polyuria, polydipsia, weight loss, abdominal pain, nausea, and vomiting. Children with DKA typically present with tachycardia and tachypnea. Signs of hypoperfusion, such as cool extremities and delayed capillary refill time, are frequently present, but blood pressure is usually maintained in the normal range. Abdominal tenderness may mimic the acute abdomen. A fruity breath odor caused by acetone may be present and is a helpful clue to the diagnosis.

LABORATORY ABNORMALITIES

A diagnosis of DKA can be made when serum glucose concentrations are above 200 mg/dL, venous pH is below 7.30 (or serum bicarbonate concentration is below 15 mmol/L) and ketonuria is present. DKA with near-normal glucose concen-

trations has also been described, most frequently in pregnant women, but is uncommon in the pediatric population.¹⁷

Acidosis

Serum bicarbonate concentrations are decreased and the anion gap is increased. Some degree of hyperchloremic acidosis frequently coexists with increased anion gap acidosis,¹⁸ and the anion gap reflects the combination of these processes. The partial pressure of CO₂ is decreased, often markedly, as a result of respiratory compensation for metabolic acidosis, and correlates linearly with the serum bicarbonate concentration.¹⁹ One recent study demonstrated that end-tidal CO₂ measurement may be used to rapidly determine the presence of acidosis in children with suspected DKA.¹⁹

Electrolyte Abnormalities

Serum sodium concentrations are typically low because the osmotic effect of hyperglycemia draws water from the extravascular to the intravascular space. The expected decrease in measured serum sodium concentration due to hyperglycemia can be calculated as a 1.6 mEq/L decrease in sodium concentration for every 100 mg/dL increase in serum glucose above 100 mg/dL.²⁰ Hypertriglyceridemia during DKA may also contribute to factitious decreases in measured serum sodium. Serum potassium concentrations are typically normal or elevated at the time of initial presentation of DKA, because of movement of potassium ions from the intracellular to the extracellular space stimulated by acidosis. Total body potassium concentrations, however, are often profoundly depleted, and the serum potassium concentration may drop rapidly with treatment as potassium returns to the intracellular space. Phosphate concentrations are similarly elevated or normal at presentation, but tend to decrease during treatment. Blood urea nitrogen and creatinine concentrations may be elevated due to diminished renal perfusion. In the absence of preexisting renal disease, serum glucose concentrations also provide information about adequacy of renal perfusion; concentrations above 500 to 600 mg/dL imply diminished renal function with a decreased glomerular filtration rate.

Other Biochemical Abnormalities

White blood cell counts are frequently elevated in children with DKA and the differential may be left shifted. DKA in children, however, is infrequently triggered by infection; only 18% of children with DKA have viral infections, and only 13% have bacterial infections.¹² Therefore, elevation or left shift of the white blood cell count need not prompt a search for an infectious process unless fever or other symptoms or signs of infection are present. Serum amylase concentrations also may be elevated in DKA.^{21,22} The significance of these elevations, however, is not known and clinical pancreatitis is rare.

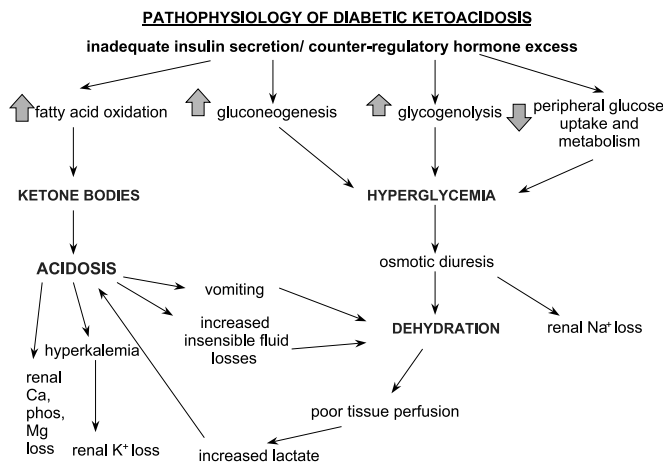


FIGURE 1. Pathophysiology of diabetic ketoacidosis.

TREATMENT

Fluid Therapy

Initial treatment should be directed at restoring perfusion and hemodynamic stability with intravenous boluses of 0.9% saline or other isotonic fluids as necessary. In patients who are well-perfused and hemodynamically stable, an initial fluid bolus may not be necessary. Subsequently, the remaining fluid deficit (assuming an average fluid deficit at presentation of approximately 7% of body weight²³) should be replaced over a 36- to 48-hour period using 0.45% to 0.9% saline.

Frequently, the serum glucose concentration will decrease substantially with rehydration alone because of restoration of renal perfusion and decreased levels of counter-regulatory hormones. This decrease in glucose concentration is to be expected and is not an indication of excessive administration of insulin.

Insulin and Dextrose

Insulin should be administered intravenously at a rate of 0.1 units/kg/h.²⁴ Administration of insulin at this dosage rapidly leads to maximal insulin activity, such that an initial bolus or loading dosage of insulin is not necessary. To prevent hypoglycemia during insulin therapy, dextrose should be added to the intravenous fluids when the serum glucose concentration falls below 250–300 mg/dL. Typically, serum glucose concentrations decrease to the normal range before ketosis and acidosis have resolved. When this occurs, it is preferable to continue insulin at the same dosage and increase the concentration of dextrose in the intravenous fluids to prevent hypoglycemia, rather than decreasing the rate of insulin administration which may result in delayed resolution of ketosis and acidosis. The “two-bag system” for administration of dextrose in children with DKA allows a more rapid response to changes in serum glucose concentration and is more cost-effective than single-bag methods.²⁵ This system employs 2 bags of intravenous fluids with identical electrolyte content, but varying dextrose concentrations (usually 0% and 10%) administered simultaneously. The relative rates of administration of the 2 fluids can be adjusted to vary the dextrose concentration while maintaining a constant overall rate of fluid and other electrolyte administration.

Electrolytes

Potassium should be administered at a concentration of 30 to 40 mEq/L of intravenous fluids to prevent hypokalemia during treatment. Adequate renal function should be insured before administration of potassium. Potassium can be administered as potassium chloride or as a combination of potassium chloride and potassium phosphate or potassium acetate. Use of combinations of potassium salts may help

to diminish the risk of development of hyperchloremic acidosis by decreasing the chloride load.

Replacement of phosphate in children with DKA is controversial. Opponents of phosphate replacement argue that aggressive phosphate replacement may cause symptomatic hypocalcemia. Conversely, hypophosphatemia may theoretically lower levels of 2,3-DPG in red blood cells, possibly resulting in reduced tissue oxygen delivery.²⁶ In addition, rhabdomyolysis and hemolytic anemia have been reported in rare cases of severe hypophosphatemia during DKA.^{27,28} Furthermore, symptomatic hypocalcemia is uncommon when phosphate is administered in more modest concentrations.²⁹ Regardless of whether phosphate replacement is given, serum phosphate concentrations during treatment should be carefully monitored.

Hypomagnesemia is common during DKA treatment and may contribute to hypocalcemia by inhibition of parathyroid hormone secretion.^{30,31} Both hypomagnesemia and hypocalcemia during DKA treatment, however, are usually mild and asymptomatic and rarely require treatment. Nonetheless, serum calcium and magnesium concentrations should be monitored during therapy.

Bicarbonate

For most children with DKA, acidosis can be corrected with insulin and fluids alone, without the administration of bicarbonate. Several adult studies and one pediatric study demonstrated minimal or no differences in the rapidity of correction of acidosis in patients with DKA treated with or without bicarbonate.^{32–34} Furthermore, there are several theoretical reasons to avoid bicarbonate administration in children with DKA. One study found that hepatic ketone production increased in patients treated with bicarbonate.³⁵ In addition, bicarbonate administration increases the risk of hypokalemia³⁶ and may lead to paradoxical acidosis of the cerebrospinal fluid.^{37,38} Finally, bicarbonate administration was associated with an increased risk of cerebral edema in one study of childhood DKA.³⁹ Therefore, routine administration of bicarbonate is not recommended. In rare circumstances, such as hemodynamic instability attributable to severe acidosis and not responding to standard measures or in the setting of symptomatic hyperkalemia, bicarbonate administration should be considered.

Monitoring

Most patients with DKA should be monitored in a pediatric intensive care unit or other unit with similar capabilities for monitoring and treating children with DKA. Specific recommendations for monitoring of children with DKA were recently developed in an international DKA consensus conference,^{40,41} and include monitoring of serum glucose concentrations hourly and electrolyte concentrations every 2 to 4 hours. Vital signs and mental status should be

monitored hourly and fluid intake and output should be accurately recorded.

COMPLICATIONS

Hypoglycemia and mild hypokalemia are the most frequent complications of DKA treatment. These complications are usually minor and clinically inapparent, and rarely result in permanent morbidity or mortality, provided that they are detected and treated promptly. More serious complications of DKA are rare, but include cerebral edema,³⁹ pulmonary edema,^{42–44} CNS hemorrhage or thrombosis,⁴⁵ other large vessel thromboses,⁴⁶ cardiac arrhythmias due to electrolyte disturbances,³⁹ pancreatitis,⁴⁷ renal failure,⁴⁸ intestinal necrosis,^{49–51} and rhinocerebral mucormycosis.⁵² DKA may stimulate a prothrombotic state and this may explain the propensity for CNS and other thromboses.^{46,53} Femoral venous catheters should be used with caution in children with DKA because of an increased tendency for deep venous thromboses.⁴⁶

Cerebral edema is the most frequent serious complication of DKA and occurs in approximately 1% of pediatric DKA episodes.^{39,54,55} Outcomes of DKA-related cerebral edema are poor with 21% to 24% mortality and 21% to 26% permanent neurologic morbidity.^{39,55} Some studies have suggested that mild, subclinical cerebral edema may be present in most patients with DKA,^{56,57} but only 1% or fewer develop cerebral edema of a degree sufficient to cause symptoms of increased intracranial pressure and CNS dysfunction. Symptoms and signs of cerebral edema include headache, altered mental status, hypertension, bradycardia, and other signs of increased intracranial pressure. Many investigators have attributed cerebral edema to rapid changes in serum osmolality or overly vigorous fluid resuscitation during treatment of DKA. Most studies which have used multivariate statistics to adjust for severity of DKA, however, have not found independent associations between osmotic factors (volume or sodium content of fluid infusion, changes in serum glucose or sodium concentrations) and the risk of cerebral edema.^{39,58,59} More recent studies suggest that cerebral edema during DKA may be predominantly vasogenic, and that osmolar factors may play a less important role.⁶⁰

Children at greatest risk for cerebral edema include those with higher blood urea nitrogen concentrations³⁹ at presentation and those presenting with greater hypocapnia.^{39,59} A lesser rise in the measured serum sodium concentration during treatment (as the serum glucose concentration falls) has also been shown to indicate increased risk for cerebral edema.^{39,61}

No pharmacologic agents have been clearly demonstrated to be effective for the treatment of DKA-related cerebral edema. Case reports have suggested that prompt treatment with mannitol (0.25–0.5 g/kg) may be

beneficial.^{62,63} Intubation with hyperventilation has been associated with poorer outcomes of DKA-related cerebral edema.⁶⁴ Therefore, routine therapeutic hyperventilation of intubated children with DKA should likely be avoided. CNS imaging in patients with suspected cerebral edema is recommended to rule out other etiologies of altered mental status such as CNS thromboses.

SUMMARY

Children with DKA present frequently to the pediatric emergency department. Most children recover uneventfully when treated with insulin, intravenous fluids, and electrolyte replacement, however, infrequent complications, such as cerebral edema, may have devastating consequences. Greater efforts are necessary to prevent DKA in children with established diabetes and to recognize and treat DKA promptly in children with new-onset diabetes. International recommendations for DKA treatment in children have recently been published and may be useful in standardizing the treatment of this condition.^{40,41}

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CME EXAM

Instructions for the *Pediatric Emergency Care* CME Program Examination

To earn CME credit, you must read the designated article and complete the examination below, answering at least 80% of the questions correctly. Mail a photocopy of the completed answer sheet to the Office of Continuing Education, Wolters Kluwer Health, 530 Walnut Street, 8th Floor East, Philadelphia, PA 19106. Only the first answer form will be considered for credit and must be received by Wolters Kluwer Health by September 15, 2004. Answer sheets will be graded and certificates will be mailed to each participant within six to eight weeks after WKH receipt. The answers for this examination will appear in the October 2004 issue of *Pediatric Emergency Care*.

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CME EXAMINATION July 2004

Please mark your answers on the ANSWER SHEET.

The Evaluation and Management of Children, *Glaser and Kuppermann*

1. The most common cause of DKA in children with known diabetes is:
 - a) Pneumonia
 - b) Gastrointestinal infection
 - c) Missed insulin
 - d) Emotional stress
 - e) Otitis media
2. One of the predominant stimuli for hepatic production of ketones in children with DKA is
 - a) Insulin
 - b) Glucose
 - c) Thyroxine
 - d) Cortisol
 - e) Bilirubin
3. A 4-year-old boy presents with a 2-week history of polyuria and polydipsia. Initial laboratory values include serum glucose of 752 mg/dl, an arterial pH of 7.1, and serum potassium of 4.6 mEq/L. After receiving an initial bolus of 20 cc/kg of normal saline, the child is hemodynamically stable and has brisk urine output. You order additional intravenous fluid with a potassium concentration of:
 - a) 0
 - b) 10 mEq/L
 - c) 20 mEq/L
 - d) 40 mEq/L
 - e) 60 mEq/L
4. In children with severe DKA, therapy with bicarbonate
 - a) Improves survival rates
 - b) Decreases ketone production
 - c) Maintains potassium levels
 - d) Reduces brain swelling
 - e) None of the above
5. A 13-year-old girl with known diabetes presents to the emergency department with DKA and appears to be 10% dehydrated. Vital signs are: T 39.6 C, P 145/min, R 36/min, BP 105/70 mm Hg. Her examination is remarkable for decreased skin turgor and rales at the right base. Initial laboratory results include: glucose 840 mg/dl, Na 131 mEq/L, K 3.1 mEq/L, and pH 7.07. After an initial bolus of 1000 cc of NS, all of the following therapeutic interventions are appropriate over the next several hours except:
 - a) Insulin 0.1 u/kg subcutaneously
 - b) $\frac{1}{2}$ normal saline IV
 - c) Potassium at 50 mEq/L
 - d) Ceftriaxone 1 gm
 - e) Potassium acetate

**ANSWER SHEET FOR THE PEDIATRIC EMERGENCY CARE
CME PROGRAM EXAM**

July 2004

Please answer the questions on page 482 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): _____

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- 1. (A) (B) (C) (D) (E)
- 2. (A) (B) (C) (D) (E)
- 3. (A) (B) (C) (D) (E)
- 4. (A) (B) (C) (D) (E)
- 5. (A) (B) (C) (D) (E)

Your evaluation of this CME activity will help guide future planning. Please respond to the following questions.

1. Did the content of the article(s) meet the stated learning objectives?
 Yes No

2. On a scale of 1 to 5, with 5 being the highest, how do you rank the overall quality of this educational activity as it pertains to your practice?
 5 4 3 2 1

3. As a result of meeting the learning objectives of this educational activity, will you be changing your practice behavior in a manner that improves your patient care? If yes, please explain.
 Yes No

4. Did you perceive any evidence of bias for or against any commercial products? If so, please explain.
 Yes No

5. Please state one or two topics that you would like to see addressed in future issues.

6. How long did it take you to complete this CME activity?
_____hour(s) _____minutes

**Mail by September 15, 2004 to
Office of Continuing Education
Wolters Kluwer Health
530 Walnut Street, 8th Floor East
Philadelphia, PA 19106**

CME EXAM ANSWERS

Answers for the Pediatric Emergency Care CME Program Exam

Below you will find the answers to the examination covering the review article in the April 2004 issue. All participants whose examinations were postmarked by June 15, 2004 and who achieved a score of 80% or greater will receive a certificate from Wolters Kluwer Health.

EXAM ANSWERS

April 2004

1. B
2. E
3. C
4. E
5. A