Management of Diabetic Ketoacidosis in Children and Adolescents

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Author Disclosure
Drs Cooke and Plotnick have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

After completing this article, readers should be able to:

1. Describe the typical presentation of diabetic ketoacidosis in children.
2. Discuss the treatment of diabetic ketoacidosis.
3. Explain the potential complications of diabetic ketoacidosis that can occur during treatment.

Introduction

Diabetic ketoacidosis (DKA) represents a profound insulin-deficient state characterized by hyperglycemia (>200 mg/dL [11.1 mmol/L]) and acidosis (serum pH <7.3, bicarbonate <15 mEq/L [15 mmol/L]), along with evidence of an accumulation of ketoacids in the blood (measurable serum or urine ketones, increased anion gap). Dehydration, electrolyte loss, and hyperosmolarity contribute to the presentation and potential complications. DKA is the most common cause of death in children who have type 1 diabetes. Therefore, the best treatment of DKA is prevention through early recognition and diagnosis of diabetes in a child who has polydipsia and polyuria and through careful attention to the treatment of children who have known diabetes, particularly during illnesses.

Presentation

Patients who have DKA generally present with nausea and vomiting. In individuals who have no previous diagnosis of diabetes mellitus, a preceding history of polyuria, polydipsia, and weight loss usually can be elicited. With significant ketosis, patients may have a fruity breath. As the DKA becomes more severe, patients develop lethargy due to the acidosis and hyperosmolarity; in severe DKA, they may present with coma. Acidosis and ketosis cause an ileus that can lead to abdominal pain severe enough to raise concern for an acutely inflamed abdomen, and the elevation of the stress hormones epinephrine and cortisol in DKA can lead to an elevation in the white blood cell count, suggesting infection. Thus, leukocytosis during DKA is not a reliable indicator of infection. On the other hand, infection can be a precipitant of DKA. Therefore, careful evaluation is important, with early treatment of any infection.

The most common cause for DKA in a patient who has known diabetes is omission of insulin doses. Such action can result from failure of an insulin pump, prolonged disconnection from an insulin pump without appropriate monitoring, and improper discontinuation of insulin during an illness associated with poor oral intake. For an older child who has the responsibility for managing his or her diabetes without adult oversight, DKA most often is caused by the child forgetting to administer insulin doses. Recurrent DKA almost always is caused by intentional omission of insulin. Improved oversight of diabetes management can eliminate this cause of DKA, but adherence can be a challenge for older teens developing independence from their parents.

Intercurrent illnesses can increase insulin requirements, and a failure to meet the increased requirement can lead to ketoacidosis in a child who has diabetes. However, careful monitoring during illnesses should identify ketosis early so proper management can

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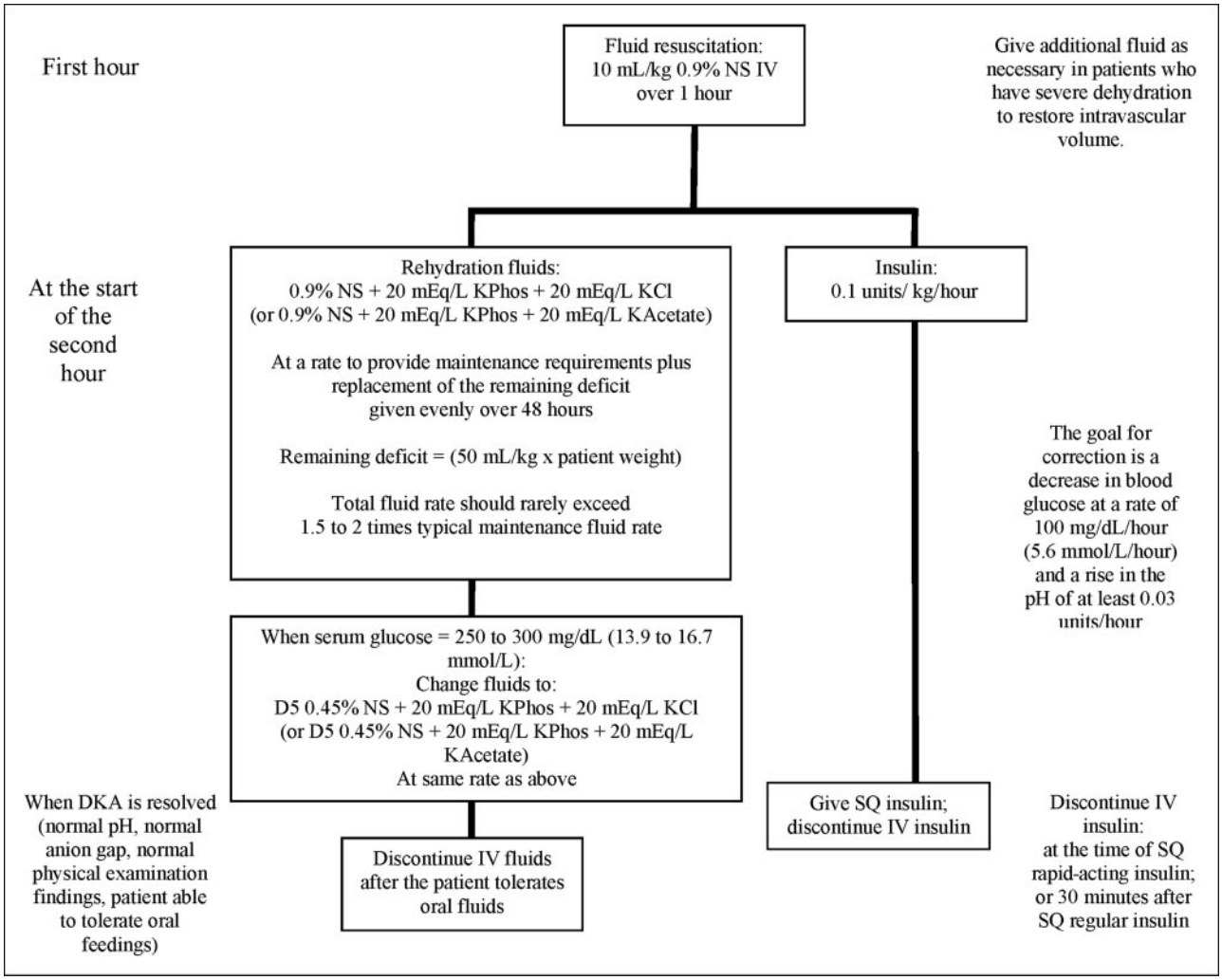

Figure. Outline of therapy that may be required for a child presenting with moderately severe diabetic ketoacidosis (DKA) (6% dehydration). No patient who has DKA should be considered "typical." Each requires determination of specific individual requirements for treatment, with adjustments to treatment based on careful monitoring. IV=intravenous, KAcetate=potassium acetate, KCl=potassium chloride, KPhos=potassium phosphate, NS=normal saline, SQ=subcutaneous

be provided to prevent deterioration to DKA or to identify DKA at an early, mild stage, when treatment can lower the risk of morbidity and mortality.

Treatment

Treatment of DKA is aimed at correcting the metabolic abnormalities while avoiding complications that can occur during correction. Therapy consists of fluid and electrolyte replacement, insulin administration, and careful ongoing monitoring of clinical and laboratory factors (Figure).

Fluid and Electrolyte Replacement

The osmotic diuresis produced by glucosuria results in large water and electrolyte losses, exacerbated by compromised intake due to nausea and vomiting. Intravenous fluid replacement is begun as soon as the diagnosis of DKA is established. Initial fluid resuscitation begins with 10 mL/kg of isotonic fluid, either 0.9% saline or lactated Ringer solution, administered over 1 hour. For more critically ill children, for whom there is concern over impending cardiovascular collapse, additional resuscitation fluid should be administered more rapidly.

After the initial fluid resuscitation, the remainder of

the fluid deficit is replaced evenly over 48 hours. Most patients who have DKA are approximately 6% dehydrated (10% for children <2 years). For patients presenting with more severe DKA (serum glucose >600 to 800 mg/dL [33.3 to 44.4 mmol/L] and pH <7.1), fluid losses are approximately 9% of body weight (15% for children <2 years). Maintenance fluid requirements are added to this deficit replacement to provide the total fluid requirements, which rarely exceed 1.5 to 2 times the usual daily fluid requirement. Urine losses generally are not replaced to avoid excessively rapid fluid delivery. However, careful attention to the fluid balance during treatment is necessary to identify the patients who will need additional fluid. The 0.9% saline (with added potassium) is continued as the hydration fluid until the blood glucose value declines to less than 300 mg/dL (16.7 mmol/L). At that time, our practice is to change the fluid to D5 0.45% saline (with added potassium). The American Diabetes Association recommendation is that deficit replacement fluids contain at least 0.45% saline with added potassium. If the blood glucose concentration declines below 150 mg/dL (8.3 mmol/L), the dextrose content may need to be increased to 10% or even 12.5%.

Patients who have DKA may present with high, normal, or low serum potassium values. However, all affected patients have total body potassium depletion. Both insulin treatment of DKA and correction of the acidosis cause potassium to move intracellularly. Because of this effect, hypokalemia is a potentially fatal complication during treatment of DKA. Unless the patient exhibits hyperkalemia or anuria, potassium should be added to the intravenous fluids at the beginning of the second hour of therapy. Otherwise, potassium is added as soon as urine output is established or the hyperkalemia abates. If the patient presents with hypokalemia, potassium replacement is initiated immediately. Most patients require 30 to 40 mEq/L of potassium in the replacement fluids, with adjustment based on serum potassium concentrations that are measured every 1 to 2 hours.

DKA results in significant phosphate depletion, and serum phosphate values decrease during treatment. Hypophosphatemia may cause metabolic disturbances. However, clinical studies have not shown benefit from phosphate replacement during the treatment of DKA, although phosphate replacement should be given if the values decrease below 1 mg/dL.

Even in the absence of severe hypophosphatemia, however, many clinicians elect to provide phosphate in intravenous fluids, typically by giving half of the potassium replacement as potassium phosphate. This practice decreases chloride delivery to the patient, minimizing the hyperchloremic metabolic acidosis that occurs in most patients. The hyperchloremia generally is of no clinical significance, although it can confound the clinician's interpretation of DKA resolution. Administration of potassium acetate to provide the other half of the potassium replacement further decreases the chloride load. The serum calcium concentration must be monitored if phosphorus is given, due to the risk of hypocalcemia. If hypocalcemia develops, phosphate administration should be stopped.

Bicarbonate losses are large in DKA. However, during the treatment of DKA, the patient can produce substantial bicarbonate as insulin stimulates the generation of bicarbonate from the metabolism of ketones. Consistent with this, clinical trials have failed to show any benefit of bicarbonate administration during the treatment of DKA. Potential risks of bicarbonate therapy include paradoxic central nervous system acidosis and exacerbation of hypokalemia. Bicarbonate treatment also has been associated with cerebral edema, the most common cause of mortality for children who have DKA. Therefore, bicarbonate treatment should be considered only in cases of extreme acidosis, such as for the patient whose pH is <6.9, when the acidosis may impair cardiovascular stability, or as treatment of life-threatening hyperkalemia. If bicarbonate administration is believed to be necessary, 1 to 2 mmol/kg (added to 0.45% saline) should be provided over 1 to 2 hours.

Insulin

Insulin treatment is begun after the initial fluid resuscitation; that is, at the beginning of the second hour of therapy (beginning insulin treatment at the same time as fluid resuscitation increases the risks of severe hypokalemia and of rapidly and excessively decreasing the serum osmolarity). Insulin is administered as a continuous intravenous infusion of regular insulin at a rate of 0.1 units/kg per hour; a bolus should not be given at the start of therapy. The infusion tubing should be prepared by running 30 to 50 mL of the insulin solution through the tube to saturate binding sites on the tube lining. If intravenous administration of insulin is not possible, short- or rapid-acting insulin injected intramuscularly or subcutaneously every 1 or 2 hours can be effective.

Resolution of the acidosis in DKA invariably takes longer than the time to achieve a normal blood glucose concentration. The temptation to decrease the rate of insulin administration based on glucose values should be resisted because this practice delays resolution of the acidosis. The dose of insulin should remain at

0.1 units/kg per hour until the acidosis resolves (pH >7.3, bicarbonate >15 mEq/L [15 mmol/L]). The insulin dose should be decreased only if hypoglycemia or a decrease in serum glucose persists despite administration of maximal dextrose concentrations in the intravenous fluid. If the acidosis is not resolving, the insulin dose should be increased to 0.15 or 0.20 units/kg per hour.

Monitoring

The initial assessment of a patient who has DKA involves evaluation of vital signs and the physical examination, including mental status and a neurologic evaluation. Such baseline assessments, along with results of laboratory testing, serve to determine if appropriate treatment for infection is necessary and to adjust fluid resuscitation based on the more in-depth evaluation of the cardiovascular status and the degree of the patient's dehydration. In addition, if the patient is markedly obtunded, a nasogastric tube should be placed to decrease the risk of aspiration. Over the ensuing hours, vital signs and mental status are monitored at least every hour, and the balance of total fluid intake and fluid output is calculated each hour. The goal of monitoring is to ascertain that the patient shows signs of rehydration and improving mental status over time along with biochemical resolution of the DKA.

Serum glucose, electrolytes (including blood urea nitrogen and creatinine), and pH and urine ketones should be measured at presentation. Subsequently, serum glucose and pH should be measured hourly, with serum electrolytes and urine ketones assessed every 2 to 3 hours. If phosphate is administered, serum calcium concentrations must be monitored. The goal for correction of hyperglycemia is to induce a 100-mg/dL (5.6-mmol/L) per hour decrease in the serum glucose value. The persistence of severe hyperglycemia suggests inadequate rehydration (or incorrect mixing of the insulin). Too rapid a decrease, however, may indicate too rapid a rate of rehydration. After the first hour, the pH should increase at least 0.03 units per hour. A slower rise suggests a need for a higher insulin dose or for increased hydration.

Hyperglycemia causes the osmotic shift of water into the intravascular compartment, causing dilutional hyponatremia. The calculation for the corrected sodium concentration accounts for this effect:

$$[Na+]_{corrected} = [Na+]_{measured} + 1.6 \times ([glucose]-100)/100$$

Both the measured and the corrected serum sodium values should increase as the serum glucose concentration decreases during treatment of DKA. A failure of the corrected sodium value to rise or, even more significantly, a fall in either sodium value suggests overly rapid rehydration.

Cerebral Edema

Cerebral edema is responsible for most of the deaths due to DKA in children, and significant neurologic morbidity persists in many survivors. Although cerebral edema typically presents 4 to 12 hours after treatment has begun, it can present later or earlier, including before treatment is initiated. The cause of cerebral edema in DKA is not known, although a number of mechanisms have been proposed. These theories include cerebral ischemia and hypoxia, fluid shifts due to inequalities in osmolarity between the extravascular and intravascular intracranial compartments, increased cerebral blood flow, and altered membrane ion transport. Risk factors that have been identified for the development of cerebral edema include young age, DKA in a child who has undiagnosed diabetes, factors indicating a more severe presentation (pH <7.2 and lower serum bicarbonate concentration, higher serum glucose concentration, higher blood urea nitrogen concentration, a calculated serum sodium concentration in the hypernatremic range, and hypocapnia), a lack of rise of the corrected sodium concentration during rehydration, and treatment with bicarbonate. Earlier uncontrolled studies had suggested that a higher rate of rehydration increased the risk of cerebral edema. Although subsequent controlled studies have not found the rate of fluid administration to be a factor for cerebral edema, current recommendations for more gradual, even fluid replacement during the treatment of DKA are related to the concern that a higher rate of rehydration may increase the risk for cerebral edema.

The signs and symptoms of cerebral edema include severe headache, sudden deterioration in mental status, bradycardia (or a sudden, persistent drop in heart rate not attributable to improved hydration), hypertension, cranial nerve dysfunction, and incontinence. If suspected, immediate treatment should be initiated with 0.25 to 1.0 g/kg of intravenous mannitol. If the patient requires intubation, hyperventilation should be avoided because it has been shown to be associated with worse outcomes.

Resolution

When the ketoacidosis has resolved, the patient may be weaned from intravenous fluids and intravenous insulin to oral intake and subcutaneous insulin. Criteria for this transition include a normal sensorium and normal vital

signs, an ability to tolerate oral intake, and resolution of the acidosis, reflected by a normal pH, a serum bicarbonate value greater than 18 mEq/L (18 mmol/L), and a normal anion gap. Because of excess chloride delivered with intravenous fluids during the treatment of DKA, many patients develop a hyperchloremic metabolic acidosis. In these patients, the pH and serum bicarbonate concentrations do not normalize completely in spite of the resolving ketoacidosis. When such patients achieve a normal anion gap, they should be "transitioned" from intravenous fluids and insulin to oral nutrition and subcutaneous insulin.

The action of intravenous insulin dissipates in minutes. Therefore, intravenous insulin should not be discontinued until a dose of insulin is administered subcutaneously. When using rapid-acting insulin analogs, subcutaneous insulin can be given just before the intravenous infusion is stopped. When administering regular insulin, the subcutaneous injection should be given 30 minutes before the infusion is stopped. It is best to make the transition from intravenous insulin to subcutaneous insulin at the time of a meal. Details on the subsequent management of diabetes mellitus can be found in our previously published article (Cooke, 2008).

Summary

- Based on some research evidence, DKA is a significant contributor to morbidity and mortality in children who have type 1 diabetes, and cerebral edema is responsible for most of the deaths during DKA in children. (Dunger, 2004)
- Based on strong research evidence, treatment of DKA requires replacement of water and electrolytes and correction of the insulin deficiency. (Dunger, 2004)
- Based on some research data and consensus opinion, after providing initial volume expansion (if needed), fluid resuscitation of children who have DKA should be calculated to rehydrate evenly over at least 48 hours. Initial fluid resuscitation should be with an isotonic solution; subsequent fluid management should be with a solution that has a tonicity of at least 0.45% saline. (Dunger, 2004)
- Based on strong research evidence, insulin treatment for DKA should begin at a dose of 0.1 units/kg per hour and generally should remain at or above this level until the ketoacidosis is resolved. (Dunger, 2004)
- Based on some research evidence, risk factors for the development of cerebral edema during treatment of DKA include the severity of acidosis, greater hypocapnia (after adjusting for the degree of acidosis), higher blood urea nitrogen concentration at presentation, and treatment with bicarbonate. (Dunger, 2004; Glaser, 2002)

Suggested Reading

American Diabetes Association. Diabetic ketoacidosis in infants, children, and adolescents. *Diabetes Care*. 2006;29:1150–1159

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Dunger DB, Sperling MA, Acerini CL, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. *Arch Dis Child*. 2004;89:188–194

Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. *N Engl J Med*. 2002;344:264–269

Marcin JP, Glaser N, Barnett P, et al. American Academy of Pediatrics. The Pediatric Emergency Medicine Collaborative Research Committee. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J Pediatr*. 2002;141:793–797

PIR Quiz

Quiz also available online at www.pedsinreview.aappublications.org.

5. The first step in managing diabetic ketoacidosis (DKA) is:

   A. Administration of potassium acetate to decrease the chloride load.
   B. Correction of acidosis with 1 to 2 mmol/kg of bicarbonate.
   C. Correction of hypokalemia with 30 to 40 mEq/L of potassium chloride.
   D. Fluid resuscitation with 0.9% saline.
   E. Replacement of phosphorus using potassium phosphate.

6. Insulin therapy in the management of DKA should begin:

   A. After the first hour of fluid therapy.
   B. After the second hour of fluid therapy.
   C. After the third hour of fluid therapy.
   D. At the initiation of fluid therapy.
   E. When the blood glucose is greater than 400 mg/dL (22.2 mmol/L).

7. Most deaths in children during DKA are due to:

   A. Cardiac arrhythmia.
   B. Cerebral edema.
   C. Hyponatremic seizures.
   D. Iatrogenic hypoglycemia.
   E. Renal failure.

8. An episode of severe DKA in a 10-year-old patient has now resolved. You plan to begin her on subcutaneous rapid-acting insulin. In relation to stopping intravenous insulin, the first dose of subcutaneous insulin should be given:

   A. 30 minutes before.
   B. 1 hour before.
   C. Just before.
   D. 30 minutes after.
   E. 1 hour after.

9. Which metabolic derangement is a potential complication that can occur due to insulin therapy for DKA?

   A. Hyperchloremia.
   B. Hyperkalemia.
   C. Hypernatremia.
   D. Hypokalemia.
   E. Hyponatremia.

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