Managing Diabetic Ketoacidosis in Children

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INTRODUCTION

Diabetic ketoacidosis is a life-threatening complication of childhood diabetes (mainly associated with type 1 or insulin-dependent diabetes).[1] Thirty percent of children with new-onset type 1 diabetes present with diabetic ketoacidosis, and an additional 6% to 8% develop diabetic ketoacidosis each year. [2,3] Presenting symptoms may be nonspecific, but laboratory findings of hyperglycemia and ketosis are diagnostic. Treatment involves administration of intravenous fluids and insulin. Children with diabetic ketoacidosis require serial laboratory studies for electrolyte derangements and close clinical monitoring for signs of cerebral edema, an uncommon but potentially fatal complication of pediatric diabetic ketoacidosis. For years, clinical guidelines for the treatment of diabetic ketoacidosis have recommended limited (if any) fluid resuscitation, isotonic fluids, and slow fluid rehydration rates in order to reduce the rate of cerebral edema.[4] A recently completed clinical trial explored the relationship between fluid replacement and cerebral injury and edema, and it provided new evidence to guide safe and effective fluid treatment for pediatric diabetic ketoacidosis.[5]

DIAGNOSIS

Clinical Presentation

Early signs and symptoms of diabetic ketoacidosis include polyuria, polydipsia, weight loss, and fatigue. These symptoms may be more difficult to recognize in younger children, particularly those who are preverbal or use diapers. A detailed history may elicit these signs and symptoms of diabetic ketoacidosis in children with new-onset diabetes and identify potential triggers, including nonadherence to insulin regimen (particularly among adolescents) or intercurrent illness.

If untreated, a child with diabetic ketoacidosis may develop abdominal pain, vomiting, and headache. Clinicians should maintain a high index of suspicion and low threshold for laboratory testing, even for children without known diabetes. Despite significant dehydration, many children with diabetic ketoacidosis present with normal blood pressure or, occasionally, hypertension.[6] Clinical signs (eg, pulse rate or peripheral perfusion) may be inaccurate for assessing the degree of dehydration in children with diabetic ketoacidosis.

As diabetic ketoacidosis progresses, respiratory compensation for the metabolic acidosis of diabetic ketoacidosis causes tachypnea and a deep and labored breathing pattern referred to as Kussmaul respirations. Changes in mental status, including drowsiness, irritability, lethargy, and confusion, may also occur.

Diabetic Ketoacidosis Definition

Based on recent international consensus, diabetic ketoacidosis is defined by hyperglycemia and metabolic acidosis with low serum bicarbonate level, high serum ketones level, or urinary ketones (Table 1).[7]

Laboratory Evaluation

Once a diagnosis of diabetic ketoacidosis is suspected, initial laboratory studies should include point-of-care glucose, venous blood gas, serum electrolyte levels (including magnesium and phosphorus), serum creatinine level, β-hydroxybutyrate level, and urinalysis and a pregnancy test in adolescent women (Table 2). Measured serum sodium level should be corrected for the presence of hyperglycemia with the following formula: corrected sodium=measured sodium+[1.6 (glucose−100)/100]. A complete blood count is frequently obtained to evaluate for an infectious trigger for diabetic ketoacidosis but may demonstrate a nonspecific leukocytosis.[8] In patients with abnormal serum potassium levels (either high or low), an electrocardiogram is indicated. Hemoglobin A1c provides a measure of glucose control over the previous several months.

Acute kidney injury is present in a substantial percentage of children with diabetic ketoacidosis. In a retrospective study of 165 and a prospective study of

Table 1. Diabetic ketoacidosis definition.

Criteria	Laboratory Test	Level
Hyperglycemia	Blood glucose	>200 mg/dL (11 mmol/L)
Metabolic acidosis	Venous pH	<7.3
	Serum bicarbonate	<15 mEq/L (15 mmol/L)
	Serum β-hydroxybutrate level	>30 mg/dL (3 mmol/L)
	Urine ketosis	Moderate to large

1,359 diabetic ketoacidosis episodes, 64% and 43%, respectively, had acute kidney injury, and most received a diagnosis at presentation.[9,10] In both studies, acute kidney injury was associated with more severe dehydration and acidosis.

TREATMENT

The mainstays of diabetic ketoacidosis treatment are intravenous fluid resuscitation and insulin administration (Figure 1).

Fluid and Electrolyte Replacement

At the time of presentation, most children in diabetic ketoacidosis are typically 5% to 10% dehydrated. The goal is repletion of the patient's fluid deficit over the first 36 to 48 hours (Table 3). Initial fluid resuscitation with 10 mL/kg normal saline solution bolus is indicated. Patients with Glasgow Coma Scale scores of 14 or 15 who exhibit persistent tachycardia or signs of poor perfusion may safely receive an additional normal saline solution bolus immediately after completion of the first bolus.

After administration of the bolus(es), additional intravenous fluids should be provided to replete the remaining fluid deficit and provide ongoing maintenance. Table 3 demonstrates a range of fluid administration rates that can safely be used based on patient weight, estimated fluid deficit, and desired duration of repletion (typically 36 to 48 hours) but not patient age.[5] Intravenous fluids are continued until the acidosis has resolved and the patient is able to tolerate oral intake and is transitioned from intravenous to subcutaneous insulin. Fluid repletion and intravenous insulin will gradually correct the marked acidosis seen in children with diabetic ketoacidosis, and sodium bicarbonate should not be administered.[11]

Even when the serum potassium level is elevated, a child with diabetic ketoacidosis will have a total potassium deficit as the intracellular exchange of hydrogen ions for potassium leads to urinary potassium loss. Therefore, the addition of 40 mEq of potassium equivalent per liter of fluid (eg, 20 mEq potassium phosphate and 20 mEq potassium acetate or potassium chloride per liter) is typical when the serum potassium level drops below 5 mEq/L (5 mmol/L) and the patient has established urine output.

Children with diabetic ketoacidosis are frequently prevented from taking anything by mouth owing to nausea and the risk of worsening mental status with inability to protect an airway. However, in the appropriate clinical scenario, small amounts of water or ice chips can improve patient comfort.

Insulin Infusion

Insulin should be started after fluid resuscitation has been initiated and the diagnosis of diabetic ketoacidosis has been confirmed. In children with mild diabetic ketoacidosis who are able to tolerate oral fluids and nutrition, rapid-acting insulin may be given subcutaneously. However, for children with moderate to severe diabetic ketoacidosis (defined by pH<7.2), regular insulin should be delivered by continuous intravenous infusion (0.05 to 0.1 units/kg per hour).[7] Insulin boluses should be avoided. The insulin infusion should not be discontinued until the acidosis resolves.

Prevention of Hypoglycemia

During diabetic ketoacidosis treatment, the serum glucose level will decrease. When serum glucose levels drop below 300 mg/dL (16.7 mmol/L), dextrose should be added to the intravenous fluids without changing the insulin dosing. The "2-bag method" can be used to titrate patient blood glucose by varying the rates of 2 fluid types (1 with and 1 without dextrose) to keep the

Table 2. Other laboratory abnormalities associated with diabetic ketoacidosis.

Laboratory Study	Expected Result	Reason
Glucose	↑	Elevated despite intracellular depletion
Sodium	↓	Hyperglycemia decreases measured serum sodium
Potassium	↑ or normal	Serum potassium increases owing to displacement from intracellular space despite total body depletion
Phosphate	↑ or normal	Serum phosphate initially increases owing to displacement from intracellular space despite total body depletion
Anion gap	↑	Elevated because of ketosis and lactic acidosis

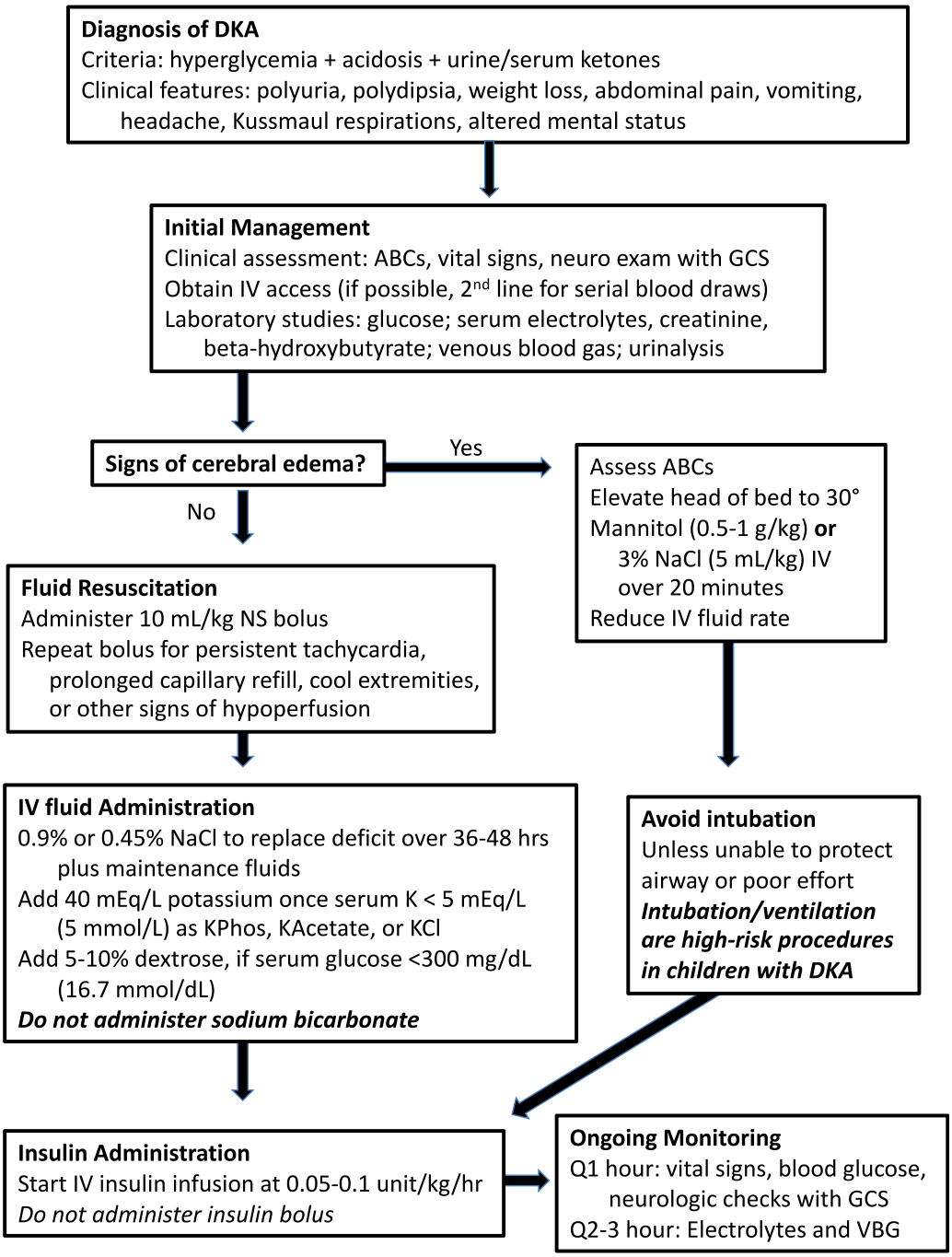

Figure 1. Diabetic ketoacidosis clinical algorithm. Concept adapted from Translating Emergency Knowledge for Kids Pediatric Diabetic Ketoacidosis Pediatric Package Algorithm. Visit www.trekk.ca/ for the complete algorithm. *ABC*, airway, breathing, circulation; *DKA*, diabetic ketoacidosis; *GCS*, Glasgow Coma Scale; *K*, potassium; *KAcetate*, potassium acetate; *KCl*, potassium chloride; *NaCl*, sodium chloride; *NS*, normal saline solution; *VBG*, venous blood gas.

serum glucose level between 150 and 250 mg/dL (8.3 to 13.9 mmol/L) (Figure 2).[12] Alternatively, clinicians can steadily increase the dextrose content of the fluid by switching the amount of dextrose as the patient's serum glucose level falls. If serum glucose level continues to decrease despite administration of fluids containing 10% dextrose, the dose of the insulin infusion may be decreased to 0.05 units/kg per hour.

Airway Management

Intubation should be avoided in children with diabetic ketoacidosis except when a child has inadequate respiratory

Table 3. Fluid deficit by patient weight with range of appropriate fluid administration rates (after initial boluses).

Weight (kg)	Estimated Deficit (5%-10% Dehydration)	Replacement of Estimated Deficit + Maintenance = Initial Fluid Rate (mL/hour)*
10	500-1,000 mL	48-78
20	1,000-2,000 mL	77-135
30	1,500-3,000 mL	95-183
40	2,000-4,000 mL	113-230
50	2,500-5,000 mL	132-278
60	3,000-6,000 mL	150-325
70	3,500-7,000 mL	168-373

*Range based on estimated deficit and desired replacement rate over 36 to 48 hours with slower rates for smaller estimated fluid deficits or longer durations of therapy.

effort or an inability to adequately protect the airway. Assuming control of ventilation runs the risk of blunting compensatory respiratory alkalosis to correct for the metabolic acidosis. If intubation is required, hyperventilation beyond this compensatory level has been associated with worse clinical outcomes and should also be avoided.[13]

Patient Monitoring

Close monitoring of mental status with hourly measurements of the patient's Glasgow Coma Scale score is essential for rapid identification of neurologic deterioration. Regular laboratory studies include hourly serum glucose level as well as venous blood gas and serum electrolyte levels every 2 to 3 hours. The placement of a second peripheral intravenous line for serial laboratory draws avoids additional needlesticks. Central venous catheter placement is associated with an increased risk of deep venous thrombosis in pediatric diabetic ketoacidosis and should be avoided.[14,15]

Disposition and Transfer Considerations

Disposition of patients with diabetic ketoacidosis depends on the severity of the disease and the resources available. Patients with established diabetes and mild diabetic ketoacidosis (pH 7.2 to 7.3) are candidates for potential discharge home after emergency department treatment. To be safely managed as outpatients, children need to demonstrate improvement with regard to laboratory abnormalities and the ability to tolerate oral fluids with adequate resources for home monitoring and close follow-up. Otherwise, children require hospitalization in a center that can provide close clinical and laboratory monitoring until diabetic ketoacidosis resolves.

Owing to the need for hourly glucose testing, close neurologic monitoring, and frequent laboratory studies, many children with diabetic ketoacidosis are managed in intensive care units. Patients with severe diabetic ketoacidosis (pH<7.1), altered mental status, young age, or severe electrolyte abnormalities always require intensive care. When transferring a child with diabetic ketoacidosis, the use of a critical care transport team should be considered in all cases and is necessary for children with altered mental status or prolonged transport time when monitoring of blood glucose or titration of intravenous fluids may be necessary en route.

CEREBRAL EDEMA

Although <1% of pediatric episodes of diabetic ketoacidosis are associated with the development of clinically overt cerebral edema with altered mental status, subclinical cerebral edema occurs more frequently and may be associated with long-term neurocognitive deficits.[16] Although some children present for care with existing signs of cerebral injury or edema, most cases develop within 12 to 24 hours of treatment initiation.[11,16] The diagnosis of cerebral edema is made clinically based on neurologic abnormalities, vital sign changes, and symptoms of increased intracranial pressure.[17] Cranial computed tomography is not required for diagnosis and should not delay treatment with hyperosmolar therapy (mannitol or hypertonic saline solution).[18]

Prevention

Historically, cerebral edema in children with diabetic ketoacidosis was assumed to be caused by osmotic shifts from rapid correction of dehydration or electrolyte abnormalities. In recognition of this potential association, pediatric diabetic ketoacidosis treatment protocols have limited the rate and volume of intravenous fluid administration. However, a decade of high-quality evidence has challenged these assumptions.

First, a 10-center case control study of 61 cases (children with diabetic ketoacidosis associated with

Figure 2. Two-bag fluid system. One bag contains 0.9% or 0.45% saline solution with 10% dextrose, and the other bag contains 0.9% or 0.45% saline solution without dextrose. To prevent hypoglycemia, an infusion of the dextrose-containing fluid is initiated when serum glucose level drops below 300 mg/dL (16.7 mmol/L) and increased to keep serum glucose levels between 150 and 250 mg/dL (8.3 to 13.9 mmol/L). The rate of the nondextrose-containing fluid is decreased accordingly to maintain a constant total fluid infusion rate.

cerebral edema) and 355 selected controls (children with diabetic ketoacidosis without cerebral edema) investigated treatment-related risk factors of cerebral edema.[11] After adjusting for diabetic ketoacidosis severity and degree of dehydration, the rate of fluid administration was not associated with cerebral edema. The only modifiable factor associated with cerebral edema identified after adjustment for diabetic ketoacidosis severity was the administration of sodium bicarbonate, which should be avoided.

Following this observation, Pediatric Emergency Care Applied Research Network investigators completed a 13-center randomized clinical trial of children younger than 18 years to compare the safety of 4 diabetic ketoacidosis fluid rehydration protocols.[5] After the initial 0.9% sodium chloride fluid bolus, children were randomized to either faster or slower fluid administration rate (0.9% or 0.45% sodium chloride fluids) for subsequent rehydration. In this study of nearly 1,400 children with diabetic ketoacidosis, rates of acute neurologic deterioration as well as short- and longer-term neurocognitive outcomes were similar between treatment groups, suggesting that neither the rate of fluid administration nor the sodium content within the ranges studied caused the brain injury.[5]

Based on the findings of this high-quality clinical trial, clinicians should use hydration status to guide the fluid resuscitation of children with diabetic ketoacidosis. Specifically, restricting fluid administration because of concerns about causing cerebral edema appears unfounded in children with initial Glasgow Coma Scale scores of 14 or 15.

Treatment

Once recognized, cerebral edema should be treated rapidly. Precautions for increased intracranial pressure, including elevation of the head of the bed, should be instituted. Either intravenous mannitol (0.5 to 1 mg/kg) or hypertonic 3% saline solution (5 mL/kg) can be rapidly administered, although hypertonic saline solution is being used increasingly as a first-line therapy.[19] One small study found an association between hypertonic saline solution and mortality, but this was likely owing to unmeasured confounding.[20] We believe that clinicians should not hesitate to use this therapy to treat cerebral edema in children.

In conclusion, children with diabetic ketoacidosis, particularly those with previously undiagnosed diabetes, may present with nonspecific symptoms. Early recognition with appropriate laboratory screening can identify children with diabetic ketoacidosis and drive appropriate therapy. Fluid hydration coupled with continuous insulin infusion is the cornerstone of therapy. Frequent clinical and laboratory monitoring is essential for clinicians to recognize and address complications, including cerebral edema. In contrast with prior teachings, intravenous fluid administration can be liberalized to appropriately treat dehydration associated with diabetic ketoacidosis in patients without evidence of cerebral edema prior to treatment.

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REFERENCES

1. A. Amaize and K.B. Mistry. Emergency Department Visits for Children and Young Adults With Diabetes, 2012. HCUP Statistical Brief #203. April 2016. Agency for Healthcare Research and Quality, Rockville, MD. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb203-Emergency-Department-Children-Diabetes.pdf. Accessed March 29, 2021
2. Divers J, Mayer-Davis EJ, Lawrence JM, et al. Trends in incidence of type 1 and type 2 diabetes among youths — selected counties and Indian reservations, United States, 2002-2015. *MMWR Morb Mortal Wkly Rep*. 2020;69:161-165.
3. Cengiz E, Xing D, Wong JC, et al. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. *Pediatr Diabetes*. 2013;14:447-454.
4. 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.
5. Kuppermann N, Ghetti S, Schunk JE, et al. Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. *N Engl J Med*. 2018;378:2275-2287.
6. DePiero A, Kuppermann N, Brown KM, et al. Hypertension during diabetic ketoacidosis in children. *J Pediatr*. 2020;223:156-163.e5.
7. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2018;19(Suppl 27):155-177.
8. Flood RG, Chiang VW. Rate and prediction of infection in children with diabetic ketoacidosis. *Am J Emerg Med*. 2001;19:270-273.
9. Hursh BE, Ronsley R, Islam N, et al. Acute kidney injury in children with type 1 diabetes hospitalized for diabetic ketoacidosis. *JAMA Pediatr*. 2017;171:e170020.
10. Myers SR, Glaser NS, Trainor JL, et al. Frequency and risk factors of acute kidney injury during diabetic ketoacidosis in children and association with neurocognitive outcomes. *JAMA Netw Open*. 2020;3:e2025481.
11. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med*. 2001;344:264-269.
12. Munir I, Fargo R, Garrison R, et al. Comparison of a "two-bag system" versus conventional treatment protocol ("one-bag system") in the management of diabetic ketoacidosis. *BMJ Open Diabetes Res Care*. 2017;5:e000395.
13. Marcin JP, Glaser N, Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J Pediatr*. 2002;141:793-797.
14. Gutierrez JA, Bagatell R, Samson MP, et al. Femoral central venous catheter-associated deep venous thrombosis in children with diabetic ketoacidosis. *Crit Care Med*. 2003;31:80-83.
15. Worly JM, Fortenberry JD, Hansen I, et al. Deep venous thrombosis in children with diabetic ketoacidosis and femoral central venous catheters. *Pediatrics*. 2004;113:e57-e60.
16. Glaser NS, Wootton-Gorges SL, Buonocore MH, et al. Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. *Pediatr Diabetes*. 2006;7:75-80.
17. Muir AB, Quisling RG, Yang MC, et al. Cerebral edema in childhood diabetic ketoacidosis: natural history, radiographic findings, and early identification. *Diabetes Care*. 2004;27:1541-1546.
18. Soto-Rivera CL, Asaro LA, Agus MS, et al. Suspected cerebral edema in diabetic ketoacidosis: is there still a role for head CT in treatment decisions? *Pediatr Crit Care Med*. 2017;18:207-212.
19. Decourcey DD, Steil GM, Wypij D, et al. Increasing use of hypertonic saline over mannitol in the treatment of symptomatic cerebral edema in pediatric diabetic ketoacidosis: an 11-year retrospective analysis of mortality*. *Pediatr Crit Care Med*. 2013;14:694-700.
20. Tasker RC, Burns J. Hypertonic saline therapy for cerebral edema in diabetic ketoacidosis: no change yet, please. *Pediatr Crit Care Med*. 2014;15:284-285.