

# Pediatric Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

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Diabetic ketoacidosis (DKA) is an important complication of childhood diabetes mellitus and the most frequent diabetes-related cause of death in children [1,2]. In various population-based studies, reported rates of DKA at presentation of type 1 diabetes have ranged from as low as 15% to as high as 83% [3–7], with most North American and European studies reporting rates of approximately 40%. Although DKA occurs less frequently in children with type 2 diabetes, case series have documented frequencies of DKA at diagnosis of type 2 diabetes in children ranging from 6% to 33% [8–11]. A diagnosis of type 2 diabetes cannot be excluded based on the occurrence of DKA.

Young children with new onset of type 1 diabetes are more likely to present with DKA [4,6,12], as are children who reside in countries with a low overall prevalence of type 1 diabetes [5]. The higher frequency of DKA at presentation in these groups likely reflects the greater difficulty in recognizing symptoms of diabetes in these populations. In a European study, an educational program directed at parents and primary care pediatricians was shown to decrease the frequency of DKA at diagnosis of type 1 diabetes from almost 80% to just 12.5%, which supported the concept that the frequency of DKA at presentation of diabetes is related to recognition of symptoms of diabetes in the population studied [7].

In children who have established diabetes, DKA may occur with episodes of infection or other illnesses or with insulin omission or malfunction of diabetes care equipment, such as insulin pumps. In children who have established diabetes, DKA occurs at a rate of approximately 1% to 8% per year [4,13–15]. DKA in patients who have established diabetes occurs more frequently in persons with

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lower socioeconomic status, lack of adequate health insurance, higher HbA1c levels, and psychiatric disorders [13]. Insulin omission is the most frequent cause of DKA in children who have known diabetes. One study investigated the frequency of viral and bacterial infections in children who have DKA. Among all children who presented with DKA, bacterial infections were present in only 13% and viral infections in 18% [16]. In the subgroup of children who have known diabetes, bacterial infections were present in 17% and viral infections in 20%. These data contrast with data for adult populations, in which higher frequencies of infection or other illnesses as precipitating factors for DKA have been reported [17,18].

Although the risk of mortality from childhood DKA is less than 0.5%, DKA is still the most frequent diabetes-related cause of death in children [1,2]. Most of these DKA-related deaths are caused by cerebral edema (62%–87%), a complication that is discussed in more detail later.

### **Pathophysiology of diabetic ketoacidosis**

The physiologic abnormalities in patients who have DKA may be viewed as an exaggeration of the normal physiologic mechanisms responsible for maintaining adequate fuel supply to the brain and other tissues during periods of fasting and physiologic stress. The relative concentration of insulin in relation to glucagon and other counterregulatory hormones or stress hormones (eg, epinephrine, norepinephrine, cortisol, and growth hormone) primarily mediates these physiologic abnormalities rather than the absolute concentration of insulin itself [19,20].

#### *Pathophysiologic abnormalities early in the development of diabetic ketoacidosis*

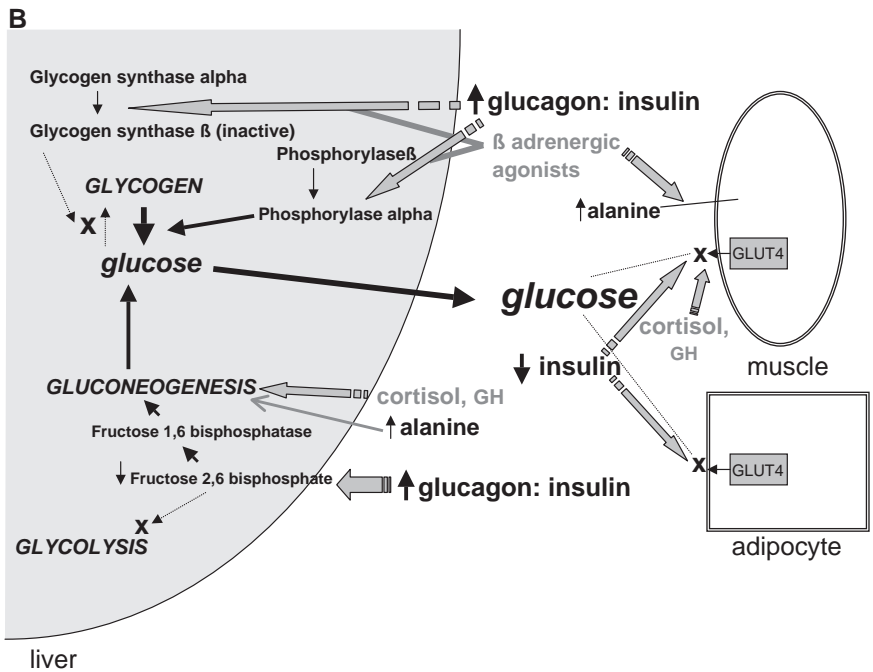
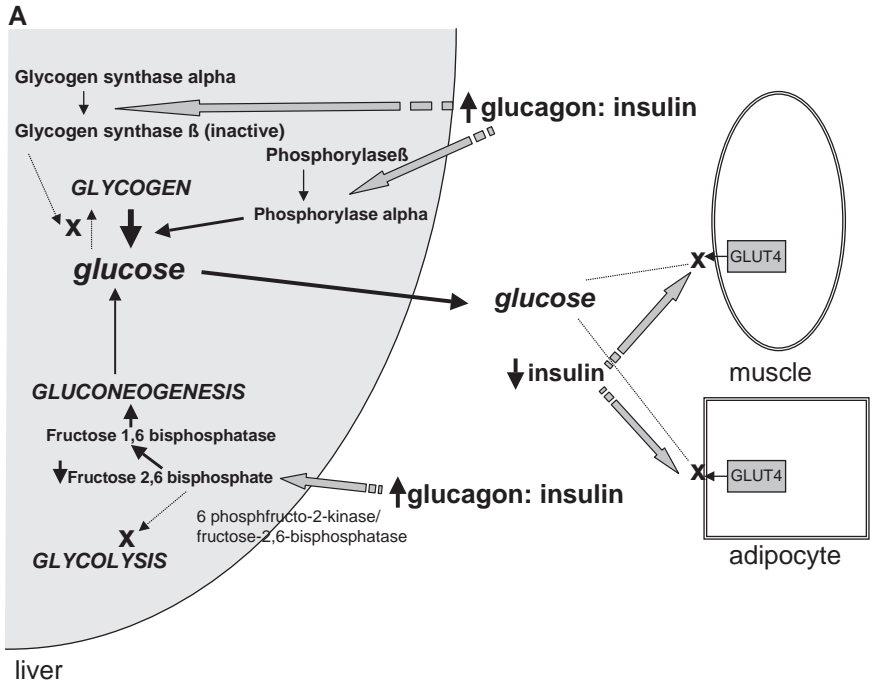
In a child who has new onset of type 1 diabetes, declining insulin production lowers the ratio of insulin to glucagon. This decrease in relative insulin concentration leads to excess hepatic glucose production (Fig. 1A). Early in the course of evolving DKA, when levels of epinephrine and other stress hormones are normal or minimally elevated, increased hepatic glucose output is mainly caused by stimulation of glycogenolysis, with a smaller contribution from increased gluconeogenesis [21–23]. Low serum insulin concentrations also contribute to hyperglycemia by decreasing peripheral glucose uptake in muscle and adipose tissue. This effect is mediated by diminished translocation of glucose transporter (GLUT)4 glucose transporters to the cell membrane [24,25]. Increased hepatic glucose output and decreased peripheral glucose use contribute to hyperglycemia [26]. When the serum glucose concentration rises above approximately 180 to 200 mg/dL, which exceeds the renal threshold for glucose reabsorption [27,28], osmotic diuresis results, with an increase in urine output. Fluid losses then stimulate compensatory oral intake of fluids, which leads to polydipsia.

Low insulin concentrations also stimulate the release of free fatty acids (FFA) from adipose tissue by allowing activation of hormone-sensitive lipase (Fig. 2). This increase in FFA delivery to the liver is necessary but not sufficient for the stimulation of ketone body formation [29]. For ketogenesis to occur, activation of the hepatic  $\beta$ -oxidative enzyme sequence is also necessary [20,30,31]. It is mainly a further decline in insulin concentration relative to glucagon that allows this activation to occur. A larger decline in insulin concentration relative to counter-regulatory hormones is necessary to promote lipolysis and ketogenesis, compared with that required to cause hyperglycemia [32]. These findings in part explain the lesser tendency toward the development of DKA in patients who have type 2 diabetes, despite the occurrence of substantial hyperglycemia.

Under fasting conditions in a normal individual, modest ketosis occurs, but marked ketoacidosis is prevented by direct ketone-induced stimulation of insulin, which limits further release of FFAs from adipose tissue [33]. In children who have type 1 diabetes, however, this “hormonal brake” is lacking and ketone production proceeds unchecked, eventually resulting in acidosis with an elevated anion gap.

#### *Pathophysiologic abnormalities later in the development of diabetic ketoacidosis*

Physiologic stress caused by acidosis and progressive dehydration eventually stimulates release of the counterregulatory hormones, cortisol, catecholamines, and growth hormone (see Fig. 1B) [26,34,35]. Coexisting infection or other illness or injury likewise can accelerate the development of ketosis via further elevations in counterregulatory hormone concentrations. Elevated cortisol concentrations augment FFA release from adipose tissue to fuel ketogenesis and decrease peripheral glucose uptake via effects on insulin-dependent mechanisms of glucose uptake and insulin-independent mechanisms (Fig. 2) [36–38]. Increased epinephrine concentrations directly increase glycogenolysis and stimulate release of gluconeogenic precursors from muscle, which allows gluconeogenesis to make a more substantial contribution to hyperglycemia [22,23,39]. Epinephrine and norepinephrine also stimulate lipolysis and  $\beta$ -oxidation of FFAs to form ketone bodies [40,41]. Catecholamines also may inhibit insulin secretion directly via stimulation of  $\alpha$ -adrenergic receptors and cause a further decline in serum insulin concentrations [42,43]. Although this effect is inconsequential in children who have longstanding type 1 diabetes (and absent or minimal endogenous insulin production), it may accelerate the development of DKA in patients with a new diagnosis of type 1 diabetes in whom some insulin-producing capacity remains, and it likely contributes more substantially to the development of DKA in children who have type 2 diabetes. Elevated growth hormone concentrations likewise contribute to worsening hyperglycemia, mainly via further decreasing peripheral glucose uptake, and enhance ketone production by increasing FFA release [23,44]. Growth hormone effects occur over a longer time course than those of other counterregulatory hormones that lead to more acute elevations in glucose and FFAs.



With the increase in hepatic glucose production, ketogenesis, and peripheral insulin resistance stimulated by elevations in counterregulatory hormone concentrations, acidosis and dehydration worsen. These changes then accelerate the development of DKA by stimulating further increases in the concentrations of counterregulatory hormones. A vicious cycle is created and is responsible for the eventual development of severe ketoacidosis.

Other physiologic processes also contribute to worsening acidosis and dehydration (Fig. 3). Intestinal ileus occurs as a consequence of acidosis, potassium depletion, and diminished splanchnic perfusion caused by dehydration. Intestinal ileus causes abdominal pain and vomiting, which impairs a patient's ability to compensate for osmotic diuresis by increased intake of fluids. More substantial dehydration eventually leads to diminished tissue perfusion, which enhances acidosis via accumulation of lactic acid [45,46]. Severe dehydration eventually compromises renal function and diminishes the capacity for clearance of glucose and ketones, which causes concentrations of both to rise further. Ongoing osmotic diuresis and ketonuria in the setting of acidosis also result in urinary losses of electrolytes, particularly potassium, sodium, chloride, calcium, phosphate, and magnesium. Urinary losses of sodium and potassium as ketone salts may result in excess chloride retention, such that hyperchloremic acidosis is superimposed on the increased anion gap acidosis [47]. Elevated aldosterone concentrations that result from dehydration also serve to further enhance potassium loss [46]. Typical electrolyte deficits in patients who have DKA include approximately 5 to 13 mmol/kg of sodium, 3 to 5 mmol/kg of potassium, and 0.5 to 1.5 mmol/kg of phosphate [48,49].

### Clinical manifestations of diabetic ketoacidosis

Classic symptoms of DKA include polyuria, polydipsia, weight loss, abdominal pain, nausea, and vomiting. Abdominal tenderness, absence of bowel sounds, and guarding may be present and may mimic the acute abdomen [50].

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Fig. 1. (A) Early in the development of DKA, a decrease in the concentration of insulin relative to glucagon results in stimulation of glycogenolysis by promoting conversion of glycogen synthase  $\alpha$  to inactive glycogen synthase  $\beta$  and conversion of phosphorylase  $\beta$  to active phosphorylase  $\alpha$ . Gluconeogenesis is also stimulated but plays a lesser role in the increase in hepatic glucose output at this stage than does glycogenolysis. An increase in the ratio of glucagon to insulin stimulates a decrease in fructose 2,6 bisphosphate concentrations mediated by phosphorylation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase. The decreased concentration of fructose 2,6 bisphosphate inactivates the rate-limiting enzyme for glycolysis (6-phosphofructo-1-kinase) and stimulates gluconeogenesis via activation of fructose-2,6-bisphosphatase. Decreased insulin concentrations also result in a lower peripheral glucose uptake by muscle and adipose tissue with diminished transport of GLUT4 to the cell membrane. (B) Later in the development of DKA, elevated concentrations of other counterregulatory hormones (eg, cortisol, norepinephrine, epinephrine, growth hormone) further increase hepatic glucose output and decrease peripheral glucose uptake.  $\beta$ -Adrenergic agonists enhance glycogenolysis and promote release of gluconeogenic substrate from muscle. Elevated cortisol and growth hormone concentrations cause further declines in peripheral glucose uptake and augment gluconeogenesis.

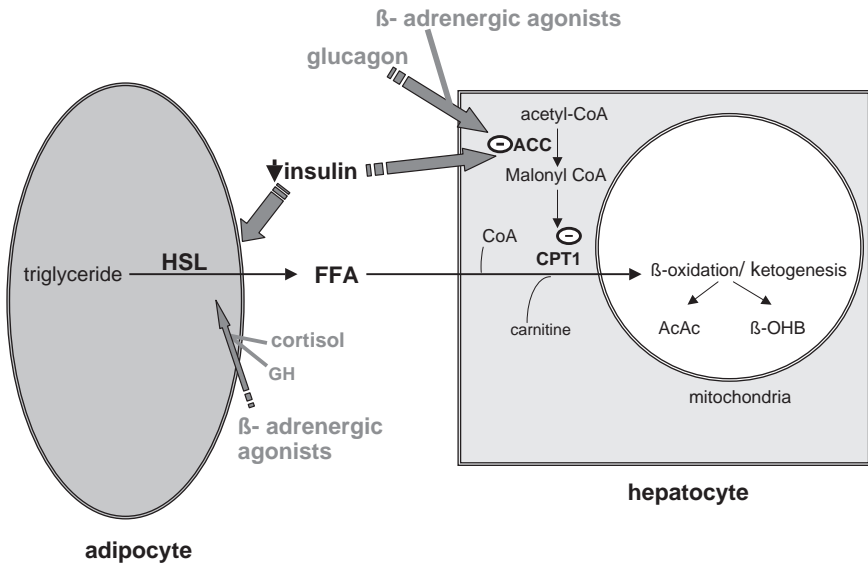


Fig. 2. Decreased insulin concentrations result in increased activity of hormone-sensitive lipase in adipose tissue with release of FFA. As concentrations of stress hormones (eg, cortisol, growth hormone (GH), catecholamines) increase later in the course of DKA, hormone-sensitive lipase activity is further stimulated. FFAs are taken up by the liver, where they are esterified to fatty acyl-CoA. Transport of the CoA ester across the mitochondrial membrane for  $\beta$ -oxidation requires transesterification with carnitine, which is accomplished by carnitine palmitoyl transferase 1 (CPT-1). Once inside the mitochondria, esterification to carnitine is reversed, and fatty acyl-CoA undergoes  $\beta$ -oxidation to form ketones (AcAc) and ( $\beta$ -OHB). CPT-1 is regulated by the concentration of malonyl CoA, which inhibits CPT-1 activity. Malonyl CoA is produced from acetyl-CoA by acetyl-CoA carboxylase (ACC), whose activity is increased by insulin and decreased by glucagon and  $\beta$ -adrenergic agents. Glucagon also decreases the concentration of malonyl CoA by diminishing the rate of glycolysis and the rate of production of citrate, the substrate for malonyl CoA production.

Tachycardia is frequent, and signs of hypoperfusion, such as delayed capillary refill time and cool extremities, are also common. Other signs of dehydration also may be present, including dry mucous membranes, absence of tears, and poor skin turgor. Hypothermia also has been described [51]. Although profound acidosis may depress myocardial contractility and vascular smooth muscle tone, the occurrence of these effects to a clinically relevant degree has not been demonstrated in DKA [52], and hypotension in children who have DKA is rare. Tachypnea occurs in response to metabolic acidosis as a result of stimulation of chemoreceptors in the central nervous system (CNS). Tachypnea may be extreme and may cause DKA to be initially misdiagnosed as respiratory illness. Acetone (produced from nonenzymatic decarboxylation of acetoacetate [AcAc]) typically causes a fruity breath odor, which may be a helpful initial clue to the diagnosis of DKA. Despite profound systemic acidosis, most children who have DKA present with normal mentation or only minimal depression of mental status. The lack of substantial neurologic depression reflects the fact that brain pH in patients who

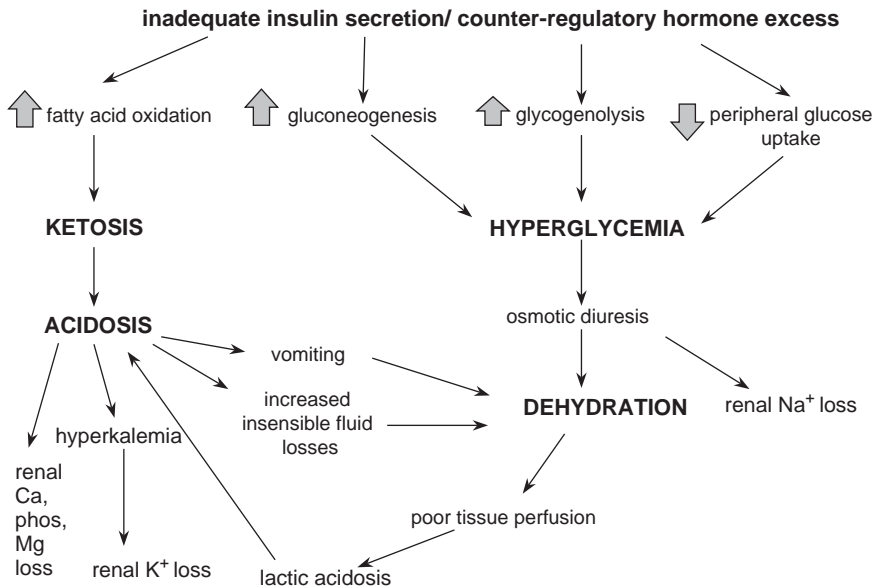


Fig. 3. Pathophysiology of diabetic ketoacidosis. (From Glaser NS, Styne DM. Endocrine disorders. In: Behrman R, Kliegman R, editors. Nelson essentials of pediatrics. 3<sup>rd</sup> edition. Philadelphia: WB Saunders; 1997; with permission.)

present with DKA is generally preserved within the normal range because of the impermeability of the blood-brain barrier to hydrogen ions [53,54].

## Laboratory abnormalities in diabetic ketoacidosis

### *Hyperglycemia*

A diagnosis of DKA can be made when the serum glucose concentration is more than 200 mg/dL and venous pH is less than 7.30 (or the serum bicarbonate concentration is less than 15 mmol/L) in the presence of elevated urine or serum ketone concentrations. DKA with near-normal glucose concentrations also has been described but occurs infrequently [55–57]. This euglycemic DKA may occur in pregnancy and in patients who have known diabetes who have administered insulin before coming to the emergency department. Children who have DKA who have prolonged vomiting and minimal oral intake before presentation also may present with lower initial glucose concentrations. Much of the variability in serum glucose concentrations at presentation may be explained by differences in hydration and nutritional status [35]. Prolonged fasting or poor nutrient intake before the development of DKA decreases substrate availability and results in lower serum glucose concentrations at presentation, whereas more severe dehydration favors higher glucose concentrations. In the absence of pre-

existing renal disease or unusually high carbohydrate intake, blood glucose concentrations of 500 to 600 mg/dL imply that dehydration is of sufficient severity to diminish the glomerular filtration rate by approximately 30% to 40%. Blood glucose concentrations more than 800 mg/dL suggest that the glomerular filtration rate is decreased by 50% or more [58].

### *Acidosis*

Concentrations of ketone bodies (beta-hydroxybutyrate [ $\beta$ OHB] and AcAc) are elevated in DKA. The serum bicarbonate concentration is low because bicarbonate is used as a buffer against metabolic acidosis, which results in increased anion gap acidosis. Some degree of hyperchloremic acidosis frequently coexists with increased anion gap acidosis in DKA [47], and the anion gap reflects the combination of these processes. Although concentrations of  $\beta$ OHB and AcAc are elevated in patients who have DKA, the ratio of  $\beta$ OHB:AcAc is increased during DKA as a result of changes in the redox potential (NADH/NAD<sup>+</sup> ratio) in hepatic mitochondria [59]. Although the ratio of  $\beta$ OHB:AcAc is typically 1:1 in a normal individual, this ratio rises to as high as 10:1 in persons who have DKA. These changes are important mainly because the nitroprusside reaction used to test urine ketone concentrations detects only AcAc and not  $\beta$ OHB. Although urine testing can be relied on to help diagnose DKA, the urine ketone concentration should not be relied on as an indication of DKA severity or treatment response, particularly because the ratio of  $\beta$ OHB:AcAc decreases during DKA treatment. Bedside blood ketone meters recently were developed and provide a rapid means for accurately measuring  $\beta$ OHB rather than AcAc in children who have DKA [60]. How these measurements might best be used to enhance diagnosis and treatment of DKA, however, remains to be determined.

Metabolic acidosis stimulates chemoreceptors in the CNS, which results in partial correction of the metabolic acidosis via hyperventilation and a decrease in the partial pressure of CO<sub>2</sub>. There is a linear relationship between serum bicarbonate concentration and pCO<sub>2</sub>, and this relationship suggests that end-tidal CO<sub>2</sub> measurements may be used as a rapid screen for acidosis in children who have suspected DKA or to follow the course of acidosis in children who have DKA (Fig. 4) [61].

### *Electrolyte abnormalities*

Hyperglycemia results in fluid movement from the extravascular to the intravascular space and a decrease in the serum sodium concentration. This decrease can be calculated as a 1.6 mEq/L decrease in sodium concentration for every 100 mg/dL increase in serum glucose more than 100 mg/dL [62]. Hyperlipidemia caused by lipolysis also may affect serum sodium measurements and result in a decrease in measured serum sodium concentrations [63].

Typically, serum potassium concentrations at presentation are in the high-normal range or even above the normal range. Redistribution of potassium ions

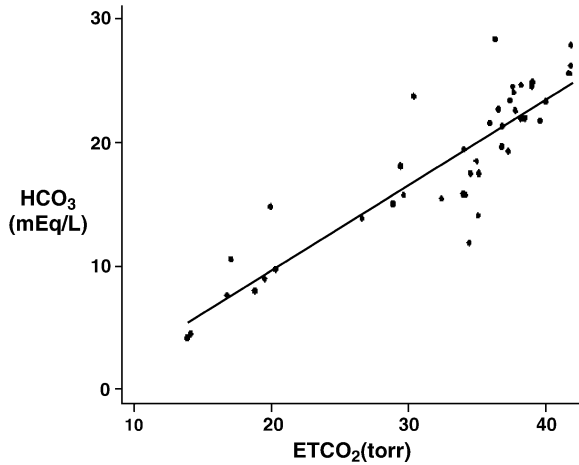


Fig. 4. End-tidal  $\text{CO}_2$  levels versus serum bicarbonate concentrations in children with diabetic ketoacidosis. (From Fearon DM, Steele DW. End-tidal carbon dioxide predicts the presence and severity of acidosis in children with diabetes. *Acad Emerg Med* 2002;9:1373–8; with permission.)

from the intracellular to the extracellular space in DKA results from a combination of factors, including direct effects of low insulin concentrations, intracellular protein and phosphate depletion, and buffering of hydrogen ions in the intracellular fluid compartment [64]. Despite normal or elevated initial potassium concentrations, total body potassium concentrations are depleted, often profoundly, and serum potassium concentrations usually drop rapidly with insulin treatment. The initial serum potassium concentration should not be taken as an indication of total body potassium stores. Serum phosphate concentrations are similarly elevated or normal at presentation but tend to decrease during treatment.

#### *Other biochemical abnormalities*

White blood cell counts are frequently elevated in children who have DKA, and the differential may be left shifted. The precise mechanism responsible for leukocytosis in DKA is not fully understood, but elevated catecholamine concentrations may play a role [65,66]. Another contributing factor may be an elevation in proinflammatory cytokines (eg, tumor necrosis factor- $\alpha$ , interleukin-6, interleukin-8, interleukin-1 $\beta$ ) and C-reactive protein caused by DKA. [67–69] Cytokine concentrations are substantially increased during DKA and decrease promptly with the initiation of insulin therapy. C-reactive protein concentrations, although also frequently elevated in patients who have DKA, show a less consistent decrease with treatment [68]. Infection is infrequently the cause of DKA in children [16], and an elevated or left-shifted 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 or lipase concentrations are elevated in 40% of children who have DKA and in 40% to 80% of adults who have DKA [70–72]. The cause and significance of these elevations, however, are not known. Clinical pancreatitis in children who have DKA is rare, and elevated amylase or lipase concentrations need not prompt further investigation for pancreatitis unless abdominal pain persists after resolution of ketosis.

## **Treatment of diabetic ketoacidosis**

### *Fluids*

Intravenous fluids (0.9% saline or other isotonic fluids) should be administered as soon as possible to restore adequate perfusion and hemodynamic stability. An intravenous fluid bolus of 10 to 20 mL/kg is often required. In patients who are well perfused and hemodynamically stable, an initial fluid bolus may not be necessary. A recent study indicated that physicians' clinical assessments of the degree of dehydration in children who have DKA correlate poorly with the actual percentage dehydration and often underestimate dehydration severity [73]. Difficulties in clinical estimation of dehydration may result in part from osmotically mediated water movement from the tissues to the intravascular space. This fluid movement results in preservation of intravascular volume and may obscure some of the clinical signs of dehydration. Because severity of dehydration is difficult to estimate clinically, it may be most appropriate to assume an average degree of dehydration for most patients (approximately 7%–9% of body weight [73,74]). This estimated fluid deficit, along with maintenance fluid requirements, should be replaced evenly over a 36- to 48-hour period using 0.45% to 0.9% saline. Because the serum glucose concentration typically decreases to levels near the renal threshold for glucose reabsorption within a few hours of initiating treatment, replacement of ongoing fluid losses from osmotic diuresis is usually unnecessary. Ongoing fluid losses caused by profuse vomiting or diarrhea may need to be replaced on rare occasion.

The serum glucose concentration often decreases substantially with rehydration alone as a result of improvements in the glomerular filtration rate and decreased concentrations of counterregulatory hormones [46,75]. This decline in glucose concentration early in treatment should not be interpreted as an indication of excessive insulin administration.

### *Insulin and dextrose*

Insulin is required to resolve acidosis and hyperglycemia via suppression of ketogenesis, gluconeogenesis, and glycogenolysis and promotion of peripheral glucose uptake and metabolism. Insulin should be administered intravenously at a rate of 0.1 U/kg/h [75]. An initial bolus or loading dose of insulin is unnecessary because maximal reductions in ketogenesis and lipolysis are achieved rapidly

with the insulin infusion rate specified previously [26,32]. More rapid declines in serum glucose concentration may be achieved with insulin administered at rates in excess of 0.1 U/kg/h, but these higher insulin dosages may increase the frequency of hypoglycemia during therapy [32,75]. The risk of hypokalemia also is greater at higher insulin infusion rates [32,75]. Thus, there seems to be no benefit to higher insulin dosages, and the potential for adverse effects may increase. The use of insulin dosages less than 0.1 U/kg/h have not been studied extensively, but available data suggest that these lower dosages may not suppress ketogenesis adequately [76].

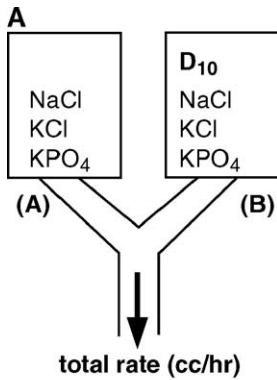
With insulin treatment, serum glucose concentrations often normalize before ketosis and acidosis have resolved. When the serum glucose concentration declines to approximately 250 to 300 mg/dL, dextrose should be added to the intravenous fluids to avoid hypoglycemia as the insulin infusion is continued to promote resolution of ketosis and acidosis. The two-bag system is an effective and efficient method for administering dextrose in children who have DKA. This system allows a more rapid response to changes in serum glucose concentration and is more cost effective than single-bag methods [77]. Two bags of intravenous fluids with identical electrolyte content but varying dextrose concentrations (usually 0% and 10%) are administered simultaneously. The relative rates of administration of the two fluids can be adjusted to vary the dextrose concentration while maintaining a constant overall rate of administration of fluid and other electrolytes (Fig. 5). Once this system is established, the blood glucose concentration should be maintained between 150 and 250 mg/dL to strike a balance between avoidance of hypoglycemia during treatment and prevention of ongoing fluid losses from osmotic diuresis.

### *Electrolytes*

With insulin treatment and resolution of acidosis, there is substantial movement of potassium from the extracellular space to the intracellular space, and serum potassium concentrations may decrease precipitously. Intravenous administration of potassium is essential, and concentrations of 30 to 40 mEq/L intravenous fluids are usually required. Adequate renal function should be ensured before administration of potassium. Potassium chloride may be used alone or in combination with 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.

Studies have demonstrated that some degree of hyperchloremic acidosis develops during treatment of DKA in most patients, and the severity of hyperchloremic acidosis correlates with serum urea nitrogen concentrations [47]. Patients who are less dehydrated and have better preservation of renal function have a greater tendency to develop hyperchloremic acidosis during treatment. This tendency is likely caused by the increased urinary loss of bicarbonate precursors (ketoacid and lactic acid anions) and diminished conversion of these precursors to bicarbonate with insulin administration [47,78].

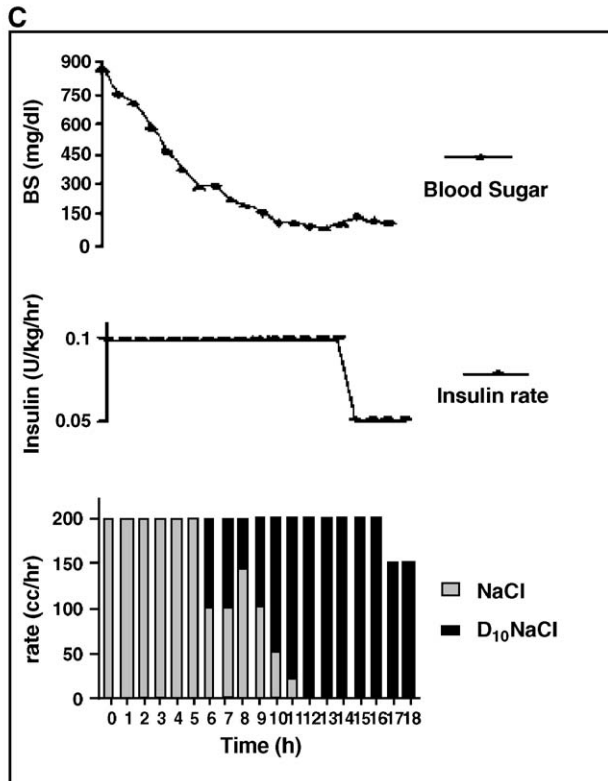
Whether phosphate replacement should be given routinely in children who have DKA is controversial. It is known that 2,3-diphosphoglycerate levels in red blood cells are decreased in patients who have DKA, and hypophosphatemia may result in persistence of low 2,3-diphosphoglycerate levels. This situation theoretically may lead to reduced tissue oxygen delivery, particularly during therapy when correction of acidosis increases the affinity of hemoglobin for oxygen,



**B**

**EXAMPLE:**  
total rate = 200 cc/hr

final glc conc'n	rate of Bag (A)	rate of Bag (B)
D <sub>0</sub>	200 cc/hr	0 cc/hr
D <sub>5</sub>	100 cc/hr	100 cc/hr
D <sub>7.5</sub>	50 cc/hr	150 cc/hr
D <sub>10</sub>	0 cc/hr	200 cc/hr



reversing the Bohr effect [79,80]. Occurrence of this effect to a degree that would be clinically relevant, however, has been difficult to demonstrate [80,81]. Conversely, although hypocalcemia can result from phosphate replacement, symptomatic hypocalcemia has been documented mainly with aggressive or rapid phosphate replacement and is uncommon when phosphate is administered slowly in more modest concentrations [81,82]. It is difficult to make a strong case either in favor of or against phosphate replacement. Case reports, however, have documented rhabdomyolysis and hemolytic anemia as results of severe hypophosphatemia during DKA [83,84]. Therefore, regardless of whether phosphate replacement is given routinely, it is necessary to monitor serum phosphate concentrations during treatment and administer phosphate replacement if severe hypophosphatemia develops.

Hypomagnesemia is common during DKA treatment and may contribute to hypocalcemia by inhibition of parathyroid hormone secretion [85,86]. Although monitoring of serum calcium and magnesium concentrations is recommended to detect rare cases of severe hypomagnesemia or hypocalcemia, decreases in the concentrations of these electrolytes are usually mild and asymptomatic and rarely require treatment.

### *Bicarbonate*

Bicarbonate should not be administered routinely in children who have DKA because acidosis usually can be corrected with insulin and fluids alone, and hemodynamic instability that results from acidosis is rare [52]. Most studies have found minimal or no differences in the rapidity of correction of acidosis in patients who have DKA treated with or without bicarbonate [87–89]. One reason for the apparent lack of effect of bicarbonate on rapidity of resolution of acidosis is that bicarbonate administration may cause an increase in hepatic ketone production [90]. It is believed that this increase results from pH-dependent stimulation of ketogenesis via increased mitochondrial uptake of fatty acyl-CoA.

Bicarbonate administration also increases the likelihood of hypokalemia during DKA treatment [91] and theoretically may increase tissue hypoxia as a result of leftward shifts in the hemoglobin-oxygen dissociation curve [79]. Bicarbonate

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Fig. 5. Two-bag system and illustrative typical course. (A) Two-bag system allows independent manipulation of glucose and total fluid volume, because electrolyte content of two bags is identical except for dextrose. (B) Differential rates of two bags modulate glucose delivery, which can be any concentration ranging from 0% to 10%. Total fluid volume is based on a patient's degree of dehydration and ongoing fluid requirement. (C) In this typical course, insulin therapy is instituted as continuous infusion of 0.1 U/kg/h, and total fluid rate is set at 200 mL/h. Because patient is markedly hyperglycemic, no dextrose is given initially. As insulin action lowers patient's glucose level, dextrose is titrated into intravenous fluid without changing administered fluid volume. Glucose titration aims to control rate of blood glucose decline (possible risk factor for cerebral edema) and prevent hypoglycemia in the face of continued insulin requirement. Later, when a patient's dehydration and ketosis become partially corrected, insulin and total fluid can be independently adjusted. (From Grimberg A, Cerri RW, Satin-Smith M, et al. The "two bag system" for variable intravenous dextrose and fluid administration: benefits in diabetic ketoacidosis management. *J Pediatr* 1999;134:377; with permission.)

treatment also may lead to paradoxical acidosis of the cerebrospinal fluid [53,92]. This phenomenon likely occurs because administration of bicarbonate results in diminished respiratory drive and a rise in the partial pressure of CO<sub>2</sub>. Although the blood-brain barrier is impermeable to bicarbonate, CO<sub>2</sub> crosses the blood-brain barrier readily and generates carbonic acid and cerebrospinal fluid acidosis. Bicarbonate administration also has been associated with an increased risk of cerebral edema in childhood DKA [93]. Routine administration of bicarbonate is not recommended. In rare cases in which hemodynamic instability is believed to be caused by severe acidosis and does not respond to standard measures or in rare cases of symptomatic hyperkalemia, however, bicarbonate administration should be considered.

### *Monitoring*

Specific recommendations for monitoring of children who have DKA are outlined in the report of the European Society for Pediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society international DKA consensus conference [94,95]. Most patients who have DKA should be treated in a pediatric intensive care unit or other unit with similar capacities for managing children who have DKA. Blood glucose concentrations should be measured hourly and electrolyte concentrations should be monitored every 2 to 4 hours. Venous pH measurements are helpful because serum bicarbonate concentrations may not increase over the first several hours despite improvements in acidosis. Arterial blood gas measurements, however, are generally unnecessary. Lack of appropriate improvement in acidosis with treatment suggests inadequate insulin infusion, inadequate rehydration, renal failure, sepsis, or other intercurrent condition.

Vital signs and mental status should be monitored hourly, and fluid intake and output should be recorded accurately. Cardiac monitoring is recommended because cardiac arrhythmias may occur during treatment, albeit infrequently. Recent data demonstrated a high frequency of prolonged QT interval corrected for heart rate (QTc) in children who have DKA (N. Kuppermann, MD, personal communication, 2005).

### **Complications**

The most frequent complications of DKA treatment are hypoglycemia and hypokalemia. With adequate monitoring of serum glucose and potassium concentrations, however, these complications are usually detected at an early stage, are easily treated, and rarely result in permanent morbidity or mortality. More serious complications of DKA are rare but may be life threatening, including cerebral edema [93,96], pulmonary edema [97–99], CNS hemorrhage or thrombosis [100], other large vessel thromboses [101], cardiac arrhythmias caused by electrolyte disturbances [93,102,103], pancreatitis [104], renal failure [105], and intestinal necrosis [106–108]. Patients who have DKA are also uniquely sus-

ceptible to rhinocerebral and pulmonary mucormycosis, a rare fungal infection [109]. Acidosis interferes with an important host defense mechanism against this fungus by disrupting the capacity of transferrin to bind iron. Mucormycosis occurs most frequently in children with longstanding poor blood glucose control. This infection carries a poor prognosis with high mortality rates. Aggressive treatment with antifungal agents and early resection of involved tissue is recommended [110].

Although severe dehydration and electrolyte depletion likely cause some of the complications of DKA, the mechanisms responsible for several others are not well understood. Recent studies have suggested that  $\beta$ -OHB may cause pulmonary vascular endothelial dysfunction and that perfusion of rabbit lungs with either  $\beta$ -OHB or AcAc results in edema and hemorrhage [111]. DKA also may cause a prothrombotic state, which may predispose children to CNS and other thromboses [101,112]. Studies have reported increased levels of von Willibrand factor and decreased free protein S and protein C activity in DKA and enhanced platelet aggregation associated with hyperglycemia [112–114]. Case series have suggested that deep venous thromboses may develop in as many as 50% of children with femoral central venous catheters [101,115]. Central venous catheters, particularly femoral venous catheters, should therefore be used with caution in children who have DKA.

Cardiac arrhythmias occur infrequently during DKA treatment and generally have been attributed to electrolyte disturbances. Recent data, however, documented a consistent increase in the QT interval corrected for heart rate (QTc) in children during acute DKA, with 47% of children having a QTc above 450 msec, the threshold generally considered to indicate prolongation of QTc [96]. In the recent study, the increase in QTc did not correlate with electrolyte concentrations, and the frequency of abnormal electrolyte concentrations in the study group was low, which raised the possibility that ketosis per se might have an effect on the myocardium. QTc intervals normalized after treatment of DKA.

The most frequent serious complication of DKA is cerebral edema, which occurs in 0.3% to 1% of pediatric DKA episodes [93,96,116,117]. Symptoms and signs of cerebral edema include headache, altered mental status, recurrence of vomiting, hypertension, inappropriate slowing of the heart rate, and other signs of increased intracranial pressure. Recent studies have documented a 21% to 24% mortality rate for DKA-related cerebral edema and a 21% to 26% rate of permanent neurologic morbidity [93,96].

Although less than 1% of children who have DKA develop symptomatic cerebral edema, studies that used sequential CT scans or other imaging technologies in children who have DKA showed that mild, asymptomatic cerebral edema is likely present in most children who have DKA (Fig. 6) [118–120]. The pathophysiologic mechanisms that cause cerebral edema during DKA remain unclear and have been the source of much controversy. Many investigators have attributed cerebral edema to rapid changes in serum osmolality or overly vigorous fluid resuscitation during DKA treatment. This hypothesis, however, has not been supported by data from clinical studies. In studies that used appropriate multi-

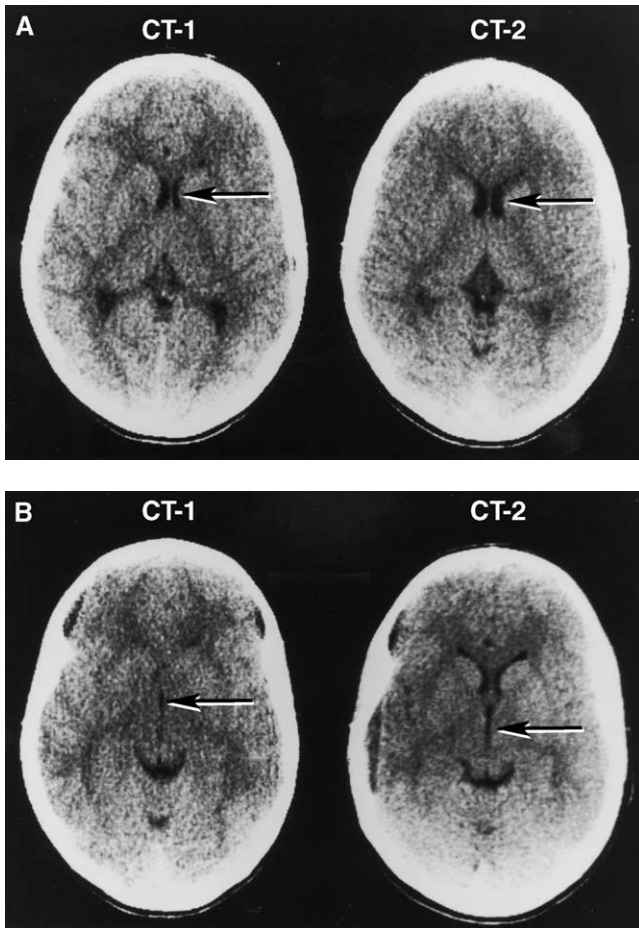


Fig. 6. CT scans of the same patient during DKA treatment (A) and after recovery from DKA (B). Narrowing of the ventricles during DKA indicates cerebral edema, although the patient was asymptomatic. (From Krane EJ, Rockoff MA, Wallman JK, et al. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. *N Engl J Med* 1985;312:1147–51; with permission.)

variate statistical techniques to adjust for DKA severity, an association between the rate of change in serum glucose concentration or the volume or sodium content of fluid infusions and risk for cerebral edema was not demonstrated [93,121,122]. Several case reports also described symptomatic and even fatal cerebral edema that occurred before hospital treatment for DKA [1,123,124]. This information suggests that DKA-related cerebral edema likely cannot be explained simply by osmotically mediated fluid shifts. More recent data suggested that cerebral edema during DKA may be predominantly vasogenic and may result from activation of ion transporters in the blood-brain barrier [118,125]. Cerebral hypoperfusion during DKA or direct effects of ketosis or inflammatory

cytokines on blood-brain barrier endothelial cell function might play a role in stimulating this process [69,118,126].

Epidemiologic studies have shown that children at greatest risk for symptomatic cerebral edema are children with high blood urea nitrogen concentrations [93] at presentation and children who present with more profound hypocapnia [93,122]. A lesser rise in the measured serum sodium concentration during treatment (as the serum glucose concentration falls) also indicates increased risk for cerebral edema [93,127]. More intensive monitoring of neurologic state and vital signs for children who present with these risk factors is recommended.

Clinical studies have not demonstrated a clear beneficial effect of any pharmacologic agent in treating DKA-related cerebral edema. Case reports, however, suggest that prompt administration of mannitol (0.25–1 g/kg) may be beneficial [128,129]. Intubation with associated hyperventilation has been correlated with poorer outcomes of DKA-related cerebral edema [130]. Therapeutic hyperventilation that attempts to decrease pCO<sub>2</sub> below a patient's own compensation for metabolic acidosis likely should be avoided in intubated children who have DKA except when absolutely necessary to treat clinically overt elevated intracranial pressure. CNS imaging in patients with suspected cerebral edema is recommended to rule out other causes of altered mental status, such as CNS thromboses; however, treatment for suspected cerebral edema should not be delayed while awaiting imaging studies.

### Differential diagnosis

In children, findings of hyperglycemia, increased anion gap acidosis, and ketonuria or ketonemia generally indicate a diagnosis of DKA, and other disorders that result in this constellation of biochemical abnormalities are rare. Occasionally, however, other disorders may have a similar presentation. Rare metabolic defects may cause ketoacidosis, including succinyl-CoA: 3-ketoacid coenzyme A transferase deficiency, a defect in ketolysis, and beta-ketothiolase deficiency, a defect in L-isoleucine catabolism. These conditions, however, are most frequently associated with hypoglycemia or normoglycemia rather than hyperglycemia [30,131–133].

In the setting of gastroenteritis, hyperglycemia may occur when stress hormone concentrations are markedly elevated in response to dehydration. Lactic acidosis results from dehydration, and the combination of hyperglycemia with acidosis initially may suggest a diagnosis of DKA. FFA concentrations also may be elevated, and modest ketonemia occasionally occurs [134–138]. These findings have been documented most frequently in infants and toddlers. In rare cases, extreme elevations in serum glucose concentration (>800–1000 mg/dL) have been reported in infants with gastroenteritis without diabetes mellitus [139]. Rapid resolution of hyperglycemia with hydration alone can be helpful in differentiating this situation from DKA [134].

## Hyperglycemic hyperosmolar state without ketosis

Extreme hyperglycemia and hyperosmolality can occur without ketosis in patients who have diabetes (hyperglycemic hyperosmolar state [HHS]). This condition occurs much more frequently in adults than in children and more frequently in patients who have type 2 diabetes than in persons who have type 1 diabetes. Among pediatric patients, case series have suggested that obese African-American children who have type 2 diabetes may be at greatest risk for HHS [140,141]. HHS also has been documented to occur with increased frequency in patients who are predisposed to dehydration because of limited access to fluids, including infants and children with cognitive deficits [139, 142]. Although HHS has been viewed as a condition separate from DKA, it may be more appropriate to view HHS as one extreme in the various presentations of altered glucose and fat metabolism in patients who have diabetes. DKA with near-normal glucose concentrations (euglycemic DKA) may be viewed as the opposite extreme on this continuum. Where a particular patient falls in this spectrum is determined by the relative concentrations of insulin and counterregulatory hormones and by the states of hydration and nutrition of the patient. The clinical picture in many patients may have elements of DKA and HHS [143].

The pathogenesis of HHS is similar to that of DKA; however, some important differences should be noted. Hyperglycemia without ketosis generally occurs in patients who retain some ability to produce insulin, most commonly persons who have type 2 diabetes. Ketogenesis and lipolysis are suppressed at lower serum insulin concentrations than the levels required to suppress hepatic glucose production, and patients develop hyperglycemia without ketosis [32,144]. In patients who do not develop ketoacidosis, osmotic diuresis with electrolyte and water loss may persist for prolonged periods and result in profound dehydration. Without ketosis, urinary cation excretion is not necessary to balance ketoanion excretion, and less electrolyte loss relative to free water loss occurs in HHS than in DKA, which contributes to the hyperosmolar state. Nonetheless, because the duration of osmotic diuresis in HHS may be lengthy, patients who have HHS may have greater electrolyte deficits than patients who have DKA [145]. Diminished renal function that results from severe dehydration is particularly important in the pathogenesis of HHS because diminished capacity for glucose excretion is necessary for the development of marked hyperglycemia.

The criteria for diagnosis of HHS include blood glucose concentration more than 600 mg/dL, serum osmolality more than 330 mOsm/kg, and lack of significant ketosis [146]. The serum sodium concentration, when corrected for the blood glucose concentration, is generally above the normal range [146,147]. The clinical presentation of HHS is otherwise similar to that of DKA, with some exceptions. Children who have HHS often have a more prolonged history of polyuria and polydipsia than children who have DKA [140,142]. Because of the absence of ketosis, fruity breath odor is not present, and tachypnea is not a prominent feature, except in patients in whom substantial lactic acidosis occurs.

In adults, approximately 10% to 20% of patients who have HHS present in coma, and other mental status abnormalities at presentation are more frequent than in DKA. Seizures may occur, and focal neurologic deficits (eg, hemiparesis, hemianopsia, chorea-ballismus) also have been described with HHS [139,142, 146,148].

Because HHS occurs infrequently in children, data regarding the optimal approach to treatment are lacking. Some authors have suggested that it may be preferable to delay insulin therapy in patients who have HHS because the serum glucose concentration decreases considerably with rehydration alone [142]. Patients who have HHS are not ketotic, and insulin is not needed for resolution of acidosis [142]. Delaying insulin treatment in these patients may result in more gradual declines in serum glucose concentration and serum osmolality. Use of 0.9% saline for intravenous fluid replacement rather than hypotonic saline also has been recommended to promote a more gradual decline in serum sodium concentration. Because patients with HHS may have had ongoing osmotic diuresis for prolonged periods before presentation, electrolyte deficits may be particularly pronounced. Close monitoring of serum electrolyte concentrations (particularly potassium and phosphate) is recommended [146]. Hyponatremia frequently develops during therapy as the serum glucose concentration declines and water returns to the extravascular tissues. Hyponatremia occasionally may be difficult to treat in patients who have HHS, in part because of ongoing free water losses caused by osmotic diuresis and persistent stimulation of sodium retention by aldosterone [149].

In contrast to DKA, in which complications occur infrequently and the mortality rate is less than 1%, HHS is associated with more frequent complications and a high mortality rate. Although limited epidemiologic data are available on HHS in children, one report documented a mortality rate of 14% [150], similar to the approximately 15% to 20% mortality rate of HHS in adults [143]. Thromboembolic complications, including pulmonary emboli and deep venous thromboses, occur frequently in patients who have HHS as a result of severe dehydration and increased blood viscosity [151]. Routine use of anticoagulant therapy, however, is controversial. A malignant hyperthermia-like syndrome with hyperpyrexia and rhabdomyolysis also was described in several children who had HHS [141]. The cause of this syndrome is unclear. Cardiac arrhythmias caused by severe electrolyte disturbances, cerebral edema, and pulmonary edema also may occur [140,141].

## Summary

DKA occurs frequently in children who have diabetes, particularly at the time of diagnosis. Greater efforts are necessary to promote earlier recognition of new onset of diabetes so that DKA can be prevented and to avoid subsequent occurrences of DKA in children who have established diabetes. Further research

is also necessary to understand and prevent cerebral edema, the most serious complication of DKA. International recommendations for DKA treatment in children recently were published and will be helpful in standardizing the treatment of this condition [94,95].

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