Diabetic Ketoacidosis in Infants, Children, and Adolescents

A consensus statement from the American Diabetes Association

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The adage "A child is not a miniature adult" is most appropriate when considering diabetic ketoacidosis (DKA). The fundamental pathophysiology of this potentially life-threatening complication is the same as in adults. However, the child differs from the adult in a number of characteristics.

1) The younger the child, the more difficult it is to obtain the classical history of polyuria, polydipsia, and weight loss. Infants and toddlers in DKA may be misdiagnosed as having pneumonia, reactive airways disease (asthma), or bronchiolitis and therefore treated with glucocorticoids and/or sympathomimetic agents that only compound and exacerbate the metabolic derangements. Because the diagnosis of diabetes is not suspected as it evolves, the duration of symptoms may be longer, leading to more severe dehydration and acidosis and ultimately to obtundation and coma. Even in developed countries, some 15–70% of all newly diagnosed infants and children with diabetes present with DKA (1–8). Generally, the rates of DKA are inversely proportional to rates of diabetes in that community, but throughout the U.S., the overall rates of DKA at diagnosis have remained fairly constant at ~25% (6). DKA, defined by blood bicarbonate <15 mmol/l and/or pH <7.25 (<7.3 if arterial or capillary), was present in 23.3% of a carefully analyzed cohort. However, the prevalence of DKA decreased significantly with age from 36% in children <5 years of age to 16% in those >14 years but did not differ significantly by sex or ethnicity (6).

2) The higher basal metabolic rate and large surface area relative to total body mass in children requires greater precision in delivering fluids and electrolytes. The degree of dehydration is expressed as a function of body weight, i.e., 10% dehydration implies 10% loss of total body weight as water. However, the calculation of basal requirements, although a constant per unit of surface area, must be carefully adjusted when calculating per unit mass because the amount of fluid per kilogram declines as the infant or child grows.

3) Cerebral and other autoregulatory mechanisms may not be as well developed in younger children. Hence, greater severity at presentation in younger children together with less maturity of autoregulatory systems combine to predispose children to cerebral edema, which occurs in ~0.5–1% of all episodes of DKA in children and is the most common cause of mortality in children with DKA (9–12). Only a minority of deaths in DKA are attributable to other causes, such as sepsis, other infections (including mucormycosis), aspiration pneumonia, pulmonary edema, acute respiratory distress syndrome, pneumomediastinum, hypo- or hyperkalemia, cardiac arrhythmias, central nervous system (CNS) hematoma or thrombosis, and rhabdomyolysis. Currently, the etiology, pathophysiology, and ideal treatment are poorly understood, but these are areas of intense investigation. Because cerebral edema occurs in the context of DKA, reduction of the incidence of DKA should be a major goal of treating children with diabetes. The reported mortality rates in children with DKA are constant in national population-based studies varying from ~0.15 to 0.3%. Once cerebral edema develops, death occurs in some 20–25%, and significant morbidity, including pituitary insufficiency, occurs in 10–25% of survivors. Where medical services are less well developed, the risk of dying from DKA is greater, and children may die before receiving treatment. Overall, cerebral edema accounts for ~60–90% of all DKA-related deaths in children.

4) Whereas delay in diagnosis is the major cause of DKA in previously unrecognized disease in younger children, omission of insulin is the leading cause of recurrent DKA, most prevalent among adolescents. In this group, some 5% of patients account for >25% of all admission for DKA (11).

These important differences between children and adults require careful attention to issues of management. Here, we briefly review the pathophysiology of DKA in childhood and discuss recommended treatment protocols. Current concepts of cerebral edema are presented. We conclude with recommendations and strategies for the prediction and prevention of DKA and, hence, its complications in infants, children, and adolescents.

These considerations and recommendations are in agreement with those recently endorsed by the Lawson Wilkins Pediatric Endocrine Society (LWPES), European Society for Pediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD).

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

Abbreviations: β-OHB, β-hydroxybutyrate; CNS, central nervous system; DKA, diabetic ketoacidosis; ECF, extracellular fluid.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-9909

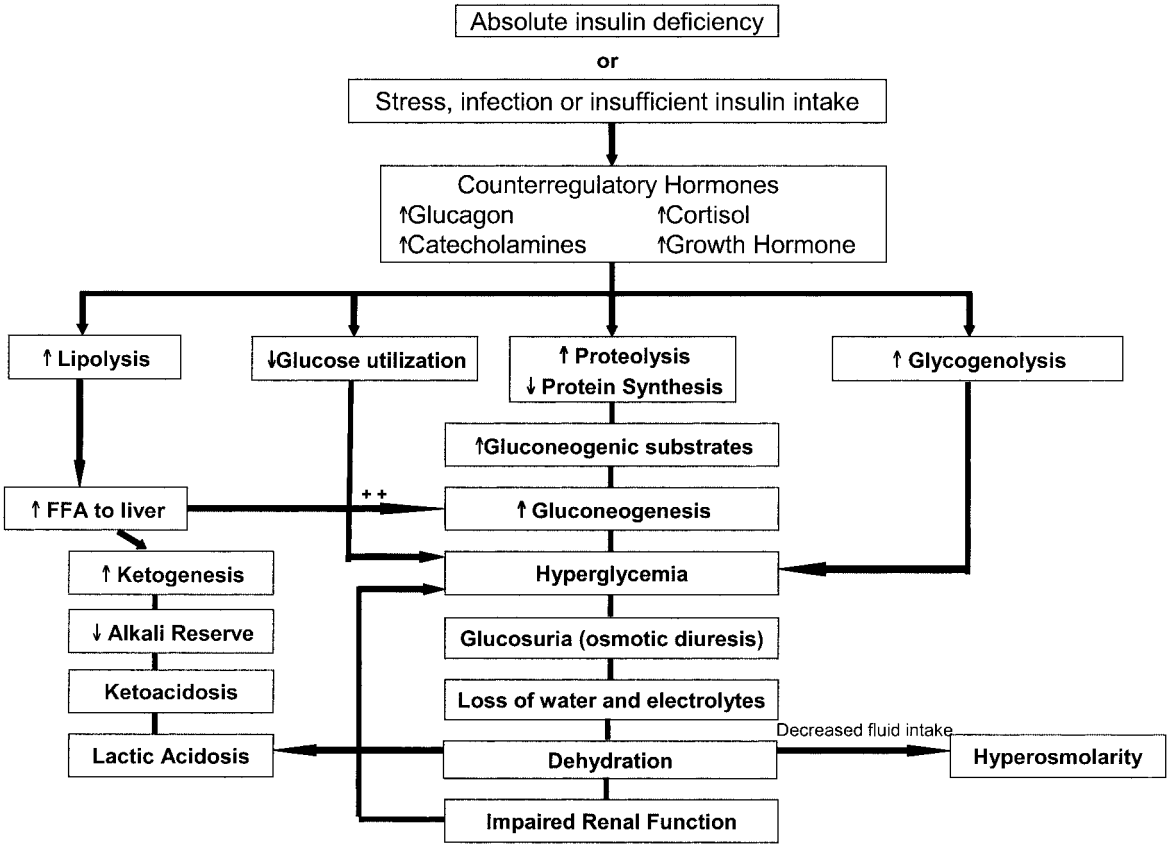

Figure 1—*Pathophysiology of DKA. FFA, free fatty acid.*

PATHOPHYSIOLOGY OF DKA

— The pathophysiology of DKA in children is summarized in Fig. 1. The interacting factors are insulin deficiency as the initial primary event in progressive β-cell failure, its omission in a patient with established disease, or its relative ineffectiveness when insulin action is antagonized by physiological stress such as sepsis and in the context of counterregulatory hormone excess. Together, these hormonal changes augment glucose production from glycogenolysis and gluconeogenesis while limiting glucose utilization, resulting in hyperglycemia (>11 mmol/l [200 mg/dl]), osmotic diuresis, electrolyte loss, dehydration, decreased glomerular filtration (further compounding hyperglycemia), and hyperosmolarity. Simultaneously, lipolysis provides increased free fatty acids, the oxidation of which facilitates gluconeogenesis and generates acetoacetic and β-hydroxybutyric acids (ketones) that overwhelm buffering capacity, resulting in metabolic acidosis (pH < 7.3), which is compounded by lactic acidosis from poor tissue perfusion. Progressive dehydration, hyperosmolarity, acidosis, and electrolyte disturbances exaggerate stress hormone secretion and establish a self-perpetuating cycle of progressive metabolic decompensation. The clinical manifestations are polyuria, polydipsia, signs of dehydration, deep sighing respirations to reduce pCO_2 and buffer acidosis, and progressive obtundation leading to coma.

The severity of DKA is defined by the degree of acidosis: mild, venous pH 7.2–7.3; moderate, pH 7.1–7.2; and severe, pH <7.1.

Frequency of DKA and precipitating factors

There is wide geographic variation in the frequency of DKA at onset of diabetes; rates inversely correlate with the regional incidence of type 1 diabetes. Frequencies range from ~15 to 70% in Europe, Australia, and North America (1–8). DKA at diagnosis is more common in younger children (<5 years of age) and in children whose families do not have ready access to medical care for social or economic reasons (5,13–15). A recent survey throughout the U.S. showed that the rate of DKA is ~25% at the time of diagnosis (6). Lower income and lower parental educational achievement were associated with higher risk of DKA. Lack of health insurance also is associated with higher rates (and greater severity) of DKA at diagnosis, presumably because uninsured subjects delay seeking timely medical care (15). Thus, younger and poorer children are disproportionately affected (6).

The risk of DKA in children and adolescents with established type 1 diabetes is 1–10 per 100 person-years (5,16–19). Insulin omission, either inadvertently or deliberately, is the cause in most cases. There usually is an important psychosocial reason for omitting insulin. Risk is increased in children with poor metabolic control or previous episodes of DKA, peripubertal and adolescent girls, children with clinical depression or other psychiatric disorders (including those with eating disorders), children with difficult or unstable family circumstances (e.g., parental abuse), children with limited access to medical services, and those on insulin pump therapy (as only rapid- or short-acting insulin is used in pumps, interruption of insulin delivery for any reason rapidly leads to insulin deficiency) (5,19). An intercurrent infection is seldom the cause when the patient/family is properly educated in diabetes management and is receiving appropriate fol-

low-up care by a diabetes team with a 24-h telephone helpline (20–23).

MANAGEMENT OF DKA

Emergency assessment

- Perform a clinical evaluation to confirm the diagnosis and determine its cause. (Carefully look for evidence of infection; in recurrent DKA, insulin omission or failure to follow sick day or pump failure management guidelines accounts for almost all episodes.)
- Weigh the patient. (If body surface area is used for fluid therapy calculations, measure height or length to determine surface area.) This weight should be used for calculations and not the weight from a previous office visit or hospital record.
- Look for acanthosis nigricans suggesting insulin resistance and type 2 diabetes.
- Assess clinical severity of dehydration. Accurate clinical assessment of dehydration may be difficult in DKA, at least in part due to the hyperosmolar state and polyuria caused by osmotic diuresis. Some findings that may be helpful include:
  - 5%: reduced skin turgor, dry mucous membranes, tachycardia
  - 10%: capillary refill ≥3 s, sunken eyes
  - >10%: weak or impalpable peripheral pulses, hypotension, shock, oliguria
- Assess level of consciousness (Glasgow coma scale; see online appendix for details [available at http://care.diabetesjournals.org]) (24,25).
- Obtain a blood sample for laboratory measurement of serum or plasma glucose; electrolytes (including bicarbonate or total carbon dioxide [TCO_2]); urea nitrogen; creatinine; osmolality; venous (arterial only in critically ill patient) pH; pCO_2; pO_2; hemoglobin and hematocrit or complete blood count*; calcium, phosphorus, and magnesium concentrations; HbA_{1c}; and blood β-hydroxybutyrate (β-OHB) concentration (26). (*An increased white blood cell count in response to stress is characteristic of DKA and is not indicative of infection.)
- Perform a urinalysis for ketones.
- If there is evidence of infection, obtain appropriate specimens for culture (blood, urine, and throat).
- If laboratory measurement of serum potassium is delayed, perform an electrocardiogram for baseline evaluation of potassium status (27,28).

Supportive measures

- In the unconscious or severely obtunded patient, secure the airway and empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration.
- A peripheral intravenous catheter should be placed for convenient and painless repetitive blood sampling.
- A cardiac monitor should be used for continuous electrocardiographic monitoring to assess T waves for evidence of hyper- or hypokalemia and monitor for arrhythmias (27,28).
- Give oxygen to patients with severe circulatory impairment or shock.
- Give antibiotics to febrile patients after obtaining appropriate cultures of body fluids.
- Catheterization of the bladder is usually not necessary, but if the child is unconscious or unable to void on demand (e.g., infants and very ill young children), the bladder should be catheterized.
- Central venous pressure monitoring rarely may be required to guide fluid management in the critically ill, obtunded, or neurologically compromised patient. (Central lines in children with DKA are frequently associated with thrombosis and should be resorted to only when absolutely necessary.)

Where should the child be managed?

- The child should receive care in a unit that has:
  - Experienced nursing staff trained in monitoring and management
  - Written guidelines for DKA management in children
  - Access to laboratories for frequent and timely evaluation of biochemical variables
- A specialist with training and expertise in the management of DKA should direct inpatient management.
- Children with severe DKA (long duration of symptoms, compromised circulation, or depressed level of consciousness) or those who are at increased risk for cerebral edema (e.g., <5 years of age, low pCO_2, high urea nitrogen) should be considered for immediate treatment in an intensive care unit (pediatric if available) or in a unit that has equivalent resources and supervision, such as a children's ward specializing in diabetes care (29,30).
- In a child with established diabetes, whose parents have been trained in sick day management, hyperglycemia and ketosis without vomiting or severe dehydration can be managed at home or in an outpatient health care facility (e.g., emergency ward), provided an experienced diabetes team supervises the care (31–33).

Table 1—*Symptoms and signs of cerebral edema*

Headache
Recurrence of vomiting
Inappropriate slowing of heart rate
Rising blood pressure
Decreased oxygen saturation
Change in neurological status:
• Restlessness, irritability, increased drowsiness, incontinence
• Specific neurologic signs, e.g., cranial nerve palsies, abnormal pupillary responses, posturing

Clinical and biochemical monitoring

Successful management of DKA and hyperglycemic hyperosmolar syndrome requires meticulous monitoring of the patient's clinical and biochemical response to treatment so that timely adjustments in treatment can be made when indicated by the patient's clinical or laboratory data.

There should be documentation on a flow chart of hour-by-hour clinical observations, intravenous and oral medications, fluids, and laboratory results. Monitoring should include:

- Hourly (or more frequently as indicated) vital signs (heart rate, respiratory rate, and blood pressure).
- Hourly (or more frequently as indicated) neurological observations for warning signs and symptoms of cerebral edema (Table 1).
- Amount of administered insulin.
- Hourly (or more frequently as indicated) accurate fluid input (including all oral fluid) and output.
- Capillary blood glucose should be measured hourly (but must be cross checked against laboratory venous glucose because capillary methods may be inaccurate in the presence of poor peripheral circulation and acidosis).
- Laboratory tests: serum electrolytes, glucose, calcium, magnesium, phosphorus, and blood gases should be repeated every 2–4 h (or more frequently, as clinically indicated) in more severe cases. Blood urea nitrogen, creatinine, and hematocrit

Table 2—*Usual losses of fluids and electrolytes in DKA and normal maintenance requirements*

	Average losses per kg (range)	Maintenance requirements
Water	70 (30–100) ml	1,500 ml/m^2
Sodium	~6 (5–13) mmol	45 mmol/m^2
Potassium	~5 (3–6) mmol	35 mmol/m^2
Chloride	~4 (3–9) mmol	30 mmol/m^2
Phosphate	~0.5–2.5 mmol	0.5–1.5 mmol/kg*

Data are from measurements in only a few children and adolescents (ref. 30). *See ref. 114.

should be repeated at 6- to 8-h intervals until they are normal.
- Urine ketones until cleared.
- If the laboratory cannot provide timely results, a portable biochemical analyzer that measures plasma glucose, serum electrolytes, and blood ketones on fingerstick blood samples at the bedside is a useful adjunct to laboratory-based determinations.
- Calculations:
  - Anion gap = Na − (Cl + HCO_3); normal is 12 ± 2 mmol/l
  - Corrected sodium = measured Na + 2 × [(glucose mmol/l − 5.6) ÷ 5.6] or Na + 2 × [(glucose mg/dl − 100) ÷ 100]
  - Effective osmolality = 2 × (Na + K) + glucose mmol/l (mg/dl ÷ 18)

Fluid and electrolyte therapy

DKA is characterized by severe depletion of water and electrolytes from both the intracellular fluid and extracellular fluid (ECF) compartments; the range of losses is shown in Table 2. Despite their dehydration, patients continue to have considerable urine output until extreme volume depletion leads to a critical decrease in renal blood flow and glomerular filtration. At presentation, the magnitude of specific deficits in an individual patient varies depending upon the duration and severity of illness, the extent to which the patient was able to maintain intake of fluid and electrolytes, and the content of food and fluids consumed before coming to medical attention (34).

Children with DKA have a deficit in ECF volume that is usually in the range of 5–10% (35,36). Shock is rare in pediatric DKA. Clinical estimates of the volume deficit are subjective and inaccurate; frequently, they either under- or overestimate the deficit (37,38). Therefore, use 5–7% dehydration in moderate DKA and 10% dehydration in severe DKA. The effective osmolality (formula above) is frequently in the 300- to 350-mosm/l range. Increased serum urea nitrogen and hematocrit may be useful markers of the severity of ECF contraction (33,39). The serum sodium concentration is an unreliable measure of the degree of ECF contraction for two reasons: *1*) glucose, largely restricted to the extracellular space, causes osmotic movement of water into the extracellular space, thereby inducing dilutional hyponatremia (40,41); and *2*) the elevated lipid fraction of the serum in DKA has a low sodium content. Therefore, it is important to calculate the corrected sodium (using the above formula) and monitor its changes throughout the course of therapy. As the plasma glucose concentration decreases after administering fluid and insulin, the measured and corrected serum sodium concentration should increase appropriately.

The objectives of fluid and electrolyte replacement therapy are restoration of circulating volume, replacement of sodium and the ECF and intracellular fluid deficit of water, restoration of glomerular filtration with enhanced clearance of glucose and ketones from the blood, and avoidance of excessive rates of fluid administration so as not to exacerbate the risk of cerebral edema (Table 3).

If needed, volume expansion to restore peripheral circulation (resuscitation) should begin immediately with an isotonic solution (0.9% saline or balanced solution such as Ringer's lactate). The volume and rate of administration depends on circulatory status, and, where it is clinically indicated, the volume is typically 10–20 ml/kg over 1–2 h and may be repeated if necessary. Subsequent fluid management (deficit replacement) should be with 0.9% saline or a balanced salt solution such as Ringer's lactate (or acetate) for at least 4–6 h. Thereafter, deficit replacement should be with a solution that has a tonicity ≥0.45% saline with added potassium chloride, phosphate, or acetate (see below under potassium replacement). The rate of intravenous fluid should be calculated to rehydrate evenly over at least 48 h (42,43).

In addition to clinical assessment of dehydration, calculation of effective osmolality may be valuable to guide fluid and electrolyte therapy. As the severity of dehydration may be difficult to determine and frequently is either under- or overestimated (38), infuse fluid each day at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement based on age and weight or body surface area. Urinary losses should not be added to the calculation of replacement fluid. The sodium content of the fluid may need to be increased if serum corrected sodium is low and/or the measured serum sodium does not rise appropriately as the plasma glucose concentration falls (44,45). The use of large amounts of 0.9% saline has been associated with the development of hyperchloremic metabolic acidosis. A replacement procedure in a patient weighing 30 kg who is 1 m^2 is illustrated in Table 4.

Insulin

DKA is caused by a decrease in effective circulating insulin associated with increases in counterregulatory hormones (glucagon, catecholamines, growth hormone, cortisol). Although rehydration alone causes some decrease in blood glucose concentration (46,47), insulin ther-

Table 3—*Fluid and electrolyte losses based on assumed 10% dehydration in a child (weight 30 kg, surface area 1 m^2) with DKA*

Fluid and electrolyte	Approximate accumulated losses with 10% dehydration	Approximate requirements for maintenance (48 h)	Working total (48 h)
Water (ml)	3,000	3,000	6,000
Sodium (mEq)	180	90	270
Potassium (mEq)	150	70	220
Chloride (mEq)	120	60	180
Phosphate (mmol)	75	20	95

apy is essential to normalize blood glucose and suppress lipolysis and ketogenesis (48).

Extensive evidence indicates that "low-dose" intravenous insulin administration should be the standard of care (49). Start insulin infusion after the patient has received initial volume expansion; i.e., ~1–2 h after starting fluid replacement therapy (50). The dose is 0.1 unit · kg^{-1} · h^{-1} (50 units regular insulin diluted in 50 ml normal saline; 1 unit = 1 ml) (51). An intravenous insulin bolus (0.1 unit/kg) is unnecessary (52), may increase the risk of cerebral edema (50), and should not be used at the start of therapy. The dose of insulin should remain at 0.1 unit · kg^{-1} · h^{-1} at least until resolution of DKA (pH >7.30, bicarbonate >15 mmol/l, and/or closure of the anion gap), which invariably takes longer than normalization of blood glucose concentrations (53).

During initial volume expansion, the plasma glucose concentration may fall steeply (46). Thereafter, the plasma glucose concentration typically decreases at a rate of ~3–5 mmol · l^{-1} · h^{-1} (54–90 mg · dl^{-1} · h^{-1}) (54). To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia, 5% glucose should be added to the intravenous fluid when the plasma glucose falls to ~17 mmol/l (300 mg/dl). If blood glucose falls very rapidly (>5 mmol · l^{-1} · h^{-1}) (after the initial period of volume expansion), consider adding glucose even before plasma glucose has decreased to 17 mmol/l. It may be necessary to use 10% or even 12.5% dextrose to prevent hypoglycemia while continuing to infuse insulin to correct the metabolic acidosis. If the patient demonstrates marked sensitivity to insulin (e.g., some young children with DKA and patients with hyperglycemic hyperosmolar syndrome), the dose may be decreased to 0.05 units · kg^{-1} · h^{-1}, or less, provided that metabolic acidosis continues to resolve. If biochemical parameters of DKA (pH, anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin (e.g., infection, errors in insulin preparation). If no obvious cause is found, increase the insulin infusion rate and adjust the rate of glucose infusion as needed to maintain a glucose concentration of ~17 mmol/l (300 mg/dl).

In circumstances where continuous intravenous administration is not possible and in patients with uncomplicated DKA, hourly or 2-hourly subcutaneous or intramuscular administration of a short- or rapid-acting insulin analog (insulin lispro or insulin aspart) is a safe and effective alternative to intravenous regular insulin infusion (54–58).

Potassium

Children with DKA suffer total-body potassium deficits of the order of 3–6 mmol/kg (35,36,59–61). The major loss of potassium is from the intracellular pool. Intracellular potassium is depleted because of transcellular shifts of this ion caused by hypertonicity. Increased plasma osmolality results in osmotic water transport from cells to the ECF, thereby concentrating cellular potassium. As a result of the increased potassium gradient, potassium is drawn out of cells. Glycogenolysis and proteolysis secondary to insulin deficiency also cause potassium efflux from cells. Acidosis may play a minor role in the distribution of potassium to the ECF.

Potassium is lost from the body as a consequence of vomiting, urinary ketoanion excretion (which requires excretion of cations, particularly sodium and potassium), and osmotic diuresis. Volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion. Thus, total-body depletion of potassium occurs, but at presentation serum potassium levels may be normal, increased, or decreased (62). Renal dysfunction, by enhancing hyperglycemia and reducing potassium excretion, contributes to hyperkalemia (62). Administration of insulin and the correction of acidosis drives potassium back into the cells, decreasing serum levels (63). The serum potassium concentration may decrease abruptly, predisposing the patient to cardiac arrhythmias.

Potassium replacement therapy is required regardless of the serum potassium concentration; start replacing potassium after initial volume expansion and concurrent with starting insulin therapy. However, if the patient is hypokalemic, start potassium replacement immediately after initial volume expansion and before starting insulin therapy. If the patient is hyperkalemic, defer potassium replacement therapy until urine output is documented. If immediate serum potassium measurements are unavailable, an electrocardiogram may help to determine whether the child has hyper- or hypokalemia (27,28). Flattening of the T wave, widening of the QT interval, and the ap-

Table 4—*Replacement procedure for a child (weight 30 kg, surface area 1 m^2) with DKA estimated to be 10% dehydrated*

Approximate duration and rate	Fluid composition and volume	Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Phosphate (mmol)
Hour 1 (300 ml/h)	300 ml 0.9% NaCl (normal saline)	46	—	46	—
Hours 2–4 (125 ml/h); start regular insulin at 0.1 unit · kg^{-1} · h^{-1}	375 ml (normal saline) + 20 mEq potassium acetate/l + 20 mEq potassium phosphate/l	58	15	58	5.1
Hours 5–48 (125 ml/h); continue regular insulin (0.1 unit · kg^{-1} · h^{-1} until pH ≥7.3 or HCO_3 ≥18 mEq/l)	5,500 ml (one-half normal saline + dextrose) + 20 mEq potassium acetate/l + 20 mEq potassium phosphate/l	424	220	424	75
Total in 48 h	6,175 ml fluid	528	235	528	80

Normal saline (10 ml/kg) is given over 1 h for initial volume expansion; thereafter, the child is rehydrated over 48 h at an even rate at two times the maintenance rate of fluid requirement. Potassium phosphate: 4.4 mEq potassium and 3 mmol phosphate (1 mEq potassium and 0.68 mmol phosphate).

Table 5—*Insulin regimens for newly diagnosed diabetes after resolution of DKA*

Prepubertal	TDD 0.75–1.0 unit/kg
Pubertal	TDD 1.0–1.2 unit/kg
Before breakfast	Two-thirds of TDD • One-third rapid-acting insulin* • Two-thirds intermediate-acting insulin
Before dinner	• One-third to one-half of the remainder of the TDD as rapid-acting insulin*
Before bedtime	• One-half to two-thirds of the remainder of the TDD as intermediate-acting insulin
An alternative, basal-bolus method, consists of administering	• One-half of the TDD as basal insulin (using insulin glargine) AND • One-half of the TDD as rapid-acting insulin; the dose before each meal comprises ~15–20% of the TDD

*In infants, toddlers, and preschool-age children, some clinicians use relatively smaller proportions of rapid-acting insulin before breakfast and dinner (e.g., one-quarter to one-third rather than one-third to one-half) and relatively larger amounts of intermediate-acting insulin. TDD, total daily dose.

pearance of U waves indicate hypokalemia. Tall, peaked, symmetrical T waves and shortening of the QT interval are signs of hyperkalemia. The starting potassium concentration in the infusate should be 40 mmol/l; subsequent potassium replacement therapy should be based on serum potassium measurements. Potassium administration should continue throughout the period of intravenous fluid therapy. Potassium phosphate may be used together with potassium chloride or acetate (e.g., 20 mmol/l potassium chloride and 20 mmol/l potassium phosphate or 20 mmol/l potassium phosphate and 20 mmol/l potassium acetate). The maximum recommended rate of intravenous potassium replacement is usually 0.5 $\text{mmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.

Phosphate

Depletion of intracellular phosphate occurs in DKA, and phosphate is lost as a result of osmotic diuresis (35,36,60). Plasma phosphate levels fall after starting treatment, and this is exacerbated by insulin, which promotes entry of phosphate into cells (64–66). Total-body phosphate depletion has been associated with a variety of metabolic disturbances (67–69). Clinically significant hypophosphatemia may occur if intravenous therapy without food intake is prolonged beyond 24 h (35,36,60). Prospective studies have not shown clinical benefit from phosphate replacement (70–75); however, severe hypophosphatemia (<1 mg/dl), which may manifest as muscle weakness, should be treated even in the absence of symptoms (76). Administration of phosphate may induce hypocalcemia (77,78), and if hypocalcemia develops, administration of phosphate should be stopped. Potassium phosphate salts may be safely used as an alternative to or combined with potassium chloride or acetate provided that careful monitoring is performed to avoid hypocalcemia (77,78).

Acidosis

Severe acidosis is reversible by fluid and insulin replacement. Insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate. Treatment of hypovolemia improves tissue perfusion and renal function, increasing the excretion of organic acids. Controlled trials have shown no clinical benefit from bicarbonate administration (79–82), and there are well-recognized adverse effects of bicarbonate therapy, including paradoxical CNS acidosis (83,84) and hypokalemia from rapid correction of acidosis (83,85,86). Failure to account for the sodium being administered and appropriately reducing the NaCl concentration of the fluids can result in increasing osmolality (83). Nevertheless, there may be selected patients who may benefit from cautious alkali therapy. These include patients with severe acidemia (arterial pH <6.9), in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion, and patients with life-threatening hyperkalemia (87). Bicarbonate administration is not recommended for resuscitation unless the acidosis is profound and likely to adversely affect the action of epinephrine during resuscitation. If bicarbonate is considered necessary, cautiously administer 1–2 mmol/kg over 60 min.

Introduction of oral fluids and transition to subcutaneous insulin injections

Oral fluids should be introduced only when substantial clinical improvement has occurred (mild acidosis/ketosis may still be present) and the patient indicates a desire to eat. When oral fluid is tolerated, intravenous fluid should be reduced. The change to subcutaneous insulin should occur when ketoacidosis has resolved (serum bicarbonate ≥18 mEq/l and venous pH >7.3), plasma glucose is <200 mg/dl, and oral intake is tolerated. The most convenient time to change to subcutaneous insulin is just before a meal. To prevent rebound hyperglycemia, the first subcutaneous injection should be given 15–60 min (with rapid-acting insulin) or 1–2 h (with regular insulin) before stopping the insulin infusion, depending on the plasma glucose concentration, to allow sufficient time for the injected insulin to be absorbed. The dose and type of subcutaneous insulin should be according to local preferences and circumstances.

In patients with established diabetes, the patient's usual insulin regimen may be resumed. Two methods of starting subcutaneous insulin after resolution of DKA in newly diagnosed patients are presented in Table 5. After transitioning to subcutaneous insulin, frequent blood glucose monitoring is required to avoid marked hyperglycemia and hypoglycemia. Supplemental rapid-acting insulin is given at ~4-h intervals to correct blood glucose levels that exceed 200 mg/dl.

Cerebral edema

Symptomatic cerebral edema occurs in 0.5–1% of pediatric DKA episodes (9–12). This complication has a high mortality rate (21–24%), and a substantial percentage of survivors (15–26%) are left with permanent neurological injury (9,11,12). The pathophysiology of this complication is not well understood, but some have hypothesized that various aspects of DKA treatment may cause or accelerate the development of cerebral edema (88). Concerns about the avoidance of cerebral edema have exerted a strong influence on treatment recommendations for pediatric DKA, underscoring the need for better understanding of this condition.

Clinical manifestations

The signs and symptoms of cerebral edema are shown in Table 1. Typically, symptomatic cerebral edema occurs 4–12 h after the initiation of treatment for DKA, but cases have also occurred before initiation of therapy (9,12,89–93) and as late as 24–28 h after the initiation of therapy (9,88,94). Cerebral imaging studies may show focal or diffuse cerebral edema, but up to 40% of initial computed tomography scans on children with DKA and clinically diagnosed "cerebral edema" are normal (95). Subsequent imaging studies on these patients often demonstrate edema, hemorrhage, or infarction.

Pathophysiological mechanisms

Several hypotheses have been proposed to account for the occurrence of cerebral edema during DKA, but the cause remains poorly understood. Fluid influx into the brain caused by rapid declines in serum osmolality and/or overly vigorous fluid resuscitation has often been cited as a potential cause of DKA-related cerebral edema (96–99). Evidence from clinical studies, however, suggests that this mechanism may not play a central role. Case reports have documented the occurrence of symptomatic and even fatal cerebral edema before initiation of DKA treatment (9,12,89–93). In addition, studies employing sequential cerebral imaging in children with uncomplicated DKA have shown that mild, asymptomatic cerebral edema is likely present in most children with DKA, both at the time of presentation and during therapy (100–102). Finally, studies investigating associations between treatment variations and risk for cerebral edema have yielded mixed results. Only a few studies have employed multivariate statistical techniques to adjust for differences in DKA severity among patients, thereby attempting to address bias attributable to variation in treatment of DKA among patients with varying disease severity (9,12,50,103). In these studies, associations between the rate of fluid administration and risk for cerebral edema were found in some (50,103), but not others (9,12), and none of these studies found an association between the rate of change in serum glucose concentration or change in osmolality and risk for cerebral edema. All of these studies gathered clinical and treatment data retrospectively, however, making it difficult to fully adjust for illness severity and other sources of bias. Treatment factors unrelated to osmotic changes (bicarbonate treatment, insulin administration within the first hour of fluid therapy) have also been implicated in some studies (9,50), but the mechanism by which these treatment variations might influence risk of cerebral edema is unclear.

In contrast to previous hypotheses proposing osmotically mediated fluid shifts as a cause for DKA-related cerebral edema, recent data suggest that vasogenic, rather than cytotoxic, cerebral edema may be the predominant finding in DKA (101,104). Animal studies have suggested that activation of ion transporters in the blood-brain barrier may be responsible for fluid influx into the brain (104). Activation of these ion transporters may result from cerebral hypoperfusion and/or from direct effects of ketosis or inflammatory cytokines on blood-brain barrier endothelial cells (104,105).

Risk factors

Children at greatest risk for symptomatic cerebral edema are those who present with high blood urea nitrogen concentrations and those with more profound acidosis and hypocapnia (9,12,50,103). A lesser rise in the measured serum sodium concentration during treatment (as the serum glucose concentration falls) has also been associated with cerebral edema (9,45). Children with these characteristics as well as very young children in whom assessment of mental status may be more difficult should be more intensively monitored.

Treatment of cerebral edema

Because cerebral edema occurs infrequently, data are limited regarding the effectiveness of pharmacological interventions for treatment of cerebral edema. Case reports and small case series suggest that prompt treatment with mannitol (0.25–1.0 g/kg) may be beneficial (106,107). Recent case reports also propose the use of hypertonic saline (3%), 5–10 ml/kg over 30 min, as an alternative to mannitol (108,109). Intubation may be necessary to protect the airway and insure adequate ventilation; however, hyperventilation (pCO_2 <22 mmHg) in intubated patients with DKA-related cerebral edema has been correlated with poorer neurological outcomes (110). In intubated patients, therefore, hyperventilation beyond that which would normally occur in response to metabolic acidosis should likely be avoided unless absolutely necessary to treat elevated intracranial pressure. In patients suspected to have cerebral edema, CNS imaging studies are recommended to rule out other causes of neurological deterioration, but treatment generally should not be delayed while awaiting results.

Prevention of DKA

Management of an episode of DKA in a patient with known diabetes is not complete until its cause has been identified and an attempt made to treat it. Delayed diagnosis is the cause in new-onset diabetes, whereas insulin omission, either inadvertently or deliberately, is the cause in most cases of established diabetes. The most common cause of DKA in insulin pump users is failure to take extra insulin with a pen or syringe when hyperglycemia and hyperketonemia or ketonuria occur. Home measurement of blood β-OHB, when compared with urine ketone testing, decreases diabetes-related hospital visits (both emergency department visits and hospitalizations) by the early identification and treatment of ketosis (111). Blood β-OHB measurements may be especially valuable to prevent DKA in patients who use a pump because interrupted insulin delivery rapidly leads to ketosis. There may be dissociation between urine ketone (acetoacetate) and serum β-OHB concentrations, which may be increased to levels consistent with DKA when a urine ketone test is negative or shows only trace or small ketonuria (112).

An intercurrent infection is seldom the cause when the patient/family is properly educated in diabetes management and is receiving appropriate follow-up care by a diabetes team with a 24-h telephone helpline (21–23). There usually is an important psychosocial reason for insulin omission (see FREQUENCY OF DKA AND PRECIPITATING FACTORS above), and a psychiatric social worker or clinical psychologist should be consulted to identify the psychosocial reason(s) contributing to development of DKA. Insulin omission can be prevented by schemes that provide education, psychosocial evaluation, and treatment combined with adult supervision of insulin administration (113).

Parents and patients should learn how to recognize and treat impending DKA with additional rapid- or short-acting insulin and oral fluids. Patients should have access to a 24-h telephone helpline for emergency advice and treatment (21). When a responsible adult administers insulin, there may be as much as a 10-fold reduction in frequency of recurrent DKA (113).

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