Diabetic Ketoacidosis in Children

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Severe diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus. Approximately 15% to 67% of patients with newly diagnosed type 1 diabetes in Europe and North America present with DKA, and it accounts for 65% of all hospital admissions of patients with diabetes mellitus who are younger than 19 years old [1,2]. The frequency of DKA at onset of diabetes correlates inversely with the regional incidence of type 1 diabetes and is more common in young children, children without a first-degree relative with type 1 diabetes, and individuals whose families are of lower socioeconomic status [3,4]. The mortality rate for DKA in children is 0.15% to 0.31% [5,6]. Despite the more apparent issues of hypovolemia and acidosis, clinically significant cerebral edema, which occurs in 1% of cases, is the most serious risk to children [7,8].

In Canada and Europe, rates of hospitalization for DKA in established and new patients with type 1 diabetes have remained stable at approximately 10 per 100,000 children over the past 20 years. The risk of DKA in patients with established type 1 diabetes is 1% to 10% per patient per year [9,10]. Risk is increased in children with poor metabolic control or previous episodes of DKA, peripubertal and adolescent girls, children with psychiatric disorders, including individuals with eating disorders, and children with difficult family circumstances, including lower socioeconomic status and lack of health insurance [10]. Interruption of insulin delivery, regardless of the reason, is an important cause of DKA in patients who use continuous subcutaneous insulin infusion (insulin pump) therapy. Children rarely have DKA when insulin administration is closely

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supervised or performed by a responsible adult. In established patients, most instances of DKA are probably associated with insulin omission or treatment error, whereas the rest of the instances are caused by inadequate insulin therapy during intercurrent illness.

The biochemical criteria for the diagnosis of DKA include hyperglycemia (blood glucose > 11 mmol/L (approximately 200 mg/dL) with acidosis (venous blood pH < 7.3 or serum bicarbonate ≤ 15 mmol/L), ketonemia with total serum ketones (β-hydroxybutyrate and acetoacetate) > 3 mmol/L, and ketonuria. DKA usually is categorized by the severity of the acidosis: from mild (venous pH < 7.30, bicarbonate < 15 mmol/L), to moderate (pH < 7.2, bicarbonate < 10 mmol/L), to severe (pH < 7.1, bicarbonate < 5 mmol/L) [11]. Clinical symptoms also may vary from mild to severe (Box 1) [12].

Pathophysiology

DKA is the result of absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counterregulatory hormones, catecholamines, glucagon, cortisol, and growth hormone. Absolute insulin deficiency occurs in previously undiagnosed type 1 diabetes and when patients on treatment deliberately or inadvertently do not take insulin. Relative insulin deficiency occurs when the concentrations of counterregulatory hormones increase in response to stress in conditions such as sepsis, trauma, or gastrointestinal illness with diarrhea and vomiting.

Low serum levels of insulin and high concentrations of the counterregulatory hormones result in an accelerated catabolic state whose effects include increased glucose production by the liver and kidney (via glycolysis and gluconeogenesis), impaired peripheral glucose use that results in hyperglycemia and hyperosmolality, and increased lipolysis and ketogenesis, which cause ketonemia and metabolic acidosis. Hyperglycemia that exceeds the renal threshold of approximately 180 mg/dL and hyperketonemia cause osmotic diuresis, dehydration, and obligatory loss of electrolytes, which often is aggravated by vomiting. These
changes stimulate further catecholamine and stress hormone production, which induces more severe insulin resistance and worsening hyperglycemia and hyperketonemia. If uninterrupted with exogenous insulin, fluid, and electrolyte therapy, this cycle progresses to fatal dehydration and metabolic acidosis. Ketoacidosis may be aggravated by lactic acidosis from poor tissue perfusion or sepsis.

DKA is characterized by severe depletion of water and electrolytes from the intra- and extracellular fluid compartments; the range of losses is shown in Table 1. Despite their dehydration, patients continue to have considerable urine output until renal blood flow and glomerular filtration are critically decreased as a result of extreme volume depletion. The magnitude of specific deficits in an individual patient at the time of presentation varies depending on the duration 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 presentation.

Intracellular potassium is depleted because of transcellular shifts of this ion caused by hypertonicity (ie, increased plasma osmolality causes solvent drag in which water and potassium are pulled out of cells), and glycolysis and proteolysis secondary to insulin deficiency cause potassium efflux from cells. Potassium is lost from the body through vomiting and as a consequence of osmotic diuresis. Volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion. Total body depletion of potassium occurs, although at the time of presentation, the plasma potassium concentration may not reflect the deficit [13].

Management of diabetic ketoacidosis

During the initial evaluation, the clinician should take the following steps:

- Perform a clinical evaluation to establish the diagnosis and determine its cause (while carefully looking for evidence of infection). Weigh the patient and measure height or length. Determine body surface area. Assess the patient’s degree of dehydration.
• Determine the blood glucose concentration with a glucose meter and the blood or urine ketone concentration.
• Obtain a blood sample for laboratory measurement of serum glucose, electrolytes and total carbon dioxide (TCO₂), blood urea nitrogen, creatinine, serum osmolality, venous (or arterial in critically ill patients) pH, partial pressure of carbon dioxide (pCO₂), partial pressure of oxygen (pO₂), hemoglobin, hematocrit, total and differential white blood cell count, calcium, phosphorus and magnesium concentrations.
• Perform a urinalysis and obtain appropriate specimens for culture (eg, blood, urine, throat).
• Perform an electrocardiogram for baseline evaluation of potassium status.

In the management of DKA, several supportive measures should be undertaken:

• Secure the airway and empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration in the unconscious or severely obtunded patient.
• Give antibiotics to febrile patients after obtaining appropriate cultures of body fluids.
• Provide supplementary oxygen to patients with severe circulatory impairment or shock.
• Catheterize the bladder if a child is unconscious or unable to void on demand (eg, infants and ill young children).
• A heparin-locked peripheral intravenous catheter should be placed for convenient and painless repetitive blood sampling.
• A cardiac monitor should be used for continuous electrocardiographic monitoring.
• Use a flow chart to record a patient’s clinical and laboratory data, including vital signs (eg, heart rate, respiratory rate, blood pressure, level of consciousness [Glasgow coma scale]), details of fluid and electrolyte therapy, amount of administered insulin, and urine output. A key to successful management of DKA is meticulous monitoring of a patient’s clinical and biochemical response to treatment so that timely adjustments in the treatment regimen can be made when indicated by a patient’s clinical or laboratory data. Frequent re-examination of laboratory parameters is required to prevent serious electrolyte imbalance and administration of either insufficient or excessive fluid.

A child with DKA should be cared for in a unit that has experienced nursing staff trained in monitoring and management, clear written guidelines, and access to a laboratory that can provide frequent and timely measurements of relevant biochemical variables. A pediatrician with training and expertise in the management of DKA should supervise inpatient management of these children. Children with signs of severe DKA, including compromised circulation or depressed level of consciousness, and children who are at increased risk for cerebral edema
(<5 years of age, new onset) should be considered for treatment in a pediatric intensive care unit or in a pediatric ward that specializes in diabetes care that has equivalent resources and supervision [11].

**Fluid and electrolyte therapy**

*Sodium and water*

All patients with DKA are dehydrated and suffer total body depletion of sodium, potassium, chloride, phosphate, and magnesium (Table 1). The high effective osmolality of the extracellular fluid compartment and restriction of glucose to the extracellular space result in a shift of water from the intracellular fluid compartment to the extracellular fluid compartment, which causes a decrease in the measured serum sodium concentration. A commonly used correction factor is 1.6 mmol/L decrease in serum sodium concentration per 5.6 mmol/L (100 mg/dL) increase in blood glucose concentration above normal [14]. Experimental evaluation of its accuracy is lacking, and based on acute experimental observations, other researchers have suggested a correction factor of 2.4 mmol/L decrease in serum sodium concentration per 5.6 mmol/L (100 mg/dL) increase in blood glucose concentration above normal [15]. The presence of hyperlipidemia also may lower the measured serum sodium concentration (depending on the methodology used to measure serum sodium concentration). The serum sodium concentration may give a misleading estimate of the degree of sodium loss. The effective osmolality (see formula in following section) at the time of presentation is frequently in the range of 300 to 350 mOsm/L. Increased serum urea nitrogen and hematocrit are useful markers of severe extracellular fluid contraction [16,17]. At the time of presentation, patients are extracellular fluid contracted, and clinical estimates of the deficit in patients with severe DKA, although notoriously inaccurate, are usually in the range of 5% to 10% [18,19]. In cases of mild to moderately severe DKA, fluid deficits are more modest—in the range 30 to 50 mL/kg. Shock with hemodynamic compromise is rare in childhood.

The onset of dehydration is associated with a reduction in glomerular filtration rate, which results in decreased glucose and ketone clearance. Intravenous fluid administration expands the intravascular volume and increases glomerular filtration, which increases renal excretion of glucose and ketoanions, and results in a prompt decrease in blood glucose concentration in the first 2 to 4 hours after rehydration is initiated [20,21].

The goals of fluid and salt replacement therapy in DKA are restoration of circulating volume, replacement of sodium and the extracellular fluid and intracellular fluid water deficit, and restoration of glomerular filtration rate with enhanced clearance of glucose and ketones from the blood and avoidance of cerebral edema (Box 2). In animals and humans, intracranial pressure rises as intravenous fluids are given [22,23]. Although no compelling evidence shows superiority of any fluid regimen over another, some data suggest that rapid
Box 2. Goals of therapy

- Correct dehydration
- Restore blood glucose to near normal levels
- Correct acidosis and reverse ketosis
- Avoid complications of treatment
- Identify and treat the precipitating event

Fluid replacement with hypotonic fluid is associated with an increased risk of cerebral edema, and slower fluid deficit correction with isotonic or near-isotonic solutions results in earlier reversal of acidosis [11,24,25]. Large amounts of 0.9% saline also have been associated with the development of hyperchloremic metabolic acidosis.

Initial intravenous fluid administration and, when necessary, volume expansion should begin immediately with an isotonic solution (0.9% saline or balanced salt solution such as Ringer’s lactate). The volume and rate of administration depend on a patient’s circulatory status. When volume expansion is clinically indicated, 10 to 20 mL/kg is given over 1 to 2 hours and may be repeated if necessary. The goal of this initial fluid therapy is to re-establish adequate perfusion of end organs, not restoration of euvolemia. Success in achieving this goal may be judged best by monitoring mental status, capillary refill, and presence of urine output.

Subsequent fluid management should be with a solution that has a tonicity of 0.45% saline or more (0.9% saline or balanced salt solution [Ringer’s lactate] or 0.45% saline with added potassium). The rate of intravenous fluid administration should be calculated to rehydrate a patient at an even rate over 48 hours. Because the severity of dehydration may be difficult to determine and is often overestimated, the daily volume of fluid usually should not exceed 1.5 to 2 times the usual daily requirement based on age, weight, or body surface area (Table 1). Urinary losses should not be added to the calculation of replacement fluids. The development of hyponatremia or failure to observe a progressive rise in serum sodium concentration with a concomitant decrease of blood glucose concentration during treatment is a risk factor for cerebral edema [7,26]. The composition of the hydrating fluid should be changed appropriately to increase the serum sodium concentration.

When the blood glucose concentration reaches approximately 17 mmol/L (300 mg/dL), 5% dextrose is added to the infusion fluid. It is often necessary to use 10% or even 12.5% dextrose to prevent hypoglycemia while continuing to infuse insulin to correct the metabolic acidosis. Administration of intravenous fluids should be continued until acidosis is corrected and a patient can tolerate fluids and food. Inadequate fluid administration should be evident from examination of the cumulative fluid balance and persistent tachycardia in the absence of a fever.
Insulin and glucose

Insulin is essential for restoring blood glucose to normal and suppressing lipolysis and ketogenesis. Rehydration alone decreases the blood glucose concentration but does not reverse ketoacidosis. Several routes (ie, subcutaneous, intramuscular, and intravenous) of insulin administration and doses have been used and are effective in managing DKA [27–29]; however, “low dose” intravenous insulin administration is the current standard of care [11,27,28]. A loading dose of insulin is not required to initiate insulin therapy [30]. At a continuous dose of 0.1 U/kg/h, intravenous regular (soluble) insulin achieves steady state serum insulin levels of 50 to 200 µU/mL within 60 minutes. These serum insulin levels are adequate to offset the insulin resistance characteristic of DKA. They suppress glucose production, significantly increase peripheral glucose uptake, and inhibit lipolysis and ketogenesis. The dose of insulin should remain at 0.1 U/kg/h until resolution of ketoacidosis (pH > 7.30 and bicarbonate > 15 mmol/L or closure of the anion gap). It should be noted, however, that resolution of ketoacidemia takes longer than restoration of blood glucose concentrations to normal. Intravenous insulin therapy must not be discontinued until ketoacidosis has resolved, even if the blood glucose concentration is normal or near to normal. To prevent an unduly rapid fall in blood glucose concentration and development of hypoglycemia, dextrose should be added to the intravenous fluid when the plasma glucose has fallen to approximately 17 mmol/L (300 mg/dL), as noted previously.

The amount of dextrose in the intravenous infusion should be increased in stepwise fashion up to a maximum concentration of 12.5% to maintain the blood glucose between 100 and 200 mg/dL. If the blood glucose continues to drop, the rate of intravenous fluid administration should be increased to twice the maintenance rate. If the blood glucose still cannot be maintained and the serum bicarbonate is approaching normal, the insulin infusion rate may be decreased by decrements of 0.02 U/kg/h.

Continuous intravenous insulin should be administered via an infusion pump. Regular insulin is diluted in normal saline (50 U regular insulin in 50 mL saline) and is given at a rate of 0.1 U/kg/h. An intravenous priming dose of 0.1 U/kg is not necessary but may be used at the start of insulin therapy, particularly if insulin treatment has been delayed. This rate of insulin infusion is sufficient to reverse ketoacidosis in most patients. If the response is inadequate (especially if blood glucose level is falling but acidosis is not improving; ie, the anion gap is not decreasing) because of severe insulin resistance, the rate of insulin infusion should be increased until a satisfactory response is achieved. There are rare patients with severe insulin resistance who do not respond satisfactorily to low-dose insulin infusion and require two or three times the usual dose. It is essential to monitor the response to insulin therapy in terms of blood glucose and degree of acidosis (ie, venous or arterial pH, anion gap, or end-tidal CO₂, as detailed later). One also should consider other possible explanations for failure to respond to insulin, especially an error in insulin preparation. When intravenous adminis-
istration is not possible, the intramuscular or subcutaneous route of insulin administration may be used, and rapid-acting insulin (lispro or aspart) may be preferable to regular insulin in these circumstances. Treatment of adult patients who have uncomplicated DKA with subcutaneous insulin lispro every hour in a nonintensive care setting has been shown to be safe and more cost effective than treatment with intravenous regular insulin in the intensive care unit [29]. Poor tissue perfusion in a severely dehydrated patient may impair absorption of insulin from subcutaneous tissue, and insulin initially should be given intramuscularly.

The serum half-life of insulin is 5 minutes, so if the insulin infusion is stopped, the serum insulin concentration decreases rapidly. If the infusion were to infiltrate and was not recognized promptly, inadequate serum insulin levels would ensue rapidly. Low-dose intravenous insulin therapy must be supervised carefully.

When ketoacidosis has resolved and the change to subcutaneous insulin is planned, the first subcutaneous injection should be given at an appropriate interval before stopping the insulin infusion to allow sufficient time for the subcutaneously injected insulin to begin to be absorbed. The onset of action of rapid-acting insulin (lispro or aspart) is approximately 15 minutes, whereas that of regular insulin is 30 to 60 minutes. At the authors’ institution, the starting dose of subcutaneous insulin in new-onset patients after recovery from DKA initially is based on a total daily dose (TDD) of insulin of 0.75 U/kg/d in prepubertal children and 1 U/kg/d in pubertal patients. Two thirds of the TDD is given before breakfast (one third as rapid-acting insulin and two thirds as intermediate-acting insulin; in young children, one fourth is given as rapid-acting insulin and three fourths are given as intermediate-acting insulin). One third of the remainder of the TDD is given before dinner as rapid-acting insulin, and two thirds of the remainder of the TDD is given as intermediate-acting insulin at bedtime. Likewise, in young children, the proportion of rapid-acting insulin given before dinner usually is decreased to one fourth of the remainder of the TDD. For example, if a 10-year-old prepubertal child weighs 30 kg, the starting dose would be 5 U rapid-acting insulin and 10 U intermediate-acting insulin before breakfast, 2 to 3 U rapid-acting insulin before dinner, and 5 U intermediate-acting insulin at bedtime. Supplemental rapid-acting insulin is given at approximately 4-hour intervals to correct blood glucose levels that exceed 200 mg/dL. Alternatively, one half of the estimated TDD may be given as basal insulin using insulin glargine, and the remaining one half of the estimated TDD is given as rapid-acting insulin, with the dose before each meal comprising approximately 15% to 20% of the TDD. In the hypothetical case cited previously, a child would receive a single dose of 11 to 12 U of insulin glargine either at dinnertime or bedtime and 3 to 4 U of rapid-acting insulin before each meal.

**Potassium**

Serum potassium concentrations at the time of presentation may be normal, increased or, infrequently, decreased. Hypokalemia at presentation may be related to prolonged duration of disease and persistent vomiting, whereas hyperkalemia
primarily results from impaired renal function [13]. Adults with DKA have total body potassium deficits of the order of 4 to 6 mmol/kg and, although data in children are sparse, similar deficits have been described in a few carefully studied cases [31–35]. After treatment is started, insulin promotes cellular uptake of glucose and potassium, and correction of acidosis promotes the return of potassium to the intracellular compartment. The serum potassium concentration may decrease abruptly, which predisposes a patient to cardiac arrhythmias. Potassium replacement should be started immediately if a patient is hypokalemic. Otherwise, it should be started concurrent with commencing insulin therapy. If a patient presents with hyperkalemia, potassium administration should be deferred until urine output has been documented.

The amount of potassium administered should be sufficient to maintain serum potassium levels in the normal range. The usual starting potassium concentration in the infusate should be 40 mmol/L, and potassium administration should continue throughout the period of intravenous fluid therapy. Careful monitoring of the serum level and provision of adequate potassium are essential to prevent hypokalemia and life-threatening arrhythmias. An electrocardiogram can be used as a guide to therapy and is especially valuable while waiting for the serum potassium concentration to be measured. Flattening of the T wave, widening of the QT interval, and the appearance of U waves indicate hypokalemia. Tall, peaked, symmetrical T waves and shortening of the QT interval are signs of hyperkalemia. The plasma potassium concentration should be rechecked every 1 to 2 hours if the plasma concentration is outside the normal range. Potassium may be given as chloride, acetate, or phosphate salt. Use of potassium acetate and potassium phosphate reduces the total amount of chloride administered and partially corrects the phosphate deficit.

**Phosphate**

Depletion of intracellular phosphate occurs in DKA and phosphate is lost as a result of osmotic diuresis. In adults, deficits are in the range of 0.5 to 2.5 mmol/kg, but comparable data in children are sparse. After starting therapy, plasma phosphate levels rapidly decrease because of urinary excretion and because insulin causes phosphate to re-enter cells. Low serum phosphate levels have been associated with various metabolic disturbances; however, the effects of hypophosphatemia on 2,3-diphosphoglycerate concentrations and on tissue oxygenation are especially relevant to DKA management. Although phosphate depletion persists for several days after resolution of DKA, prospective studies have failed to show any significant clinical benefit from phosphate replacement [36–41]. Serum phosphate levels should be monitored, and severe hypophosphatemia should be treated with potassium phosphate while carefully monitoring serum calcium concentrations to avoid phosphate-induced hypocalcemia. This occurrence generally can be avoided if potassium phosphate concentration in the intravenous fluid does not exceed 20 mEq/L.
Acidosis and bicarbonate

Even severe acidosis is reversible by fluid and insulin replacement. Insulin stops further synthesis of ketoacids and promotes ketone use. The metabolism of ketoanions results in the regeneration of bicarbonate and correction of acidemia. Treatment of hypovolemia improves tissue perfusion and restores renal function, which increases the excretion of organic acids and reverses any lactic acidosis, which may account for up to 25% of the acidemia.

In DKA, the anion gap is increased primarily because of a marked increase in the concentrations of the major ketoanions, β-hydroxybutyrate and acetoacetate. Acetone is formed by spontaneous decarboxylation of acetoacetate. Acetoacetate and acetone, but not β-hydroxybutyrate, are measured by the commonly used clinical reagent strip or tablet methods that use the sodium nitroprusside reaction. At initial presentation with DKA, the concentration of β-hydroxybutyrate is four to ten times higher than that of acetoacetic acid. With insulin therapy and correction of the acidosis, the β-hydroxybutyrate is reoxidized to acetoacetate, which is eventually metabolized. Blood ketone meters only measure β-hydroxybutyrate.

The indications for bicarbonate therapy in DKA are unclear. Controlled trials of sodium bicarbonate in children and adults have been unable to show clinical benefit or any important difference in the rate of rise in the plasma bicarbonate concentration [42–44]. There are physiologic reasons not to use bicarbonate. Its use may cause paradoxic central nervous system acidosis. Bicarbonate combines with H+ and then dissociates to CO₂ and H₂O. Bicarbonate diffuses poorly across the blood-brain barrier, whereas CO₂ diffuses freely into the cerebrospinal fluid. The use of bicarbonate may worsen acidosis within the central nervous system while serum acidosis improves [45]. Rapid correction of acidosis causes hypokalemia, may aggravate sodium load, and contributes to serum hypertonicity. It also may impair tissue oxygenation by increasing the affinity of hemoglobin for oxygen (ie, shift the hemoglobin-oxygen dissociation curve to the left). Alkali therapy may increase hepatic ketone production and slow the rate of recovery from ketosis [46]. The use of bicarbonate in children with DKA is associated with an increased risk of cerebral edema (Box 3) [7].

Box 3. Complications of therapy

- Inadequate rehydration
- Hypoglycemia
- Hypokalemia
- Hyperchloremic acidosis
- Cerebral edema
Selected patients may benefit from cautious alkali therapy, including 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. Administration of bicarbonate is indicated when acidosis is severe (arterial pH≤6.9) and when there is hypotension, shock, or an arrhythmia. In these circumstances, 1 to 2 mmol/kg or 40 to 80 mmol/m² of sodium bicarbonate is infused over 2 hours and the plasma bicarbonate level is rechecked. Bicarbonate should not be given as a bolus because this may precipitate an acute cardiac arrhythmia.

**Clinical and biochemical monitoring**

Initially, plasma glucose should be measured hourly. Thereafter, plasma glucose, serum electrolytes (and calculated sodium), pH, pCO₂, TCO₂, anion gap, calcium and phosphorus levels should be measured every 2 to 4 hours for the first 8 hours and then every 4 hours until they are normal. The data must be recorded carefully on a flow sheet.

In all patients, continuous cardiovascular and respiratory monitoring should be performed. The end-tidal CO₂ has been shown to correlate well with degree of acidosis in DKA, and noninvasive capnography may be used continuously to monitor the degree of metabolic acidosis [47–49]. The end-tidal CO₂ can be expected to rise steadily toward normal (35–45 mm Hg) in the successfully treated patient. If the end-tidal CO₂ begins to trend downward, immediate investigation must be undertaken of the insulin infusion and a patient’s neurologic status. Conversely, an upward trend in end-tidal CO₂ in an increasingly somnolent patient may be a sign of hypoventilation and evolving cerebral edema.

**Investigating the cause of ketoacidosis**

The management of DKA is not complete until its cause has been identified and treated. Leukocytosis is common but most likely reflects the severity of DKA rather than the presence of infection; most children with DKA have no evidence of infection [50]. An intercurrent infection is not the usual cause when a patient is properly educated in diabetes management, is receiving regular follow-up care by a competent physician, and has access to a diabetes treatment team [51,52]. In previously diagnosed patients on treatment with insulin, omission of insulin—either inadvertently or deliberately—is the most common cause [52,53]. There is often an important psychosocial reason for insulin omission, including an attempt by an adolescent girl with an eating disorder to lose weight, a means of escaping an intolerable or abusive home situation, clinical depression, or the inability of a patient to manage his or her own diabetes unassisted [11]. A psychiatric social worker or clinical psychologist should be consulted to help identify the psychosocial reasons underlying the development of DKA.
The following calculations are useful for managing DKA [54]:

Effective osmolality: $2[Na^+ + K^+] + \text{glucose (mg/dL)}/18$

Corrected sodium: $[Na^+] + (1.6 \times [\text{plasma glucose mmol/L} - 5.6] ÷ 5.6)$

Anion gap: $[Na^+] - [\text{Cl}^- + \text{HCO}_3^-]$

Evaluation for pure metabolic acidosis:

$$\text{pCO}_2 = \text{last two numbers of the pH}$$

$$\text{pCO}_2 = 1.5 \times [\text{serum } \text{HCO}_3^-] + 8 \pm 2$$

Effective serum osmolality correlates with mental status abnormalities. Blood or serum urea nitrogen freely diffuses into cells and does not contribute to effective osmolality. Corrected serum sodium assists in estimation of free water deficits. A decreasing anion gap indicates successful therapy of metabolic acidosis. A lower than predicted pCO$_2$ indicates respiratory alkalosis and may be a clue to sepsis.

**Morbidity and mortality from diabetic ketoacidosis in children**

Reported mortality rates from DKA in national population-based studies are reasonably constant in the range of 0.15% to 0.31% [11]. In areas with sparse medical facilities, the risk of dying from DKA is greater, and children may succumb before receiving treatment. Cerebral edema accounts for 57% to 87% of all deaths from DKA. The incidence of cerebral edema has been fairly consistent between national population-based studies: 0.46% in Canada to 0.87% in the United States. Mortality rates from cerebral edema in population-based studies are 21% to 25%. Significant morbidity is evident in 10% to 26% of survivors. Other causes of DKA-related morbidity and mortality include hypokalemia, hyperkalemia, hypoglycemia, sepsis, venous thrombosis [55], and other central nervous system complications, such as cerebrovascular thrombosis with brain infarction [56].

**Cerebral edema**

Clinically significant cerebral edema may develop at any time during the first 24 hours of therapy. It is more common in children with severe DKA, new-onset type 1 diabetes, younger age, and longer duration of symptoms [7,8]. The cause(s) of CE remains poorly understood. It occurs to some extent (subclinical) in all patients with DKA [57]. Patients who require treatment are the subset of patients who have clinical symptoms or signs. The onset of symptoms typically
occurs 4 to 12 hours after commencement of treatment but can occur before treatment has begun or at any time during treatment. Symptoms and signs vary and are shown in Box 4 [58]. Children who develop significant CE during DKA usually exhibit definable signs and symptoms of neurologic collapse early enough to allow intervention to prevent brain damage. Initial cranial CT scans may be reported as normal. The diagnosis of this complication must be based on clinical criteria at the bedside.

Based on data generated in animal models, researchers have thought that because of the presence of a chronic hyperosmolar state associated with hyperglycemia, the cerebral cells compete with the osmotic force of the serum by

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**Box 4. Bedside evaluation of neurologic state of children with diabetic ketoacidosis**

**Diagnostic criteria**

- Abnormal motor or verbal response to pain
- Decorticate or decerebrate postures
- Cranial nerve palsy (especially III, IV, and VI)
- Abnormal neurogenic respiratory pattern (eg, grunting, tachypnea, Cheyne-Stokes respiration, apneusis)

**Major criteria**

- Altered mentation/fluctuating level of consciousness
- Sustained heart rate deceleration (decrease >20 beats/min) not attributable to improved intravascular volume or sleep state
- Age-inappropriate incontinence

**Minor criteria**

- Vomiting
- Headache
- Lethargic or not easily arousable
- Diastolic blood pressure more than 90 mm Hg
- Age younger than 5 years

One diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity rate of 92% and a false-positive rate of 4% [58].
storing intracellular osmoles (primarily taurine). It has been thought that with therapy plasma glucose concentrations decline over several hours and the cytosolic osmolality becomes disproportionately high; water is attracted by osmosis, and cellular swelling occurs. This longstanding theory was challenged recently when MRI with diffusion-weighted analysis demonstrated that among 12 subjects with DKA, none demonstrated significant cellular edema [59]. The edema in this series of patients was vasogenic, or extracellular. Because none of the patients studied had severe cerebral edema, the possibility that cellular edema complicates vasogenic edema only in those patients who develop clinical symptomatology has not been ruled out.

**Treatment of cerebral edema**

Treatment of cerebral edema should be initiated as soon as the condition is suspected. The rate of fluid administration should be reduced. Intravenous mannitol (0.25–1 g/kg) should be given over 20 minutes and can be repeated, if necessary, in 2 hours if there is no initial response. Hypertonic saline (3%), 5 to 10 mL/kg over 30 minutes, may be an alternative to mannitol [60]. Intubation may be necessary for a patient with impending respiratory failure, but aggressive hyperventilation (to a pCO₂ < 22 mm Hg) has been associated with poor outcome and is not recommended [61].

**Summary**

Although DKA should, theoretically, be largely preventable in patients with established diabetes, a recent report from the Barbara David Center for Childhood Diabetes in Denver, Colorado showed that children with type 1 diabetes remain at high risk for DKA, with an incidence of 8 per 100 patient-years [10]. Children who are uninsured or underinsured, have psychiatric disorders, have poorly controlled diabetes, and live in dysfunctional families are most vulnerable. The efficacy and cost effectiveness of strategies to reduce the incidence of DKA, before diagnosis and in patients with established diabetes, are important issues for future investigation.

**References**


