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Guidelines For The ED Management Of Pediatric Diabetic Ketoacidosis (DKA)

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CME Objectives

Upon completing this article, you should be able to:

1. Define diabetic ketoacidosis;
2. Discuss the pathophysiology of pediatric diabetic ketoacidosis;
3. Describe the risk factors associated with the development of cerebral edema in children who are diagnosed with diabetic ketoacidosis; and
4. Discuss the management of children who are diagnosed with diabetic ketoacidosis.

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See "Physician CME Information" on back page.

An adolescent girl is brought to your ED by her mother for another episode of diabetic ketoacidosis (DKA). This 14-year-old has had diabetes since 7 years of age and has had multiple episodes of DKA over the past 3 or 4 years. The mother describes her as increasingly rebellious and "tired of having diabetes." She frequently goes to the mall with her friends and eats "junk." She has become inconsistent with checking her glucose levels and sometimes "forgets" to take her insulin. She now complains of abdominal pain. She is Kussmaul breathing with fast and deep breaths. Her bedside glucose check registers "high" on the monitor. She has ketones on a dip urinalysis. As the nurse prepares to place an intravenous (IV) catheter, you begin to consider the issues involved in treating a child who is experiencing DKA. What are the greatest pitfalls in treatment? What about electrolytes, such as potassium? When is sodium bicarbonate indicated? Should bolus insulin be given prior to starting a continuous drip? Which children are at risk for cerebral edema?

ON January 11, 1922, astounded physicians watched blood sugar fall following the first human injection of insulin. Leonard Thompson, a 65-pound, 14-year-old boy, received 15 cc of an impure, thick, brown muck extracted from bovine pancreas. Until that day, the diagnosis of diabetes had been a death sentence with a very short life expectancy. Since 1922, we have come a long way. Protamine zinc insulin was introduced in the 1930s. The United States Food and Drug Administration approved insulin for human use in 1939.[1] Neutral protamine Hagedorn (NPH) insulin was introduced in the 1940s. NPH offered the advantage of prolonged insulin activity, so that early morning hyperglycemia could be blunted with an injection in the evening. The Lente series was introduced in the 1960s, and the 1970s brought the purification of insulin.[2] In the 1980s human insulin generated through

recombinant DNA technology appeared. More recently, insulin pumps have become available. Yet despite the many advances in diabetes care that have occurred over the last 8 decades, children still die from complications associated with DKA.

In this issue of *Pediatric Emergency Medicine Practice*, an organized approach to the diagnosis, evaluation, and management of children with DKA will be presented.

Abbreviations Used in this Article

ACTH — Adrenocorticotropic hormone
BUN — Serum blood, urea, nitrogen
CT — Computed tomography or computed tomographic
DKA — Diabetic ketoacidosis
ED — Emergency department
HLA — Human leukocyte antigen
MRI — Magnetic resonance imaging
NPH — Neutral protamine Hagedorn

Critical Appraisal Of The Literature

Consensus Documents

There are abundant consensus documents regarding pediatric DKA available in the literature,[3-6] and these can provide much helpful evidence and expert opinion regarding the treatment of pediatric DKA. Because of the work done to develop consensus documents such as these, the management of DKA is one of the most widely agreed upon and standardized in pediatrics. Still, the agreement is not universal. Physicians from multiple specialties, including general pediatricians, pediatric endocrinologists, emergency physicians, pediatric emergency physicians, and pediatric intensivists, all manage children with DKA. There is some evidence that their management practices vary to a degree based on their training and experience.[7]

Cerebral Edema

Since DKA-associated cerebral edema has a low incidence, occurring in about 1% of all episodes of DKA, study of this relatively rare complication is problematic. Most studies, therefore, are retrospective case-control studies, small case series, or case reports. I was unable to identify any prospective, randomized controlled studies of the treatment for DKA-associated cerebral edema. The main focus of the available studies is identifying potential risk factors for cerebral edema in children with DKA.[8,9]

One well-designed study was a multicenter case-control study involving 61 children with DKA-associated cerebral edema and, for each of these cases, 6 control children who had DKA without developing cerebral edema.[8] There were 3 risk factors for cerebral edema identified: a higher serum blood, urea, nitrogen (BUN) on initial presentation, more severe hypocapnia on initial presentation, and the administration of sodium bicarbonate. If the patient had a low rate of increase of serum sodium during the treatment, there was a somewhat higher risk of cerebral edema in this study. More interesting, perhaps, were the factors *not* associated with an increased risk of cerebral edema. Neither the initial serum glucose concentration, nor the rates of fluid, sodium, or insulin administration were associated with the development of cerebral edema in this study. This evidence flies in the face of the traditional teaching that overzealous fluid administration is a key factor in the development of cerebral edema in young children with DKA.

Another case-control study included 24 patients with cerebral edema associated with DKA who were matched with 69 episodes of uncomplicated DKA.[10] The analysis provided a bedside evaluation protocol that was then applied to 17 children who subsequently developed symptomatic cerebral edema. The protocol allowed a better than 90% sensitivity and 96% specificity of cerebral edema resulting in timely intervention. The study points out that initial head CT scans were often normal.

One small study investigated the mechanism of cerebral edema in children with DKA.[11] This study by Glaser et al suggests that the mechanism of cerebral edema is vasogenic and not oncotic. The researchers evaluated the neuroimaging of 14 children during treatment of their DKA with magnetic resonance imaging (MRI) using both perfusion- and diffusion-weighted MRI techniques. They found that perfusion MRI studies had significantly shorter mean transit times, indicating increased cerebral blood flow. The authors note that the observed changes may reflect differences in the hemodynamic states between the dehydrated DKA patient and the resuscitated DKA patient. The authors also note that patients with greater dehydration and more profound hypocapnia had increased risk of symptomatic cerebral edema. They concluded that cerebral hypoperfusion before treatment may play an important role in the development of cerebral edema.

Infection as a Cause of DKA in Children

One retrospective study, published in 2001, reinforced the concept that leukocytosis does not correlate well with the presence of a bacterial infection. In this study, 12.9% of 247 admissions of children 21 years of age or younger were found to have a bacterial infection associated with DKA.[12] The results of this study challenge the statement that "infections are the most frequent cause of DKA" found in many texts.

Epidemiology, Etiology, And Pathophysiology

Epidemiology and Etiology

"Type 1" and "Type 2" Diabetes in Children

Type 1 diabetes is the most common type of diabetes seen in children today. The primary metabolic derangement in type 1 diabetes is an absolute insulin deficiency. These patients will have a life-long dependence on insulin injections. The overall incidence of insulin-dependent diabetes is about 15 cases per 100,000 people per year (about 50,000 are diagnosed with type 1 diabetes each year). An estimated 3 children of every 1000 will develop insulin-dependent diabetes by the age of 20. Type 1 diabetes is primarily a disease of Caucasians. The worldwide incidence is highest in Finland and Sardinia and lowest in the Asian and black populations. Type 1 diabetes is more frequently diagnosed

in the winter months (the reason for this is not known.) Interestingly, twins affected by type 1 diabetes are often discordant in the development of the disease.[13] About 95% of cases of type 1 diabetes are the result of a genetic defect of the immune system, exacerbated by environmental factors.[13] The autoimmune destruction of the beta cells of the pancreas results in the inability to produce insulin. Inheritance of type 1 diabetes is carried in genes of the major histocompatibility complex, the human leukocyte antigen (HLA) system. Eventually, this research may lead to a vaccine using the insulin B chain 8-24 peptides to actually prevent type 1 diabetes.[13] It is currently thought that islet cells damaged by a virus produce a membrane antigen that may stimulate a response by T killer cells of the immune system in the genetically susceptible patient. The T killer cells misidentify the beta cell as foreign and destroy it. As the beta cells in the pancreas are destroyed, the remaining beta cells must increase their metabolism, and thus the turnover of membrane antigen, in order to keep up with insulin demands. More membrane antigen means that more T killer cells are activated, hence more islet cell destruction. This sets up a vicious cycle that ends in the destruction of the entire beta cell mass and the symptoms of clinical diabetes. This chronic destructive process involves humoral and cellular components that are detectable in the peripheral blood months, or even years, before the onset of clinical diabetes. Throughout this long "prediabetic" period, metabolic changes, including decrease in insulin secretion with altered glucose tolerance, develop at variable rates, leading to full-blown diabetes. Early recognition of diabetes and adequate supplemental insulin may reverse this process and prevent the immune response.[13] This preservation and possible recovery of the beta cell mass is thought to be the basis of the "honeymoon period" seen after insulin is started in the patient with new-onset type 1 diabetes. Early identification and adequate treatment with insulin may initiate, sustain, and even extend this partial remission.

Type 2 diabetes is a heterogeneous glucose disorder, found most often in adults over 40 years of age and associated with a family history of diabetes. Type 2 diabetes was originally considered a disease only affecting adults. In the late 1970s, type 2 diabetes was recognized as a disease of the pediatric age group.[4,14] It has since turned into an "epidemic," with a 10-fold increase during the 1990s alone. The problem is not limited to North America; it has also been reported in children from Europe, Asia, Africa, and Australia.[15-25] In fact, type 2 diabetes is usually characterized by a resistance to the patient's own insulin that may or may not be coupled with a defect in insulin secretion of varying severity. These defects lead to increase in liver production of glucose and subsequent fasting hyperglycemia. As emergency physicians, we are seeing increasing numbers of older school-aged children, adolescents, and young adults with type 2 diabetes.[4,14]

The major risk factor for type 2 diabetes appears to be obesity, which has become an epidemic in the United States for all ethnic subtypes.[26] Obesity is associated with insulin resistance, which worsens diabetes in any case. If the type 2 diabetic loses weight and adheres to a strict diet, often no medication at all is required. Since the majority of these patients do have some insulin secretion, diabetic ketoacidosis is uncommon in the type 2 diabetic, but it can occur. The type 2 diabetic patient is often considered to require insulin for control, but not to be "insulin-dependent." Prolonged high blood sugars will also reduce the effect of insulin (ie, insulin resistance) and decrease the secretion of insulin.[27] When the pancreas quits making insulin, then the type 2 diabetic needs insulin as much as the type 1 diabetic.[28] Given the heterogeneity of the clinical presentation of type 2 diabetes in children, classification of patients into type 1 and type 2 cannot always be reliably made.[29]

DKA-associated Cerebral Edema

Diabetic ketoacidosis is the most common cause of diabetes-related death in childhood. Despite the plethora of guidelines and protocols, all covering meticulous details of fluid and electrolyte replacement and insulin therapy, the mortality associated with diabetic emergencies has remained unchanged for the last 10 years. Cerebral edema associated with DKA is the most common cause of these diabetic-related deaths in young patients.[11] Cerebral edema is found in about 1% of patients who present with DKA, but is responsible for about 30% of deaths due to diabetic complications in children.[30-33] It is almost always a disease of children. In the largest reported series to date, over 95% of cases occurred in patients under 20 years of age, and one third of cases occurred in children younger than 5 years of age.[30] As many as one fourth of the children who develop DKA-associated cerebral edema will die from this complication.

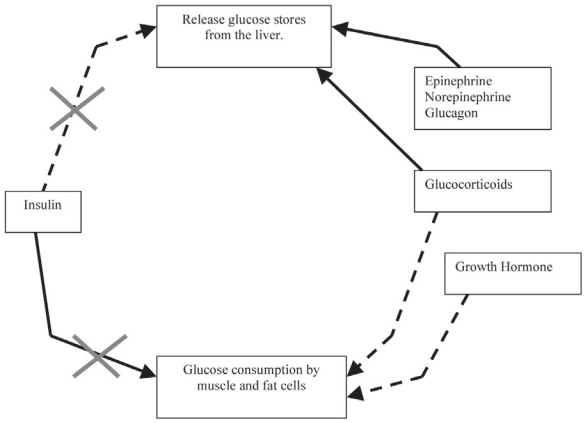
"The terms 'insulin dependent,' 'non-insulin dependent,' 'juvenile onset,' and 'adult onset' are no longer used to describe patients with diabetes."

Pathophysiology

Normal Glucose Physiology

Maintenance of blood glucose homeostasis is of paramount importance to human survival. The brain requires 75% of the glucose circulating in the blood. If for no other reason, the needs of the brain for this oxidizable glucose require the human body to closely regulate the level of glucose in the blood. Both elevated and reduced levels of blood glucose trigger hormonal responses to restore

Figure 1. Overall Regulation Of Blood Glucose And The Impact Of Type 1 Diabetes.*



*The solid lines indicate positive effects. Dashed lines indicate negative or inhibitory effects. The large gray X's indicate the derangements caused by type 1 diabetes.

glucose homeostasis. Low blood glucose triggers release of glucagons from pancreatic alpha cells. High blood glucose triggers release of insulin from pancreatic beta cells. Additional signals, adrenocorticotropic hormone (ATCH) and growth hormone released from the pituitary, increase blood glucose levels by inhibition of glucose uptake by extrahepatic tissues. (**Figure 1**) Glucocorticoids also act to increase blood glucose levels by inhibition of glucose uptake. Cortisol is secreted by the adrenal cortex in response to the increased ACTH levels. The adrenal medullary hormone, epinephrine, stimulates the production of glucose by activation of glycogenolysis in response to stress. The term "diabetes" refers to a group of diseases consisting of different errors or faults in metabolic processes that culminate in a high sugar. The implications, treatment, and short-term complications seen with these various diseases can be quite different, yet all are designated "diabetes." The terms "insulin dependent," "non-insulin dependent," "juvenile onset," and "adult onset" are no longer used to describe patients with diabetes.

Diabetic Ketoacidosis

The basic underlying mechanism of DKA is a reduction in the net effective action of circulating insulin, coupled with a concomitant elevation of counterregulatory hormones, such as glucagon, catecholamines, cortisol, and growth hormone. Insulin is the most significant hormone of blood glucose regulation. Insulin increases the ability of the cell to take in glucose and stimulates manufacture of glycogen. Increased hepatic glucose production is the major cause of the hyperglycemia seen in diabetes. Decreased peripheral uptake of glucose further increases the serum glucose. Blood glucose levels will rise above the renal threshold for glucose reabsorption, so an osmotic diuresis occurs. The counterregulatory hormones (cortisol, catecholamines, and growth hormones) are increased by the stress of the illness, including both the profound dehydration caused by the osmotic diuresis and the acidosis caused by fatty acid oxidation. In the absence of insulin, glucagon becomes the primary driving hormone for hepatic carbohydrate metabolism. Glucagon stimulates release of glucose from the liver by gluconeogenesis and glycogenolysis. Liver glycogen stores are broken down into sugar and released into the bloodstream. Deficiency of insulin and concomitant increases in glucagon will enhance the liver production of glucose by breakdown of fat and protein. The fatty acid oxidation leads to ketone body formation and inhibits the conversion of acetyl coenzyme A (CoA), by acetyl CoA carboxylase, to malonyl CoA, which is the first intermediate in the lipogenesis pathway. This inhibition means that fatty acids are unable to enter the citric acid cycle and move instead into the mitochondria, where they are oxidized and further ketone bodies — acetoacetate and beta-hydroxybutyrate — are formed.[34] At the same time, peripheral uptake of glucose is impaired by both lack of insulin and excess of glucagon, so the excess glucose accumulates in the blood stream. Insulin deficiency alone, or in combination with the insulin counterregulatory hormone increases, will increase protein breakdown, providing amino acids for increased gluconeogenesis.

Diabetic ketoacidosis can be caused by either an absolute or relative deficiency of insulin and is exacerbated by the concomitant increase in the insulin counterregulatory hormones: glucagon, epinephrine, cortisol, and growth hormone. Not surprisingly, the classic triad of DKA is

Table 1. Severity Grading For Diabetic Ketoacidosis.*

	Mild	Moderate	Severe
Venous pH	7.25–7.30	7.00–7.24	<7.00
Serum bicarbonate (mEq/L)	15-18	10-14	<10
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma

*Adapted from American Diabetes Association. Hyperglycemic Crises in Patients with Diabetes Mellitus. *Diabetes Care* 2002;25:S100-S108.

Note: An alternative grading scheme has been advocated by the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society. They suggest that mild DKA is defined by a venous pH <7.30 and a bicarbonate concentration <15 mmol/L; moderate DKA is defined by a venous pH <7.2 and a bicarbonate concentration <10 mmol/L; and severe DKA is defined by pH <7.1 and a bicarbonate <5 mmol/L. Adapted from Dunger DB, Sperling MA, Acerini CL, et al. See Reference 3.

hyperglycemia, ketosis, and acidosis. As untreated DKA worsens, the counterregulatory hormones further shift metabolism toward hyperglycemia, acidosis, and ketosis. Although DKA was formerly thought to occur only in type 1 diabetics, up to 25% of pediatric patients presenting with type 2 diabetes may have DKA at the time of diagnosis.[35]

Diabetic ketoacidosis is defined by hyperglycemia, ketosis, and acidosis. Obviously, these features occur along a continuum. There is no universal agreement as to the exact definition of DKA, nor is there exact agreement as to how to grade the severity of DKA. (**Table 1**) Some patients (eg, pregnant adolescents) may present with only mild hyperglycemia and marked ketoacidosis.[36-38]

Insulin inhibits the lipolytic action of cortisol and growth hormone. A deficiency of insulin will increase the circulating levels of fatty acids. These fatty acids are metabolized by alternative metabolic pathways. The breakdown products of the alternative metabolic pathways cause the characteristic acetone byproducts and a resultant metabolic acidosis. The acidosis of diabetic ketoacidosis is mostly due to the ketoacids, although excess fatty acids and lactic acid from poor tissue perfusion also play a role. These increased ketoacids include acetone, beta-hydroxybutyric acid, and acetoacetic acid, although the major derangement in DKA is an increased level of beta-hydroxybutyric acid, rather than acetone or acetoacetate (on the order of 10:1).

Abdominal pain may be a prominent complaint in children experiencing DKA. The abdominal pain may be severe enough to mimic an acute "surgical abdomen."[39] The exact cause of the abdominal pain associated with DKA is not known. One theory involves prostaglandins. Prostaglandins I2 and E2, which are generated in adipose tissue, are increased during DKA.[40] These prostaglandins decrease peripheral vascular resistance and may cause tachycardia, hypotension, nausea, vomiting, and abdominal pain. The same symptoms occur when PGI2 is infused over several hours into normal humans.

Physiologic stress may precipitate DKA. Several cytokines involved in stress responses, such as IL1, IL6, and TNF-alpha, antagonize the effects of insulin. Therefore, it is not surprising that many causes of stress and/or the systemic inflammatory responses can precipitate DKA in patients who are lacking insulin.

The kidney plays an important role in the development of DKA. The normal renal threshold for glucose reabsorption is greater than 240 mg/dL.[41] When this threshold is exceeded, glucose spills into the urine (along with obligatory fluid). When the patient is well hydrated and normal kidney function is maintained, the serum glucose level is maintained at about 240 mg/dL by spillage into the urine. The osmotic diuresis results in significant volume depletion, unless the patient drinks copious amounts of fluids. When hypovolemia occurs, the glomerular filtration rate falls and the hyperglycemia is exacerbated. The diuresis also leads to significant urinary losses of potassium, sodium, phosphate, chloride, and magnesium ions.

Differential Diagnosis

Condition	Features Differentiating Condition from DKA
Starvation ketosis	Serum bicarbonate level ≥18 mmol/L
Chronic renal failure	Hyperchloremia
Paraldehyde ingestion	Characteristic strong odor on the breath
Ethylene glycol ingestion	Crystals in the urine
Salicylate ingestion	Elevated serum salicylate level

Prehospital Care

Prehospital care of the child with diabetes and suspected DKA is limited to starting an intravenous (IV) line, checking or confirming a home glucose check, and initiating a judicious fluid bolus of normal saline (10 mL/kg is probably reasonable). Obtaining a high fingerstick glucose on a young child with altered mental status and clinical dehydration may allow the ED staff to begin considering DKA as the probable cause of the child's acute illness.

ED Evaluation

History

The most common association found with diabetic ketoacidosis is, of course, the prior history of diabetes. Unfortunately, as many as 20-30% of cases of diabetic ketoacidosis may be the initial presentation of previously undiagnosed diabetes. The patient with DKA may have fatigue, malaise, thirst, and polyuria. The patient may note weight loss, if there is a long onset prior to frank DKA. As the patient becomes more ill, they will begin to vomit and may complain of abdominal pain. When diabetic ketoacidosis occurs as the initial presentation in the newly diagnosed diabetic, the symptoms are often gradual in onset, with progressive dehydration and slowly developing ketosis. The onset of symptoms may be more rapid in children with established diabetes.

Risk Factors for DKA

Sex

There is no difference in DKA rates between the sexes at diagnosis and during early childhood. During adolescence, females with diabetes are twice as likely to develop DKA as males with diabetes.

Age

Preschool-aged children are at the greatest risk of presenting with diabetic ketoacidosis. The use of insulin pumps and continuous subcutaneous insulin infusion hold great promise in decreasing this risk.

Inadequate Insulin Use

Failure to take insulin is the most common cause of recurrent DKA, particularly in adolescents. The patient may also run out of insulin, have a calibration error in the

injection device, use the wrong concentration or type of insulin, or inadvertently inject an inadequate dose of insulin. A change of diet or exercise may also mean that the insulin administered is inadequate.

Eating Disorders

In adolescents with type 1 diabetes, psychological problems complicated by eating disorders may be a contributing factor in as many as 20% of recurrent ketoacidosis cases. Factors that decrease compliance in adolescents include fear of weight gain with improved metabolic control, fear of hypoglycemia, rebellion, and the stress of chronic disease.[5]

Stress Due to Coexistent Illnesses or Infections

Pneumonia and urinary infections are common coexistent illnesses associated with DKA in adults.[42-44] Trauma, febrile illnesses, or even psychological turmoil may elevate the counterregulatory hormones (glucagon, epinephrine, growth hormone, and cortisol) and precipitate DKA. In a study of 247 admissions for pediatric DKA, bacterial infections were only identified in 8 cases (3.2%).[12]

Poor Sick Day Management

Difficulty in regulating blood sugar during episodes of vomiting, decreased activity, and other illnesses may precipitate DKA.

Physical Examination

The physical signs of DKA can be quite variable. (**Table 2**) Uniformly, the patient with DKA will be dehydrated. Typical signs include reduced skin elasticity (poor skin turgor), dry mucous membranes, hypotension, Kussmaul respiration, and tachycardia from the volume deficits. The typical deficit in body water in one series was 7-10%. Other literature has quoted up to 15% in infants.[45] Protracted vomiting may markedly increase the water loss. Some water loss may also occur due to the compensatory hyperventilation from the metabolic acidosis. The respiratory rate may be normal or somewhat rapid. If the patient is carefully examined, the rapid, deep breathing typical of Kussmaul respirations is often found. If Kussmaul respirations are present, serum CO_2 is likely to be <10. A fruity odor to the breath is often cited as due to the acetone and ketone bodies associated with DKA.[46]

Lethargy is common, and some patients experiencing DKA will present in a coma. Mental status changes may occur in DKA — these may be the result of DKA or may be due to an underlying process that caused the patient to develop DKA. If a mental status change is present, it is important to consider cerebral edema as the potential cause. (**Table 3**)

Diagnostic Studies

The laboratory diagnosis and management of DKA is straightforward. (**Table 1** on page 4) The tests of greatest utility include blood glucose measurement, serum bicarbonate, serum potassium, a venous blood gas, and measurement of ketones in the blood or urine.

Serum Glucose

Although laboratory measurement of serum glucose is customary and confirmatory, most ongoing management of DKA can be done with bedside glucose testing. In the vast majority of cases of DKA, the glucose value will be ≥250 mg/dL. Relative normoglycemia may be seen in patients who were given or took insulin before being seen in the ED, those who were starving or had reduced food intake, and those who have impaired gluconeogenesis from liver failure.

Electrolytes

Electrolyte abnormalities are very common and should be expected in cases of DKA. The massive diuresis may contribute significantly to the electrolyte abnormalities seen in DKA. Free water, sodium, potassium, magnesium, and phosphate electrolytes are excreted into the urine along with the glucose. Ketoacids act as nonresorbable ions in the kidney and are excreted as potassium and sodium salts. Because urine contains about 70-80 mEq/L of cations, most of which are sodium and potassium, massive total body deficiencies in sodium and potassium may result. (**Clinical Pathway**) Despite this urinary potassium loss and total body deficits of potassium, children may have an elevated potassium value in the initial set of laboratory tests, because of a shift of intracellular potassium into the serum.

Table 2. Signs And Symptoms Commonly Associated With Diabetic Ketoacidosis.

- Polyuria
- Polydipsia
- Polyphagia
- Weight loss
- Fatigue and weakness
- Abdominal pain
- Nausea and vomiting
- Hyperventilation

Cost-Effective Strategies: Pediatric DKA

The most important cost-effective strategy is to initiate proper therapy promptly, coordinate care with the inpatient physicians who will care for the patient, and return the child to their baseline physiology through a deliberate plan. Prolonged hospitalization, increased risk of complications, and undue burden on the patient and family may arise if a treatment plan is not developed and followed carefully by everyone involved in the care of the child with DKA. ▲

Complete Blood Count

In a study of adult patients with DKA, an elevated band count was associated with bacterial infections.[47] In a similar study of children, of the total white blood cell count, the differential, and the presence of leukocytosis, none were associated with bacterial infections.[12] In this study, leukocytosis was common regardless of the absence of infection, the presence of a presumed viral infection, or the presence of a bacterial infection. It has been proposed that this leukocytosis is proportional to the blood ketone body concentration.[5]

Blood Gas Analysis

A venous gas should be sent early in the evaluation of the patient believed to have DKA.[48,49] This will help determine the severity of the DKA. (**Table 1** on page 4) A venous blood gas is typically preferred over an arterial blood gas in children. For the majority of children in DKA, there is no need to assess the arterial PaO_2 — an arterial puncture is painful and can be technically difficult, the pH measurement from a venous blood gas is an accurate measure of the child's acid-base status, and a venous blood gas can easily be obtained along with other blood laboratory tests at the time of intravenous catheter placement.

BUN and Creatinine

The patient will often have some elevation of the BUN due to dehydration. The clinician should carefully consider the possibility of chronic renal failure. The patient with both diabetes and renal failure may be quite difficult to manage. Fluid losses may be smaller than when the patient has normal renal function, and fluid replacement must be much more conservative. Therapeutic emphasis will switch to insulin, careful monitoring of potassium, and consideration of dialysis.

Urinalysis and Urine Culture

A dipstick urinalysis is useful for identifying ketonuria. However, according to the American Diabetes Association guidelines, a serum measurement of beta-hydroxybutyrate is the preferred method of measuring ketones in children with suspected or confirmed DKA.[5] The reason given in support of this recommendation is that the nitroprusside method for measuring ketones in the urine only measures acetoacetic acid and acetone, not beta-hydroxybutyrate, the dominant acid in DKA. Because beta-hydroxybutyrate is converted to acetoacetic acid during successful treatment of DKA, acetoacetic acid levels rise, which may lead to confusion as to whether the acidosis is improving or worsening. A urine culture may be ordered for children with DKA. The indications for ordering a urine culture have not been directly studied. It certainly seems reasonable to order a urine culture on children who would otherwise meet the indications for ordering a urine culture in children without DKA. In a study specifically examining 247 pediatric admissions for DKA and infections, 8 children had bacterial infections, and only 3 (1.2%) had urinary tract infections.[12]

Ketones

Serum ketone testing may not correlate with the degree of ketoacidosis. Beta-hydroxybutyric acid is the major

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Table 3. Bedside Evaluation For DKA-Associated Cerebral Edema.*

Evaluation and treatment for cerebral edema are necessary if a patient has 2 major criteria, or 1 major criteria plus 2 minor criteria, or ANY diagnostic criteria.†

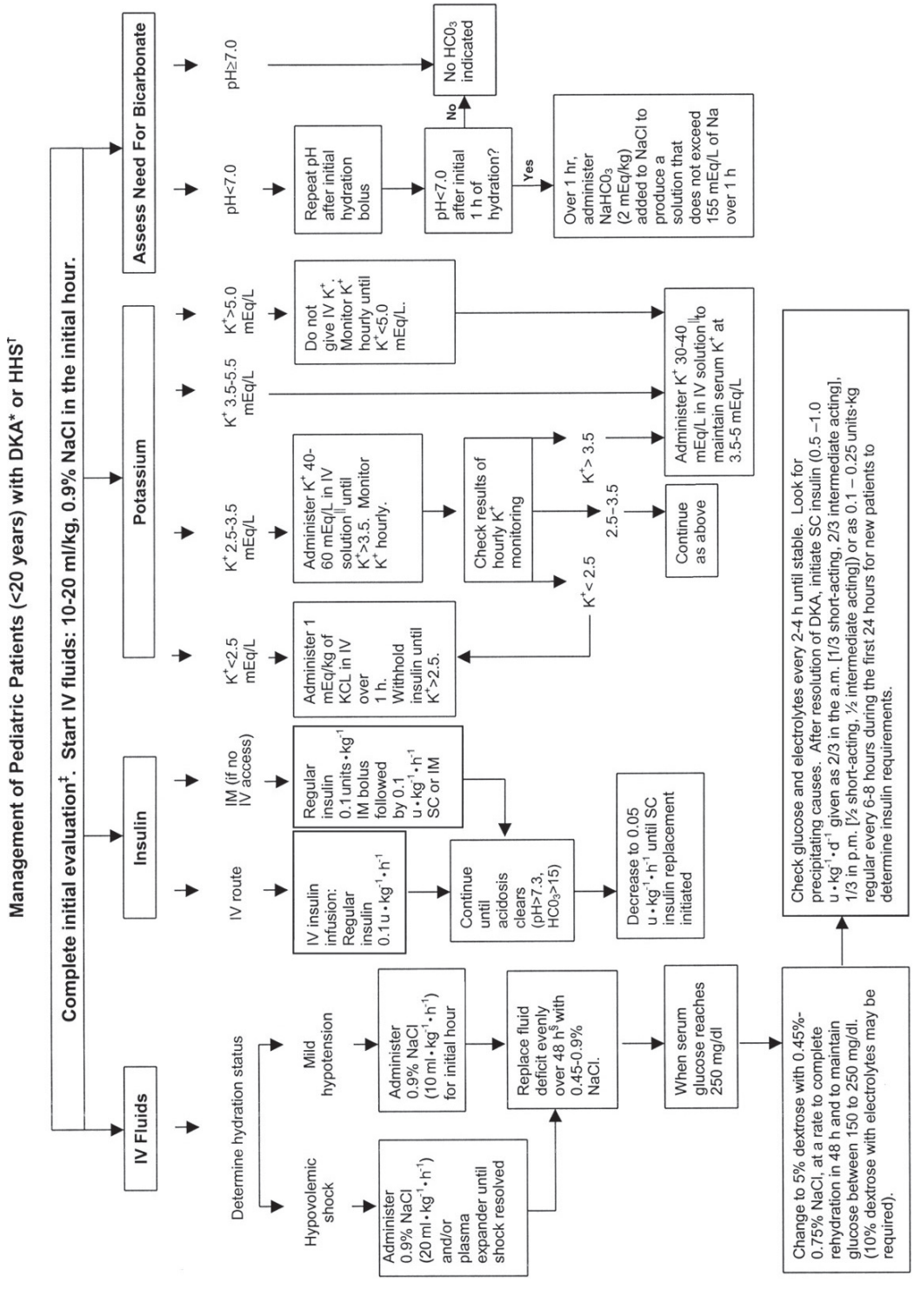
Major criteria
Altered mentation/fluctuating level of consciousness
Bradycardia‡
Age-inappropriate incontinence

Minor criteria
Vomiting
Headache
Lethargy or not easily aroused
Diastolic hypertension (determined by age- and gender-based norms)
Age <5 years

Diagnostic criteria
Abnormal motor or verbal response to pain
Decorticate or decerebrate posture
Cranial nerve palsy (particularly III, IV, and VI)
Abnormal respiratory pattern

*Adapted from Glaser N, Barnett P, McCaslin I, et al and from Muir AB, Quisling RG, Yang MC, et al. See Reference 8 and Reference 10.
†Signs that occur before the initiation of treatment suggest an alternative diagnosis to DKA-associated cerebral edema.
‡Sustained heart rate deceleration (decline of more than 20 bpm) not attributable to improved intravascular volume or sleep state. This must be of sudden onset and persistent (recorded over at least 15 minutes).

Clinical Pathway: Management Of Pediatric Patients (<20 years) With DKA* Or HHS†



*DKA diagnostic criteria: blood glucose >250 mg/dL, venous pH <7.3, bicarbonate <15 mEq/L, moderate ketonuria or ketonemia.
†HHS diagnostic criteria: blood glucose >600 mg/dL, venous pH >7.3, bicarbonate >15 mEq/L and altered mental status or severe dehydration.
‡After the initial history and physical examination, obtain blood glucose, venous blood gases, electrolytes, blood urea nitrogen (BUN), creatinine, calcium, phosphorous, and urine analysis STAT.
§Usually 1.5 times the 24 h maintenance requirements (5 mL · kg^{-1} · h^{-1}) will accomplish a smooth rehydration; do not exceed two times the maintenance requirement.
‖The potassium in solution should be 1/3 KPO_4 and 2/3 KCl or Kacetate. IM, intramuscular; IV, intravenous; SC subcutaneous.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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ketoacid produced in DKA. It does not react with the nitroprusside, so urine or blood testing for ketones may be negative or only slightly positive. Sepsis, accumulation of lactate, and poor tissue perfusion prevent the formation of acetoacetate, which does react with nitroprusside.

During treatment of DKA, beta-hydroxybutyric acid will be converted to acetoacetic acid. The resultant increase in acetoacetic acid may make the serum or urine testing for ketones more positive, despite clinical improvement and an increasing pH and decreasing anion gap.

Treatment

Successful treatment of DKA includes correction of the dehydration and hyperglycemia, resolution and anticipation of electrolyte abnormalities, identification of precipitating and comorbid illnesses, and frequent patient monitoring. The clinician should be aware of the types of insulin available. (**Table 4**) Regular insulin is used in the ED to treat DKA. The use of sodium bicarbonate is controversial.[50]

The specific treatment goals of the patient with DKA are to improve tissue perfusion, correct dehydration, decrease the serum glucose, reverse acidosis, and correct electrolyte disturbances. (**Clinical Pathway**)

Special Circumstances

Hyperglycemic Hyperosmolar Syndrome

There are so few cases of hyperosmolar nonketotic coma in children and adolescents that all studies are case reports of only a few children in any center.[35] There are no randomized studies of this disease in children. An article in the 2005 *Pediatric Clinics of North America* by Glaser et al summarizes the state of research for this rare condition.[51]

Coma is the most common presentation in pediatric patients. Adult patients with hyperosmolar hyperglycemic syndrome often present with neurologic abnormalities that are rarely seen in the patient with diabetic ketoacidosis.[52] These abnormalities include seizures, transient hemiparesis, movement disorders, and other focal neurologic findings. Seizures are seen in up to 25% of patients and can be either generalized or focal.[53,54]

In contrast to DKA, where complications are infrequent and the mortality rate is usually less than 1%, HHS is associated with a high frequency of complications and a high mortality rate.[51] Since the only literature describing HHS is limited in size, epidemiologic data are likewise limited. One pediatric study reported a mortality rate of 14% (1 of 7 children).[55] This is a lethal disease, and mortality rates as high as 12% to 46% have been recorded in adults.[56-58] Subclinical rhabdomyolysis, possibly owing to shrinkage of muscle cells and impaired glucose use, is a common finding in patients with HHS, and to a lesser degree with DKA, but secondary acute renal failure is extremely rare. Many patients do not develop myoglobinuria; thus, monitoring serum creatinine phosphokinase levels is the most sensitive way to screen for this potentially serious complication. In at least 1 series, rhabdomyolysis was seen in 50% of children with HHS.[59] A malignant, hyperthermia-like syndrome with hyperpyrexia and

Table 4. Comparison Of Insulin Types.*

Insulin		Onset of Action	Peak Action	Duration of Action
Humalog Insulin lispro		10 minutes	1 hour	4 hours
Regular		30 minutes	2-5 hours	8 hours
NPH		90 minutes	4-12 hours	22-24 hours
Lente		2.5 hours	6-16 hours	24 hours
Ultralente		4 hours	8-18 hours	30 hours
70/30 70% NPH, 30% regular	blend	30 minutes	2-12 hours	24 hours
50/50 50% regular, 50% NPH	blend	30 minutes	2-6 hours	24 hours
Insulin Lantus	glargine	1.5 hours	Flat	24 hours
Insulin Aspart		Within 15 minutes	1-3 hours	3-5 hours

*Table derived from data furnished by Eli Lilly and Novo Nordisk pharmaceuticals in their product information. Supplemental information from Endotext.com. See Reference 76.

Note: The standard insulin concentration in the United States is U-100 insulin. There are several insulins not charted above. Buffered insulins from Eli Lilly and Novo Nordisk and special U-400 insulin from Hoechst of Germany are designed for use in insulin pumps. U-40 insulin is available in some foreign countries, and users need to be aware of the different volume needed to achieve the same dose. The duration of action and time of onset of these insulin concentrations do not differ from those above.

Note: Glargine insulin must not be mixed in the same syringe as any other insulin or solution, because this will alter the pH of the insulin and affect absorption rates. The flat biological activity of glargine insulin is due to its absorption kinetics and not due to different pharmacodynamic activity.

rhabdomyolysis has been described in several children with HHS.[35,60] The cause of this is not yet known.

Because HHS is so infrequent in children, the optimal approach to treatment has yet to be determined. Some authors have suggested that it may be appropriate to delay insulin administration until fluid resuscitation is well underway, since the glucose will decrease markedly with rehydration alone. Patients who have HHS, by definition, are not ketotic; hence, insulin is not needed for resolution of the ketosis. This delay in treatment with insulin will therefore result in a more gradual decline in serum glucose and serum osmolality. The patient with HHS always needs admission to the intensive care unit or a special diabetic unit that has the same capacity to monitor vital signs, laboratory data, neurological status, and blood glucose on an hourly basis.

Controversies/Cutting Edge

Insulin Pumps

The continuous infusion of insulin via a pump has been available for at least 20 years, but has come into more common use for young children only relatively recently.[61-68] Children and families are carefully selected for this treatment modality. Families who have difficulty with glycemic control for whatever reason are typically not selected for implantation of an insulin pump. Unless the pump malfunctions, it is unusual to see a child or adolescent who has an insulin pump present to the ED in DKA.

Islet Cell Transplants and Gene Therapy

Islet cell transplants[69-71] are still quite rare. Transplanting islet cells has the potential to actually cure diabetes. It is unclear if this procedure will become more common in the future and to what extent children who receive these transplants will be immunocompromised following the transplant. Gene therapy is experimental, but offers another potential cure for diabetes.[72]

Inhaled Insulin

The United States Food and Drug Administration has very recently approved inhaled insulin for human use.[73] This insulin delivery method has been studied in and approved for adults.[74] Pediatric use of inhaled insulin awaits future studies.

Hypertonic Saline to Treat Cerebral Edema

A small case series has examined the utility of 3% (hypertonic) saline for treating DKA-associated cerebral edema.[75] Whether this treatment will replace traditional therapy with mannitol requires further study.

Disposition

In general, children with DKA are admitted to a pediatric intensive care unit. Obviously, critically ill children should be admitted or transferred to a pediatric intensive care unit. Alternative management plans depend on the available resources, institutional experience, and family dynamics. Some large pediatric centers have a sufficient volume of children with diabetes admitted to their hospital to support a "diabetes ward." Children with milder cases of DKA can be successfully managed on these wards. In other instances, such as remote hospitals, a pediatric ward, the ED, or the adult intensive care unit may be an acceptable admission location, depending on the experience and preference of the local health care providers. Finally, with very experienced families in which a child with known diabetes has a very mild case of DKA, management in the ED followed by close management at home may be appropriate.[3]

"Just a hundred years ago, the onset of DKA heralded the end of a child's life."

Summary

Just a hundred years ago, the onset of DKA heralded the end of a child's life. Throughout the twentieth century, tremendous advances were made in the care of children with diabetes, including DKA. Now, DKA has become a common and recurrent problem for children with diabetes. Physicians caring for children in an ED are likely to see several children a year with DKA.

Fortunately, our collective experience and that of our colleagues in endocrinology has led to a better understanding of how DKA develops and how complications arise. Perhaps the biggest change in recent years has been the suggestion that DKA-associated cerebral edema is not

Key Points For Pediatric DKA

- DKA should be considered in the differential diagnosis of children with otherwise unexplained altered mental status.
- The most common cause of DKA in adolescents is poor compliance with their diet or insulin regimen.
- Children with DKA may have elevated serum potassium on the initial set of ED laboratory tests, but they actually have a total body depletion of potassium.
- Children with DKA are dehydrated. ▲

caused by excessive fluid administration. The concept of "idiogenic osmoles" is finally being questioned with reasonable methodology.

The care of children with DKA has become standardized to a significant extent. With relatively little fanfare, without advocating the use of new pharmaceutical agents, and with reasonable evidence, well-respected organizations, such as the American Diabetes Association, have developed guidelines for the management of children experiencing DKA. Although not perfect and certainly open to future modifications, the **Clinical Pathway** provided in this issue of *Pediatric Emergency Medicine Practice*, based on recommendations from the American Diabetes Association, offers very practical advice for the practicing clinician who cares for children in the ED. ▲

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in the paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

1. Bliss M. *The Discovery of Insulin*. Chicago, IL: The University of Chicago Press; 1982:112-113. **(Review)**

2. [No authors listed]. The History of Insulin, 2002. Available at: http://www.caerlas.demon.co.uk/insulin.htm. Accessed March 22, 2006. **(Historical review)**

3.* Dunger DB, Sperling MA, Acerini CL, et al. European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis in children and adolescents. *Pediatrics* 2004;113:133-140. **(Consensus statement/review)**

4. [No authors listed]. Type 2 diabetes in children and adolescents. American Diabetes Association. *Diabetes Care* 2000;23:381-389. **(Consensus statement)**

5. Kitabchi AE, Umpierrez GE, Murphy MB, et al; American Diabetes Association. Hyperglycemic crises in patients with diabetes mellitus. *Diabetes Care* 2002;25: S100-S108. **(Consensus statement)**

6. Kitabchi AE, Umpierrez GE, Murphy MB, et al; American Diabetes Association. Hyperglycemic Crises in Diabetes. *Diabetes Care* 2004;27(90001):S94-S102. **(Consensus statement)**

7. Glaser NS, Kuppermann N, Yee CK, et al. Variation in the management of pediatric diabetic ketoacidosis by specialty training. *Arch Pediatr Adolesc Med* 1997;151:1125-1132. **(Mail survey; 581 physicians from 5 specialties)**

8.* Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med* 2001;344(4):264-269. **(Case-control study; 61 children with cerebral edema, 181 random control, 174 matched case-controls)**

9. Mallare JT, Cordice CC, Ryan BA, et al. Identifying risk

Five Pitfalls To Avoid

1. "The child was obese, so I thought it was type 2 diabetes. I prescribed an oral hypoglycemic and discharged him home."

Type 2 diabetes, although increasingly seen in children, remains relatively rare in children. In general, children should be presumed to have new-onset type 1 diabetes and be admitted to the hospital.

2. "I wanted my insulin therapy to work for a long time, so I used NPH insulin."

The treatment of DKA in the ED is with regular insulin.

3. "I really restricted fluids. How could the child have developed cerebral edema?"

Recent research has suggested that the amount of fluid given is not associated with the development of cerebral edema.

4. "The child was pretty sick when she arrived. When her mental status deteriorated, I immediately performed a lumbar puncture. I figured that she had developed DKA because she also had meningitis."

Unlike adults, coexisting infections are uncommon in children with DKA. A child with DKA who has deteriorating mental status should be assumed to be developing cerebral edema.

5. "Insulin pump? What's that?"

Familiarity with current therapy, such as insulin pumps, will gain the confidence of the patient and their family. ▲

factors for the development of diabetic ketoacidosis in new onset type 1 diabetes mellitus. *Clin Pediatr (Phila)* 2003;42:591-597. **(Retrospective medical record review; 139 children)**

10. Muir AB, Quisling RG, Yang MC, et al. Cerebral edema in childhood diabetic ketoacidosis: natural history, radiographic findings, and early identification. *Diabetes Care* 2004;27:1541-1546. **(Clinical decision rule; 26 subjects in the derivation component of the study and 17 Subjects in the validation component of the study)**

11.* Glaser NS, Wootton-Gorges SL, Marcin JP, et al. Mechanism of cerebral edema in children with diabetic ketoacidosis. *J Pediatr* 2004;145(2):164-171. **(Case-control study; 14 subjects)**

12.* Flood RG, Chiang VW. Rate and prediction of infection in children with diabetic ketoacidosis. *Am J Emerg Med* 2001;19:270-273. **(Retrospective medical review; 247 pediatric admissions for DKA)**

13. Kukreja A, Maclaren NK.. Autoimmunity and diabetes. *J Clin Endocrinol Metab* 1999;84:4371-4378. **(Review)**

14. Fagot-Campagna A, Pettit DJ, Engelgau MM. Type 2 diabetes among North American children and adolescents: An epidemiologic review and a public health perspective. *J Pediatr* 2000;136:664-672. **(Epidemiologic study and review of the literature)**

15. Ehtisham S, Barrett TG, Shaw NJ. Type 2 diabetes mellitus in UK children: An emerging problem. *Diabetes Med* 2000;17:867-871. **(Case series; 8 subjects)**

16. Ehtisham S, Kirk J, McEvilly A, et al. Prevalence of type 2 diabetes in children in Birmingham. *BMJ* 2001;322(7299):1428. **(Letter)**

17. Ehtisham S, Hattersley AT, Dunger DB, et al. First UK survey of paediatric type 2 diabetes and MODY. *Arch Dis Child* 2004;89:526-529. **(Survey; 25 subjects)**

18. Drake AJ, Smith A, Betts PR. Type 2 diabetes in obese white children. *Arch Dis Child* 2002;86(3):207-208. **(Case series; 4 children)**

19. Holl RW, Grabert M, Krause U. Prevalence and clinical characteristics of patients with non-type 1 diabetes in the pediatric age range: analysis of a multicenter database including 20,410 patients from 148 centers in Germany and Austria. *Diabetologia* 2003;46(Suppl 2): A26. **(Database review; 20,410 subjects)**

20. Rami B, Schober E, Nachbauer E. Austrian Diabetes Incidence Study Group. Type 2 diabetes mellitus is rare, but not absent in children under 15 years of age in Austria. *Eur J Pediatr* 2003;162(12):850-852. **(Prospective, population-based epidemiological study; 529 subjects including 10 adolescents with type 2 diabetes)**

21. Ortega-Rodriguez E, Levy-Marchal C, Tubiana N, et al. Emergence of type 2 diabetes in a hospital based cohort of children with diabetes mellitus. *Diabet Metab* 2001;27(1):574-578. **(Retrospective review; 382 patients)**

22. Zachrisson I, Tibell C, Bang P, et al. Prevalence of type 2 diabetes among known cases of diabetes aged 0-18 years in Sweden (Abstract). *Diabetologia* 2003;46(Suppl 2):A66.

23. Kitagawa T, Owada M, Urakami T et al. Epidemiology of type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in Japanese children. *Diabetes Res Clin Pract* 1994;24(Suppl 1):S7-S13. **(Epidemiologic review)**

24. Chan JC, Hawkins BR, Cockram CS. A Chinese family with non-insulin-dependent diabetes of early onset and severe diabetic complications. *Diabet Med* 1990;7(3):211-214. **(Case report)**

25. Wei J-N, Sung F-C, Lin C-C, et al. National Surveillance for Type 2 Diabetes Mellitus in Taiwanese Children. *JAMA* 2003;290(10):1345-1350. **(Epidemiologic study; 137 pediatric cases of type 2 diabetes)**

26. Crawford PB, Story M, Wang MC, et al. Ethnic issues in the epidemiology of childhood obesity. *Pediatr Clin North Am* 2001;48(4):855-878. **(Epidemiologic study)**

27. Le Roith D, Zick Y. Recent Advances in Our Understanding of Insulin Action and Insulin Resistance. *Diabetes Care* 2001;24(3):588-597. **(Review)**

28. Buse JB. The use of insulin alone and in combination with oral agents in type 2 diabetes. *Prim Care* 1999;26(4):931-950. **(Review)**

29.* Gungor N, Hannon T, Libman I, et al. Type 2 diabetes mellitus in youth: the complete picture to date. *Pediatr Clin North Am* 2005;52(6):1579-1609. **(Review)**

30. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. *Diabetes Care* 1990;13(1):22-33. **(Retrospective medical record review; 69 subjects)**

31. Edge JA. Cerebral oedema during treatment of diabetic ketoacidosis: are we any nearer finding a cause? *Diabetes Metab Res Rev* 2000;16(5):316-324. **(Review)**

32. Mel JM, Werther GA. Incidence and outcome of diabetic cerebral oedema in childhood: are there predictors? *J Paediatr Child Health* 1995;31(1):17-20. **(Retrospective medical record review; 6507 Subjects including 12 cases of cerebral edema)**

33. McNally PG, Raymond NT, Burden ML, et al. Trends in mortality of childhood-onset insulin-dependent diabetes mellitus in Leicestershire: 1940-1991. *Diabet Med* 1995;12(11):961-966. **(Database review; 844 subjects)**

34. Fleckman AM. Diabetic ketoacidosis. *Endocrinol Metab Clin North Am* 1993;22:181-207. **(Review)**

35. Morales AE, Rosenbloom AL. Death caused by hyperglycemic hyperosmolar state at the onset of type 2 diabetes. *J Pediatr* 2004;144(2):270-273. **(Case report)**

36. Munro JF, Campbell JW, McCuish AC, et al. Euglycaemic diabetic ketoacidosis. *Brit J Med* 1973;2:578-580. **(Retrospective review; 722 cases of DKA, including 23 cases in which the subjects were euglycemic)**

37. Jenkins D, Close CF, Krentz AJ, et al. Euglycaemic diabetic ketoacidosis: does it exist? *Acta Diabetol* 1993;30(4):251-253. **(Case report)**

38. De P, Child DF. Euglycaemic diabetic ketoacidosis - is it on the rise? *Pract Diabetes Int* 2001;18(7):239-240. **(Case report)**

39. Valerio D. Acute diabetic abdomen in childhood. *Lancet* 1976;1(7950):66-68. **(Case series; 3 children)**

40. Axelrod L. Insulin, prostaglandins, and the pathogenesis of hypertension. *Diabetes* 1991;40:1223-1227. **(Review)**

41. Rose BD. Proximal tubule. In: Rose BD, ed. *Clinical Physiology of Acid-Base and Electrolyte Disorders*. 3rd ed. New York, NY: McGraw-Hill; 1989. **(Textbook chapter)**

42. Wachtel TJ, Tetu-Mouradjain LM, Goldman DL et al. Hyperosmolarity and acidosis in diabetes mellitus: A three year experience in Rhode Island. *J Gen Intern Med* 1991;6:495-502. **(Retrospective medical record review; 613 cases)**

43. Elleman K, Sorensen JN, Pedersen L et al. Epidemiology and treatment of diabetic ketoacidosis in a community population. *Diabetes Care* 1984;7:528-532. **(Epidemiological study)**

44. Umpierrez GE, Kelly JP, Navarrete MD et al. Hyperglycemic crises in urban blacks. *Arch Intern Med* 1997;157:669-675. **(Prospective observational study; 144 patients)**

45. Rosenbloom AL, Hanas R. Diabetic ketoacidosis (DKA): treatment guidelines. *Clin Pediatr (Phila)* 1996;35(5):261-266. **(Review)**

46. Axelrod L. Diabetic ketoacidosis. *Endocrinologist* 1992;2:375-383. **(Review)**

47. Slovis CM, Mork VG, Slovis RJ, et al. Diabetic ketoacidosis and infection. Leukocyte count and differential as early predictors of serious infection. *Am J Emerg Med* 1987;5(1):1-5. **(Retrospective review; 153 subjects)**

48.* Brandenburg M, Dire D. Comparison of arterial and venous blood gas values in the initial emergency department evaluation of patients with diabetic ketoacidosis. *Ann Emerg Med* 1998;31:459-465. **(Retrospective review; 38 subjects with 44 episodes of DKA)**

49. Gokel Y, Paydas S, Koseoglu Z, et al. Comparison of blood gas and acid-base measurements in arterial and venous blood samples in patients with uremia acidosis and diabetic ketoacidosis in the emergency room. *Am J Nephrology* 2000;20:319-323. **(Retrospective record review; 100 uremic subjects, 21 diabetic subjects, and 31 control subjects, including a total of 152 venous and arterial samples)**

50. Green SM, Rothrock SG, Ho JD, et al. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. *Ann Emerg Med* 1998;31:41-48. **(Retrospective medical record review; 146 admissions involving 106 children)**

51.* Glaser N. Pediatric diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Clin North Am* 2005;52(6):1611-1635. **(Review)**

52. Morres CA, Dire DJ. Movement disorders as a manifestation of nonketotic hyperglycemia. *J Emerg Med* 1989;7(4):359-364. **(Case series; 2 subjects)**

53. Harden CL, Rosenbaum DH, Daras M. Hyperglycemia presenting with occipital seizures. *Epilepsia* 1991;32(2):215-220. **(Case series; 3 subjects)**

54. Duncan MB, Jabbari B, Rosenberg ML. Gaze-evoked visual seizures in nonketotic hyperglycemia. *Epilepsia* 1991;32(2):221-224. **(Case report)**

55. Fourtner SH, Weinzimer SA, Levitt Katz LE. Hyperglycemic hyperosmolar non-ketotic syndrome in children with type 2 diabetes. *Pediatr Diabetes* 2005;6(3):129-135. **(Retrospective database review; 7 children)**

56. Khardori R, Soler NG. Hyperosmolar hyperglycemic nonketotic syndrome. Report of 22 cases and brief review. *Am J Med* 1984;77(5):899-904. **(Case series; 22 cases)**

57. Arieff AI, Carroll HJ. Nonketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. *Medicine (Baltimore)* 1972;51(2):73-94. **(Retrospective medical record review; 37 subjects)**

58. MacIsaac RJ, Lee LY, McNeil KJ, et al. Influence of age on the presentation and outcome of acidotic and hyperosmolar diabetic emergencies. *Intern Med J* 2002;32(8):379-385. **(Retrospective review; 312 subjects)**

59. Carchman RM, Dechert-Zeger M, Calikoglu AS, et al. A new challenge in pediatric obesity: pediatric hyperglycemic hyperosmolar syndrome. *Pediatr Crit Care Med* 2005;6(1):20-24. **(Case series; 4 subjects)**

60. Hollander AS, Olney RC, Blackett PR. Fatal malignant hyperthermia-like syndrome with rhabdomyolysis complicating the presentation of diabetes mellitus in adolescent males. *Pediatrics* 2003;111:1447-1452. **(Case series; 6 subjects)**

61. Litton J, Rice A, Friedman N, et al. Insulin pump therapy in toddlers and preschool children with type 1 diabetes mellitus. *J Pediatr* 2002;141:490-495. **(Prospective observational study; 9 toddlers)**

62. Fox LA, Buckloh LM, Smith SD, et al. A randomized controlled trial of insulin pump therapy in young children with type 1 diabetes. *Diabetes Care* 2005;28:1277-1281. **(Randomized controlled trial; 22 children)**

63. Hanas R, Adolfsson P. Insulin pumps in pediatric routine care improve long-term metabolic control without increasing the risk of hypoglycemia. *Pediatr Diabetes* 2006;7:25-31. **(Prospective observational comparative study; 89 children)**

64. Hohenhaus SM. Insulin pumps in the emergency department. *J Emerg Nurs* 2004;30:248-249. **(Review)**

65. Pickupu J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomized controlled trials. *BMJ* 2002;324:705. Available at: http://www.bmj.com/cgi/content/full/324/7339/705. Accessed March 22, 2006. **(Meta-analysis of 12 randomized controlled trials)**

66. Torrance T, Franklin V, Greene S. Insulin pumps. *Arch Dis Child* 2003;88:949-953. **(Review)**

67. Toni S, Reali MF, Fasulo A, et al. The use of insulin pumps improves the metabolic control in children and adolescents with type 1 diabetes. *Arch Dis Child* 2004;89:796-797. **(Prospective observational study; 34 children)**

68. Weintrob N, Benzaquen H, Galatzer A, et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: A randomized open crossover trial. *Pediatrics* 2003;112:559-564. **(Prospective, randomized, open-label, crossover trial; 23 children)**

69. O'Connell PJ, Hawthorne WJ, Holmes-Walker DJ, et al. Clinical test transplantation in type 1 diabetes mellitus: Results of Australia's first trial. *Med J Aust* 2006;184:221-225. **(Prospective observational study; 6 subjects)**

70. Hering BJ, Kandaswamy R, Ansite JD, et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. *JAMA* 2005;293:830-835. **(Prospective trial; 8 women)**

71. Scharp DW, Lacy PE, Santiago JV, et al. Results of our first nine intraportal islet allografts in type 1, insulin-dependent diabetic patients. *Transplantation* 1991;51:76-85. **(Case series; 9 subjects)**

72. Giannoukakis N, Robbins PD. Gene and cell therapies for diabetes mellitus: Strategies and clinical potential. *Biodrugs* 2002;16:149-173. **(Review)**

73. FDA Approves First Ever Inhaled Insulin Combination Product for Treatment of Diabetes. FDA News. Revised version based on original release of January 27, 2006. Available at: http://www.fda.gov/bbs/topics/news/2006/NEW01304.html. Accessed March 17, 2006. **(Governmental report)**

74. Garg S, Rosenstock J, Silverman BL, et al. Efficacy and safety of preprandial human insulin inhalation powder versus injectable insulin in patients with type 1 diabetes. *Diabetologia* 2006 Feb 28; Epub ahead of print. **(Randomized, open-label crossover study; 137 adult diabetics)**

75. Kamat P, Vats A, Gross M, et al. Use of hypertonic saline for the treatment of altered mental status associated with diabetic ketoacidosis. *Pediatr Crit Care Med* 2003;4:239-242. **(Case series; 4 children)**

76. Kroon L. Insulin - Pharmacology, types of regimens, and adjustments, 2003. Available at: http://www.endotext.org/diabetes/diabetes17/diabetes17.htm. Accessed March 22, 2006. **(Review)**

Physician CME Questions

33. Which of the following best differentiates starvation ketosis from DKA?

a. A history of obesity
b. The absence of leukocytosis
c. A serum bicarbonate of 20 mmol/L
d. Crystals in the urine
e. Hyperchloremia

34. Which of the following is true regarding the recommended treatment of DKA (according to the American Diabetes Association Clinical Pathway in this issue of *Pediatric Emergency Medicine Practice*)?

a. Intravenous potassium should be provided in a rapid bolus push.
b. Intravenous potassium is only indicated if hypovolemic shock is present.
c. Intravenous potassium should immediately begin whenever a continuous infusion of insulin is begun.
d. Intravenous insulin is not indicated for children with DKA.
e. Intravenous potassium should not be administered until the serum potassium falls below 5 mEq/L.

35. Which of the following is true regarding the body of literature pertinent to pediatric DKA diagnosis and treatment?
a. The majority of studies are randomized, controlled trials.
b. There are no relevant consensus practice guidelines relevant to pediatric DKA.
c. Most studies of DKA have both adult and pediatric study subjects included in them.
d. The best study to date regarding risk factors for DKA-associated cerebral edema is a multicenter case-control study.
e. Overzealous fluid administration has been proven to be the cause of DKA-associated cerebral edema.

36. Leukocytosis identified in a child with DKA indicates that a bacterial infection must be present.
a. True
b. False

37. Hyperglycemic hyperosmolar syndrome is more common in children than adults.
a. True
b. False

38. As described in this issue of *Pediatric Emergency Medicine Practice*, which of the following is a specific treatment goal regarding the ED treatment of children with DKA?
a. Improve tissue perfusion
b. Avoid pediatric intensive care unit admission
c. Identify children with acute appendicitis
d. Initiate behavior modification for noncompliant adolescents
e. Identify children appropriate for insulin pumps

39. Which of the follow is true regarding islet cell transplants for children with type 1 diabetes mellitus?
a. This treatment is currently uncommon.
b. Initial trials failed, and the children involved died.
c. Islet cell transplants take place through insulin pumps.
d. Human trials of islet cell transplants have not yet occurred.
e. Islet cell transplants are only appropriate for children with type 2 diabetes.

40. Children with DKA are dehydrated.
a. True
b. False

41. For a child with DKA, the initial serum potassium measurement may be low, normal, or high.
a. True
b. False

42. Which of the following best differentiates ethylene glycol poisoning from DKA?
a. Crystals in the urine
b. Fever
c. A distinct fruity odor on the breath
d. A salty taste to the skin
e. Evidence of retinal hemorrhages

43. Which of the following is true regarding the recommended treatment of DKA (according to the American Diabetes Association Clinical Pathway in this issue of *Pediatric Emergency Medicine Practice*)?
a. The starting dose of a continuous intravenous infusion of insulin is 0.1 units/kg/h.
b. NPH insulin is the preferred type of insulin for the treatment of pediatric DKA.
c. Due to the risk of cerebral edema, sodium bicarbonate is not indicated for the treatment of pediatric DKA.
d. A child in hypovolemic shock from DKA should receive no more than 10 mL/kg per hour of normal saline.
e. Sodium bicarbonate is only indicated for children with a venous blood gas pH ≥7.0.

44. Abdominal pain in a child with DKA suggests a surgical etiology.
a. True
b. False

45. As presented in this issue of *Pediatric Emergency Medicine Practice*, according to the American Diabetes Association, which of the following is suggestive of moderate DKA?
a. Coma
b. A venous pH of 7.10
c. A serum bicarbonate of 16 mEq/L
d. Fever
e. An elevated peripheral white blood cell count

46. Which of the following best describes the characteristic odor on the breath of some children with DKA?
a. Sweaty feet
b. Dew drop on a rose petal
c. Like stool
d. Fruity
e. Like blue cheese dressing

47. Which of the following characteristics best describe Kussmaul respirations?
a. Slow and deep
b. Rapid and deep
c. Slow and shallow
d. Rapid and shallow

Physician CME questions conclude on back page

48. **Which of the following is true regarding initial ED glucose testing for children with DKA?**
    a. In the vast majority of cases, the glucose value is ≥250 mg/dL.
    b. Hypoglycemia is very common.
    c. In most cases, the glucose value is between 200 and 250 mg/dL.
    d. A glucose value of ≥250 is life-threatening.
    e. A glucose level is not measured in the ED. A dextrose level is measured, instead.

Coming in Future Issues:

Pain Control And Sedation • Drowning • Eye Injuries

Class Of Evidence Definitions

Each action in the clinical pathways section of *Pediatric Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case-
- control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA* 1992;268(16):2289-2295.

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Target Audience: This enduring material is designed for emergency medicine physicians.

Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

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