

PEDIATRICS®

European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society Consensus Statement on Diabetic Ketoacidosis in Children and Adolescents

David B. Dunger, Mark A. Sperling, Carlo L. Acerini, Desmond J. Bohn, Denis Daneman, Thomas P.A. Danne, Nicole S. Glaser, Ragnar Hanas, Raymond L. Hintz, Lynne L. Levitsky, Martin O. Savage, Robert C. Tasker and Joseph I. Wolfsdorf

Pediatrics 2004;113;133-140

DOI: 10.1542/peds.113.2.e133

This information is current as of April 18, 2005

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/113/2/e133>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2004 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society Consensus Statement on Diabetic Ketoacidosis in Children and Adolescents

David B. Dunger, MD*‡; Mark A. Sperling, MD‡§; Carlo L. Acerini, MD*; Desmond J. Bohn, MD§; Denis Daneman, MD‡§; Thomas P.A. Danne, MD*‡; Nicole S. Glaser, MD§; Ragnar Hanas, MD*‡; Raymond L. Hintz, MD§; Lynne L. Levitsky, MD§; Martin O. Savage, MD*‡; Robert C. Tasker, MD*; and Joseph I. Wolfsdorf, MD§

ABBREVIATIONS. DKA, diabetic ketoacidosis; T1DM, type 1 diabetes mellitus; LWPES, Lawson Wilkins Pediatric Endocrine Society; ESPE, European Society for Paediatric Endocrinology; β -OHB, β -hydroxybutyrate; CNS, central nervous system; IV, intravenous; ICP, intracranial pressure; ECF, extracellular fluid; ICF, intracellular fluid; GFR, glomerular filtration rate.

INTRODUCTION

Diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in children with type 1 diabetes mellitus (T1DM). Mortality is predominantly related to the occurrence of cerebral edema; only a minority of deaths in DKA are attributed to other causes. Cerebral edema occurs in

From the *European Society for Paediatric Endocrinology, West Smithfield, London, United Kingdom; §Lawson Wilkins Pediatric Endocrine Society, Stanford, CA; and ‡International Society for Paediatric and Adolescent Diabetes, Leicester, United Kingdom.

Received for publication Oct 22, 2003; accepted Oct 22, 2003.

‡Participants were: Carlo L. Acerini, Cambridge, United Kingdom; Dorothy J. Becker, Pittsburgh, Pennsylvania; Desmond Bohn, Toronto, Ontario, Canada; Stuart J. Brink, Waltham, Massachusetts; Francesco Chiarelli, Chieti, Italy; Maria Craig, Kogarth, Australia; Gisela Dahlquist, Umea, Sweden; Denis Daneman, Toronto, Ontario, Canada; Thomas Danne, Hanover, Germany; David B. Dunger, Cambridge, United Kingdom; Julie A. Edge, Oxford, United Kingdom; Irma Fiordalisi, Greenville, North Carolina; Nicole S. Glaser, Sacramento, California; John Gregory, Cardiff, United Kingdom; Mitchell Halperin, Toronto, Ontario, Canada; Ragnar Hanas, Uddevalla, Sweden; Glenn Harris, Greenville, North Carolina; Morey W. Haymond, Houston, Texas; Ray L. Hintz, Stanford, California; Carol Inward, Cardiff, United Kingdom; Chris Kelnar, Edinburgh, United Kingdom; Wieland Kiess, Leipzig, Germany; Mikael Knip, Helsinki, Finland; Elliot J. Krane, Stanford, California; Nathan Kuppermann, Sacramento, California; Sarah Muirhead Lawrence, Ottawa, Ontario, Canada; Lynne Levitsky, Boston, Massachusetts; Marc Maes, Brussels, Belgium; Henrik Mortensen, Glostrup, Denmark; Andrew Muir, Augusta, Maine; Andreas Neu, Tübingen, Germany; Jose Ramet, Brussels, Belgium; Robert Rapaport, New York, New York; Arleta Rewers, Denver, Colorado; Marian J. Rewers, Denver, Colorado; Arlan L. Rosenbloom, Gainesville, Florida; Martin O. Savage, London, United Kingdom; Mark A. Sperling, Pittsburgh, Pennsylvania; Peter Swift, Leicester, United Kingdom; William V. Tamborlane, New Haven, Connecticut; Robert C. Tasker, Cambridge, United Kingdom; Nadia Tubiana-Rufi, Paris, France; Maurizio Vanelli, Parma, Italy; Diane K. Wherrett, Toronto, Ontario, Canada; Neil H. White, St Louis, Missouri; and Joseph I. Wolfsdorf, Boston, Massachusetts.

Address correspondence to David B. Dunger, Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital, Level 8, Box 116, Cambridge CB2 2QQ, United Kingdom. E-mail: dbd25@cam.ac.uk; or Mark A. Sperling, Department of Pediatrics/Endocrinology, Children's Hospital of Pittsburgh, 3705 Fifth Ave, Pittsburgh, PA 15213. E-mail: masp@pitt.edu
PEDIATRICS (ISSN 0031 4005). Copyright © 2004 by the American Academy of Pediatrics.

~0.3% to 1% of all episodes of DKA, and its etiology, pathophysiology, and ideal method of treatment are poorly understood. There is debate as to whether physicians treating DKA can prevent or predict the occurrence of cerebral edema and the appropriate site(s) for children with DKA to be managed. There is agreement that prevention of DKA and reduction of its incidence should be a goal in managing children with diabetes.

To explore these issues, the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE) convened a panel of expert physicians for a consensus conference. The meeting was chaired by Mark A. Sperling, MD, representing LWPES, and David B. Dunger, MD, representing ESPE. The Consensus statement was developed with close partnership between the ESPE and LWPES and the International Society for Pediatric and Adolescent Diabetes, all 3 organizations being represented by members who participated in the writing process. The statement also was endorsed by related organizations; the Juvenile Diabetes Research Foundation International, the World Federation of Pediatric Intensive and Critical Care Societies, the European Society for Pediatric Critical Care, the European Society of Pediatric and Neonatal Intensive Care, and the Australian Pediatric Endocrine Group were represented by invited participants.

Each of the major topics had a presenter and recorder, responsible for review of the literature and providing evidence-based recommendations according to criteria used by the American Diabetes Association (see Appendix; levels of evidence are indicated in capital letters, in parentheses).¹ Type 2 diabetes was not considered. All participants contributed significantly to the development of consensus.

This document summarizes the final consensus reached and represents the current "state of the art."

DEFINITION OF DKA

DKA is caused by a decrease in effective circulating insulin associated with elevations in counter-regulatory hormones including glucagon, catecholamines, cortisol, and growth hormone. This leads to increased glucose production by the liver

and kidney and impaired peripheral glucose utilization, with resultant hyperglycemia and hyperosmolality. Increased lipolysis, with ketone body (β -hydroxybutyrate [β -OHB] and acetoacetate) production causes ketonemia and metabolic acidosis. Hyperglycemia and acidosis result in osmotic diuresis, dehydration, and obligate loss of electrolytes. The biochemical criteria for the diagnosis of DKA include hyperglycemia (blood glucose: >11 mmol/L [~ 200 mg/dL]) with a venous pH <7.3 and/or bicarbonate <15 mmol/L. There is associated glycosuria, ketonuria, and ketonemia. Rarely, young or partially treated children as well as pregnant adolescents may present with near-normal glucose values ("euglycemic ketoacidosis").²

DKA is generally categorized by the severity of the acidosis, varying from mild (venous pH: <7.30 ; bicarbonate concentration: <15 mmol/L) to moderate (pH: <7.2 ; bicarbonate: <10) to severe (pH: <7.1 ; bicarbonate: <5).^{3,4}

FREQUENCY OF DKA

At Disease Onset

There is wide geographic variation in the frequency of DKA at diabetes onset, and rates correlate inversely with regional incidence of T1DM. Reported frequencies range between 15% and 67% in Europe and North America and may be more common in developing countries (A).^{5,6} In Canada and Europe, hospitalization rates for DKA in established and new patients with T1DM have remained stable at ~ 10 per 100 000 children over the past 20 years, but severity may be decreasing (B).^{7,8}

DKA at onset of T1DM is more common in younger children (<4 years of age), children without a first-degree relative with T1DM, and those from families of lower socioeconomic status (A).^{4,9} High-dose glucocorticoids, atypical antipsychotics, diazoxide, and some immunosuppressive drugs have been reported to precipitate DKA in individuals not diagnosed previously with T1DM (B).^{10,11}

In Children With Established T1DM

The risk of DKA in established T1DM is 1% to 10% per patient per year (A).¹²⁻¹⁵ Risk is increased in children with poor metabolic control or previous episodes of DKA, peripubertal and adolescent girls, children with psychiatric disorders (including those with eating disorders), and those with difficult family circumstances (including lower socioeconomic status and lack of appropriate health insurance).¹⁶ Inappropriate interruption of insulin-pump therapy also leads to DKA.^{12,14}

Children whose insulin is administered by a responsible adult rarely have episodes of DKA (C),¹⁷ and 75% of episodes of DKA beyond diagnosis probably are associated with insulin omission or treatment error.^{17,18} The remainder are due to inadequate insulin therapy during intercurrent illness (B).¹⁸⁻²⁰

MORBIDITY AND MORTALITY OF DKA IN CHILDREN

Reported mortality rates from DKA in national population-based studies are reasonably constant:

0.15% (C) (United States),²¹ 0.18% (C) (Canada),⁷ 0.25% (C) (Canada),²² to 0.31% (B) (United Kingdom).²³ In places with less developed medical facilities, the risk of dying from DKA is greater, and children may die before receiving treatment.²³

Cerebral edema accounts for between 57% and 87% of all DKA deaths.^{24,25} The incidence of cerebral edema has been fairly consistent between national population-based studies: 0.46% (C) (Canada),²² 0.68% (B) (United Kingdom),²⁴ and 0.87% (B) (United States).²⁵ Single-center studies often report higher frequencies because of ascertainment bias arising from secondary referral patterns: 1.1% (C) (United States)²⁶ to 4.6% (United States).²⁷

Reported mortality rates from cerebral edema in population-based studies are 21% (C),²⁵ 25% (C),²² and 24% (B).²⁴ Significant morbidity is evident in 10% (C),²² 21% (B),²⁵ and 26% (B)²⁴ of survivors. However, some individual centers have reported markedly lower mortality and serious morbidity after DKA and cerebral edema (B [United States²⁸], C [United States²⁹]).

Other possible causes of mortality and morbidity include hypokalemia, hyperkalemia, hypoglycemia, other central nervous system (CNS) complications, hematoma (C),³⁰ thrombosis (C),³¹ sepsis, infections (including rhinocerebral mucormycosis) (C),³² aspiration pneumonia, pulmonary edema (C),³³ adult respiratory distress syndrome (C),³⁴ pneumomediastinum and subcutaneous emphysema (C),³⁵ and rhabdomyolysis (C).³⁶ Late sequelae relate to cerebral edema and other CNS complications including hypothalamopituitary insufficiency,^{37,38} isolated growth hormone deficiency,³⁹ and combined growth hormone and thyroid-stimulating hormone deficiency.⁴⁰

CEREBRAL EDEMA

Presentation

Cerebral edema typically occurs 4 to 12 hours after treatment is activated^{25,41} but can be present before treatment has begun (B,²³ C,^{42,43} B²⁵) or may develop any time during treatment for DKA. Symptoms and signs of cerebral edema are variable and include onset of headache, gradual decrease or deterioration in level of consciousness, inappropriate slowing of the pulse rate, and an increase in blood pressure (C).^{44,45}

Pathophysiology

In vitro experiments and studies in animals and humans presenting with cerebral edema due to other causes (eg, trauma or stroke) suggest that the etiological mechanisms may be complex. A number of mechanisms have been proposed, including the role of cerebral ischemia/hypoxia and the generation of various inflammatory mediators,^{46,47} increased cerebral blood flow,⁴⁸ and disruption of cell membrane ion transport^{49,50} and aquaporin channels.⁵¹ The generation of intracellular organic osmolytes (myoinositol and taurine) and subsequent cellular osmotic imbalance has also been implicated.⁵² Preliminary imaging studies in children with

DKA using ultrasound, computed tomography, or magnetic resonance imaging indicate that some degree of cerebral edema may be present even in patients without clinical evidence of raised intracranial pressure (ICP).⁵³⁻⁵⁶

Demographics

Various demographic factors have been associated with an increased risk of cerebral edema including: presentation with new-onset T1DM (B, C)^{23,44} younger age (C),⁴⁴ and longer duration of symptoms (C).²⁶ These associations may be a consequence of the greater likelihood of presenting with severe DKA (C).²⁵

Risk Factors

Several potential risk factors, at diagnosis or during treatment, have been identified through epidemiologic studies.

- There is evidence that an attenuated rise in measured serum sodium concentrations during therapy for DKA may be associated with increased risk of cerebral edema (C).^{25,57,58} There is little evidence, however, to show associations between the volume or sodium content of intravenous (IV) fluids or rate of change in serum glucose and risk for cerebral edema (C).^{25-27,58,59} Therefore, it is unclear whether the association between sodium change and cerebral edema reflects variations in fluid administration or the effects of cerebral injury on renal salt handling.
- There is some evidence to support an association between severity of acidosis and risk of cerebral edema (C).⁶⁰ There is also evidence for an association between bicarbonate treatment for correction of acidosis and increased risk of cerebral edema (C).^{25,61}
- Greater hypocapnia at presentation of DKA, after adjusting for the degree of acidosis, has been associated with cerebral edema in 2 studies (C).^{25,27} This association correlates well with the observed detrimental effects of hypocapnia in other conditions (B).⁶²
- Elevated serum urea nitrogen at presentation of DKA is associated with increased risk of cerebral edema (C),²⁵ and this association may reflect greater dehydration in these patients.

Most studies show no association between the degree of hyperglycemia at presentation of DKA with risk of cerebral edema after correcting for other covariates (C).^{25,27}

MANAGEMENT OF DKA

General Issues

Children with ketosis and hyperglycemia without vomiting or severe dehydration can be managed at home or in an outpatient health care setting (eg, emergency ward or units with similar facilities), but the level of care needs to be reevaluated frequently and supervised by an experienced diabetes team (C,^{3,63,64} E).

A specialist/consultant pediatrician with training

and expertise in the management of DKA should direct inpatient management. The child also should be cared for in a unit that has experienced nursing staff trained in monitoring and management, clear written guidelines, and access to laboratories for frequent evaluation of biochemical variables.

Children with signs of severe DKA (long duration of symptoms, compromised circulation, or depressed level of consciousness) or those who are at increased risk for cerebral edema (including <5 years of age and new onset) should be considered immediately for treatment in an intensive care unit (pediatric, if available) or a children's ward specializing in diabetes care with equivalent resources and supervision (C,⁶⁵ E). If transfer by ambulance to another unit is required, caution should be exercised in the use of sedatives and antiemetics.

Monitoring

There should be documentation of hour-by-hour clinical observations, IV and oral medication, fluids, and laboratory results during the entire treatment period (E).

Monitoring should include:

- Hourly heart rate, respiratory rate, and blood pressure.
- Hourly (or more frequent), accurate fluid input and output (when there is impaired level of consciousness, urinary catheterization may be necessary).
- In severe DKA, electrocardiogram monitoring may be helpful to assess T-waves for evidence of hyperkalemia/hypokalemia.
- Capillary blood glucose should be monitored hourly (but must be cross-checked against laboratory venous glucose, because capillary methods may be inaccurate in the presence of poor peripheral circulation and acidosis).
- Laboratory tests: electrolytes, urea, hematocrit, blood glucose, and blood gases should be repeated every 2 to 4 hours. (However, electrolytes should be monitored hourly as clinically indicated in the more-severe cases.) An elevated white blood cell count may be due to stress and cannot be taken as a sign of infection.
- Hourly or more-frequent neurologic observations for warning signs and symptoms of cerebral edema:

Headache

Inappropriate slowing of heart rate

Recurrence of vomiting

Change in neurologic status (restlessness, irritability, increased drowsiness, or incontinence), or specific neurologic signs (eg, cranial nerve palsies or pupillary response)

Rising blood pressure

Decreased oxygen saturation

Those monitoring should be instructed to alert the physician of any of these manifestations, because it may be difficult to clinically discriminate cerebral edema from other causes of altered mental status.

Fluids and Salt (Table 1)

The high effective osmolality of the extracellular fluid (ECF) compartment results in a shift of water

from the intracellular fluid (ICF) compartment to the ECF. Studies performed in adults with T1DM in whom insulin therapy was withheld have shown fluid deficits of ~5 L⁶⁶ together with ~20% loss of total body sodium and potassium.⁶⁷ At the time of presentation, patients are ECF contracted, and clinical estimates of the deficit are usually in the range of 7% to 10%, although these estimates can be subjective and may overestimate the problem.⁶⁸ Shock with hemodynamic compromise is a rare event in DKA. The serum sodium measurement is an unreliable measure of the degree of ECF contraction due to the dilutional effect of fluid shift. The effective osmolality (2 [Na + K] + glucose) at the time of presentation is frequently in the range of 300 to 350 mOsm/L. Elevated serum urea nitrogen and hematocrit may be useful markers of severe ECF contraction.^{28,64}

The onset of dehydration is associated with a reduction in glomerular filtration rate (GFR), which results in decreased glucose and ketone clearance from the blood. Studies in humans have shown that IV fluid administration alone results in substantial falls in blood glucose levels because of an increase in GFR.^{69,70} The objectives of fluid and sodium replacement therapy in DKA are 1) restoration of circulating volume, 2) replacement of sodium and the ECF and ICF deficit of water, 3) restoration of GFR with enhanced clearance of glucose and ketones from the blood, and 4) avoidance of cerebral edema.

Both animal and human studies have shown that ICP rises as IV fluids are administered.^{71,72} There are also animal models of DKA that show that the use of hypotonic fluids, compared with isotonic, is associated with greater rises in ICP.⁷¹ Although there are no category A studies that demonstrate superiority of any fluid regimen over another, there are category C data that suggest that rapid fluid replacement with hypotonic fluid is associated with an increased risk of cerebral edema (see "Risk Factors" above). There are both adult (category A) and pediatric (level B) studies that show that a less-rapid fluid-deficit correction with isotonic or near-isotonic solutions results in earlier reversal of acidosis.^{29,73} However, the use of large amounts of 0.9% saline has also been associated with the development of hyperchloremic metabolic acidosis.^{74,75}

There are no data to support the use of colloids in preference to crystalloids in the treatment of DKA. There also are no data to support the use of solutions more dilute than 0.45% NaCl; the use of these solutions, which contain a large amount of electrolyte-free water, is likely to lead to a rapid osmolar change and movement of fluid into the ICF compartment.

Insulin (Table 2)

Although rehydration alone causes some decrease in blood glucose concentration, insulin therapy is essential to normalize the blood glucose concentration and suppress lipolysis and ketogenesis. Although different routes (subcutaneous, intramuscular, and IV) and doses have been used, extensive evidence indicates that "low-dose" IV insulin administration should be the standard of care.⁷⁶

Physiologic studies indicate that IV insulin at a

TABLE 1. Water and Salt Replacement in DKA

- Water and salt deficits must be replaced. IV or oral fluids that may have been given before the child presents for treatment and prior to assessment should be factored into calculation of deficit and repair (A).
- Initial IV fluid administration and, if needed, volume expansion should begin immediately with an isotonic solution (0.9% saline or balanced salt solutions such as Ringer's lactate). The volume and rate of administration depend on circulatory status, and where it is clinically indicated, the volume is typically 10 to 20 ml/kg over 1 to 2 hours, repeated if necessary (E).
- Use crystalloid (C).
- Subsequent fluid management should be with a solution with a tonicity $\geq 0.45\%$ saline (C):
 - This can be achieved by administering 0.9% saline or balanced salt solution (Ringer's lactate or 0.45% saline with added potassium) (E).
 - Rate of IV fluid should be calculated to rehydrate evenly over at least 48 hours (E).
- In addition to clinical assessment of dehydration, calculation of effective osmolality may be valuable to guide fluid and electrolyte therapy (E).
- Because the severity of dehydration may be difficult to determine and can be overestimated, infuse fluid each day at a rate rarely in excess of 1.5 to 2 times the usual daily requirement based on age, weight, or body surface area. Urinary losses should not be added to the calculation of replacement fluids (E).

dose of 0.1 unit/kg per hour, which achieves steady-state plasma insulin levels of ~100 to 200 $\mu\text{U}/\text{mL}$ within 60 minutes, is effective.⁷⁷ Such plasma insulin levels are able to offset insulin resistance and, in most circumstances, inhibit lipolysis and ketogenesis, exerting maximal or near-maximal effects on suppression of glucose production and stimulated peripheral glucose uptake.⁷⁸ The resolution of acidemia invariably takes longer than normalization of blood glucose concentrations.⁷⁹

Potassium (Table 3)

Adults with DKA have total body potassium deficits on the order of 3 to 6 mmol/kg; data in children

TABLE 2. Insulin Therapy for DKA

- Correction of insulin deficiency (A):
 - Dose: 0.1 U/kg per hour (A)
 - Route of administration: IV (A)
- The dose of insulin should remain at least 0.1 U/kg per hour at least until resolution of ketoacidosis (pH: $>.30$; HCO_3^- : >5 mmol/L and/or closure of anion gap). To prevent an unduly rapid decrease in plasma glucose concentration and possible development of hypoglycemia, glucose should be added to the IV fluid when the plasma glucose falls to ~14 to 17 mmol/L (250–300 mg/dL) (B).
- There may be circumstances in which the insulin dose may be safely reduced earlier, but the criteria have not been defined (E).
- If biochemical parameters of ketoacidosis (pH and anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin (eg, infection, errors in insulin preparation, or adhesion of insulin to tubing with very dilute solutions) (E).
- There is evidence that an IV bolus of insulin is not necessary^{80,81} (C). However, a bolus may be used at the start of insulin therapy, particularly if insulin treatment has been delayed (E).
- In unusual circumstances in which IV administration is not possible, the intramuscular or subcutaneous route of insulin administration has been used effectively⁷⁶ (C). However, poor perfusion will impair absorption of insulin.⁷⁹

are sparse.^{66,67,82–85} The major loss of potassium is from the intracellular pool as a result of hypertonicity, insulin deficiency, and buffering of hydrogen ions within the cell. Serum potassium levels at the time of presentation may be normal, increased or decreased: Hypokalemia at presentation may be related to prolonged duration of disease, whereas hyperkalemia primarily results from reduced renal function.⁸⁶ Administration of insulin and the correction of acidosis will drive potassium back into the cells, decreasing serum levels.

Phosphate

Depletion of intracellular phosphate occurs 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,^{66,67,84} but comparable data in children are unavailable. The fall in plasma phosphate levels after starting treatment is exacerbated by insulin administration as phosphate reenters cells.⁸⁷ Low plasma phosphate levels, when indicative of total body depletion in other conditions, have been associated with a wide array of metabolic disturbances; however, particular interest has focused on erythrocyte 2,3-diphosphoglycerate concentrations and effects on tissue oxygenation.⁸⁸ Phosphate depletion persists for several days after resolution of DKA.^{66,82,84} However, prospective studies have failed to show significant clinical benefit from phosphate replacement.^{89–94} Nevertheless, provided that careful monitoring is performed to avoid hypocalcemia,^{95,96} potassium phosphate may be used safely in combination with potassium chloride or acetate to avoid hyperchloremia.

Acidosis

Even severe acidosis is reversible by fluid and insulin replacement. Administration of insulin stops

further ketoacid synthesis and allows excess ketoacids to be metabolized. The metabolism of keto-anion results in the regeneration of bicarbonate (HCO_3^-) and spontaneous correction of acidemia. Also, treatment of hypovolemia will improve decreased tissue perfusion and renal function, thus increasing the excretion of organic acids (see “Fluids and Salt”) and reversing any lactic acidosis, which may account for 25% of the acidemia.

In DKA, there is an increased anion gap. The major retained anions are β -OHB and acetoacetate.

$$\text{anion gap} = [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-]): \text{normally } 12 \pm 2 \text{ mmol/L}$$

The indications for bicarbonate therapy in DKA are unclear. Several controlled trials of sodium bicarbonate in small numbers of children and adults (B, C) have been unable to demonstrate clinical benefit or any important difference in the rate of rise in the plasma bicarbonate concentration (C).^{25,97–100}

There are potential arguments against the use of bicarbonate.^{25,97,101,102} Of concern is that bicarbonate therapy may cause paradoxical CNS acidosis and that rapid correction of acidosis caused by bicarbonate will result in hypokalemia and may accentuate sodium load and contribute to serum hypertonicity. In addition, alkali therapy may increase hepatic ketone production, thus slowing the rate of recovery from the ketosis.

These findings, however, do not address the issue that there may be select patients who may benefit from cautious alkali therapy, including those with severe acidemia (arterial pH: <6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion and patients with potentially life-threatening hyperkalemia.

TABLE 3. Potassium, Phosphate, and Acid-Base Management

Potassium
• Replacement is required (A).
• Replacement therapy should be based on serum potassium measurements (E).
• Start potassium replacement immediately if the patient is hypokalemic; otherwise, start potassium concurrent with starting insulin therapy. If the patient is hyperkalemic, defer potassium until urine output is documented (E).
• Starting potassium concentration in the infusate should be 40 mmol/L (E), and potassium replacement should continue throughout IV fluid therapy (E).
Phosphate
• There is no evidence that replacement has clinical benefit (A). Severe hypophosphatemia should be treated (C).
• Potassium phosphate salts may be used as an alternative to or combined with potassium chloride/acetate (C).
• Administration of phosphate may induce hypocalcemia (C).
Acid base
• Other acute resuscitation protocols no longer recommend bicarbonate administration unless the acidosis is “profound” and “likely to affect the action of adrenaline/epinephrine during resuscitation” (A).
• Fluid and insulin replacement without bicarbonate administration corrects ketoacidosis (A).
• Data show that treatment with bicarbonate confers no clinical benefit (B).
• Repair fluids containing various buffering agents (bicarbonate, acetate, and lactate) have been used (C). The efficacy and safety of these agents have not been established.

Treatment of Cerebral Edema

Treatment should be initiated as soon as the condition is suspected. The rate of fluid administration should be reduced. Although mannitol has been shown to have possible beneficial effects in case reports,^{103–105} there has been no definite beneficial or detrimental effect in retrospective epidemiologic studies.¹⁰⁶ The response may be altered by timing of administration, delayed administration being less effective. IV mannitol should be given (0.25–1.0 g/kg over 20 minutes) in patients with signs of cerebral edema before impending respiratory failure (C, E). Repeat 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 (C).¹⁰⁷

Intubation and ventilation may be necessary. However, aggressive hyperventilation has been associated with poor outcome in one retrospective study of DKA-related cerebral edema¹⁰⁶; similarly detrimental effects have been reported in numerous other conditions such as head trauma and high-altitude exposure.⁶² There are no data regarding glucocorticoid use in DKA-related cerebral edema.

PREVENTION OF DKA

Before Diagnosis

Earlier diagnosis through genetic and immunologic screening of high-risk children such as in the recent DPT-1 study¹⁰⁸ decrease DKA incidence at diabetes onset (A).^{14,109} High levels of awareness related to the existence of other members of families with T1DM also reduce the risk of DKA. A school and physician awareness campaign, targeted at 6- to 14-year-olds, reduced rates of DKA from 78% to almost 0% over a 6-year period (B).¹¹⁰ Increased public awareness of signs and symptoms of diabetes should lead to earlier diagnosis, particularly in children <5 years; checking urine or blood for glucose may prevent misdiagnosis (E). Although such strategies are intuitively obvious, programs to decrease DKA at onset need to be designed and evaluated in diverse populations and age groups.

Beyond Diagnosis

Studies of the effects of comprehensive diabetes programs and telephone help lines report a reduction in the rates of DKA from 15–60 to 5–5.9/100 patient-years (B).^{19,111,112} In patients on continuous subcutaneous insulin pumps, episodes of DKA can be reduced with the introduction of educational algorithms (E). Therefore, it is likely that episodes of DKA after diagnosis could be reduced if all children with diabetes receive comprehensive diabetes health care and education and have access to a 24-hour diabetes telephone help line (A).¹⁹ The value of home measurement of β -OHb as a mechanism for earlier diagnosis and thus prevention of hospitalization needs to be assessed.

Multiple episodes of recurrent DKA are more problematic: In a recent United Kingdom study, 4.8% of patients accounted for 22.5% of all episodes over a 3-year period.²⁴ Insulin omission has been identified as the major factor in most of these cases and may be confirmed by finding low free-insulin levels on admission (C).^{13,113} There is no evidence that mental health interventions alone can impact on the frequency of DKA in these children (B),^{14,17,111} but insulin omission can be prevented by sequential schemes providing education, psychosocial evaluation, and treatment combined with adult supervision of insulin administration (B).¹⁷ When responsible adults administer insulin, a 10-fold reduction in episodes of DKA has been reported (B).¹⁷

KEY ISSUES FOR FUTURE INVESTIGATION

- Prevention: efficacy and cost-effectiveness of strategies to reduce DKA incidence; frequency and evaluation of ketoacidosis in childhood type 2 diabetes mellitus.
- Management: improved assessment of dehydration; systematic evaluation of rehydration solutions such as those containing bicarbonate, acetate, lactate, and phosphate; use of lower doses of insulin in younger children; clarification of criteria for reducing dose of insulin during treatment of DKA; need for bicarbonate therapy in those with pH <6.9 and the very young.

- Cerebral edema: meta-analysis of existing epidemiologic studies to identify factors related to increased risk in infants and the newly diagnosed; monitoring of DKA and earlier detection of signs of cerebral edema; efficacy of hypertonic saline versus mannitol.

APPENDIX

The American Diabetes Association evidence-grading system for clinical practice recommendations is as follows¹:

Level of Evidence	Description
A	Clear evidence from well-conducted, generalizable, randomized, controlled trials that are adequately powered, including: <ul style="list-style-type: none">• Multicenter trial• Meta-analysis incorporating quality ratings• Compelling nonexperimental evidence, (ie, "all-or-none" rule) developed by the Center for Evidence-Based Medicine at Oxford* Supportive evidence from well-conducted, randomized, controlled trials that are adequately powered, including: <ul style="list-style-type: none">• Well-conducted trials at ≥ 1 institutions
B	Supportive evidence from well-conducted cohort studies including: <ul style="list-style-type: none">• Prospective cohort studies or registry• Meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study.
C	Supportive evidence from poorly controlled or uncontrolled studies including: <ul style="list-style-type: none">• Randomized clinical trials with ≥ 1 major or ≥ 3 minor methodological flaws that could invalidate the results• Observational studies with high potential for bias• Case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation.
E	Expert consensus or clinical experience.

* Either all patients died before therapy and at least some survived with therapy or some patients died without therapy and none died with therapy (eg, the use of insulin in the treatment of diabetes ketoacidosis).

ACKNOWLEDGMENTS

The LWPES and ESPE gratefully acknowledge Aventis Pharmaceuticals, Novo Nordisk, and the Society for Endocrinology for support of the consensus conference; Sten Renstad of Semser for organizing the conference; and Emily Knight and Kathy Wypychowski for assistance with preparing the consensus statement.

REFERENCES

1. American Diabetes Association position statement: hyperglycemic crises in patients with diabetes mellitus. *Diabetes Care*. 2003;26(suppl 1): S1–S2
2. International Society for Pediatric and Adolescent Diabetes. Consensus guidelines. Available at: www.ispad.org. Accessed December 11, 2003
3. Chase HP, Garg SK, Jelley DH. Diabetic ketoacidosis in children and the role of outpatient management. *Pediatr Rev*. 1990;11:297–304
4. Pinkney JH, Bingley PJ, Sawtell PA, Dunger DB, Gale EA. Presentation and progress of childhood diabetes mellitus: a prospective population-based study. The Bart's-Oxford Study Group. *Diabetologia*. 1994;37: 70–74
5. Levy-Marchal C, Papoz L, de Beaufort C, et al. Clinical and laboratory features of type 1 diabetic children at the time of diagnosis. *Diabet Med*. 1992;9:279–284
6. Komulainen J, Lounamaa R, Knip M, Kaprio EA, Akerblom HK. Ketoacidosis at the diagnosis of type 1 (insulin dependent) diabetes mellitus is related to poor residual beta cell function. Childhood Diabetes in Finland Study Group. *Arch Dis Child*. 1996;75:410–415

7. Curtis JR, To T, Muirhead S, Cummings E, Daneman D. Recent trends in hospitalization for diabetic ketoacidosis in Ontario children. *Diabetes Care*. 2002;25:1591–1596
8. Hirasing RA, Reeser HM, de Groot RR, Ruwaard D, van Buuren S, Verloove-Vanhorick SP. Trends in hospital admissions among children aged 0–19 years with type I diabetes in The Netherlands. *Diabetes Care*. 1996;19:431–434
9. Komulainen J, Kulmala P, Savola K, et al. Clinical, autoimmune, and genetic characteristics of very young children with type 1 diabetes. Childhood Diabetes in Finland (DiMe) Study Group. *Diabetes Care*. 1999;22:1950–1955
10. Alavi IA, Sharma BK, Pillay VK. Steroid-induced diabetic ketoacidosis. *Am J Med Sci*. 1971;262:15–23
11. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics*. 1999;40:438–443
12. Smith CP, Firth D, Bennett S, Howard C, Chisholm P. Ketoacidosis occurring in newly diagnosed and established diabetic children. *Acta Paediatr*. 1998;87:537–541
13. Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit [see comments]. *Lancet*. 1997;350:1505–1510
14. Rewers A, Chase HP, Mackenzie T, et al. Predictors of acute complications in children with type 1 diabetes. *JAMA*. 2002;287:2511–2518
15. Rosilio M, Cotton JB, Wieliczko MC, et al. Factors associated with glycemic control. A cross-sectional nationwide study in 2, 579 French children with type 1 diabetes. The French Pediatric Diabetes Group. *Diabetes Care*. 1998;21:1146–1153
16. Keenan HT, Foster CM, Bratton SL. Social factors associated with prolonged hospitalization among diabetic children. *Pediatrics*. 2002;109:40–44
17. Golden MP, Herrold AJ, Orr DP. An approach to prevention of recurrent diabetic ketoacidosis in the pediatric population. *J Pediatr*. 1985;107:195–200
18. Flood RG, Chiang VW. Rate and prediction of infection in children with diabetic ketoacidosis. *Am J Emerg Med*. 2001;19:270–273
19. Hoffman WH, O'Neill P, Khoury C, Bernstein SS. Service and education for the insulin-dependent child. *Diabetes Care*. 1978;1:285–288
20. Glasgow AM, Weissberg-Benchell J, Tynan WD, et al. Readmissions of children with diabetes mellitus to a children's hospital. *Pediatrics*. 1991;88:98–104
21. Levitsky L, Ekwo E, Goselink CA, Solomon IL, Aceto T. Death from diabetes (DM) in hospitalized children (1970–1988) [abstract]. *Pediatr Res*. 1991;29:A195
22. Cummings E, Lawrence S, Daneman D. Cerebral edema (CE) in pediatric diabetic ketoacidosis (DKA) in Canada [abstract]. *Diabetes*. 2003;52:A400
23. Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes 1990–96. *Arch Dis Child*. 1999;81:318–323
24. Edge JA, Hawkins MM, Winter DL, Dunger DB. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. *Arch Dis Child*. 2001;85:16–22
25. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med*. 2001;344:264–269
26. Bello FA, Sotos JF. Cerebral oedema in diabetic ketoacidosis in children. *Lancet*. 1990;336:64
27. Mahoney CP, Vlcek BW, DelAguila M. Risk factors for developing brain herniation during diabetic ketoacidosis. *Pediatr Neurol*. 1999;21:721–727
28. Harris GD, Fiordalisi I. Physiologic management of diabetic ketoacidemia. A 5-year prospective pediatric experience in 231 episodes. *Arch Pediatr Adolesc Med*. 1994;148:1046–1052
29. Felner EI, White PC. Improving management of diabetic ketoacidosis in children. *Pediatrics*. 2001;108:735–740
30. Atluru VL. Spontaneous intracerebral hematomas in juvenile diabetic ketoacidosis. *Pediatr Neurol*. 1986;2:167–169
31. Kanter RK, Oliphant M, Zimmerman JJ, Stuart MJ. Arterial thrombosis causing cerebral edema in association with diabetic ketoacidosis. *Crit Care Med*. 1987;15:175–176
32. Moll GW Jr, Raila FA, Liu GC, Conlry AW Sr. Rhinocerebral mucormycosis in IDDM. Sequential magnetic resonance imaging of long-term survival with intensive therapy. *Diabetes Care*. 1994;17:1348–1353
33. Young MC. Simultaneous acute cerebral and pulmonary edema complicating diabetic ketoacidosis. *Diabetes Care*. 1995;18:1288–1290
34. Breidbart S, Singer L, St Louis Y, Saenger P. Adult respiratory distress syndrome in an adolescent with diabetic ketoacidosis. *J Pediatr*. 1987;111:736–738
35. Watson JP, Barnett AH. Pneumomediastinum in diabetic ketoacidosis. *Diabet Med*. 1989;6:173–174
36. Casteels K, Beckers D, Wouters C, Van Geet C. Rhabdomyolysis in diabetic ketoacidosis. *Pediatr Diabetes*. 2003;4:29–31
37. Tubiana-Rufi N, Thizon-de Gaulle I, Czernichow P. Hypothalamopituitary deficiency and precocious puberty following hyperhydration in diabetic ketoacidosis. *Horm Res*. 1992;37:60–63
38. Lufkin EG, Reagan TJ, Doan DH, Yanagihara. Acute cerebral dysfunction in diabetic ketoacidosis: survival followed by panhypopituitarism. *Metabolism*. 1977;26:363–369
39. Keller RJ, Wolfsdorf JL. Isolated growth hormone deficiency after cerebral edema complicating diabetic ketoacidosis. *N Engl J Med*. 1987;316:857–859
40. Dunlop KA, Woodman D, Carson DJ. Hypopituitarism following cerebral oedema with diabetic ketoacidosis. *Arch Dis Child*. 2002;87:337–338
41. Edge JA. Cerebral oedema during treatment of diabetic ketoacidosis: are we any nearer finding a cause? *Diabetes Metab Res Rev*. 2000;16:316–324
42. Deeb L. Development of fatal cerebral oedema during outpatient therapy for diabetic ketoacidosis. *Pract Diabetes Int*. 1989;6:212–213
43. Glasgow AM. Devastating cerebral edema in diabetic ketoacidosis before therapy. *Diabetes Care*. 1991;14:77–78
44. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. *Diabetes Care*. 1990;13:22–33
45. Muir A. Therapeutic controversy. Cerebral edema in diabetic ketoacidosis: a look beyond rehydration. *J Clin Endocrinol Metab*. 2000;85:509–513
46. Abbott NJ. Inflammatory mediators and modulation of blood-brain barrier permeability. *Cell Mol Neurobiol*. 2000;20:131–147
47. Sarker MH, Fraser PA. The role of guanylyl cyclases in the permeability response to inflammatory mediators in pial venular capillaries in the rat. *J Physiol*. 2002;540:209–218
48. Yang GY, Betz AL. Reperfusion-induced injury to the blood-brain barrier after middle cerebral artery occlusion in rats. *Stroke*. 1994;25:1658–1664, 1664–1665 [discussion]
49. O'Donnell ME, Martinez A, Sun D. Endothelial Na-K-Cl cotransport regulation by tonicity and hormones: phosphorylation of cotransport protein. *Am J Physiol*. 1995;269:C1513–C1523
50. Kimelberg HK, Rutledge E, Goderie S, Charniga C. Astrocytic swelling due to hypotonic or high K⁺ medium causes inhibition of glutamate and aspartate uptake and increases their release. *J Cereb Blood Flow Metab*. 1995;15:409–416
51. Manley GT, Fujimura M, Ma T, et al. Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. *Nat Med*. 2000;6:159–163
52. McManus ML, Churchwell KB, Strange K. Regulation of cell volume in health and disease. *N Engl J Med*. 1995;333:1260–1226
53. Krane EJ, Rockoff MA, Wallman JK, Wolfsdorf JL. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. *N Engl J Med*. 1985;312:1147–1151
54. Hoffman WH, Steinhart CM, el Gammal T, Steele S, Cuadrado AR, Morse PK. Cranial CT in children and adolescents with diabetic ketoacidosis. *AJNR Am J Neuroradiol*. 1988;9:733–739
55. Hoffman WH, Casanova MF, Bauza JA, Passmore GG, Sekul EA. Computer analysis of magnetic resonance imaging of the brain in children and adolescents after treatment of diabetic ketoacidosis. *J Diabetes Complications*. 1999;13:176–181
56. Hoffman WH, Pluta RM, Fisher AQ, Wagner MB, Yanovski JA. Transcranial Doppler ultrasound assessment of intracranial hemodynamics in children with diabetic ketoacidosis. *J Clin Ultrasound*. 1995;23:517–523
57. Harris GD, Fiordalisi I, Harris WL, Mosovich LL, Finberg L. Minimizing the risk of brain herniation during treatment of diabetic ketoacidemia: a retrospective and prospective study [published correction appears in *J Pediatr*. 1991;118:166–167] [see comments]. *J Pediatr*. 1990;117:22–31
58. Hale PM, Rezvani I, Braunstein AW, Lipman TH, Martinez N, Garibaldi L. Factors predicting cerebral edema in young children with diabetic ketoacidosis and new onset type I diabetes. *Acta Paediatr*. 1997;86:626–631
59. Mel JM, Werther GA. Incidence and outcome of diabetic cerebral oedema in childhood: are there predictors? *J Paediatr Child Health*. 1995;31:17–20
60. Durr JA, Hoffman WH, Sklar AH, el Gammal T, Steinhart CM. Correlates of brain edema in uncontrolled IDDM. *Diabetes*. 1992;41:627–632
61. Bureau MA, Begin R, Berthiaume Y, Shapcott D, Khoury K, Gagnon N. Cerebral hypoxia from bicarbonate infusion in diabetic acidosis. *J Pediatr*. 1980;96:968–973

62. Roberts J, Schierhout G. Hyperventilation therapy for acute traumatic brain injury (Cochrane Review). The Cochrane Library; 2003. Available at: www.cochrane.org/cochrane/revabstr/ab000566.htm. Accessed December 11, 2003
63. Bonadio WA, Gutzeit MF, Losek JD, Smith DS. Outpatient management of diabetic ketoacidosis. *Am J Dis Child*. 1988;142:448-450
64. Linares MY, Schunk JE, Lindsay R. Laboratory presentation in diabetic ketoacidosis and duration of therapy. *Pediatr Emerg Care*. 1996;12:347-351
65. Monroe KW, King W, Atchison JA. Use of PRISM scores in triage of pediatric patients with diabetic ketoacidosis. *Am J Manag Care*. 1997;3:253-258
66. Atchley D, Loeb R, Richards D. On diabetic acidosis. A detailed study of electrolyte balances following withdrawal and reestablishment of therapy. *J Clin Invest*. 1933;12:297-326
67. Nabarro JDN, Spencer AG, Stowers JM. Metabolic studies in severe diabetic ketosis. *Q J Med*. 1952;82:225-248
68. Mackenzie A, Barnes G, Shann F. Clinical signs of dehydration in children. *Lancet*. 1989;2(8663):605-607
69. Waldhausl W, Kleinberger G, Korn A, Dudczak R, Bratusch-Marrain P, Nowotny P. Severe hyperglycemia: effects of rehydration on endocrine derangements and blood glucose concentration. *Diabetes*. 1979;28:577-584
70. Owen OE, Licht JH, Sapir DG. Renal function and effects of partial rehydration during diabetic ketoacidosis. *Diabetes*. 1981;30:510-518
71. Harris GD, Fiordalisi I, Yu C. Maintaining normal intracranial pressure in a rabbit model during treatment of severe diabetic ketoacidemia. *Life Sci*. 1996;59:1695-1702
72. Clements RS Jr, Blumenthal SA, Morrison AD, Winegrad AI. Increased cerebrospinal-fluid pressure during treatment of diabetic ketosis. *Lancet*. 1971(7726);2:671-675
73. Adrogué HJ, Barrero J, Eknoyan G. Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis. Use in patients without extreme volume deficit. *JAMA*. 1989;262:2108-2113
74. Adrogué HJ, Eknoyan G, Suki WK. Diabetic ketoacidosis: role of the kidney in the acid-base homeostasis re-evaluated. *Kidney Int*. 1984;25:591-598
75. Oh MS, Carroll HJ, Uribarri J. Mechanism of normochloremic and hyperchloremic acidosis in diabetic ketoacidosis. *Nephron*. 1990;54:1-6
76. Kitabchi AE. Low-dose insulin therapy in diabetic ketoacidosis: fact or fiction? *Diabetes Metab Rev*. 1989;5:337-363
77. Schade DS, Eaton RP. Dose response to insulin in man: differential effects on glucose and ketone body regulation. *J Clin Endocrinol Metab*. 1977;44:1038-1053
78. Luzzi L, Barrett EJ, Groop LC, Ferrannini E, DeFronzo RA. Metabolic effects of low-dose insulin therapy on glucose metabolism in diabetic ketoacidosis. *Diabetes*. 1988;37:1470-1477
79. Soler NG, FitzGerald MG, Wright AD, Malins JM. Comparative study of different insulin regimens in management of diabetic ketoacidosis. *Lancet*. 1975;2(7947):1221-1224
80. Fort P, Waters SM, Lifshitz F. Low-dose insulin infusion in the treatment of diabetic ketoacidosis: bolus versus no bolus. *J Pediatr*. 1980;96:36-40
81. Lindsay R, Bolte RG. The use of an insulin bolus in low-dose insulin infusion for pediatric diabetic ketoacidosis. *Pediatr Emerg Care*. 1989;5:77-79
82. Nabarro J, Spencer A, Stowers J. Treatment of diabetic ketoacidosis. *Lancet*. 1952;i:983-983
83. Danowski T, Peters J. Studies in diabetic acidosis and coma, with particular emphasis on the retention of administered potassium. *J Clin Invest*. 1949;28:1-9
84. Butler A, Talbot N. Metabolic studies in diabetic coma. *Trans Assoc Am Physicians*. 1947;60:102-109
85. Darrow DC, Pratt EL. Retention of water and electrolyte during recovery in a patient with diabetic acidosis. *J Pediatr*. 1952;41:688-696
86. Adrogué HJ, Lederer ED, Suki WN, Eknoyan G. Determinants of plasma potassium levels in diabetic ketoacidosis. *Medicine*. 1986;65:163-172
87. Riley MS, Schade DS, Eaton RP. Effects of insulin infusion on plasma phosphate in diabetic patients. *Metabolism*. 1979;28:191-194
88. Alberti KG, Emerson PM, Darley JH, Hockaday TD. 2,3-Diphosphoglycerate and tissue oxygenation in uncontrolled diabetes mellitus. *Lancet*. 1972;2(7774):391-395
89. Gibby OM, Veale KE, Hayes TM, Jones JG, Wardrop CA. Oxygen availability from the blood and the effect of phosphate replacement on erythrocyte 2,3-diphosphoglycerate and haemoglobin-oxygen affinity in diabetic ketoacidosis. *Diabetologia*. 1978;15:381-385
90. Keller U, Berger W. Prevention of hypophosphatemia by phosphate infusion during treatment of diabetic ketoacidosis and hyperosmolar coma. *Diabetes*. 1980;29:87-95
91. Wilson HK, Keuer SP, Lea AS, Boyd AE 3rd, Eknoyan G. Phosphate therapy in diabetic ketoacidosis. *Arch Intern Med*. 1982;142:517-520
92. Becker DJ, Brown DR, Steranka BH, Drash AL. Phosphate replacement during treatment of diabetic ketosis. Effects on calcium and phosphorus homeostasis. *Am J Dis Child*. 1983;137:241-246
93. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab*. 1983;57:177-180
94. Clerbaux T, Reynaert M, Willems E, Frans A. Effect of phosphate on oxygen-hemoglobin affinity, diphosphoglycerate and blood gases during recovery from diabetic ketoacidosis. *Intensive Care Med*. 1989;15:495-498
95. Winter RJ, Harris CJ, Phillips LS, Green OC. Diabetic ketoacidosis. Induction of hypocalcemia and hypomagnesemia by phosphate therapy. *Am J Med*. 1979;67:897-900
96. Zipf WB, Bacon GE, Spencer ML, Kelch RP, Hopwood NJ, Hawker CD. Hypocalcemia, hypomagnesemia, and transient hypoparathyroidism during therapy with potassium phosphate in diabetic ketoacidosis. *Diabetes Care*. 1979;2:265-268
97. Soler NG, Bennett MA, Dixon K, FitzGerald MG, Malins JM. Potassium balance during treatment of diabetic ketoacidosis with special reference to the use of bicarbonate. *Lancet*. 1972;2(7779):665-667
98. Hale PJ, Crase J, Natrass M. Metabolic effects of bicarbonate in the treatment of diabetic ketoacidosis. *Br Med J (Clin Res Ed)*. 1984;289:1035-1038
99. Okuda Y, Adrogué HJ, Field JB, Nohara H, Yamashita K. Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. *J Clin Endocrinol Metab*. 1996;81:314-320
100. Green SM, Rothrock SG, Ho JD, Gallant RD, Borger R, Thomas TL, Zimmerman GJ. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. *Ann Emerg Med*. 1998;31:41-48
101. Ohman JL Jr, Marliss EB, Aoki TT, Munichoodappa CS, Khanna VV, Kozak GP. The cerebrospinal fluid in diabetic ketoacidosis. *N Engl J Med*. 1971;284:283-290
102. Assal JP, Aoki TT, Manzano FM, Kozak GP. Metabolic effects of sodium bicarbonate in management of diabetic ketoacidosis. *Diabetes*. 1974;23:405-411
103. Franklin B, Liu J, Ginsberg-Fellner F. Cerebral edema and ophthalmoplegia reversed by mannitol in a new case of insulin-dependent diabetes mellitus. *Pediatrics*. 1982;69:87-90
104. Shabbir N, Oberfield SE, Corrales R, Kairam R, Levine LS. Recovery from symptomatic brain swelling in diabetic ketoacidosis. *Clin Pediatr (Phila)*. 1992;31:570-573
105. Roberts MD, Slover RH, Chase HP. Diabetic ketoacidosis with intracerebral complications. *Pediatr Diabetes*. 2001;2:109-114
106. Marcin JP, Glaser N, Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J Pediatr*. 2002;141:793-797
107. Kamat P, Vats A, Gross M, Checchia PA. Use of hypertonic saline for the treatment of altered mental status associated with diabetic ketoacidosis. *Pediatr Crit Care Med*. 2003;4:239-242
108. Diabetes Prevention Trial-Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med*. 2002;346:1685-1691
109. Levy-Marchal C, Patterson CC, Green A; EURODIAB ACE Study Group. Europe and Diabetes. Geographical variation of presentation at diagnosis of type 1 diabetes in children: the EURODIAB study. *European and Diabetes*. *Diabetologia*. 2001;44(suppl 3):B75-B80
110. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. *Diabetes Care*. 1999;22:7-9
111. Grey M, Boland EA, Davidson M, Li J, Tamborlane WV. Coping skills training for youth with diabetes mellitus has long-lasting effects on metabolic control and quality of life. *J Pediatr*. 2000;137:107-113
112. Drozda DJ, Dawson VA, Long DJ, Freson LS, Sperling MA. Assessment of the effect of a comprehensive diabetes management program on hospital admission rates of children with diabetes mellitus. *Diabetes Educ*. 1990;16:389-393
113. Malone JI, Root AW. Root, Plasma free insulin concentrations: key-stone to effective management of diabetes mellitus in children. *J Pediatr*. 1981;99:862-867

European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society Consensus Statement on Diabetic Ketoacidosis in Children and Adolescents

David B. Dunger, Mark A. Sperling, Carlo L. Acerini, Desmond J. Bohn, Denis Daneman, Thomas P.A. Danne, Nicole S. Glaser, Ragnar Hanas, Raymond L. Hintz, Lynne L. Levitsky, Martin O. Savage, Robert C. Tasker and Joseph I. Wolfsdorf

Pediatrics 2004;113;133-140
DOI: 10.1542/peds.113.2.e133

This information is current as of April 18, 2005

Updated Information & Services	including high-resolution figures, can be found at: http://www.pediatrics.org/cgi/content/full/113/2/e133
References	This article cites 111 articles, 35 of which you can access for free at: http://www.pediatrics.org/cgi/content/full/113/2/e133#BIBL
Citations	This article has been cited by 4 HighWire-hosted articles: http://www.pediatrics.org/cgi/content/full/113/2/e133#otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Endocrinology http://www.pediatrics.org/cgi/collection/endocrinology
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.pediatrics.org/misc/Permissions.shtml
Reprints	Information about ordering reprints can be found online: http://www.pediatrics.org/misc/reprints.shtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

