

In Brief

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS) are two acute complications of diabetes that can result in increased morbidity and mortality if not efficiently and effectively treated. Mortality rates are 2–5% for DKA and 15% for HHS, and mortality is usually a consequence of the underlying precipitating cause(s) rather than a result of the metabolic changes of hyperglycemia. Effective standardized treatment protocols, as well as prompt identification and treatment of the precipitating cause, are important factors affecting outcome.

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

Guillermo E. Umpierrez, MD, FACP;
Mary Beth Murphy, RN, MS, CDE,
MBA; and Abbas E. Kitabchi, PhD,
MD, FACP, FACE

The two most common life-threatening complications of diabetes mellitus include diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS). Although there are important differences in their pathogenesis, the basic underlying mechanism for both disorders is a reduction in the net effective concentration of circulating insulin coupled with a concomitant elevation of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone).

These hyperglycemic emergencies continue to be important causes of morbidity and mortality among patients with diabetes. DKA is reported to be responsible for more than 100,000 hospital admissions per year in the United States¹ and accounts for 4–9% of all hospital discharge summaries among patients with diabetes.¹ The incidence of HHS is lower than DKA and accounts for <1% of all primary diabetic admissions.¹

Most patients with DKA have type 1 diabetes; however, patients with type 2 diabetes are also at risk during the catabolic stress of acute illness.² Contrary to popular belief, DKA is more common in adults than in children.¹ In community-based studies, more than 40% of African-American patients with DKA were >40 years of age and more than 20% were >55 years of age.³ Many of these adult patients with DKA were classified as

having type 2 diabetes because 29% of patients were obese, had measurable insulin secretion, and had a low prevalence of autoimmune markers of β -cell destruction.⁴

Treatment of patients with DKA and HHS utilizes significant health care resources. Recently, it was estimated that treatment of DKA episodes accounts for more than one of every four health care dollars spent on direct medical care for adults with type 1 diabetes, and for one of every two dollars for those patients experiencing multiple episodes of DKA.⁵

Despite major advances in their management, recent series have reported a mortality rate of 2–5% for DKA, and ~15% for HHS.^{1,2} DKA is the most common cause of death in children and adolescents with type 1 diabetes and accounts for half of all deaths in diabetic patients <24 years of age.⁶

The cause of death in patients with DKA and HHS rarely results from the metabolic complications of hyperglycemia or metabolic acidosis but rather relates to the underlying medical illness that precipitated the metabolic decompensation. Thus, successful treatment requires a prompt and careful search for the precipitating cause(s).

This review discusses the pathogenesis, clinical presentation, complications, and recommendations for treatment of DKA and HHS.

PATHOGENESIS

DKA is characterized by hyperglycemia, metabolic acidosis, and increased circulating total body ketone concentration. Ketoacidosis results from the lack of, or ineffectiveness of, insulin with concomitant elevation of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone).^{7,8} The association of insulin deficiency and increased counterregulatory hormones leads to altered glucose production and disposal and to increased lipolysis and production of ketone bodies. Hyperglycemia results from increased hepatic and renal glucose production (gluconeogenesis and glycogenolysis) and impaired glucose utilization in peripheral tissues.⁷ Increased gluconeogenesis results from the high availability of noncarbohydrate substrates (alanine, lactate, and glycerol in the liver and glutamine in the kidney)⁹ and from the increased activity of gluconeogenic enzymes (phosphoenolpyruvate carboxykinase [PEPCK], fructose-1,6-bisphosphatase, and pyruvate carboxylase). From a quantitative standpoint, increased hepatic glucose production represents the major pathogenic disturbance responsible for hyperglycemia in patients with DKA.⁷ In addition, both hyperglycemia and high ketone levels cause osmotic diuresis that leads to hypovolemia and decreased glomerular filtration rate. The latter further aggravates hyperglycemia.

The mechanisms that underlie the increased production of ketones have recently been reviewed.⁸ The combination of insulin deficiency and increased concentration of counterregulatory hormones causes the activation of hormone-sensitive lipase in adipose tissue. The increased activity of tissue lipase causes breakdown of triglyceride into glycerol and free fatty acids (FFA). While glycerol becomes an important substrate for gluconeogenesis in the liver, the massive release of FFA assumes pathophysiological predominance, as they are the hepatic precursors of the ketoacids. In the liver, FFA are oxidized to ketone bodies, a process predominantly stimulated by glucagon. Increased concentration of glucagon lowers the hepatic levels of malonyl coenzyme A (CoA) by blocking the conversion of pyruvate to acetyl CoA through inhibition of acetyl CoA carboxylase, the first rate-limiting enzyme in de novo fatty acid

synthesis. Malonyl CoA inhibits carnitine palmitoyl-transferase I (CPT I), the rate-limiting enzyme for transesterification of fatty acyl CoA to fatty acyl carnitine, allowing oxidation of fatty acids to ketone bodies. CPT I is required for movement of FFA into the mitochondria where fatty acid oxidation takes place. The increased activity of fatty acyl CoA and CPT I in DKA leads to accelerated ketogenesis.⁸

Studies in animals and humans with diabetes have shown that lower insulin levels are needed for antilipolysis than for peripheral glucose uptake.^{10,11} HHS is characterized by a relative deficiency of insulin concentration to maintain normoglycemia but adequate levels to prevent lipolysis and ketogenesis.¹¹ To date, very few studies have been performed comparing differences in counterregulatory response in DKA versus HHS. Patients with HHS have been reported to have higher insulin concentration (demonstrated by basal and stimulated C-peptide levels),¹² and reduced concentrations of FFA, cortisol, growth hormone, and glucagon compared to patients with DKA.¹²⁻¹⁴ However, one study reported similar levels of FFA in patients with DKA and HHS,¹² indicating that further studies are needed to characterize metabolic responses in such patients.

PRECIPITATING CAUSES

DKA is the initial manifestation of diabetes in 20% of adult patients¹ and 30-40% of children^{15,16} with type 1 diabetes. In patients with established diabetes, precipitating factors for DKA include infections, intercurrent illnesses, psychological stress, and poor compliance with therapy. Infection is the most common precipitating factor for DKA, occurring in 30-50% of cases. Urinary tract infection and pneumonia account for the majority of infections. Other acute conditions that may precipitate DKA include cerebrovascular accident, alcohol/drug abuse, pancreatitis, pulmonary embolism, myocardial infarction, and trauma. Drugs that affect carbohydrate metabolism, such as corticosteroids, thiazides, sympathomimetic agents, and pentamidine, may also precipitate the development of DKA.

Recent studies have emphasized the importance of noncompliance and psychological factors in the incidence of DKA. In a survey of 341 female patients with type 1 diabetes,¹⁷ it was

reported that psychological problems complicated by eating disorders were a contributing factor in 20% of recurrent ketoacidosis in young women. More recently, it was reported that up to one-third of young women with type 1 diabetes have eating disturbances,¹⁸ which affect the management of diabetes and increase the risk of microvascular complications. Factors that may lead to insulin omission in young subjects included fear of gaining weight with good metabolic control, fear of hypoglycemia, rebellion from authority, and diabetes-related stress. Noncompliance with therapy has also been reported to be a major precipitating cause for DKA in urban black and medically indigent patients. A recent study reported that in urban black patients, poor compliance with insulin accounted for more than 50% of DKA cases admitted to a major urban hospital.³

Most patients with HHS have type 2 diabetes. HHS is the initial manifestation of diabetes in 7-17% of patients.^{1,3} Infection is the major precipitating factor, occurring in 30-60% of patients, with urinary tract infections and pneumonia being the most common infections.¹⁹ In many instances, an acute illness, such as cerebrovascular accident or myocardial infarction, provokes the release of counterregulatory hormones, resulting in hyperglycemia. Furthermore, in many cases, the patient or caregiver is unaware of the signs and symptoms of decompensated diabetes, or the patient is unable to treat the progressive dehydration. Certain medications that cause DKA may also precipitate the development of HHS, including glucocorticoids, thiazide diuretics, dilantin, and β -blockers.

DIAGNOSIS

Symptoms and Signs

The clinical presentation of DKA usually develops rapidly, over a period of <24 hours. Polyuria, polydipsia, and weight loss may be present for several days before the development of ketoacidosis, and vomiting and abdominal pain are frequently the presenting symptoms. Abdominal pain, sometimes mimicking an acute abdomen, is reported in 40-75% of cases of DKA.²⁰ In our institution, we have observed that the presence of abdominal pain is associated with a more severe metabolic acidosis and

with a history of alcohol or cocaine abuse, but not with the severity of hyperglycemia or dehydration. Although the potential of an acute abdominal problem requiring surgical intervention should not be overlooked, in the majority of patients, the abdominal pain spontaneously resolves after correction of the metabolic disturbance.

Physical examination reveals signs of dehydration, including loss of skin turgor, dry mucous membranes, tachycardia, and hypotension. Mental status can vary from full alertness to profound lethargy; however, <20% of patients are hospitalized with loss of consciousness.^{2,21} Most patients are normothermic or even hypothermic at presentation. Acetone on breath and labored Kussmaul respiration may also be present on admission, particularly in patients with severe metabolic acidosis.

Typical patients with HHS have undiagnosed diabetes, are between 55 and 70 years of age, and frequently are nursing home residents. Most patients who develop HHS do so over days to weeks during which they experience polyuria, polydipsia, and progressive decline in the level of consciousness. The most common clinical presentation for patients with HHS is altered sensorium.¹⁹

Physical examination reveals signs of volume depletion. Fever due to underlying infection is common, and signs of acidosis (Kussmaul respiration, acetone breath) are usually absent. Gastrointestinal manifestations (abdominal pain, vomiting) frequently reported in patients with DKA are not typically present in HHS. Thus, the presence of abdominal pain in patients without significant metabolic acidosis needs to be investigated. In some patients, focal neurological signs (hemiparesis, hemianopsia) and seizures (partial motor seizures more common than generalized) may be the dominant clinical features, resulting in a common misdiagnosis of stroke.²¹ Despite the focal nature of neurological findings, these manifestations often reverse completely after correction of the metabolic disorder.

Laboratory Findings

Although the diagnoses of DKA and HHS can be suspected on clinical grounds, confirmation is based on laboratory tests. The syndrome of DKA consists of the triad of hyper-

glycemia, hyperketonemia, and metabolic acidosis.

In the past, the most widely used diagnostic criteria for DKA included a blood glucose level >250 mg/dl, a moderate degree of ketonemia, serum bicarbonate <15 mEq/l, arterial pH <7.3, and an increased anion gap metabolic acidosis. Although these criteria served well for research purposes, they have significant limitations in clinical practice because the majority of patients with DKA present with mild metabolic acidosis despite elevated serum glucose and β -hydroxybutyrate concentrations. Thus, the biochemical criteria for diagnosis were recently modified.² Table 1 summarizes the biochemical criteria for the diagnosis and empirical subclassification of DKA and HHS.

The diagnostic criteria for HHS include a plasma glucose concentration >600 mg/dl, a serum osmolality >320 mOsm/kg of water, and the absence of significant ketoacidosis. Although by definition patients with HHS have a serum pH >7.3, a serum bicarbonate >18 mEq/l, and negative ketone bodies in urine and plasma, mild ketonemia may be present. Approximately 50% of patients with HHS have an increased anion gap metabolic acidosis as the result of concomitant ketoacidosis and/or an increase in serum lactate levels.²

The assessment of ketonemia, the key diagnostic feature of ketoacidosis, is usually performed by the nitroprusside reaction. However, clinicians should be aware that the nitroprusside

reaction provides a semiquantitative estimation of acetoacetate and acetone levels but does not recognize the presence of β -hydroxybutyrate, which is the main ketoacid in DKA. Therefore, this test may underestimate the level of ketosis. Direct measurement of β -hydroxybutyrate is now available by fingerstick method, which is a more accurate indicator of ketoacidosis.

Common Laboratory Pitfalls

Patients with DKA frequently present with leukocytosis in the absence of infection. However, a leukocyte count >25,000 mm³ or the presence of >10% neutrophil bands is seldom seen in the absence of bacterial infection.²² The admission serum sodium is usually low because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia. To assess the severity of sodium and water deficit, serum sodium may be corrected by adding 1.6 mg/dl to the measured serum sodium for each 100 mg/dl of glucose above 100 mg/dl. An increase in serum sodium concentration in the presence of hyperglycemia indicates a rather profound degree of water loss. Extreme hypertriglyceridemia, which may be present during DKA due to impaired lipoprotein lipase activity, may cause lipemic serum with spurious lowering of serum glucose (pseudonormoglycemia)²³ and serum sodium (pseudohyponatremia)²⁴ in laboratories still using volumetric testing or dilution of samples with ion-specific electrodes.

Table 1. Diagnostic Criteria for DKA and HHS

	Diagnostic Criteria and Classification			
	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dl)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–<7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10–<15	<10	>15
Urine ketone*	Positive	Positive	Positive	Small
Serum ketone*	Positive	Positive	Positive	Small
Effective serum osmolality**	Variable	Variable	Variable	>320 mOsm/kg
Anion gap***	>10	>12	>12	<12
Alteration in sensorium or mental obtundation	A	A/D	S/C	S/C

*Nitroprusside reaction method

**Calculation: Effective serum osmolality: 2[measured Na (mEq/L)] + glucose (mg/dl)/18

***Calculation: Anion gap: (Na⁺) – (Cl⁻ + HCO₃⁻) (mEq/L). See text for details.

A, alert; D, drowsy; S, stuporous, C, comatose.

The admission serum potassium concentration is usually elevated in patients with DKA. In a recent series,³ the mean serum potassium in patients with DKA and those with HHS was 5.6 and 5.7 mEq/l, respectively. These high levels occur because of a shift of potassium from the intracellular to the extracellular space due to acidemia, insulin deficiency, and hypertonicity. Similarly, the admission serum phosphate level may be normal or elevated because of metabolic acidosis. Dehydration also can lead to increases in total serum protein, albumin, amylase, and creatine phosphokinase concentration in patients with acute diabetic decompensation. Finally, serum creatinine, which is measured by a colorimetric method, may be falsely elevated as a result of interference by blood acetoacetate levels.²⁵

Clinicians should remember that not all patients who present with

ketoacidosis have DKA. Patients with chronic ethanol abuse with a recent binge culminating in nausea, vomiting, and acute starvation may present with alcoholic ketoacidosis. The key diagnostic feature that differentiates diabetic and alcohol-induced ketoacidosis is the concentration of blood glucose.²⁶ While DKA is characterized by severe hyperglycemia, the presence of ketoacidosis without hyperglycemia in an alcoholic patient is virtually diagnostic of alcoholic ketoacidosis. In addition, some patients with decreased food intake (<500 kcal/day) for several days may present with starvation ketosis. However, a healthy subject is able to adapt to prolonged fasting by increasing ketone clearance by peripheral tissue (brain and muscle) and by enhancing the kidney's ability to excrete ammonia to compensate for the increased acid production. Therefore, a patient with starvation ketosis rarely presents with a

serum bicarbonate concentration <18 mEq/l.

TREATMENT

Figures 1 and 2 show the recommended algorithm suggested by the recent American Diabetes Association position statement on treatment of DKA and HHS.²⁷ In general, treatment of DKA and HHS requires frequent monitoring of patients, correction of hypovolemia and hyperglycemia, replacement of electrolyte losses, and careful search for the precipitating cause(s). A flow sheet is invaluable for recording vital signs, volume and rate of fluid administration, insulin dosage, and urine output and to assess the efficacy of medical therapy. In addition, frequent laboratory monitoring is important to assess response to treatment and to document resolution of hyperglycemia and/or metabolic acidosis. Serial laboratory measurements include glucose and electrolytes

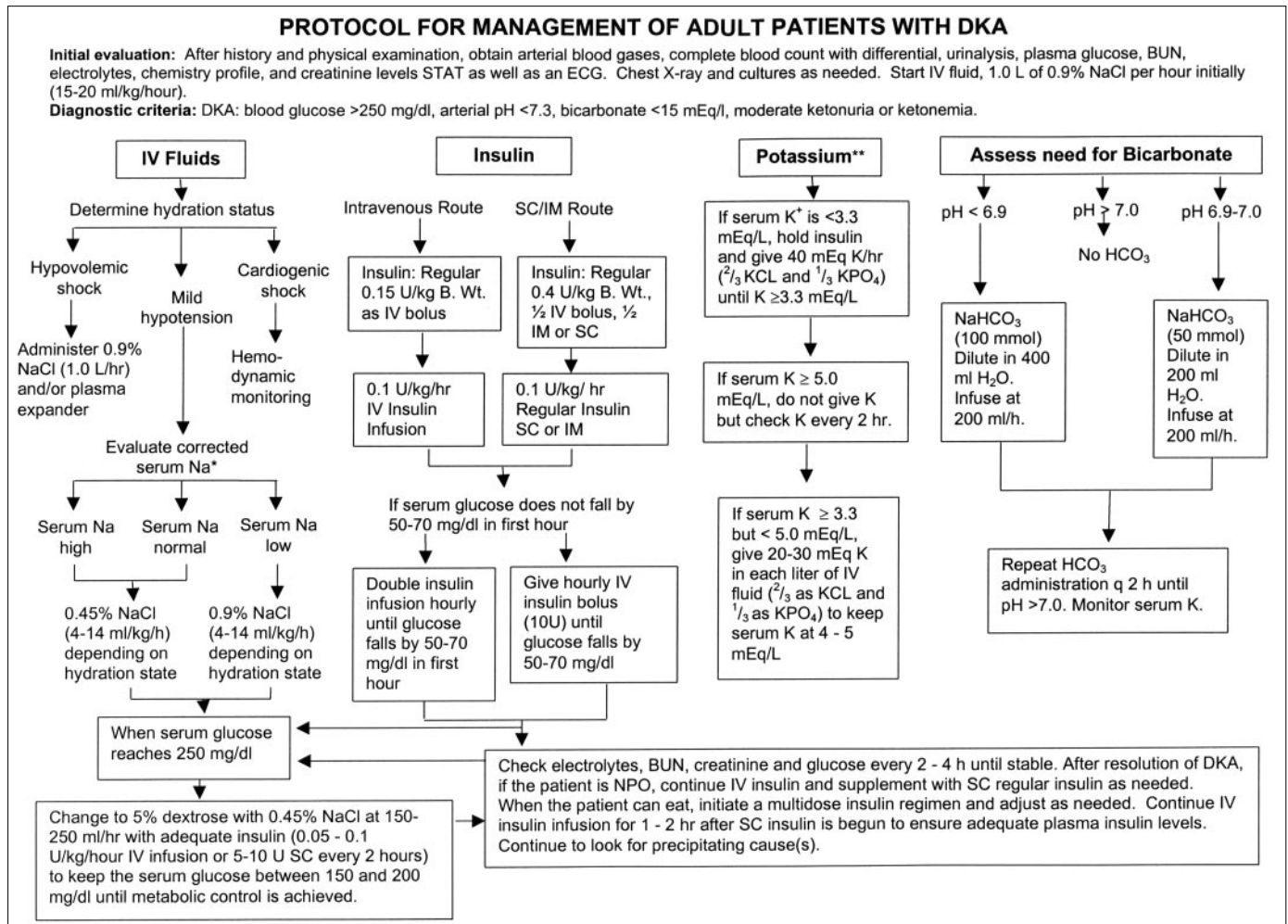


Figure 1. Protocol for Management of Adult Patients with Diabetic Ketoacidosis

*Serum Na⁺ should be corrected for hyperglycemia (for each 100 mg/dl glucose above 100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value).

**Upper limits for serum potassium may vary by laboratory.

Adapted with permission from reference 27.

and, in patients with DKA, venous pH, bicarbonate, and anion gap values until resolution of hyperglycemia and metabolic acidosis.

Fluid Therapy

Patients with DKA and HHS are invariably volume depleted, with an estimated water deficit of ~100 ml/kg of body weight.²⁸ The initial fluid therapy is directed toward expansion of intravascular volume and restoration of renal perfusion. Isotonic saline (0.9% NaCl) infused at a rate of 500–1,000 mL/h during the first 2 h is usually adequate, but in patients with hypovolemic shock, a third or fourth liter of isotonic saline may be needed to restore normal blood pressure and tissue perfusion.

After intravascular volume depletion has been corrected, the rate of normal saline infusion should be reduced to 250 mL/h or changed to

0.45% saline (250–500 mL/h) depending on the serum sodium concentration and state of hydration. The goal is to replace half of the estimated water deficit over a period of 12–24 h. See Table 2 for typical total body deficits of water and electrolytes in DKA and HHS.

Once the plasma glucose reaches 250 mg/dl in DKA and 300 mg/dl in HHS, replacement fluids should contain 5–10% dextrose to allow continued insulin administration until ketonemia is controlled while avoiding hypoglycemia.² An additional important aspect of fluid management in hyperglycemic states is to replace the volume of urinary losses. Failure to adjust fluid replacement for urinary losses may delay correction of electrolytes and water deficit.

Insulin Therapy

The cornerstone of DKA and HHS

management is insulin therapy. Prospective randomized studies have clearly established the superiority of low-dose insulin therapy in that smaller doses of insulin result in less hypoglycemia and hypokalemia.^{29,30} Insulin increases peripheral glucose utilization and decreases hepatic glucose production, thereby lowering blood glucose concentration. In addition, insulin therapy inhibits the release of FFAs from adipose tissue and decreases ketogenesis, both of which lead to the reversal of ketogenesis.

In critically ill and mentally obtunded patients, regular insulin given intravenously by continuous infusion is the treatment of choice. Such patients should be admitted to an intensive care unit or to a step down unit where adequate nursing care and quick turnaround of laboratory tests results are available. An initial intravenous bolus of regular

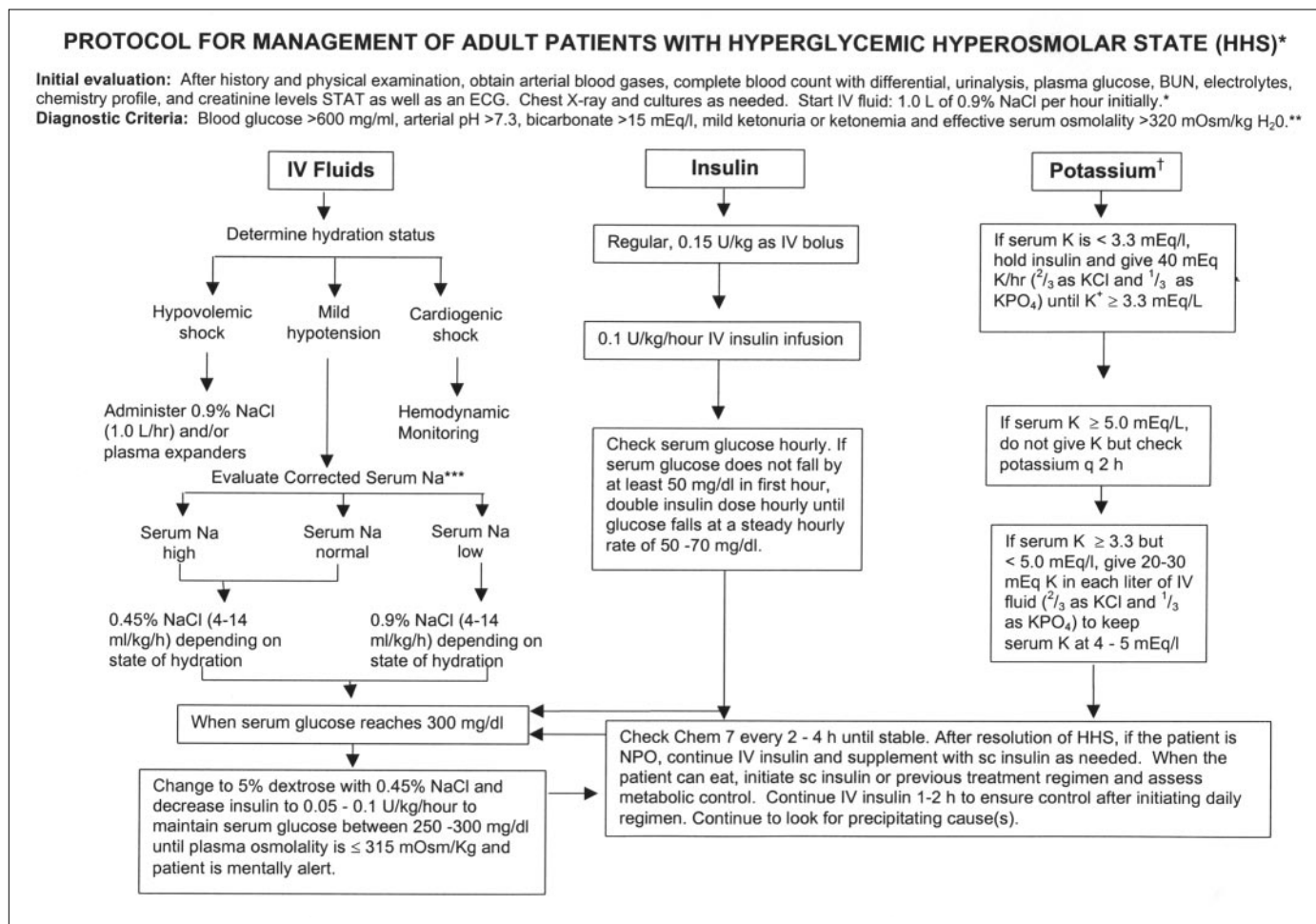


Figure 2. Management of Adult Patients with Hyperosmolar Hyperglycemic Syndrome

*This protocol is for patients admitted with mental status change or severe dehydration who require admission to an ICU.

**Effective serum osmolality calculation: $2[\text{measured Na (mEq/l)}] + \text{glucose (mg/dl)}/18$

***Serum Na⁺ should be corrected for hyperglycemia (for each 100 mg/dl glucose above 100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value).

†Upper limits for serum potassium may vary by laboratory.

Adapted with permission from reference 27.

Table 2. Typical Total Body Deficits of Water and Electrolytes Seen in DKA and HHS²⁸

	Typical Deficit	
	DKA	HHS
Total water (L)	6	9
Water (ml/kg)*	100	100–200
Na ⁺ (mEq/kg)*	7–10	5–13
Cl ⁻ (mEq/kg)*	3–5	5–15
K ⁺ (mEq/kg)*	3–5	4–6
PO ₄ (mEq/kg)*	5–7	3–7
Mg ⁺⁺ (mEq/kg)*	1–2	1–2
Ca ⁺⁺ (mEq/kg)*	1–2	1–2

*Per kg of body weight

insulin of 0.15 unit/kg of body weight, followed by a continuous infusion of regular insulin at a dose of 0.1 unit/kg/h (5–10 unit/h) should be administered. This will result in a fairly predictable decrease in plasma glucose concentration at a rate of 65–125 mg/h.³¹

When plasma glucose levels reach 250 mg/dl in DKA or 300 mg/dl in HHS, the insulin infusion rate is reduced to 0.05 unit/kg/h (3–5 units/h), and dextrose (5–10%) should be added to intravenous fluids. Thereafter, the rate of insulin administration may need to be adjusted to maintain the above glucose values until ketoacidosis or mental obtundation and hyperosmolality are resolved. During therapy, capillary blood glucose should be determined every 1–2 hours at the bedside using a glucose oxidase reagent strip. Blood should be drawn every 2–4 h for determination of serum electrolytes, glucose, blood urea nitrogen, creatinine, magnesium, phosphorus, and venous pH.

A conscious patient with mild DKA could be admitted to a general hospital ward. In such patients, the administration of regular insulin every 1–2 h by subcutaneous or intramuscular route has been shown to be as effective in lowering blood glucose and ketone bodies concentration as giving the entire insulin dose by intravenous infusion.^{32,33} Furthermore, it has been shown that the addition of albumin in the infusate was not necessary to prevent adsorption of insulin to the IV tubing or bag.³³ Such patients should receive the recommended hydrating solution and an initial “priming” dose of regular insulin of 0.4 unit/kg of body weight, given half as intravenous bolus and half as a subcutaneous or

intramuscular injection (Figures 1 and 2). The effectiveness of intramuscular or subcutaneous administration has been shown to be similar; however, subcutaneous injections are easier and less painful.

Potassium

Despite a total body potassium deficit of ~3–5 mEq/kg of body weight, most patients with DKA have a serum potassium level at or above the upper limits of normal.² These high levels occur because of a shift of potassium from the intracellular to the extracellular space due to acidemia, insulin deficiency, and hypertonicity. Both insulin therapy and correction of acidosis decrease serum potassium levels by stimulating cellular potassium uptake in peripheral tissues. Therefore, to prevent hypokalemia, most patients require intravenous potassium during the course of DKA therapy. Replacement with intravenous potassium (two-thirds as potassium chloride [KCl] and one-third as potassium phosphate [KPO₄]) should be initiated as soon as the serum potassium concentration is below 5.0 mEq/L. The treatment goal is to maintain serum potassium levels within the normal range of 4–5 mEq/L.

In some hyperglycemic patients with severe potassium deficiency, insulin administration may precipitate profound hypokalemia,³⁴ which can induce life-threatening arrhythmias and respiratory muscle weakness. Thus, if the initial serum potassium is lower than 3.3 mEq/L, potassium replacement should begin immediately by an infusion of KCl at a rate of 40 mEq/h, and insulin therapy should be delayed until serum potassium is ≥3.3 mEq/L (Figure 1).

Bicarbonate

Bicarbonate administration in patients with DKA remains controversial. Severe metabolic acidosis can lead to impaired myocardial contractility, cerebral vasodilatation and coma, and several gastrointestinal complications. However, rapid alkalization may result in hypokalemia, paradoxical central nervous system acidosis, and worsened intracellular acidosis (as a result of increased carbon dioxide production) with resultant alkalosis. Controlled studies have failed to show any benefit from bicarbonate therapy in patients with DKA with an arterial pH between 6.9 and 7.1.³⁵ However, most experts in the field recommend bicarbonate replacement in patients with a pH <7.0. In patients with DKA with arterial pH ≥7.0, or in patients with HHS, bicarbonate therapy is not recommended.² See Figures 1 and 2 for dosing guidelines.

Phosphate

Total body phosphate deficiency is universally present in patients with DKA, but its clinical relevance and benefits of replacement therapy remain uncertain. Several studies have failed to show any beneficial effect of phosphate replacement on clinical outcome.³⁶ Furthermore, aggressive phosphate therapy is potentially hazardous, as indicated in case reports of children with DKA who developed hypocalcemia and tetany secondary to intravenous phosphate administration.³⁷ Theoretical advantages of phosphate therapy include prevention of respiratory depression and generation of erythrocyte 2,3-diphosphoglycerate.

Because of these potential benefits, careful phosphate replacement may be indicated in patients with cardiac dysfunction, anemia, respiratory depression, and in those with serum phosphate concentration lower than 1.0–1.5 mg/dl. If phosphate replacement is needed, it should be administered as a potassium salt, by giving half as KPO₄ and half as KCl. In such patients, because of the risk of hypocalcemia, serum calcium and phosphate levels must be monitored during phosphate infusion.

TRANSITION TO SUBCUTANEOUS INSULIN

Patients with moderate to severe DKA should be treated with continuous intravenous insulin until ketoacidosis is resolved. Criteria for resolution of ketoacidosis include a blood glucose

<200 mg/dl, a serum bicarbonate level ≥ 18 mEq/L, a venous pH > 7.3 , and a calculated anion gap ≤ 12 mEq/L. The criteria for resolution of HHS include improvement of mental status, blood glucose < 300 mg/dL, and a serum osmolality of < 320 mOsm/kg.

When these levels are reached, subcutaneous insulin therapy can be started. If patients are able to eat, split-dose therapy with both regular (short-acting) and intermediate-acting insulin may be given. It is easier to make this transition in the morning before breakfast or at dinnertime.

Patients with known diabetes may be given insulin at the dosage they were receiving before the onset of DKA. In patients with newly diagnosed diabetes, an initial insulin dose of 0.6 unit/kg/day is usually sufficient to achieve and maintain metabolic control. Two-thirds of this total daily dose should be given in the morning and one-third in the evening as a split-mixed dose. If patients are not able to eat, intravenous insulin should be continued while an infusion of 5% dextrose in half-normal saline is given at a rate of 100–200 mL/h.

A critical element to avoid recurrence of hyperglycemia or ketoacidosis during the transition period to subcutaneous insulin is to allow a 1- or 2-h overlap of intravenous insulin infusion during the initiation of subcutaneous regular insulin to ensure adequate plasma insulin levels.

COMPLICATIONS

Hypoglycemia is the most common complication during insulin infusion. Despite the use of low-dose insulin protocols, hypoglycemia is still reported in 10–25% of patients with DKA.³ The failure to reduce insulin infusion rate and/or to use dextrose-containing solutions when blood glucose levels reach 250 mg/dl is the most important risk factor associated with hypoglycemia during insulin infusion.

Frequent blood glucose monitoring (every 1–2 h) is mandatory to recognize hypoglycemia and serious complications. Many patients with hyperglycemic crises who experience hypoglycemia during treatment do not experience adrenergic manifestations of sweating, nervousness, fatigue, hunger, and tachycardia despite low blood glucose levels (GEU, unpublished observations). Clinicians should be aware that recurrent episodes of hypoglycemia might be associated with a state of hypoglycemia unawareness (loss of

perception of warning symptoms of developing hypoglycemia), which may complicate diabetes management after resolution of hyperglycemic crises.

Hypoglycemia is not frequently observed in patients with HHS. Blood glucose values < 60 mg/dl have been reported in $< 5\%$ of HHS patients during intravenous insulin therapy.³

Although the admission serum potassium concentration is commonly elevated in patients with DKA and HHS, during treatment, plasma concentration of potassium will invariably decrease. Both insulin therapy and correction of acidosis decrease serum potassium levels by stimulating cellular potassium uptake in peripheral tissues. Thus, to prevent hypokalemia, replacement with intravenous potassium as soon as the serum potassium concentration is ≤ 5.0 mEq/L is indicated (upper limits may vary by laboratory).

In patients admitted with normal or reduced serum potassium, insulin administration may precipitate profound hypokalemia.³⁴ Thus, if the initial serum potassium is < 3.3 mEq/L, intravenous potassium replacement should begin immediately, and insulin therapy should be held until serum potassium is ≥ 3.3 mEq/L (see Figures 1 and 2).

Cerebral edema is a rare but serious complication of DKA. It occurs in $\sim 1\%$ of episodes of DKA in children^{38,39} and is associated with a mortality rate of 40–90%.⁴⁰ Clinically, cerebral edema is characterized by a decreasing level of consciousness and headache, followed by seizures, sphincter incontinence, pupillary changes, papilledema, bradycardia, and respiratory arrest.

It has been hypothesized that cerebral edema in children with DKA may be caused by the rapid shift in extracellular and intracellular fluids and changes in osmolality due to accumulation of osmolytes in brain cells exposed to hyperosmolar conditions.⁴¹ A rapid decrease in extracellular osmolality during treatment would then result in osmotically mediated swelling of the brain. Although osmotic factors and other mechanisms may play a part in the development of cerebral edema, recent data suggest that cerebral edema in children with DKA is related to brain ischemia.⁴² In children with DKA, both hypocapnia (which causes cerebral vasoconstriction) and extreme dehydration (as determined by a high initial serum urea nitrogen concentration) were

associated with increased risk for cerebral edema. Hyperglycemia superimposed on an ischemic insult increases the extent of neurological damage, blood-brain barrier dysfunction, and edema formation.

In addition, it has been shown that a lower serum sodium concentration that does not resolve during therapy may be associated with increased risk of cerebral edema.^{42,43} The more frequent occurrence of cerebral edema in children than in adults may be explained in part by the fact that children's brains have higher oxygen requirements than those of adults and are thus more susceptible to ischemia.

Measures that may decrease the risk of cerebral edema in high-risk patients are gradual replacement of sodium and water deficits in patients with high serum osmolality (maximal reduction in osmolality 3 mOsm/kg/h) and the addition of dextrose to the hydrating solutions once blood glucose reaches 250 mg/dl in DKA and 300 mg/dl in HHS.²

Patients with cerebral edema should be transferred to an intensive care unit setting. If signs of increased intracranial pressure or brain herniation are present, only 7–14% of patients recover without permanent significant neurological disabilities.

Treatment includes the immediate use of intravenous mannitol,⁴⁰ reduction of fluid administration rate, and possible mechanical ventilation to help reduce brain swelling.⁴⁴ Corticosteroid and diuretic therapy have no proven benefit over the immediate use of intravenous mannitol.⁴⁰

PREVENTION

The financial burden of DKA and HHS is estimated to exceed \$1 billion per year. The most common precipitating causes of DKA and HHS include infection, intercurrent illness, psychological stress, and noncompliance with therapy. Many episodes could be prevented through better and novel approaches to patient education and effective outpatient treatment programs.

Paramount in this effort is improved education regarding sick-day management. Education on sick-day management should review:

- the importance of early contact with the health care provider
- the importance of insulin during an illness and the reasons never to discontinue insulin without contacting the health care team

- blood glucose goals and the use of supplemental short- or rapid-acting insulin
- availability of medications to suppress a fever and treat an infection
- initiation of an easily digestible liquid diet containing carbohydrates and salt when nauseated
- information for family members on sick-day management and record keeping, including assessing and documenting temperature, respiration and pulse, blood glucose and urine/blood ketones, insulin taken, oral intake, and weight
- information for primary care providers and school personnel on the signs and symptoms of new-onset and decompensated diabetes.

Approximately 50% of DKA admissions may be preventable with improved outpatient treatment programs and better adherence to self-care. Outpatient management is more cost effective and can minimize missed days of school or work for patients with diabetes and their family members.⁴⁵ The frequency of hospitalizations for DKA have been reduced following diabetes education programs, improved follow-up care, and access to medical advice.^{15,45,46}

Additionally, an alarming rise in insulin discontinuation because of economic reasons as the precipitating cause for DKA in urban African Americans illustrates the need for health care legislation guaranteeing reimbursement for medications to treat diabetes.

Novel approaches to patient education incorporating a variety of health care beliefs and socioeconomic issues are critical to an effective prevention program.

Home blood ketone monitoring systems, which measure β -hydroxybutyrate levels on a fingerstick blood specimen, are now commercially available.⁴⁷ These systems measure β -hydroxybutyrate levels in 30 seconds with a detection range of 0–6 mmol/L. Clinical studies have shown that elevations of β -hydroxybutyrate levels are extremely common in patients with poorly controlled diabetes, even in the absence of positive urinary ketones.⁴⁸ The use of home glucose-ketone meters may allow early recognition of impending ketoacidosis, which may help to guide insulin therapy at home and may possibly prevent hospitalization for DKA.

HHS occurs frequently in elderly or debilitated patients who do not recog-

nize or cannot treat the symptoms of diabetes and dehydration or, in many cases, who have caregivers who are not knowledgeable about the signs and symptoms of diabetes and the conditions, procedures, and medications that can lead to decompensation. Therefore, additional education as well as the use of glucose and ketone monitoring may decrease the incidence and severity of HHS in this susceptible group.

References

¹Graves EJ, Gillium BS: Detailed diagnosis and procedures: National Discharge Survey, 1995. National Center for Health Statistics. *Vital Health Stat* 13 (no. 133), 1997

²Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM: Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 24:31–53, 2001

³Umpierrez GE, Kelly JP, Navarrete JE, Casals MMC, Kitabchi AE: Hyperglycemic crises in urban Blacks. *Arch Int Med* 157:669–675, 1997

⁴Umpierrez GE, Woo W, Hagopian WA: Immunogenetic analysis suggests different pathogenesis for obese and lean African-Americans with diabetic ketoacidosis. *Diabetes Care* 22:1517–1523, 1999

⁵Javor KA, Kotsanos JG, McDonald RC, Baron AD, Kesterson JG, Tierney WM: Diabetic ketoacidosis charges relative to medical charges of adult patients with type I diabetes. *Diabetes Care* 20:349–354, 1997

⁶Basu A, Close CF, Jenkins D, Krentz AJ, Natrass M, Wright AD: Persisting mortality in diabetic ketoacidosis. *Diabet Med* 10:282–289, 1992

⁷Gerich JE, Lorenzi M, Bier DM, Tsalikian E, Schneider V, Karam JH, Forsham PH: Effects of physiologic levels of glucagon and growth hormone on human carbohydrate and lipid metabolism: studies involving administration of exogenous hormone during suppression of endogenous hormone secretion with somatostatin. *J Clin Invest* 57:875–884, 1976

⁸McGarry JD: Regulation of ketogenesis and the renaissance of carnitine palmitoyltransferase. *Diabetes Metab Rev* 5:271–284, 1989

⁹Felig P, Wahren J: Influence of endogenous insulin secretion on splanchnic glucose and amino acid metabolism in man. *J Clin Invest* 50:1702–1711, 1971

¹⁰Yu SS, Kitabchi AE: Biological activity of proinsulin and related polypeptides in the fat tissue. *J Biol Chem* 248:3753–3761, 1973

¹¹Shade DS, Eaton RP: Dose response to insulin in man: differential effects on glucose and ketone body regulation. *J Clin Endocrinol Metab* 44:1038–1053, 1977

¹²Chupin M, Charbonnel B, Chupin F: C-peptide blood levels in ketoacidosis and in hyperosmolar non-ketotic diabetic coma. *Acta Diabet* 18:123–128, 1981

¹³Gerich JE, Martin MM, Recant LL: Clinical

and metabolic characteristics of hyperosmolar nonketotic coma. *Diabetes* 20:228–238, 1971

¹⁴Lindsey CA, Falooma GR, Unger RH: Plasma glucagon in nonketotic hyperosmolar coma. *JAMA* 229:1771–1773, 1974

¹⁵Kaufman FR, Halvorson M: The treatment and prevention of diabetic ketoacidosis in children and adolescents with type 1 diabetes mellitus. *Pediatr Ann* 28:576–582, 1999

¹⁶Kauffman FR, Halvorson M: Strategies to prevent diabetic ketoacidosis in children with known type 1 diabetes. *Clin Diabetes* 15:236–239, 1997

¹⁷Polonsky WH, Anderson BJ, Lohrer PA, Aponte JE, Jacobson AM, Cole CF: Insulin omission in women with IDDM. *Diabetes Care* 17:1178–1185, 1994

¹⁸Rydall AC, Rodin GM, Olmsted MP, Devenyi RG, Daneman D: Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. *N Engl J Med* 336:1849–1854, 1997

¹⁹Wachtel TJ, Tetu-Mouradjain LM, Goldman DL, Ellis SE, O'Sullivan PS: Hyperosmolality and acidosis in diabetes mellitus: a three-year experience in Rhode Island. *J Gen Int Med* 6:495–502, 1991

²⁰Campbell IW, Duncan LJ, Innes JA, MacCuish AC, Munro JF: Abdominal pain in diabetic metabolic decompensation: clinical significance. *JAMA* 233:166–168, 1975

²¹Guisado R, Arieff AI: Neurologic manifestations of diabetic comas: correlation with biochemical alterations in the brain. *Metabolism* 24:665–669, 1975

²²Slovic CM, Mark VG, Slovic RJ, Bain RP: Diabetic ketoacidosis and infection: leukocyte count and differential as early predictors of infection. *Am J Emerg Med* 5:1–5, 1987

²³Rumbak MJ, Hughes TA, Kitabchi AE: Pseudonormoglycaemia in diabetic ketoacidosis with elevated triglycerides. *Am J Emerg Med* 9:61–63, 1991

²⁴Kaminska ES, Pourmatabbed G: Spurious laboratory values in diabetic ketoacidosis and hyperlipidemia. *Am J Emerg Med* 11:77–80, 1993

²⁵Assadi FK, John EG, Formell L, Rosenthal IM: Falsely elevated serum creatinine concentration in ketoacidosis. *J Pediatr* 107:562–564, 1985

²⁶Umpierrez GE, DiGirolamo M, Tuvlin JA, Issacs SD, Bhoollasm SM, Kokko JP: Differences in metabolic and hormonal milieu in diabetic- and alcohol-induced ketoacidosis. *J Crit Care* 15:52–59, 2000

²⁷American Diabetes Association: Hyperglycemic crises in patients with diabetes mellitus (Position Statement). *Diabetes Care* 24:1988–1996, 2001

²⁸Ennis ED, Stahl EJVB, Kreisberg RA: The hyperosmolar hyperglycemic syndrome. *Diabetes Rev* 2:115–126, 1994

²⁹Kitabchi AE, Fisher JN, Murphy MB, Rumbak MJ: Diabetic ketoacidosis and the hyperglycemic hyperosmolar nonketotic state. In *Joslin's Diabetes Mellitus* 13th ed. Kahn CR, Weir GC, Eds. Philadelphia, Pa., Lea & Febiger, 1994, p. 738–770

³⁰Kitabchi AE, Ayyagari V, Guerra SMO, Medical House Staff: The efficacy of low dose

versus conventional therapy of insulin for treatment of diabetic ketoacidosis. *Ann Int Med* 84:633-638, 1976

³¹Morris LR, Kitabchi AE: Efficacy of low-dose insulin therapy for severely obtunded patients in diabetic ketoacidosis. *Diabetes Care* 3:53-56, 1980

³²Fisher JN, Shahshahani MN, Kitabchi AE: Diabetic ketoacidosis: low-dose insulin therapy by various routes. *N Engl J Med* 297:238-241, 1977

³³Sacks HS, Shahshahani M, Kitabchi AE, Fisher JN, Young RT: Similar responsiveness of diabetic ketoacidosis to low-dose insulin by intramuscular injection and albumin-preinfusion. *Ann Int Med* 90:36-42, 1979

³⁴Abramson E, Arky R: Diabetic acidosis with initial hypokalemia: therapeutic implications. *JAMA* 196:401-403, 1966

³⁵Morris LR, Murphy MB, Kitabchi AE: Bicarbonate therapy in severe diabetic ketoacidosis. *Ann Intern Med* 105:836-840, 1986

³⁶Fisher JN, Kitabchi AE: A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab* 57:177-180, 1983

³⁷Zipf MB, Bacon GE, Spencer ML, Kelch RP, Hopwood NJ, Hawker CD: Hypocalcemia, hypomagnesemia, and transient hypoparathyroidism during therapy with potassium phos-

phate in diabetic ketoacidosis. *Diabetes Care* 2:265-268, 1979

³⁸Bello FA, Sotos JF: Cerebral oedema in diabetic ketoacidosis in children. *Lancet* 336:64, 1990

³⁹Duck SC, Wyatt DT: Factors associated with brain herniation in the treatment of diabetic ketoacidosis. *J Pediatr* 113:10-14, 1988

⁴⁰Rosenbloom AL: Intracerebral crises during treatment of diabetic ketoacidosis. *Diabetes Care* 13:22-33, 1990

⁴¹Finberg L: Why do patients with diabetic ketoacidosis have cerebral swelling, and why does treatment sometimes make it worse? *Arch Pediatr Adolesc Med* 150:785-786, 1996

⁴²Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M: 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* 344:264-269, 2001

⁴³Silver SM, Clark EC, Schroeder BM, Sterns RH: Pathogenesis of cerebral edema after treatment of diabetic ketoacidosis. *Kidney Int* 51:1237-1244, 1997

⁴⁴White NH: Diabetic ketoacidosis in children. *Endocrinol Metab Clin North Am* 29:657-682, 2000

⁴⁵Laffel LM, Brachett J, Kaufman F, Ho J,

Anderson BJ: Changing the process of diabetes care improves metabolic outcomes and reduces hospitalizations. *Qual Manag Health Care* 6:53-62, 1998

⁴⁶Runyan JW: The Memphis chronic disease program: comparisons in outcome and the nurse's extended role. *JAMA* 231:264-267, 1975

⁴⁷Byrne HA, Tieszen KL, Hollis S, Dornan TL, New JP: Evaluation of an electrochemical sensor for measuring blood ketones. *Diabetes Care* 23:500-503, 2000

⁴⁸MacGillivray MH, Li PK, Lee JT, Mills BJ, Vourhess ML, Putnam TI, Schaeffer PA: Elevated plasma beta-hydroxybutyrate concentrations without ketonuria in healthy insulin-dependent diabetic patients. *J Clin Endocrinol Metab* 54:665-668, 1982

Guillermo E. Umpierrez, MD, FACP, is an associate professor of medicine, Mary Beth Murphy, RN, MS, CDE, MBA, is research nurse director, and Abbas E. Kitabchi, PhD, MD, FACP, FACE, is a professor of medicine and director of the Division of Endocrinology, Diabetes, and Metabolism at the University of Tennessee Health Science Center in Memphis.