

# Management of Hyperglycemic Crises in Patients With Diabetes

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**D**iabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are two of the most serious acute complications of diabetes. These hyperglycemic emergencies continue to be important causes of morbidity and mortality among patients with diabetes in spite of major advances in the understanding of their pathogenesis and more uniform agreement about their diagnosis and treatment. The annual incidence rate for DKA estimated from population-based studies ranges from 4.6 to 8 episodes per 1,000 patients with diabetes (1,2), and in more recent epidemiological studies in the U.S., it was estimated that hospitalizations for DKA during the past two decades are increasing (3). Currently, DKA appears in 4–9% of all hospital discharge summaries among patients with diabetes (4,5). The incidence of HHS is difficult to determine because of the lack of population-based studies and the multiple combined illnesses often found in these patients. In general, it is estimated that the rate of hospital admissions due to HHS is lower than the rate due to DKA and accounts for <1% of all primary diabetic admissions (4–6).

Treatment of patients with DKA and HHS uses significant health care resources, which increases health care costs. In 1983, the cost of hospitalization for DKA in

Rhode Island for 1 year was estimated to be \$225 million (2). It was recently reported that treatment of DKA episodes represents more than one of every four health care dollars spent on direct medical care for adult patients with type 1 diabetes and for one of every two dollars in those patients experiencing multiple episodes of ketoacidosis (7). Based on an annual average of ~100,000 hospitalizations for DKA in the U.S. (4) and estimated annual mean medical care charges of ~\$13,000 per patient experiencing a DKA episode (7), the annual hospital cost for patients with DKA may exceed \$1 billion per year.

Mortality rates, which are <5% in DKA and ~15% in HHS (4–6,8–12,13), increase substantially with aging and the presence of concomitant life-threatening illnesses. Similar outcomes of treatment of DKA have been noted in both community and teaching hospitals (14–16), and outcomes have not been altered by whether the managing physician is a family physician, general internist, house officer with attending supervision, or endocrinologist, so long as standard written therapeutic guidelines are followed (17,18).

This technical review aims to present updated recommendations for management of patients with hyperglycemic crises based on the pathophysiological basis of these conditions.

## DEFINITION OF TERMS, CLASSIFICATION, AND CRITERIA FOR DIAGNOSIS —

DKA consists of the biochemical triad of hyperglycemia, ketonemia, and acidemia (Fig. 1). As indicated, each of these features by itself can be caused by other metabolic conditions (19). Although it has been difficult to classify the degree and severity of DKA, we propose a working classification that may be useful for management of such a condition. Table 1 provides an empirical classification for DKA and HHS, with the caveat that the severity of illness will be influenced by the presence of concomitant intercurrent illnesses.

The terms “hyperglycemic hyperosmolar nonketotic coma” and “hyperglycemic hyperosmolar nonketotic state” have been replaced with the term “hyperglycemic hyperosmolar state” (HHS) (20) to reflect the facts that 1) alterations of sensoria may often be present without coma and 2) the hyperosmolar hyperglycemic state may consist of moderate to variable degrees of clinical ketosis as determined by the nitroprusside method. As indicated, the degree of hyperglycemia in DKA is quite variable and may not be a determinant of the severity of DKA. Serum osmolality has been shown to correlate significantly with mental status in DKA and HHS (5,6,20–23) and is the most important determinant of mental status, as demonstrated by several studies. Table 2 provides estimates of typical deficits of water and electrolytes in DKA and HHS (20,24,25).

## PRECIPITATING EVENTS —

Although it has been repeatedly shown that infection is a common precipitating event in DKA and HHS in this country and abroad (4,12), recent studies suggest that omission of insulin or undertreatment with insulin may be the most important precipitating factor in urban African-American populations (5,26). Table 3 summarizes various studies (2,5,6,27–30) describing precipitating events for DKA. It is important to note that up to 20% of patients may present in the emergency room with either DKA or HHS without a previous diagnosis of diabetes (Table 3). In the African-American population, DKA has been increasingly

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**Abbreviations:** AaO<sub>2</sub>, alveolar-to-arteriolar oxygen; AKA, alcoholic ketoacidosis; ARDS, adult respiratory distress syndrome; BUN, blood urea nitrogen; CPT, carnitine palmitoyl-transferase; CSF, cerebrospinal fluid; DKA, diabetic ketoacidosis; FFA, free fatty acid; HHS, hyperosmolar hyperglycemic state; IRI, immunoreactive insulin; Pao<sub>2</sub>, arteriolar partial pressure of oxygen; RDKA, recurrent DKA.

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

**Other Hyperglycemic States**

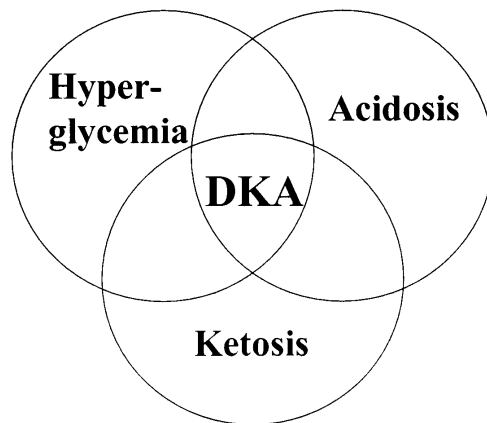
Diabetes Mellitus  
Non-Ketotic Hyperosmolar Coma  
Impaired Glucose Tolerance  
Stress Hyperglycemia

**Other Ketotic States**

Ketotic Hypoglycemia  
Alcoholic Ketosis  
Starvation Ketosis

**Other Metabolic Acidotic States**

Lactic Acidosis  
Hyperchloremic Acidosis  
Salicylism  
Uremic Acidosis  
Drug-Induced Acidosis



**Figure 1**—The triad of DKA (hyperglycemia, acidemia, and ketonemia) and other conditions with which the individual components are associated. From Kitabchi and Wall (19).

noted in newly diagnosed obese type 2 diabetic patients (5,26,31). Therefore, the concept that the presence of DKA in type 2 diabetes is a rare occurrence is incorrect.

The most common types of infections are pneumonia and urinary tract infection, accounting for 30–50% of cases (Table 4). Other acute medical illnesses as precipitating causes include alcohol abuse, trauma, pulmonary embolism, and myocardial infarction, which can occur both in type 1 and 2 diabetes (6). Various drugs that alter carbohydrate metabolism, such as corticosteroids, pentamidine, sympathomimetic agents, and  $\alpha$ - and  $\beta$ -adrenergic blockers, and excessive use of diuretics in the elderly may also precipitate the development of DKA and HHS.

The recent increased use of continuous subcutaneous insulin infusion pumps that use small amounts of short-acting insulin has been associated with an incidence of DKA that is significantly increased over the incidence seen with conventional methods of multiple daily insulin injections, in spite of the fact that most of the mechanical problems with insulin pumps have been resolved (6,32–34). In the Diabetes Control and Complications Trial, the incidence of DKA in patients on insulin pumps was about twofold higher than that in the multiple-injection group over a comparable time period (35). This may be due to the exclusive use of short-acting insulin in the pump, which if interrupted leaves no reservoir of insulin for blood glucose control.

Psychological factors and poor compliance, leading to omission of insulin therapy, are important precipitating factors for recur-

rent ketoacidosis. In young female patients with type 1 diabetes, psychological problems complicated by eating disorders may be contributing factors in up to 20% of cases of recurrent ketoacidosis (36,37). Factors that may lead to insulin omission in younger patients include fear of weight gain with good metabolic control, fear of hypoglycemia, rebellion against authority, and stress related to chronic disease (36). Noncompliance with insulin therapy has been found to be the leading precipitating cause for DKA in urban African-Americans and medically indigent patients (5,26). In addition, a recent study showed that diabetic patients without health insurance or with Medicaid alone had hospitalization rates for DKA that were two to three times higher than the rate in diabetic individuals with private insurance

(38). In addition to the above-mentioned precipitating causes of DKA and HHS, there are numerous additional medical procedures and medications that may precipitate HHS. Some of these drugs trigger the development of hyperglycemic crises by causing a reversible deficiency in insulin action or insulin secretion (e.g., diuretics,  $\beta$ -adrenergic blockers, and dilantin), whereas other conditions cause hyperglycemic crises by inducing insulin resistance (e.g., hypercortisolism, acromegaly, and thyrotoxicosis). Some of the major causes of HHS are included in Table 4 (20).

**PATHOGENESIS** — Although the pathogenesis of DKA is better understood than that of HHS, 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 stress hormones (glucagon, catecholamines, cortisol, and growth hormone). Thus, DKA and HHS are extreme manifestations of impaired carbohydrate regulation that can occur in diabetes. Although many patients manifest overlapping metabolic clinical pictures, each condition can also occur in relatively pure form. In patients with DKA, the deficiency in insulin can be absolute, or it can be insufficient relative to an excess of counterregulatory hormones. In HHS, there is a residual amount of insulin secretion that minimizes ketosis but does not control hyperglycemia. This leads to severe dehydration and impaired renal function, leading to decreased excretion of glucose. These factors coupled with the presence of a stressful condition result in more severe hyperglycemia than that

**Table 1**—Diagnostic criteria for DKA and HHS

	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 ketones*	Positive	Positive	Positive	Small
Serum ketones*	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)†	Variable	Variable	Variable	>320
Anion gap‡	>10	>12	>12	<12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/Coma

\*Nitroprusside reaction method; †calculation:  $2[\text{measured Na (mEq/l)}] + \text{glucose (mg/dl)}/18$ ; ‡calculation:  $(\text{Na}^+) - (\text{Cl}^- - \text{HCO}_3^-) \text{ (mEq/l)}$ . See text for details.

**Table 2—Typical total body deficits of water and electrolytes in DKA and HHS**

	DKA	HHS
Total water (liters)	6	9
Water (ml/kg)*	100	100–200
Na <sup>+</sup> (mEq/kg)	7–10	5–13
Cl <sup>−</sup> (mEq/kg)	3–5	5–15
K <sup>+</sup> (mEq/kg)	3–5	4–6
PO <sub>4</sub> (mmol/kg)	5–7	3–7
Mg <sup>2+</sup> (mEq/kg)	1–2	1–2
Ca <sup>2+</sup> (mEq/kg)	1–2	1–2

\*Per kilogram of body weight. †From Ennis et al. (20) and Kreisberg (24).

seen in DKA. In addition, inadequate fluid intake contributes to hyperosmolality without ketosis, the hallmark of HHS. These pathogenic topics will be discussed under various subheadings.

### Carbohydrate metabolism

When insulin is deficient (absolute or relative), hyperglycemia develops as a result of three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues (39–44). Increased hepatic glucose production results from the high availability of gluconeogenic precursors, such as amino acids (alanine and glutamine; as a result of accelerated proteolysis and decreased protein synthesis) (45), lactate (as a result of increased muscle glycogenolysis), and glycerol (as a result of increased lipolysis), and from the increased activity of gluco-

neogenic enzymes. These include PEPCK, fructose-1,6-biphosphatase, pyruvate carboxylase, and glucose-6-phosphatase, which are further stimulated by increased levels of stress hormones in DKA and HHS (46–50). From a quantitative standpoint, increased glucose production by the liver and kidney represents the major pathogenic disturbance responsible for hyperglycemia in these patients, and gluconeogenesis plays a greater metabolic role than glycogenolysis (46–50,51). Although the detailed biochemical mechanisms for gluconeogenesis are well established, the molecular basis and the role of counterregulatory hormones in DKA are the subject of debate; very few studies have attempted to establish a temporal relationship between the increase in the level of counterregulatory hormones and the metabolic alterations in DKA (52). However, studies of insulin withdrawal in previously controlled patients with type 1 diabetes indicate that a combination of increased catecholamines and glucagon (and a decreased level of free insulin) in a well-hydrated individual may be the initial event (41,43,53–56). Furthermore, in the absence of dehydration, vomiting, or other stress situations, ketosis is usually mild, while glucose levels increase with simultaneous increases in serum potassium (56).

Animal studies have shown that catecholamines stimulate glycogen phosphorylase via  $\beta$ -receptor stimulation and subsequent production of cAMP-dependent protein kinase. Decreased insulin in the presence of an ambient level of glucagon,

which is usually higher in diabetic than in nondiabetic individuals, leads to a high glucagon-to-insulin ratio, which inhibits production of an important metabolic regulator: fructose-2,6-biphosphate. Reduction of this intermediate stimulates the activity of fructose-1,6-biphosphatase (an enzyme that converts fructose-1,6-biphosphate to fructose-6-phosphate) and inhibits phosphofructokinase, the rate-limiting enzyme in the glycolytic pathway (57). Gluconeogenesis is further enhanced through stimulation of PEPCK by the increased ratio of glucagon to insulin in the presence of increased cortisol in DKA (57–59). In addition, the rapid decrease in the level of available insulin also leads to decreased glycogen synthase. These interactions can be summarized as follows:

$$\begin{aligned} &\uparrow \text{glucagon/insulin} + \uparrow \text{catecholamines} \rightarrow \\ &\uparrow \text{cAMP} \rightarrow \uparrow \text{cAMP-dependent protein} \\ &\text{kinase} \rightarrow \downarrow \text{fructose-2,6-biphosphate} \rightarrow \\ &\downarrow \text{glycolysis and } \uparrow \text{gluconeogenesis and} \\ &\downarrow \text{glycogen synthase} \end{aligned}$$

The final step of glucose production occurs by conversion of glucose-6-phosphate to glucose, which is catalyzed by another rate-limiting enzyme of gluconeogenesis, hepatic glucose-6-phosphatase, which is stimulated by increased catabolic hormones and decreased insulin levels. These metabolic alterations are depicted in Fig. 2. Major substrates for gluconeogenesis are lactate, glycerol, alanine (in the liver), and glutamine (in the kidney). Alanine and glutamine are provided by the process of excess proteolysis and decreased protein

**Table 3—Precipitating factors for DKA**

Study location/dates/reference	Number of episodes	Infections	Concomitant cardiovascular disease	Inadequate insulin treatment or noncompliance	New onset	Other medical illness	Unknown
Frankfurt, Germany/Petzold et al. (27)	472	19	6	38	+	+	+
Birmingham, U.K./1968–1972/Soler et al. (28)	258	28	3	23	+	+	+
Erfurt, Germany/1970–1971/Panzram (29)	133	35	4	21	+	+	+
Basel, Switzerland/1968–1978/Berger et al. (30)	163	56	5	31	+	+	+
Rhode Island/1975–1979/Faich et al. (2)	152	43	—	26	+	+	+
Memphis, TN/1974–1985/Kitabchi et al. (6)	202	38	—	28	22	10	4
Atlanta, GA/1993–1994/Umpierrez et al. (5)	144	28	—	41	17	10	4

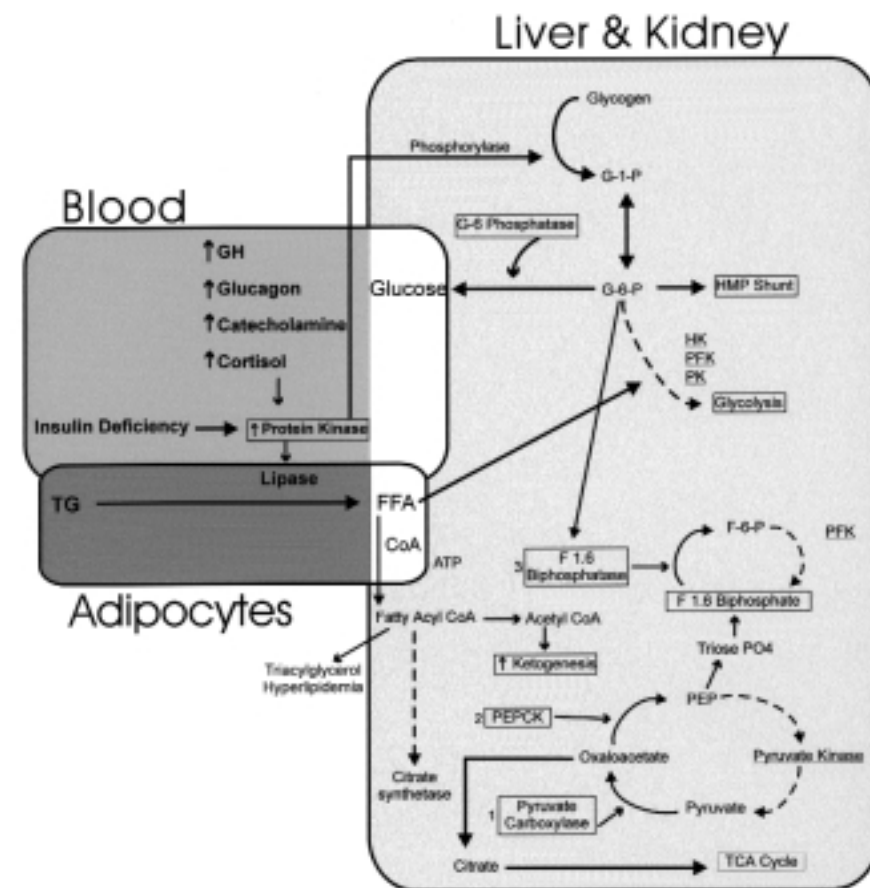
Data are % of all cases. +, complete data on these items were not given because total numbers did not reach 100%.

**Table 4—Predisposing or precipitating factors for HHS**

Acute illness
Acute infection (32–60%)
Pneumonia
Urinary tract infection
Sepsis
Cerebral vascular accident
Myocardial infarction
Acute pancreatitis
Acute pulmonary embolus
Intestinal obstruction
Dialysis, peritoneal
Mesenteric thrombosis
Renal failure
Heat stroke
Hypothermia
Subdural hematoma
Severe burns
Endocrine
Acromegaly
Thyrotoxicosis
Cushing's syndrome
Drugs/therapy
$\beta$ -Adrenergic blockers
Calcium-channel blockers
Chlorpromazine
Chlorthalidone
Cimetidine
Diazoxide
Diuretics
Encainide
Ethacrynic acid
Immunosuppressive agents
L-asparaginase
Loxapine
Phenytoin
Propranolol
Steroids
Total parenteral nutrition
Previously undiagnosed diabetes

From the review by Ennis et al. (20).

synthesis, which occurs as a result of increased catabolic hormones and decreased insulin (45,60). In DKA and HHS, hyperglycemia causes an osmotic diuresis due to glycosuria, resulting in loss of water and electrolytes, hypovolemia, dehydration, and decreased glomerular filtration rate, which further increase the severity of hyperglycemia (see below). Although increased hepatic gluconeogenesis is the main mechanism of hyperglycemia in severe ketoacidosis, recent studies have shown a significant portion of gluconeogenesis may be accomplished via the kidney (51). Decreased insulin availability and partial insulin resis-



**Figure 2—Proposed biochemical changes that occur during DKA leading to increased gluconeogenesis and lipolysis and decreased glycolysis. Note that lipolysis occurs mainly in adipose tissue. Other events occur primarily in the liver (except some gluconeogenesis in the kidney). Lighter arrows indicate inhibited pathways in DKA. F-6-P, fructose-6-phosphate; G-(X)-P, glucose-(X)-phosphate; HK, hexokinase; HMP, hexose monophosphate; PC, pyruvate carboxylase; PFK, phosphofructokinase; PEP, phosphoenolpyruvate; PK, pyruvate kinase; TCA, tricarboxylic acid; TG, triglycerides. From Kitabchi et al. (6).**

tance, which exist in DKA and HHS by different mechanisms (see below), also contribute to decreased peripheral glucose utilization and add to the overall hyperglycemic state in both conditions.

### Lipid and ketone metabolism

The increased production of ketones in DKA is the result of a combination of insulin deficiency and increased concentrations of counterregulatory hormones, particularly epinephrine, which lead to the activation of hormone-sensitive lipase in adipose tissue (61–64). The increased activity of tissue lipase causes a breakdown of triglyceride into glycerol and free fatty acids (FFAs). Although glycerol is used as a substrate for gluconeogenesis in the liver and the kidney, the massive release of FFAs assumes pathophysiological predominance in the liver, the FFAs serving as precursors

of the ketoacids in DKA (44,63). In the liver, FFAs are oxidized to ketone bodies, a process predominantly stimulated by glucagon. Increased concentration of glucagon in DKA reduces the hepatic levels of malonyl-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 (63–66). Malonyl-CoA inhibits carnitine palmitoyl-transferase (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 fatty acyl-CoA and CPT-I activity in DKA leads to increased ketogenesis in DKA (67,68). In addition to increased production of ketone bodies, there is evidence that clearance of

ketones is decreased in patients with DKA (69–71). This decrease may be due to low insulin concentration, increased glucocorticoid level, and decreased glucose utilization by peripheral tissues (72).

The role of individual counterregulatory hormones in the process of ketogenesis is reviewed below. Some of the first studies demonstrating net ketogenesis by the human liver in patients with DKA were done nearly 50 years ago (39). By combining measurements of arterial and hepatic venous ketone concentrations and estimation of splanchnic blood flow in patients with DKA, the liver was demonstrated to produce large amounts of ketones, and insulin treatment was demonstrated to reduce ketone production promptly. These findings were subsequently confirmed and extended with improved analytical techniques (73). To our knowledge, rates of ketogenesis have not been measured in hyperosmolar nonketotic patients using either organ balance or isotopic methods. Subsequent work using tracer methods (41,74) has demonstrated that even brief withdrawal of insulin from type 1 diabetic patients results in prompt development of ketosis. Insulin withdrawal from diabetic patients, however, leads to complex changes in circulating concentrations of many stress hormones. As a result, it is difficult to dissect the relative contributions of insulin deficiency and stress hormone excess in the regulation of ketogenesis. This is well illustrated in studies examining glucagon action. Numerous *in vitro* and some *in vivo* studies have demonstrated a potent role for glucagon in the stimulation of ketogenesis. However, some of these studies have used very high glucagon concentrations, and their physiological significance has been questioned. In a recent study in which blood glucose concentrations were carefully controlled (to eliminate suppressive effects of hyperglycemia on lipolysis), a lipolytic effect of glucagon was demonstrated (75). Another human study (76) demonstrated modest increases in ketogenesis when plasma glucagon was increased in insulin-deficient subjects. In contrast with the somewhat equivocal actions of physiological or near-physiological concentrations of glucagon, cortisol appears to have a more predictable stimulatory action on ketogenesis (77,78). This may result from both effects on peripheral lipolysis and increased supply of FFAs, as well as from direct hepatic effects.

Growth hormone may also play a prominent role in ketogenesis. Even modest physiological doses of growth hormone

**Table 5—Admission biochemical data in patients with HHS or DKA**

Parameters measured	HHS	DKA
Glucose (mg/dl)	930 ± 83	616 ± 36
Na <sup>+</sup> (mEq/l)	149 ± 3.2	134 ± 1.0
K <sup>+</sup> (mEq/l)	3.9 ± 0.2	4.5 ± 0.13
BUN (mg/dl)	61 ± 11	32 ± 3
Creatinine (mg/dl)	1.4 ± 0.1	1.1 ± 0.1
pH	7.3 ± 0.03	7.12 ± 0.04
Bicarbonate (mEq/l)	18 ± 1.1	9.4 ± 1.4
3-β-hydroxybutyrate (mmol/l)	1.0 ± 0.2	9.1 ± 0.85
Total osmolality*	380 ± 5.7	323 ± 2.5
IRI (nmol/l)	0.08 ± 0.01	0.07 ± 0.01
C-peptide (nmol/l)	1.14 ± 0.1	0.21 ± 0.03
FFA (nmol/l)	1.5 ± 0.19	1.6 ± 0.16
Human growth hormone (ng/ml)	1.9 ± 0.2	6.1 ± 1.2
Cortisol (ng/ml)	570 ± 49	500 ± 61
IRI (nmol/l)†	0.27 ± 0.05	0.09 ± 0.01
C-peptide (nmol/l)†	1.75 ± 0.23	0.25 ± 0.05
Glucagon (pg/ml)	689 ± 215‡	580 ± 147§
Catecholamines (ng/ml)	0.28 ± 0.09	1.78 ± 0.4¶
Growth hormone (ng/ml)	1.1#	7.9#
Δ Gap (anion gap – 12) (mEq/l)	11	17

Data are means ± SEM. From Chupin et al. (95). \*According to the formula 2(Na + K) + urea (mmol/l) + glucose (mmol/l); †values following intravenous administration of tolbutamide; ‡from Lindsey et al. (93); §from Kitabchi and Fisher (23); ||from Zadik et al. (219) in children with nonketotic hyperglycemia; ¶from Ennis et al. (20); #from Gerich et al. (92).

can markedly increase circulating levels of FFAs and ketone bodies (79,80). Because these changes with growth hormone administration are observed within 60 min, increased ketogenesis appears to be the result of the action of growth hormone itself rather than locally generated IGF-1. It has been reported that in patients with type 1 diabetes, the administration of growth hormone leads to significant increases in FFAs, ketone bodies, and glucose concentrations (81).

Adrenergic stimulation can also increase lipolysis and hepatic ketogenesis. Epinephrine secretion by the adrenal medulla is markedly enhanced in DKA (Table 5). *In vitro*, epinephrine has a marked effect to increase lipolysis in adipocytes. *In vivo*, epinephrine can increase plasma concentrations of FFAs, at least when insulin deficiency is present. In addition, epinephrine facilitates hepatic ketogenesis directly (82,83). Norepinephrine at concentrations that approximate those seen in the synaptic cleft stimulates lipolysis by adipocytes and enhances ketogenesis (84,85).

In addition to the individual effects of stress hormones, infusion of combinations of counterregulatory hormones has been observed to have synergistic effects when

compared with those seen with single hormone infusions (86,87). Indeed, in the setting of fixed levels of insulin, infusing mixtures of stress hormones to reach high physiological/severe stress levels, can precipitate marked increases in lipolysis and ketogenesis (44,67). Spontaneous DKA is characterized by simultaneous elevations of multiple insulin-antagonizing (counterregulatory) hormones (6,88–90) in the face of reduced insulin, which brings about the altered metabolic profiles seen in DKA. Thus, DKA is analogous to a fasting state, where ketosis is accompanied by elevations of counterregulatory hormones and reduction of insulin but to a lesser degree than in DKA. The condition in DKA has been referred to as a “superfasted” state (91).

Having suggested that stress hormones either singly or in combination are major contributors to ketogenesis and the development of the acidotic state in DKA, the question arises whether HHS differs from DKA with regard to stress hormone secretion. There are surprisingly few data regarding this issue. Reduced concentrations of FFAs, cortisol, and growth hormone (92) and reduced levels of glucagon have been demonstrated in HHS relative to DKA (93). In another study, the concentra-

tions of glucagon, cortisol, growth hormone, epinephrine, and norepinephrine were measured in patients presenting with acute decompensation of their diabetes (94). Some subjects were hyperglycemic with little or no ketosis, whereas others were frankly ketoacidotic. In this study, no clear-cut differences between hormonal levels in DKA and those in HHS could be identified. However, there were significant positive correlations between degree of ketonemia and plasma concentrations of growth hormone and FFAs, and there was a negative correlation with serum C-peptide. Glucagon and cortisol concentrations correlated well with plasma glucose, but not with degree of ketonemia. This study presents correlative data, but does not establish causal relationships between hormonal levels and alterations of metabolic pathways; hence, it does not settle the controversy of hormonal status in DKA and HHS. In another study, 12 HHS and 22 DKA patients showed no differences with regard to FFAs, cortisol, or glucagon (95). This work is of special interest because it demonstrated that in HHS, both basal and stimulated C-peptide levels were five- to sevenfold higher than those in the DKA group. These data are depicted in Table 5 and are contrasted with data from other authors.

The scarcity of data available in HHS prevents firm conclusions as to whether or not differences in stress hormone profiles contribute to the less prominent ketosis in that setting. Available data are consistent with multiple contributing factors, with the most consistent differences being lower growth hormone and higher insulin in HHS than in DKA (Table 5) (92,95). The higher insulin levels (demonstrated by high basal and stimulated C-peptide) in HHS provide enough insulin to inhibit lipolysis in HHS (since it takes less insulin for antilipolysis than for peripheral glucose uptake [67,96–98]) but not enough for optimal carbohydrate metabolism. Although Table 5 shows similar levels of FFAs in HHS and DKA, plasma FFAs may not be reflective of portal vein FFA levels, which in turn regulate ketogenesis. It is important to emphasize that studies performed before 1980, which showed similar blood levels of insulin in DKA and HHS (99), used assays that were not free from interference from proinsulin. Because patients with DKA and HHS present with an overlapping syndrome, the differences between DKA and HHS become matters of degree, not funda-

mental pathogenetic differences. However, it is important to remember that hyperosmolarity of severe DKA, which occurs in about one-third of DKA patients (23), is secondary to fluid losses due to osmotic diuresis and to variable degrees of impaired fluid intake due to nausea and vomiting; the hyperosmolarity in HHS patients is due to more prolonged osmotic diuresis and to inability to take fluid. This can be secondary either to mental retardation (in certain cases in children) or to chronic debilitation in elderly patients who are unaware of or unable to take adequate fluid (216,217).

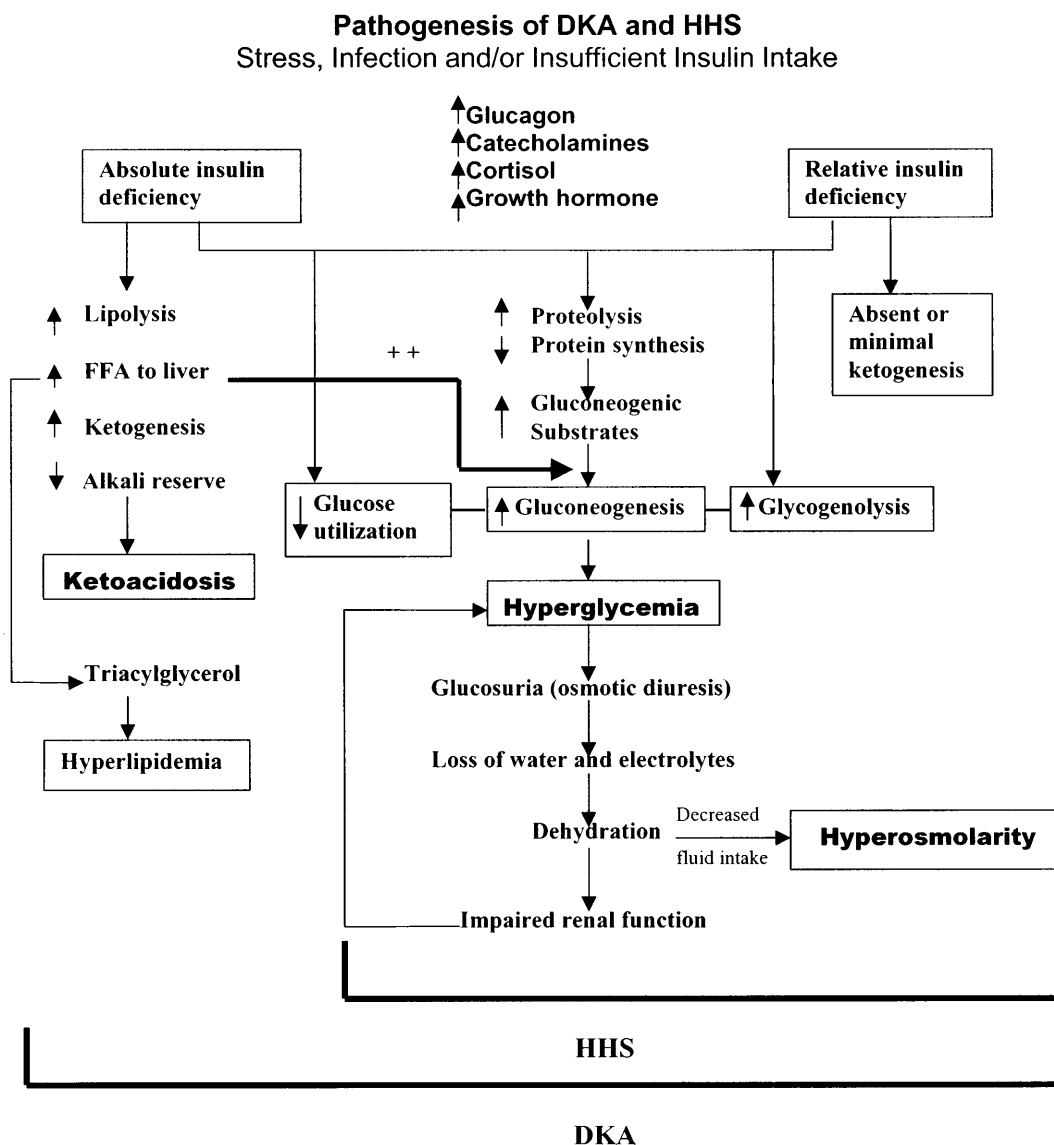
### Water and electrolyte metabolism

The development of dehydration and sodium depletion in DKA and HHS is the result of increased urinary output and electrolyte losses (25,100,101). Hyperglycemia leads to osmotic diuresis in both DKA and HHS. In DKA, urinary ketoanion excretion on a molar basis is generally less than half that of glucose. Ketoanion excretion, which obligates urinary cation excretion as sodium, potassium, and ammonium salts, also contributes to a solute diuresis. The extent of dehydration, however, is typically greater in HHS than in DKA. At first, this seems paradoxical because patients with DKA experience the dual osmotic load of ketones and glucose. The more severe dehydration in HHS, despite the lack of severe ketonuria, may be attributable to the more gradual onset and longer duration of metabolic decompensation (102) and partially to the fact that patients presenting with HHS typically have an impaired fluid intake. Other factors that may contribute to excessive volume losses include diuretic use, fever, diarrhea, and nausea and vomiting. The more severe dehydration, together with the older average age of patients with HHS and the presence of other comorbidities, almost certainly accounts for the higher mortality of HHS (102). In addition, osmotic diuresis promotes the net loss of multiple minerals and electrolytes (Na, K, Ca, Mg, Cl, and  $\text{PO}_4$ ). Although some of these can be replaced rapidly during treatment (Na, K, and Cl), others require days or weeks to restore losses and achieve balance (25,100,101).

The severe derangement of water and electrolytes in DKA and HHS is the result of insulin deficiency, hyperglycemia, and hyperketonemia (in DKA). In DKA and HHS, insulin deficiency per se may also contribute to renal losses of water and electrolytes because insulin stimulates salt and

water reabsorption in the proximal and distal nephron and phosphate reabsorption in the proximal tubule (100,101,103). During severe hyperglycemia, the renal threshold of glucose ( $\sim 200$  mg/dl) and ketones is exceeded; therefore, urinary excretion of glucose in DKA and HHS may be as much as 200 g/day, and urinary excretion of ketones in DKA may be  $\sim 20$ –30 g/day, with total osmolar load of  $\sim 2,000$  mOsm (103). The osmotic effects of glucosuria result in impairment of NaCl and  $\text{H}_2\text{O}$  reabsorption in the proximal tubule and loop of Henle (100). The ketoacids formed during DKA ( $\beta$ -hydroxybutyric and acetoacetic) are strong acids that fully dissociate at physiological pH. Thus, ketonuria obligates excretion of positively charged cations ( $\text{Na}$ ,  $\text{K}$ ,  $\text{NH}_4^+$ ). The hydrogen ions are titrated by plasma bicarbonate, resulting in metabolic acidosis. The retention of ketoanions leads to an increase in the plasma anion gap.

The losses of electrolytes and water in DKA and HHS are summarized in Tables 1 and 2. During HHS and DKA, intracellular dehydration occurs as hyperglycemia and water loss lead to increased plasma tonicity, leading to a shift of water out of cells. This shift of water is also associated with a shift of potassium out of cells into the extracellular space. Potassium shifts are further enhanced by the presence of acidosis and the breakdown of intracellular protein secondary to insulin deficiency (104). Furthermore, entry of potassium into cells is impaired in the presence of insulinopenia. Marked renal potassium losses occur as a result of osmotic diuresis and ketonuria. Progressive volume depletion leads to decreased glomerular filtration rate and greater retention of glucose and ketoanions in plasma. Thus, patients with a better history of food, salt, and fluid intake prior to and during DKA have better preservation of kidney function, greater ketonuria, lower ketonemia, and lower anion gap and are less hyperosmolar. These patients may, therefore, present with greater degrees of hyperchloremic metabolic acidosis (105). On the other hand, diabetic patients with a history of diminished fluid and solute intake during the development of acute metabolic decompensation, plus loss of fluid through nausea and vomiting, typically present with greater degrees of volume depletion, increased hyperosmolarity, and impaired renal function and greater retention of glucose and ketoanions in plasma. The greater



**Figure 3**—Pathogenesis of DKA and HHS.

retention of plasma ketoanions is reflected in a greater increment in the plasma anion gap. Such patients may present with greater alteration of sensoria, which is more commonly found in HHS than DKA (8,102). However, in HHS, as mentioned above, the inability to take fluid (often in elderly patients) plus other pathogenic mechanisms leads to greater hyperosmolarity. These pathogenic pathways and their relationship to clinical conditions of DKA and HHS are depicted in Fig. 3.

During treatment of DKA with insulin, hydrogen ions are consumed as ketoanion metabolism is facilitated. This contributes to regeneration of bicarbonate, correction of metabolic acidosis, and decrease in plasma

anion gap. The urinary loss of ketoanions, as sodium and potassium salts, therefore represents the loss of potential bicarbonate (106), which is gradually recovered within a few days or weeks (107).

#### Insulin resistance in hyperglycemic crises

Soon after insulin therapy became available, the administration of 10 U insulin every 2 h was reported to be effective for the treatment of DKA (108,109). In subsequent decades, however, large doses of insulin were recommended because two early studies suggested that larger doses of insulin were more effective (110,111). In the 1950s and 1960s, two prospective randomized studies com-

pared high-, moderate-, and intermediate-dose insulin therapy in the treatment of DKA. The results showed no difference in response to therapy regardless of insulin dose (112,113). In the early 1970s, numerous studies demonstrated that “low-dose” or “physiological” ( $0.1 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) doses of insulin were effective in controlling DKA (114–120). None of these studies used randomized prospective protocols (121). Between 1976 and 1980, however, numerous prospective randomized studies in adults and children demonstrated the efficacy of lower or physiological doses of insulin by various routes of therapy, which, unlike the high-dose protocol, were associated with a lower incidence of hypokalemia

and hypoglycemia (122–129). The average glucose decrement under such low-dose protocols was between 75 and 120 mg · dl<sup>-1</sup> · h<sup>-1</sup>, which was very similar to the response to larger doses of insulin. Because of the similar metabolic response to high or low doses of insulin, it was questioned whether DKA patients were significantly more insulin resistant than well-controlled type 1 diabetic patients (18,56).

Several studies, however, have demonstrated that when insulin's action on glucose disposal in diabetic subjects is compared with that in healthy control subjects, both DKA and HHS are associated with a significant amount of insulin resistance (130–133). One of the major reasons for the success of low-dose insulin is the fact that most of the protocols recommend that patients in DKA or HHS be aggressively hydrated before or during insulin therapy. The hyperosmolar state alone has been shown to cause insulin resistance both in vivo and in vitro (90,130). Hydration before insulin therapy has also been shown to decrease glucagon, cortisol, catecholamines, and aldosterone by at least threefold, whereas growth hormone, prolactin, and parathyroid hormone do not exhibit such changes (90). The blood glucose decrement during hydration is partially due to improvement in glomerular filtration rate and excretion of large amounts of glucose in the urine (90,134,135). Lack of blood glucose decrement may therefore indicate inadequate hydration or renal function impairment (13). Hydration therapy alone has been reported to partially correct pH and plasma bicarbonate in two studies (44,90), but in another study, pH and plasma bicarbonate were not corrected until insulin was added to the regimen (128). There are, in addition, very rare cases of DKA in which extraordinary insulin resistance is present, which results in multiple hospital admissions (23) or in which hundreds or even thousands of units of insulin are required before resolution of hyperglycemia (136).

## DIAGNOSTIC PROCEDURES

### History and physical examination

DKA and HHS are medical emergencies that require prompt recognition and treatment. The first approach to these patients consists of a rapid but careful history and physical examination with special attention to 1) patency of airway, 2) mental status, 3) cardiovascular and renal status, 4) sources of infection, and 5) state of hydration (6,137–139). These steps should allow determina-

tion of the degree of urgency and priority with which various laboratory results should be obtained so that treatment can start without delay. DKA usually develops rapidly, over a time span of <24 h, whereas HHS symptoms may occur more insidiously, with polyuria, polydipsia, and weight loss persisting for several days before admission. In patients with DKA, nausea and vomiting is a common symptom. Abdominal pain is occasionally seen in adults (and is commonly seen in children), sometimes mimicking an acute abdomen (140). Although the cause has not been elucidated, dehydration of the muscle tissue, delayed gastric emptying, and ileus induced by electrolyte disturbance and metabolic acidosis have been implicated as possible causes of abdominal pain. Acidosis, which can stimulate the medullar respiratory center, can cause rapid and deep respiration (Kussmaul breathing).

Physical examination reveals other findings, such as a fruity breath odor (similar to the odor of nail polish remover) as the result of volatile acetone and 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 with DKA or HHS are hospitalized with loss of consciousness (5,6,8,9,20,23,24). In HHS, mental obtundation and coma are more frequent because the majority of patients, by definition, are hyperosmolar (20,141). In some patients with HHS, focal neurological signs (hemiparesis or hemianopsia) and seizures may be the dominant clinical features (141–144). Although the most common precipitating event is infection, most patients are normothermic or even hypothermic at presentation, because of either skin vasodilation or low fuel-substrate availability.

The easiest and most urgent laboratory tests after a prompt history and physical examination are determination of blood glucose by finger stick and urinalysis with reagent strips to assess qualitative amounts of glucose, ketones, nitrite, and leukocyte esterase in the urine.

### Laboratory evaluation

The initial laboratory evaluation of a patient with suspected DKA or HHS should include immediate determination of arterial blood gases, blood glucose, and blood urea nitrogen (BUN); determination of serum electrolytes, osmolality, creatinine, and ketones; urinalysis; and a complete blood count with differential. Bacterial cultures of

urine, blood, and other tissues should be obtained, and appropriate antibiotics should be administered if infection is suspected. In children without heart, lung, or kidney disease, the initial evaluation may be modified, at the discretion of the physician, to include a venous pH in lieu of an arterial pH. The workup for sepsis may be omitted in children, unless warranted by initial evaluation, because the most common precipitating factor of DKA in this age-group is insulin omission.

Tables 1 and 2 summarize the biochemical criteria for diagnosis and empirical subclassification of DKA and HHS. The most widely used diagnostic criteria for DKA are blood glucose >250 mg/dl, arterial pH <7.3, serum bicarbonate <15 mEq/l, and moderate degree of ketonemia and/or ketonuria. Accumulation of ketoacids usually results in an increased anion gap metabolic acidosis. The plasma anion gap is calculated by subtracting the major measured anions (chloride and bicarbonate) from the major measured cation (sodium). Because potassium concentration may be altered by acid-base disturbances and by total-body stores, it is not routinely used in the calculation of anion gap (44,145). The normal anion gap has been historically reported to be 12 mEq/l, and values >14–15 mEq/l have been considered to indicate the presence of an increased anion gap metabolic acidosis (44,145). Most laboratories, however, currently measure sodium and chloride concentrations using ion-specific electrodes. The plasma chloride concentration typically measures 2–6 mEq/l higher with ion-specific electrodes than with prior methods; thus, the normal anion gap using the current methodology has been reported to be in the range of 7–9 mEq/l (146,147). Using these values, an anion gap of >10–12 mEq/l would indicate the presence of increased anion gap acidosis (146,147).

Although these criteria for DKA have served well for research purposes, they may be somewhat restrictive for clinical practice. For example, the majority of patients admitted with the diagnosis of DKA present with mild metabolic acidosis; however, they show elevations of both serum glucose and  $\beta$ -hydroxybutyrate concentration (5). Most of these patients with mild ketoacidosis are alert and could be managed in a general hospital ward. Milder cases of DKA in which the patient is alert and able to tolerate oral intake may be treated and observed in the emergency room for a few hours and then



discharged when stable. Patients with severe ketoacidosis typically present with a bicarbonate level  $<10$  mEq/l and/or a pH  $<7.0$ , have total serum osmolality  $>330$  mOsm/kg, usually present with mental obtundation (23), and are more likely to develop complications than are those patients with mild or moderate forms of ketoacidosis. Therefore, a classification of the severity of DKA appears to be more clinically appropriate because it may help with patient disposition and choice of therapy (see TREATMENT). This classification must be coupled with an understanding of any concomitant conditions affecting the patient's prognosis and the need for intravenous therapy for hydration.

Assessment of ketonuria and ketonemia, the key diagnostic features of ketoacidosis, is usually performed by nitroprusside reaction. However, nitroprusside reaction provides a semiquantitative estimation of acetoacetate and acetone levels. This assay underestimates the severity of ketoacidosis because it does not recognize the presence of  $\beta$ -hydroxybutyric acid, which is the main ketoacid in DKA (148). Therefore, if possible, direct measurement of  $\beta$ -hydroxybutyrate, which is now available in many hospital settings, is preferable in establishing the diagnosis of ketoacidosis (149,150).

Diagnostic criteria for HHS include plasma glucose concentration  $>600$  mg/dl, serum total osmolality  $>330$  mOsm/kg, and absence of severe ketoacidosis. However, the laboratory profiles of HHS in previous series have shown higher mean values of glucose (998 mg/dl) and osmolality (363 mOsm/l), with BUN 65 mg/dl,  $\text{HCO}_3^-$  21.6 mEq/l, sodium 143 mEq/l, creatinine 2.9 mg/dl, and anion gap 23.4 mg/l (100,151). By definition, patients with HHS have a serum pH  $\geq 7.3$ , a serum bicarbonate  $>18$  mEq/l, and mild ketonemia and ketonuria. Approximately 50% of the patients with HHS have an increased anion gap metabolic acidosis as the result of concomitant ketoacidosis and/or an increase in serum lactate levels (151). Table 6 provides methods for measurement of anion gap and serum total and effective osmolality from serum chemistries.

In some cases, the diagnosis of DKA can be confounded by the coexistence of other acid-base disorders. Arterial pH may be normal or even increased, depending on the degree of respiratory compensation and the presence of metabolic alkalosis from frequent vomiting or diuretic use (152). Similarly, blood glucose concentration may

**Table 6—Calculations from serum chemistries**

**Anion gap**

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

$$\text{Normal} = 7\text{--}9 \text{ mEq/l}$$

$$\Delta \text{ Gap} = [\text{patient gap} - 8]$$

$$\text{Average} = 8 \text{ mEq/l}$$

$$\text{Primary gap acidosis} = \Delta \text{ anion gap} / \Delta \text{HCO}_3^- \geq 0.8$$

$$\text{Primary nongap acidosis} = \Delta \text{ anion gap} / \Delta \text{HCO}_3^- \leq 0.4$$

$$\text{Serum sodium correction} = \text{add } 1.6 \text{ mEq sodium for each } 100 \text{ mg plasma glucose } >100 \text{ mg/dl to the measured serum sodium value}$$

**Total and effective serum osmolality**

$$\text{Total: } 2 \left[ \text{measured serum Na}^+ (\text{mEq/l}) \right] + \frac{\text{glucose (mg/dl)}}{18} + \frac{\text{BUN (mg/dl)}}{2.8} = \text{mOsm/kg H}_2\text{O}$$

$$\text{Normal} = 290 \pm 5$$

$$\text{Effective: } 2 \left[ \text{measured serum Na}^+ (\text{mEq/l}) \right] + \frac{\text{glucose (mg/dl)}}{18} = \text{mOsm/kg H}_2\text{O}$$

$$\text{Normal} = 285 \pm 5$$

Adapted from Ennis et al. (20).

be normal or only minimally elevated in 15% of patients with DKA ( $<300$  mg/dl), such as in alcoholic subjects or patients receiving insulin. In addition, wide variability in the type of metabolic acidosis has been reported. It has been reported that 46% of patients admitted for DKA had high anion gap acidosis, 43% had mixed anion gap acidosis and hyperchloremic metabolic acidosis, and 11% had only hyperchloremic metabolic acidosis (105).

The majority of patients with hyperglycemic emergencies present with leukocytosis. Admission serum sodium concentration is usually low in DKA 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 deficits, serum sodium may be corrected by adding 1.6 mEq to the measured serum sodium for each 100 mg/dl of glucose above 100 mg/dl (153). Admission serum potassium concentration is usually elevated because of a shift of potassium from the intracellular to the extracellular space caused by acidemia, insulin deficiency, and hypertonicity. On the other hand, in HHS, the measured serum sodium concentration is usually normal or elevated because of severe dehydration. In this setting, the corrected serum sodium concentration would be very high. Admission serum phosphate level in DKA may be elevated despite total-body phosphate depletion.

**Pitfalls of laboratory diagnosis**

In assessment of blood glucose and electrolytes in DKA, certain precautions need to

be taken in interpreting results. Severe hyperlipidemia, which is occasionally seen in DKA, could reduce serum glucose (154) and sodium (155) levels, factitiously leading to pseudohypo- or normoglycemia and pseudohyponatremia, respectively, in laboratories still using volumetric testing or dilution of samples with ion-specific electrodes. This should be rectified by clearing lipemic blood before measuring glucose or sodium or by using undiluted samples with ion-specific electrodes. Creatinine, which is measured by a colorimetric method, may be falsely elevated as a result of acetoacetate interference with the method (156,157). Hyperamylasemia, which is frequently seen in DKA, may be the result of extrapancreatic secretion (158) and should be interpreted cautiously as a sign of pancreatitis. The usefulness of urinalysis is only in the initial diagnosis for glycosuria and ketonuria and detection of urinary tract infection. For quantitative assessment of glucose or ketones, the urine test is unreliable, because urine glucose concentration has poor correlation with blood glucose levels (159,160) and the major urine ketone,  $\beta$ -hydroxybutyrate, cannot be measured by the standard nitroprusside method (148).

**Differential diagnosis**

Not all patients 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 (AKA). In virtually all reported series of AKA, the elevation of total ketone body concentration

Table 7—Laboratory evaluation of metabolic causes of acidosis and coma

	Starvation or high fat intake	DKA	Lactic acidosis	Uremic acidosis	Alcoholic ketosis (starvation)	Salicylate intoxication	Methanol or ethylene glycol intoxication	Hyperosmolar coma	Hypoglycemic coma	Rhabdomyolysis
pH	Normal	↓	↓	Mild ↓	↓ ↑	↓ ↑*	↓	Normal	Normal	Mild ↓ may be ↓↓
Plasma glucose	Normal	↑	Normal	Normal	↓ or normal	Normal or ↓	Normal	↑↑ >500 mg/dl	↓↓ <30 mg/dl	Normal
Glycosuria	Negative	++	Negative	Negative	Negative	Negative†	Negative	++	Negative	Negative
Total plasma ketones‡	Slight ↑	↑ ↑	Normal	Normal	Slight to moderate ↑	Normal	Normal	Normal or slight ↑	Normal or slight ↑	Normal
Anion gap	Slight ↑	↑	↑	Slight ↑	↑	↑	↑	Normal	Normal or slight ↑	↑ ↑
Osmolality	Normal	↑	Normal	↑	Normal	Normal	↑ ↑	↑ ↑ >330 mOsm/kg	Normal	Normal or slight ↑
Uric acid	Mild (starvation)	↑	Normal	Normal ↑	↑	Normal	Normal	Normal	Normal	↑
Miscellaneous		May give false-positive for ethylene glycol§	Serum lactate >7 mmol/l	BUN >200 mg/dl		Serum salicylate positive	Serum levels positive			Myoglobinuria, hemoglobinuria

+, positive; —, negative. \*Acetest and Ketostix measure acetoacetic acid only; thus, misleading low values may be obtained because the majority of “ketone bodies” are  $\beta$ -hydroxybutyrate; †respiratory alkalosis/metabolic acidosis; ‡may get false-positive or false-negative urinary glucose caused by the presence of salicylate or its metabolites; §from Bjellerup et al. (220). All other data are from Morris and Kitabchi (167).

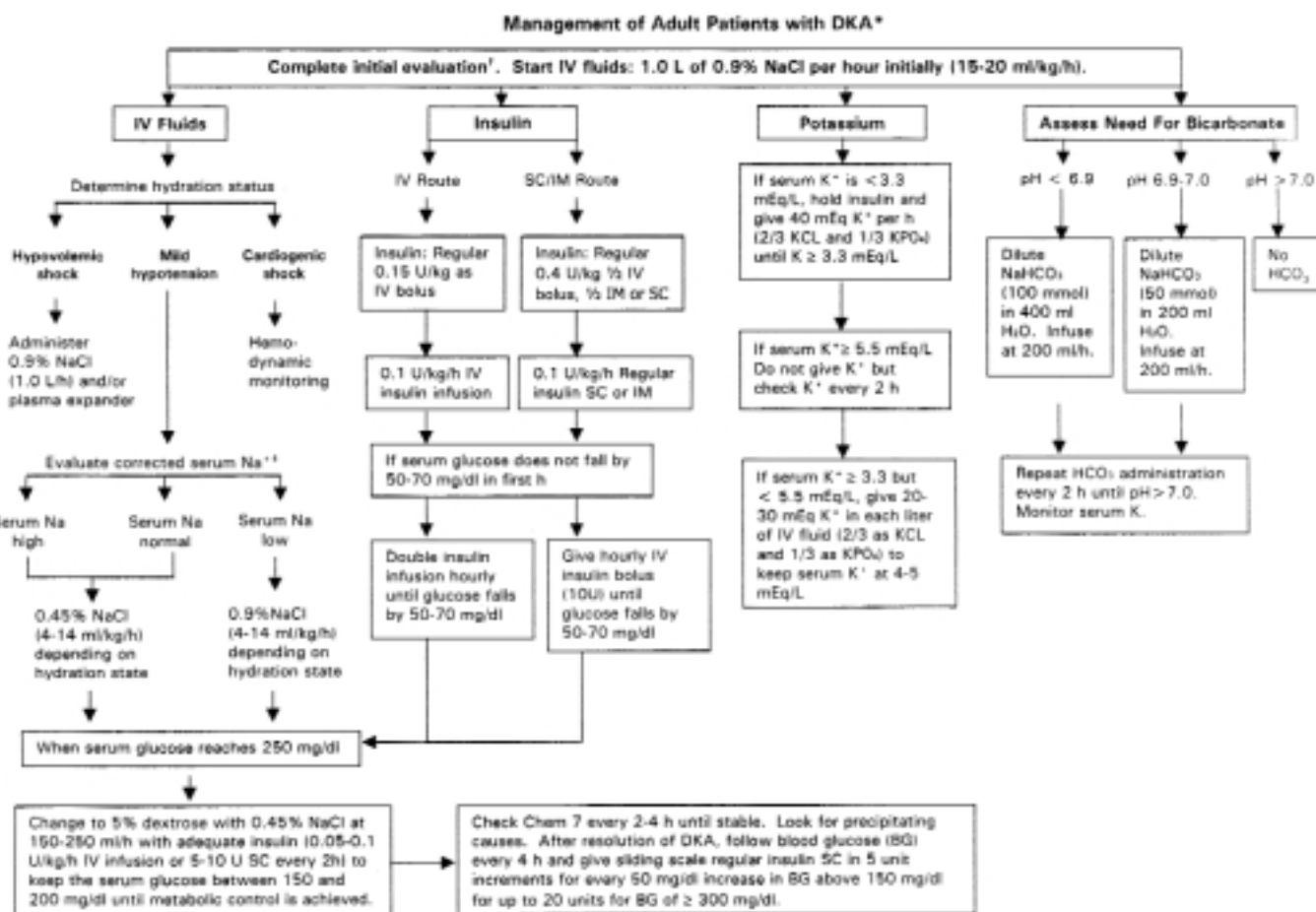
(7–10 mmol/l) is comparable to that reported in patients with DKA (161,162). However, in in vitro studies, the altered redox cellular state in AKA caused by an increased ratio of NADH to NAD levels leads to a reduction of pyruvate and oxaloacetate, which results in impaired gluconeogenesis (163). Additionally, low levels of malonyl-CoA stimulate ketoacidosis and high catecholamines, which result in decreased insulin secretion and increased ratio of glucagon to insulin. This sets the stage for a shift in the equilibrium reaction toward  $\beta$ -hydroxybutyrate production (163,164). Consequently, AKA patients usually present with normal or even low plasma glucose levels and much higher levels of  $\beta$ -hydroxybutyrate than of acetoacetate. The average  $\beta$ -hydroxybutyrate-to-acetoacetate ratio observed in AKA might be as high as 7–10:1, as opposed to the 3:1 ratio observed in DKA (165). The variable that differentiates diabetes-induced and alcohol-induced ketoacidosis is the concentration of blood glucose. Whereas DKA is characterized by hyperglycemia (plasma glucose >250 mg/dl), the presence of ketoacidosis without hyperglycemia in an alcoholic patient is virtually diagnostic of AKA. Additionally, AKA patients frequently have hypomagnesemia, hypokalemia, and hypophosphatemia, as well as hypocal-

cemia, due to decreased PTH as a result of hypomagnesemia (165).

Some patients with decreased food intake (<500 kcal/day) for several days may present with mild ketoacidosis (starvation ketosis). However, a healthy subject is able to adapt to prolonged fasting by increasing the clearance of ketone bodies in peripheral tissues (brain and muscle) and by enhancing the kidneys' ability to excrete ammonium to compensate for the increased ketoacid production (91). Thus, patients with starvation ketosis rarely present with a serum bicarbonate concentration <18 mEq/l and do not exhibit hyperglycemia.

DKA must also be distinguished from other causes of high anion gap metabolic acidosis, including lactic acidosis, advanced chronic renal failure, and ingestion of such drugs as salicylate, methanol, ethylene glycol, and paraldehyde. Measuring blood lactate concentration easily establishes the diagnosis of lactic acidosis (>5 mmol/l) because DKA patients seldom demonstrate this level of serum lactate (122,127,128). However, an altered redox state may obscure ketoacidosis in diabetic patients with lactic acidosis (166). Salicylate overdose is suspected in the presence of mixed acid-base disorder (primary respiratory alkalosis and increased anion gap metabolic acidosis) in the absence of increased

ketone levels. Diagnosis is confirmed by a serum salicylate level >80–100 mg/dl. Methanol ingestion results in acidosis from the accumulation of formic acid and to a lesser extent lactic acid. Methanol intoxication develops within 24 h after ingestion, and patients usually present with abdominal pain secondary to gastritis or pancreatitis and visual disturbances that vary from blurred vision to blindness (optic neuritis). Diagnosis is confirmed by the presence of an elevated methanol level. Ethylene glycol (antifreeze) ingestion leads to excessive production of glycolic acid. The diagnosis of ethylene glycol ingestion is suggested by the presence of increased serum osmolality and high anion gap acidosis without ketonemia, as well as neurological and cardiovascular abnormalities (seizures and vascular collapse), and the presence of calcium oxalate and hippurate crystals in the urine. Because methanol and ethylene glycol are low-molecular weight alcohols, their presence in plasma may be indicated by an increased (>20 mOsm/kg) plasma osmolar gap, defined as the difference between measured and calculated plasma osmolality. Paraldehyde ingestion is indicated by its characteristic strong odor on the breath. Table 7 also summarizes the differential diagnosis of various states of coma in regard to acid-base balances, etc. (167).



**Figure 4**—Protocol for the management of adult patients with DKA. \*DKA diagnostic criteria: blood glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15 mEq/L, and moderate ketonuria or ketonemia. †After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, blood glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT as well as an electrocardiogram. Obtain chest X ray and cultures as needed. ‡Serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value).

## TREATMENT

### Therapeutic goals

The therapeutic goals for treatment of hyperglycemic crises in diabetes consist of 1) improving circulatory volume and tissue perfusion, 2) decreasing serum glucose and plasma osmolality toward normal levels, 3) clearing the serum and urine of ketones at a steady rate, 4) correcting electrolyte imbalances, and 5) identifying and treating precipitating events (Tables 2 and 3).

### Monitoring

As shown in Figs. 4 and 5, monitoring of serum glucose values must be done every 1–2 h during treatment. Serum electrolytes, phosphate, and venous pH must be assessed every 2–6 h, depending on the clinical response of the patient. Foremost, the precipitating factor must be identified

and treated. See Table 7 for a review of the laboratory evaluation of metabolic causes of acidosis and coma. A flow sheet (Fig. 6) is invaluable for recording vital signs, volume and rate of fluid administration, insulin dosage, and urine output and for assessing the efficacy of medical therapy (6). Figures 4 and 5 represent a successful protocol used by the authors for the treatment of DKA and HHS in adult patients. There are some differences in the treatment of children with DKA, which are described throughout the following sections. A protocol for the management of the pediatric patient with DKA and HHS is shown in Fig. 7.

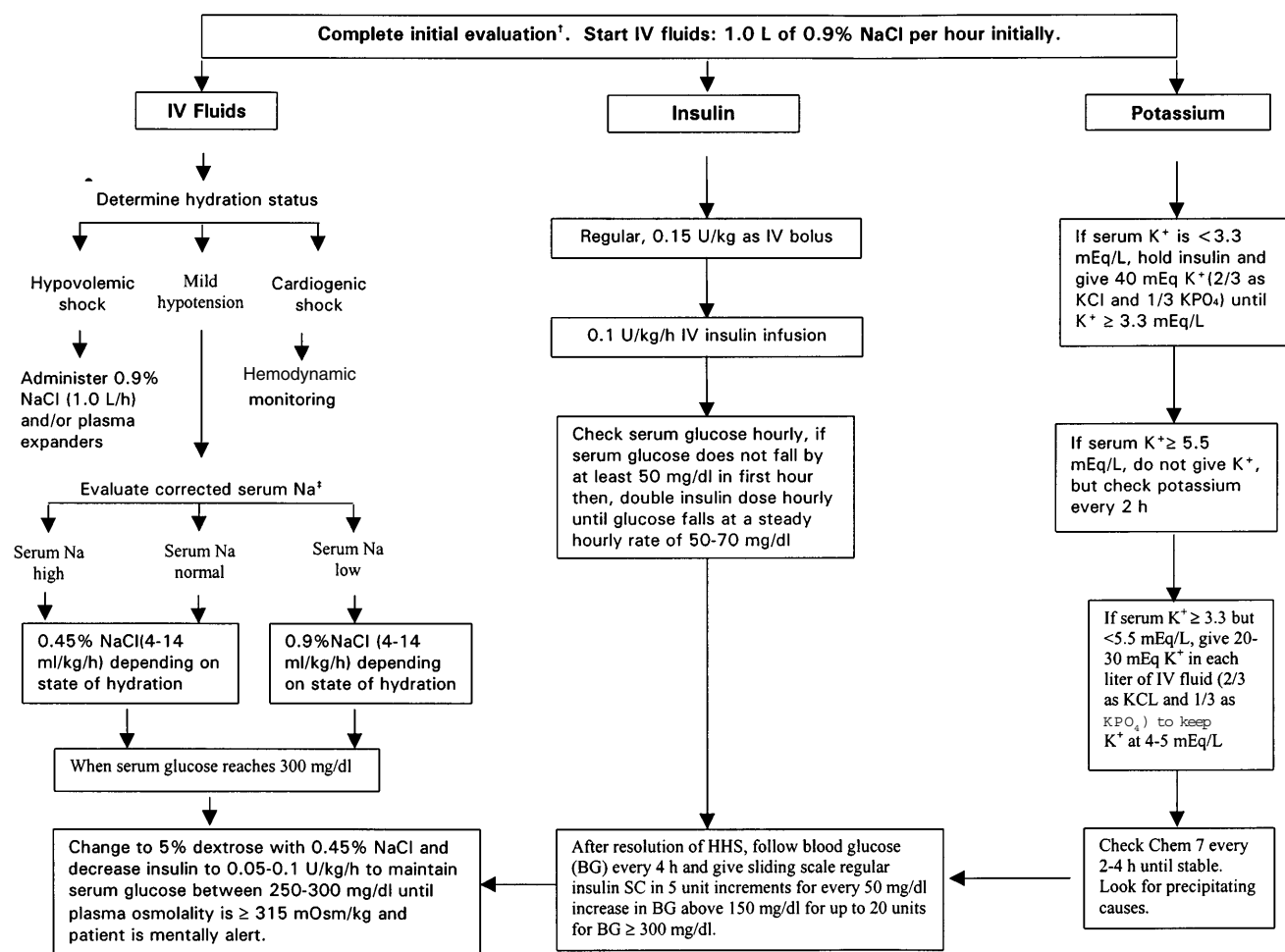
### Replacement of fluid and electrolytes

The severity of fluid and sodium deficits, as shown in Table 2, is determined primarily

by duration of hyperglycemia, level of renal function, and patient's oral intake of solute and water (23,24,44,145,167–175). The severity of dehydration and volume depletion can be estimated by clinical examination (44) using the following guidelines, with the caveat that these criteria are less reliable in patients with neuropathy and impaired cardiovascular reflexes:

1. An orthostatic increase in pulse without change in blood pressure indicates ~10% decrease in extracellular volume (i.e., ~2 liters isotonic saline).
2. An orthostatic drop in blood pressure (>15/10 mmHg) indicates a 15–20% decrease in extracellular volume (i.e., 3–4 liters).
3. Supine hypotension indicates a decrease of >20% in extracellular fluid volume (i.e., >4 liters).

# Management of Adult Patients with HHS\*



**Figure 5**—Protocol for the management of adult patients with HHS. \*Diagnostic criteria: blood glucose >600 mg/dl, arterial pH >7.3, bicarbonate >15 mEq/L, effective serum osmolality >320 mOsm/kg H<sub>2</sub>O, and mild ketonuria or ketonemia. This protocol is for patients admitted with mental status change or severe dehydration who require admission to an intensive care unit. For less severe cases, see text for management guidelines. Effective serum osmolality calculation:  $2[\text{measured Na}^+ (\text{mEq/L})] + \text{glucose} (\text{mg/dl})/18$ . †After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, plasma glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT as well as an electrocardiogram. Chest X ray and cultures as needed. ‡Serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum value).

The use of isotonic versus hypotonic saline in treatment of DKA and HHS is still controversial, but there is uniform agreement that in both DKA and HHS, the first liter of hydrating solution should be normal saline (0.9% NaCl), given as quickly as possible within the 1st hour and followed by 500–1,000 ml/h of 0.45 or 0.9% NaCl (depending on the state of hydration and serum sodium) during the next 2 h. State of hydration can also be estimated by calculating total and effective plasma osmolality and by calculating corrected serum sodium concentration. Total plasma osmolality can be calculated by the following equation:  $2(\text{measured Na}^+) (\text{mEq/L}) + \text{glucose} (\text{mg/dl})/18 + \text{BUN} (\text{mg/dl})/2.8$ . Total

osmolality, whether calculated or directly measured by freezing point depression, is not equivalent to tonicity, because only those solutes that are relatively restricted to the extracellular space are effective in causing osmotic flux of water from intracellular to extracellular space. Urea is an ineffective osmole; therefore, effective osmolality is defined as  $2(\text{measured Na}^+) (\text{mEq/L}) + \text{glucose} (\text{mg/dl})/18$  (45,172). Corrected serum sodium concentrations of >140 mEq/L and calculated total osmolality of >340 mOsm/kg H<sub>2</sub>O are associated with large fluid deficits (20,23,167–171). Calculated total and effective osmolalities can be correlated with mental status, stupor, and coma typically occurring with total

and effective osmolalities of >340 and 320 mOsm/kg H<sub>2</sub>O, respectively (21,23,174). The presence of stupor or coma in the absence of such hyperosmolality demands prompt consideration of other causes of altered mental status (145). Severe hypertonicity is also more frequently associated with large sodium deficits and hypovolemic shock (21,168–174).

The initial goal of rehydration therapy is repletion of extracellular fluid volume by intravenous administration of isotonic saline (175) to restore intravascular volume; this will decrease counterregulatory hormones and lower blood glucose (90), which should augment insulin sensitivity (130). The initial fluid of choice is isotonic

saline (0.9% NaCl), even in HHS patients or DKA patients with marked hypertonicity, particularly in patients with evidence of severe sodium deficits manifested by hypotension, tachycardia, and oliguria. Isotonic saline is hypotonic relative to the patient's extracellular fluid and remains restricted to the extracellular fluid compartment (175). Administration of hypotonic saline, which is similar in composition to fluid lost during osmotic diuresis, leads to gradual replacement of deficits in both intracellular and extracellular compartments (175). The choice of replacement fluid and the rate of administration in HHS remain controversial. Some authorities advocate the use of hypotonic fluid from the outset if effective osmolality is  $>320$  mOsm/kg  $H_2O$ . Others advocate initial use of isotonic fluid. As outlined in Fig. 5, an initial liter of 0.9% NaCl over the 1st hour is followed by either 0.45 or 0.9% NaCl, depending on the corrected serum sodium and the hemodynamic status of the patient.

Dextrose should be added to replacement fluids when blood glucose concentrations are  $<250$  mg/dl in DKA or  $<300$  mg/dl in HHS. This can usually be accomplished with the administration of 5% dextrose; however, in rare cases, a 10% dextrose solution may be needed to maintain plasma glucose levels and clear ketonemia. This allows continued insulin administration until ketogenesis is controlled in DKA and avoids too rapid correction of hyperglycemia, which may be associated with development of cerebral edema (especially in children) (176). An additional important aspect of fluid replacement therapy in both DKA and HHS is the replacement of ongoing urinary losses. Failure to adjust fluid replacement for urinary losses leads to a delay in repair of sodium, potassium, and water deficits (21,170,176). Overhydration is a concern when treating children with DKA, adults with compromised renal or cardiac function, and elderly patients with incipient congestive heart failure. Once blood pressure stability is achieved with the use of  $10\text{--}20$  ml  $\cdot$  kg $^{-1}$   $\cdot$  h $^{-1}$  0.9% NaCl for 1–2 h, one should become more conservative with hydrating fluid (Figs. 4 and 5). Reduction in glucose and ketone concentrations should result in concomitant resolution in osmotic diuresis of DKA. The resulting decrease in urine volume should lead to a reduction in the rate of intravenous fluid replacement. This reduces the risk of retention of excess free water, which contributes to brain swelling and cerebral edema, particularly in

SUGGESTED DKA/HHS FLOWSHEET												
DATE:	HOUR:	ER										
Weight (daily)												
Mental Status*												
Temperature												
Pulse												
Respiration/Depth**												
Blood Pressure												
Serum Glucose (mg/dl)												
Serum Ketones												
Urine Ketones												
<b>ELECTROLYTES</b>												
Serum Na <sup>+</sup> (mEq/L)												
Serum K <sup>+</sup> (mEq/L)												
Serum CL (mEq/L)												
Serum HCO <sub>3</sub> <sup>-</sup> (mEq/L)												
Serum BUN (mg/dl)												
Effective Osmolality 2[measured Na(mEq/L)] +Glucose (mg/dl)/18												
Anion Gap												
<b>A.B.G.</b>												
pH Venous(V) Arterial(A)												
pO <sub>2</sub>												
pCO <sub>2</sub>												
O <sub>2</sub> SAT												
<b>INSULIN</b>												
Units Past Hour												
Route												
<b>INTAKE FLUID/METABOLITES</b>												
0.45% NaCl(ml) Past Hour												
0.9% NaCl(ml) Past Hour												
5% Dextrose(ml) Past Hour												
KCL (mEq) Past Hour												
PO <sub>4</sub> (mMOLES) Past Hour												
Other (e.g., HCO <sub>3</sub> <sup>-</sup> )												
<b>OUTPUT</b>												
Urine (ml)												
Other												
* A-ALERT    D-DROWSY    S-STUPOROUS    C-COMATOSE ** D-DEEP    S-SHALLOW    N-NORMAL												

**Figure 6**—DKA/HHS flowsheet for the documentation of clinical parameters, fluid and electrolytes, laboratory values, insulin therapy, and urinary output. From Kitabchi et al. (6).

children. The duration of intravenous fluid replacement in adults and children is  $\sim 48$  h depending on the clinical response to therapy. However, in a child, once cardiovascular stability is achieved and vomiting has stopped, it is safer and as effective to pursue oral rehydration.

### Insulin therapy

The use of low-dose insulin reemerged in the 1970s in the U.S. after a prospective randomized study using high doses of intravenous and subcutaneous insulin (total dose  $263 \pm 45$  U) or low-dose insulin (total dose  $46 \pm 5$  U) administered intramuscularly after aggressive hydration demonstrated similar outcomes in the two groups. Furthermore, significant reduction in hypokalemia and no hypoglycemia were demonstrated in the low-dose group (122). These findings were confirmed in many

subsequent studies in both adults and children (23,123–128).

An important question raised during this period concerned the optimum route of insulin delivery (17). In one comparative study, 45 patients (15 in each of three groups) were randomly assigned to receive low-dose insulin intravenously, subcutaneously, or intramuscularly, with initial therapy consisting of 0.33 U/kg body wt, as either an intravenous bolus or subcutaneous or intramuscular injections, followed by 7 U/h regular insulin administered in the same manner (127). Outcome parameters were found to be similar in the three groups. However, during the first 2 h of therapy, the group receiving intravenous insulin showed a greater decline in plasma glucose and ketone bodies. In fact, the group that received subcutaneous or intramuscular



injections showed an increase rather than a decrease in ketone bodies in the 1st hour. It was of interest that the 10% glucose decrement, which was defined as an acceptable response in the 1st hour of insulin therapy, was achieved in 90% of the intravenous group but only in 30–40% of the intramuscular and subcutaneous groups. These groups required second and third doses of insulin to produce an acceptable glucose decrement. Because 15 of the 45 patients had never taken insulin, it was possible to determine their level of immunoreactive insulin (IRI) during therapy. Insulin levels during 8 h of therapy were measured with the following results: 1) the intravenous insulin bolus gave rise within a few minutes to  $>3,000 \mu\text{U/ml}$  of IRI, and 2) a similar amount of insulin given subcutaneously or intramuscularly barely doubled the initial level of IRI to

It has been well established that insulin resistance is present in many type 1 (without DKA) and most type 2 diabetic patients (44). During severe DKA, there are additional confounding factors, such as stress (elevated counterregulatory hormones), ketone bodies, FFAs, hemoconcentration, electrolyte deficiencies (132), and particularly hyperosmolality, that exaggerate the insulin resistance state. However, replacement of fluid and electrolytes alone may diminish this insulin resistance by decreasing levels of counterregulatory hormones and hyperglycemia as well as by decreasing osmolality, making the cells more responsive to insulin (90,130). Low-dose insulin therapy is therefore most effective when preceded or accompanied by initial fluid and electrolyte replacement.

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men for both DKA and HHS, but because of a greater level of mental obtundation in HHS, we have recommended only using the intravenous route for HHS (Figs. 4 and 5). The important point to emphasize in insulin treatment of patients with DKA and HHS is that insulin should be used after initial serum electrolyte values are obtained while the patient is being hydrated with 1 liter of 0.9% saline. Insulin therapy is then initiated with an intravenous bolus of 0.15 U/kg or 10 U regular insulin, followed by either intravenous infusion of insulin at a rate of  $0.1 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  or subcutaneous or intramuscular injection of 7–10 U/h. However, in children, the initial dose may be 0.1 U/kg continuous infusion with or without an insulin bolus. Some pediatric endocrinologists do not use  $>3 \text{ U/h}$  in children.

As noted earlier (26,127), the rates of absorption of regular insulin administered intramuscularly and subcutaneously are comparable, with the subcutaneous route being less painful. However, an intravenous route should be used exclusively in the case of hypovolemic shock due to poor tissue perfusion. As depicted in Figs. 4 and 5, the insulin rate is decreased to  $0.05\text{--}0.1 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  when blood glucose reaches 250–300 mg/dl. A 5% or, rarely, a 10% solution of dextrose is added to the hydrating solution at this time to keep blood glucose at its respective level (by adjusting the insulin rate) until the patient has recovered from DKA (i.e.,  $\text{HCO}_3^- > 18 \text{ mEq/L}$ , anion gap  $\leq 12$ , and pH  $> 7.3$ ) or HHS (osmolality  $< 315 \text{ mOsm/kg}$  and patient is alert). Blood glucose monitoring every 60 min will indicate whether this is sufficient to produce a consistent reduction in blood glucose. If blood glucose fails to decrease at a rate of  $50\text{--}70 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{h}^{-1}$ , the patient's volume status should be reassessed to ensure adequate volume repletion. An additional factor that may contribute to the failure of blood glucose to decline is an error in preparation of the insulin infusion mixture, which should be redone with greater care for the appropriate inclusion of insulin into the infusion solution. If the infusion continues to be ineffective, the infusion rate should be increased until the desired glucose-lowering effect is produced.

## Potassium

Table 2 shows typical potassium deficits, which represent mainly intracellular losses, in both DKA and HHS. Extracellular hyperosmolality, secondary to hyperglycemia, causes a shift of water and potassium from

the intracellular to the extracellular space, resulting in normal or elevated serum potassium concentrations despite total-body potassium deficits of 500–700 mEq/L (44,177–179). This potassium shift is further enhanced by insulin deficiency and the presence of acidosis and accelerated breakdown of intracellular protein (180).

Excessive urinary potassium losses, which occur as a result of osmotic diuresis with increased delivery of fluid and sodium to potassium secretory sites in the distal nephron, are ultimately responsible for the development of potassium depletion (177–180). Secondary hyperaldosteronism and urinary ketoanion excretion, as potassium salts, further augment potassium losses.

During treatment of DKA and HHS with hydration and insulin, there is typically a rapid decline in plasma potassium concentration as potassium reenters the intracellular compartment. However, potassium replacement should not be initiated until the serum potassium concentration is  $< 5.5 \text{ mEq/L}$ . We recommend administering one-third of the potassium replacement as potassium phosphate to avoid excessive chloride administration and to prevent severe hypophosphatemia. Others use potassium acetate to avoid an excessive chloride load. Because hypokalemia is the most life-threatening electrolyte derangement occurring during treatment, in the rare patients ( $\sim 4\text{--}10\%$ ) presenting with hypokalemia (179), potassium replacement should be initiated before insulin therapy and insulin therapy held until plasma potassium levels are  $> 3.3 \text{ mEq/L}$ . Intravenous potassium administration should not generally exceed 40 mEq in the 1st hour; thereafter, 20–30 mEq/h is needed to maintain plasma potassium levels between 4 and 5 mEq/L. We recommend electrocardiogram monitoring during potassium therapy in patients presenting with hypokalemia or in patients with any abnormal rhythms other than sinus tachycardia.

## Bicarbonate

Most current reviews do not recommend the routine use of alkali therapy in DKA because DKA tends to correct with insulin therapy. Insulin administration inhibits ongoing lipolysis and ketoacid production and promotes ketoanion metabolism. Because protons are consumed during ketoanion metabolism, bicarbonate is regenerated, leading to partial correction of metabolic acidosis. Arguments that favor

the use of alkali therapy are based on the assumption that severe metabolic acidosis is associated with intracellular acidosis, which could contribute to organ dysfunction, such as in the heart, liver, or brain. Such organ dysfunction could in turn result in increased morbidity and mortality. Potential adverse effects of alkali therapy include worsened hypokalemia, worsened intracellular acidosis due to increased carbon dioxide production, delay of ketoanion metabolism, and development of paradoxical central nervous system acidosis (181).

A retrospective review (182) has failed to identify changes in morbidity or mortality with sodium bicarbonate therapy. After reviewing the risks and benefits of bicarbonate therapy, one author concluded that the only clear indication for use of bicarbonate is life-threatening hyperkalemia (183). Another study showed that ketoanion metabolism was delayed in the presence of bicarbonate therapy, but no significant difference in response between the bicarbonate and no bicarbonate groups was noted (184). A prospective randomized study examined the effect of bicarbonate versus no bicarbonate in two groups of DKA patients with similar degrees of acidemia (pH 6.9–7.14) (185). In some patients, initial cerebrospinal fluid (CSF) chemistry was measured and compared with initial plasma chemistry. It was of interest that  $\text{HCO}_3^-$  and pH in CSF were significantly higher than those in plasma of DKA patients. Conversely, ketones and glucose were higher in plasma than in CSF. However, CSF and plasma osmolalities were similar, indicating that the blood-brain barrier provided greater protection against acidosis for the brain (185). Furthermore, regression analysis of the level of lactate, ketones, pH, bicarbonate, and glucose showed no significant difference in the two groups with regard to slopes of these variables during recovery from DKA. It was therefore concluded that administration of bicarbonate in DKA patients (with pH of 6.9–7.14) provided no measurable advantage either biochemically or clinically (181,185). However, because there were very few in a subclass of patients who had an admission pH of 6.9–7.0, additional studies are needed at this level of acidosis. No prospective randomized studies concerning the use of bicarbonate in DKA with arterial pH values  $< 6.9$  have been reported. In the absence of such studies, bicarbonate therapy in patients with pH  $< 7.0$  seems prudent. As outlined in

Fig. 4, a pH of 6.9–7.0 warrants a dose of 50 mmol of intravenous bicarbonate; a larger dose is recommended for a venous pH of <6.9 because of the increased severity of acidosis. Bicarbonate should be administered as an isotonic solution, which can be prepared by addition of one ampoule of 7.5%  $\text{NaHCO}_3$  solution (50 mmol  $\text{HCO}_3^-$ ) to 250 ml sterile  $\text{H}_2\text{O}$ . Add 15 mEq of KCl for each ampoule of bicarbonate administration (if serum potassium is <5.5 mEq/l).

Regarding the use of bicarbonate in children with DKA, no prospective randomized study has been reported. Because good tissue perfusion created with the initial fluid bolus reduces the lactic acidosis of DKA and because organic acid production is reduced as the result of administered exogenous insulin, the metabolic acid load in DKA is reduced enough that it appears to be unnecessary to add buffer  $\text{NaHCO}_3$ . Young people who are at the least risk for cardiovascular failure should not receive  $\text{NaHCO}_3$  in their rehydration fluids until there is some clinical evidence of cardiac failure. Furthermore, in a recent retrospective study of 147 admissions of severe DKA in children with pH <7.15 (two with <6.9), the effect of bicarbonate or no bicarbonate was compared. This study concluded that there was no benefit of bicarbonate and that use of bicarbonate may be disadvantageous in severe pediatric DKA (186). There have been suggestions that administration of  $\text{NaHCO}_3$  in children with DKA may be associated with altered consciousness and headache, but no definitive causal relationship has been established. It must be stated, however, that a definitive study on the efficacy of bicarbonate or no bicarbonate in DKA requires a larger number of patients to provide enough power for conclusive results. Until such a time, we recommend that adult patients with a pH of <6.9 receive 100 mmol isotonic bicarbonate with KCl and 50 mmol bicarbonate for a serum bicarbonate of 6.9–7.0. In children, the use of bicarbonate must be based on the condition of the individual patient.

### Phosphate therapy

Phosphate, along with potassium, shifts from the intracellular to the extracellular compartment in response to hyperglycemia and hyperosmolality. Osmotic diuresis subsequently leads to enhanced urinary phosphate losses (Tables 1 and 2). Because of the shift of phosphate from the intracellular

to the extracellular compartment, serum levels of phosphate at presentation with DKA or HHS are typically normal or increased (187,188). During insulin therapy, phosphate reenters the intracellular compartment, leading to mild to moderate reductions in serum phosphate concentrations. Adverse complications of hypophosphatemia are uncommon, occurring primarily in the setting of severe hypophosphatemia (phosphate <1 mg/dl).

Potential complications of severe hypophosphatemia include respiratory and skeletal muscle weakness, hemolytic anemia, and worsened cardiac systolic performance (189). Phosphate depletion may also contribute to decreased concentrations of 2,3-diphosphoglycerate, thus shifting the oxygen dissociation curve to the left and limiting tissue oxygen delivery (190). Controlled and randomized studies have not demonstrated clinical benefits from the routine use of phosphate replacement in DKA (187,188). Five days of  $\text{PO}_4$  therapy increased 2,3-diphosphoglycerate without a significant change in the oxygen dissociation curve and resulted in a significant decrease in serum ionized calcium (187). Similar studies have not been performed in patients with HHS.

Although routine phosphate replacement is unnecessary in DKA, replacement should be given to patients with serum phosphate concentrations <1.0 mg/dl and to patients with moderate hypophosphatemia and concomitant hypoxia, anemia, or cardiorespiratory compromise (189). Excessive administration of phosphate can lead to hypocalcemia with tetany and metastatic soft tissue calcifications (191). In HHS, because the duration of symptoms may be prolonged and because of comorbid conditions, the phosphate level may be lower than in DKA; therefore, it is prudent to monitor phosphate levels in these patients.

If phosphate replacement is needed, 20–30 mEq/l potassium phosphate can be added to replacement fluids and given over several hours. In such patients, because of the risk of hypocalcemia, serum calcium and phosphate levels must be monitored during phosphate infusion.

### Immediate posthyperglycemic care

Low-dose insulin therapy provides a circulating insulin concentration of ~60–100  $\mu\text{U}/\text{ml}$ . However, because of the short half-life of intravenous regular insulin, sudden interruption of insulin infusion can lead to rapid lowering of insulin concentration,

resulting in a relapse into DKA or HHS. Thus, numerous publications have emphasized the need for frequent monitoring during the posthyperglycemic period (6,19,44,56,137,139,192).

Patients with severe DKA and mental obtundation should be treated with continuous intravenous insulin or, if less severe, with hourly injection of subcutaneous insulin until ketoacidosis is resolved to maintain insulin levels at ~100  $\mu\text{U}/\text{ml}$  (124). Criteria for resolution of ketoacidosis include blood glucose <200 mg/dl, serum bicarbonate level  $\geq 18$  mEq/l, venous pH >7.3, and calculated anion gap  $\leq 12$  mEq/l. Once DKA is resolved, hydrating fluid is continued intravenously and subcutaneous regular insulin therapy is started every 4 h. An abrupt discontinuance of intravenous insulin coupled with a delayed onset of a subcutaneous insulin regimen may lead to worsened control; therefore, some overlap should occur in intravenous insulin therapy and initiation of the subcutaneous insulin regimen. When the patient is able to eat, a multiple daily injection schedule should be established that uses a combination of regular (short-acting) and intermediate or long-acting insulin as needed to control plasma glucose. Patients with known diabetes may be given insulin at the dose they were receiving before the onset of DKA and further adjusted using a multiple daily injection regimen. In patients with newly diagnosed diabetes, the initial total insulin dose should be ~0.6  $\text{U} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , divided into at least three doses in a mixed regimen including short- and long-acting insulin, until an optimal dose is established.

Although serum  $\beta$ -hydroxybutyrate levels are usually <1.5 mmol/l at resolution of DKA, we do not recommend routine measurement of ketone levels during therapy. However, in some patients with prolonged metabolic acidosis, combined diabetic and lactic acidosis, or other mixed acid-base disorders, direct measurement of  $\beta$ -hydroxybutyrate levels may be helpful. During treatment of DKA, use of the nitroprusside test, which measures acetoacetate and acetone levels but not  $\beta$ -hydroxybutyrate, should be avoided because the fall in acetone and acetoacetate lags behind the resolution of DKA (6).

## COMPLICATIONS OF THERAPY

### Hypoglycemia and hypokalemia

Before the advent of low-dose insulin protocols (193), these two complications were



seen in as many as 25% of patients treated with large doses of insulin (122). Both complications were significantly reduced with lower-dose therapy (122). In spite of this, hypoglycemia still constitutes one of the potential complications of therapy, the incidence of which may be underreported (194). The use of dextrose-containing solutions when blood glucose reaches 250 mg/dl in DKA and a simultaneous reduction in the rate of insulin delivery should further reduce the incidence of hypoglycemia. Similarly, the addition of potassium to the hydrating solution and frequent monitoring of serum potassium during the early phases of DKA and HHS therapy should reduce the incidence of hypokalemia.

### Cerebral edema

An asymptomatic increase in CSF pressure during treatment of DKA has been recognized for >25 years (195–197). Significant decreases in the size of the lateral ventricles, as determined by echoencephalogram, were noted in 9 out of 11 DKA patients during therapy (198,199). However, in another study, nine children in DKA were compared with regard to brain swelling before and after therapy, and it was concluded that brain swelling is usually present in DKA before treatment is begun (200). Symptomatic cerebral edema, which is extremely rare in adult HHS or DKA patients, has been reported to occur primarily in pediatric patients, particularly in those with newly diagnosed diabetes. No single factor has been identified that can be used to predict the development of cerebral edema (201,202). Lowering blood glucose in patients with HHS at a rate of 50–70 mg · dl<sup>-1</sup> · h<sup>-1</sup> and adding 5% dextrose to the hydrating solution when blood glucose is ~300 mg/dl are prudent until more knowledge on the mechanism of cerebral edema is obtained (203,204). A 20-year review of cerebral edema in children with DKA from the Royal Children's Hospital in Melbourne, Australia, concluded that although no predictive factors for survival of cerebral edema were identified, protocols that use slow rates of rehydration with isotonic fluids should be recommended (205).

Several other reviews have found a correlation between the development of cerebral edema and higher rates of fluid administration, especially in the first hours of fluid resuscitation. The most current recommendation is to limit fluid administration in the first 4 h of therapy to <50 ml/kg isotonic solution (206,207).

### Adult respiratory distress syndrome

A rare but potentially fatal complication of therapy is adult respiratory distress syndrome (ARDS) (208). During rehydration with fluid and electrolytes, an initially elevated colloid osmotic pressure is reduced to subnormal levels. This change is accompanied by a progressive decrease in arteriolar partial pressure of oxygen (PaO<sub>2</sub>) and an increase in alveolar-to-arteriolar oxygen (AaO<sub>2</sub>) gradient, which is usually normal at presentation in DKA (19,175,198). In a small subset of patients, this may progress to ARDS. By increasing left atrial pressure and decreasing colloid osmotic pressure, excessive crystalloid infusion favors edema formation in the lungs (even in the presence of normal cardiac function). Patients with an increased AaO<sub>2</sub> gradient or those who have pulmonary rales on physical examination may be at an increased risk for development of this syndrome. Monitoring of PaO<sub>2</sub> with pulse oximetry and monitoring of AaO<sub>2</sub> gradient may assist in the management of such patients. Because crystalloid infusion may be the major factor, we advise that such patients have lower fluid intake, with addition of colloid administration for treatment of hypotension unresponsive to crystalloid replacement.

### Hyperchloremic metabolic acidosis

Hyperchloremic normal anion gap metabolic acidosis is present in ~10% of patients admitted with DKA; however, it is almost uniformly present after resolution of ketonemia (105,209,210). This acidosis has no adverse clinical effects and is gradually corrected over the subsequent 24–48 h by enhanced renal acid excretion. The severity of hyperchloremia can be exaggerated by excessive chloride administration (211) because 0.9% NaCl contains 154 mmol/l of both sodium and chloride, which is 54 mmol/l in excess of the 100 mmol/l of chloride in serum. Further causes of non-anion gap hyperchloremic acidosis include 1) loss of potential bicarbonate due to excretion of ketoanions as sodium and potassium salts; 2) decreased availability of bicarbonate in proximal tubule, leading to greater chloride reabsorption; and 3) reduction of bicarbonate and other buffering capacity in other body compartments. In general, hyperchloremic metabolic acidosis is self-limiting with reduction of chloride load and judicious use of hydration solution (212,213). Serum bicarbonate that does not normalize with other metabolic parameters should alert

the clinician to the need for more aggressive insulin therapy or further investigation.

### RESOURCE UTILIZATION IN DKA

— The process of health care reform demands cost-efficient modes of delivering optimal care. The choice of management site (intensive care unit, step-down unit, or general medical ward) therefore becomes a critical issue. Unfortunately, there are no randomized prospective studies that have evaluated the optimal site of care for either DKA or HHS. Given the lack of such studies, the decision concerning the site of care must be based on known clinical prognostic indicators and on the availability of hospital resources.

Recent studies that have emphasized the use of standardized written guidelines for therapy have demonstrated mortality rates <5% in DKA and ~15% in HHS (6,9,10,12–16,214). The majority of deaths have occurred in patients >50 years of age because of concomitant life-threatening illnesses, suggesting that further major decreases in mortality rates may not be attainable based on treatment of DKA alone (9). As stated earlier, similar outcomes of treatment of DKA have been noted in both community and training hospitals, and outcomes have not been altered by whether the managing physician is a family physician, a general internist, a house officer with attending supervision, or an endocrinologist (14–16), so long as standard written therapeutic guidelines are followed.

The response to initial therapy, which would preferably be in the emergency ward, can be used as a guideline for choosing the most appropriate hospital site for further care. All patients with hypotension or oliguria refractory to initial rehydration and those patients with mental obtundation or coma with hyperosmolality (effective osmolality >320 mOsm/kg H<sub>2</sub>O) should be considered for admission to step-down or intensive care units in order to receive continuous intravenous insulin therapy. In the absence of indications for hemodynamic monitoring, the majority of such patients can be managed in less expensive step-down units rather than intensive care units after the initial emergency room evaluation and care (19,215).

Options of site of care for DKA patients with less mental obtundation and no hypotension following initial rehydration are based primarily on the availability of hospital resources. Those patients who are mildly ketotic can be effectively man-

aged on a general medical ward, assuming there are 1) sufficient nursing staff to allow frequent monitoring of vital signs and hourly administration of subcutaneous insulin and 2) on-site blood glucose monitoring equipment and rapid turn-around time for routine laboratory services. Continuous intravenous insulin therapy is not generally recommended for use in general medical wards unless appropriately trained personnel are available. DKA patients with a mild condition who are alert and able to tolerate oral intake may be treated in the emergency room and observed for a few hours before discharge.

Given the known high mortality rate of HHS, the frequent presence of serious concomitant illnesses, and the usually advanced age of HHS patients, it is reasonable that all such patients be admitted to either step-down or intensive care units.

**PREVENTION** — The two major precipitating factors in the development of DKA are inadequate insulin treatment (including noncompliance) and infection. In many cases, these events may be prevented by better access to medical care, including intensive patient education and effective communication with a health care provider during acute illnesses.

Goals in the prevention of hyperglycemic crises precipitated by either acute illness or stress have been outlined (216). These goals included controlling insulin deficiency, decreasing excess stress hormone secretion, avoiding prolonged fasting state, and preventing severe dehydration. Therefore, an educational program should review sick-day management with specific information on administration of short-acting insulin, including frequency of insulin administration, blood glucose goals during illness, means to suppress fever and treat infection, and initiation of an easily digestible liquid diet containing carbohydrates and salt. Most importantly, the patient should never discontinue insulin and should solicit professional advice early in the course of the illness.

Success with such a program depends on frequent interaction between the patient and the health care provider and on the level of involvement that the patient or family member is willing to take to avoid hospitalization. The patient/family must be willing to keep an accurate record of blood glucose, urine ketones, insulin administration, temperature, respiratory and pulse rate, and body weight. Indicators for hospi-

talization include >5% loss of body weight, respiratory rate >36/min, intractable elevations in blood glucose, mental status change, uncontrolled fever, and unresolved nausea and vomiting. A group of investigators reported on the successful prevention of recurrent DKA (RDKA) in a pediatric population with the introduction of a hierarchical set of medical, educational, and psychosocial interventions in a lower socioeconomic group (217). Insulin omission was documented in 31 out of 44 patients (70%) with a history of RDKA and in 13 of the 44 with inadequate education (30%). After initiation of the program, the episodes of RDKA were reduced to 2.6 episodes per 100 patient-months, compared with the initial number of 25.2 episodes before the program ( $P < 0.0001$ ). RDKA ceased with or without psychotherapy. The authors concluded that RDKA is causally related to a variety of social and economic problems, but its prevention requires recognition that its proximate cause in certain groups is omission of insulin. There is therefore a need for a support system to ensure adherence (217). In addition, an education program directed toward pediatricians and school educators that promoted the signs and symptoms of diabetes was shown to be effective in decreasing ketoacidosis at the onset of diabetes (218).

As previously mentioned, many of the admissions for HHS are nursing home residents or elderly individuals who become dehydrated and are unaware or unable to treat the increasingly dehydrated state. Better education of care givers as well as patients regarding conditions, procedures, and medications that may worsen diabetes control, use of glucose monitoring, and signs and symptoms of newly onset diabetes could potentially decrease the incidence and severity of HHS.

Beyond the educational issues, recent reports on DKA in urban African-American type 1 diabetic patients showed that the major precipitating cause of DKA was discontinuance of insulin (67%). Reasons for stopping insulin included economic reasons (50%), lack of appetite (21%), behavioral reasons (14%), or lack of knowledge about how to manage sick days (14%) (26). Because the most common reason for interrupted insulin is economic in nature, changes in the health care delivery system and in the access patients have to care and medications may be the most effective means of preventing DKA in this population. The investigators showed that of 56

DKA admissions, only two patients tried to contact the diabetes unit for assistance (26). Similarly, a study of hyperglycemic crises in an urban black population demonstrated that socioeconomic barriers, such as a low literacy rate, limited financial resources, and limited access to health care, might explain the continuing high rates of admission for DKA in this group of patients (5).

Hospitalizations for DKA in the past two decades have increased in some areas and declined in others (3). Because repeated admissions for DKA are estimated to drain approximately one out of every two health care dollars spent on adult patients with type 1 diabetes, resources need to be redirected toward prevention by funding better access to care and educational programs that address a variety of ethnicity-related health care beliefs.

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