Hyperglycemic Crises in Adult Patients With Diabetes

Abbas E. Kitabchi, phd, md[1]
Guillermo E. Umpierrez, md[2]
John M. Miles, md[3]
Joseph N. Fisher, md[1]

Diabetic ketoacidosis (DKA) and the hyperosmolar hyperglycemic state (HHS) are the two most serious acute metabolic complications of diabetes. DKA is responsible for more than 500,000 hospital days per year (1,2) at an estimated annual direct medical expense and indirect cost of 2.4 billion USD (2,3). Table 1 outlines the diagnostic criteria for DKA and HHS. The triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration characterizes DKA. HHS is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis. These metabolic derangements result from the combination of absolute or relative insulin deficiency and an increase in counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). Most patients with DKA have autoimmune type 1 diabetes; however, patients with type 2 diabetes are also at risk during the catabolic stress of acute illness such as trauma, surgery, or infections. This consensus statement will outline precipitating factors and recommendations for the diagnosis, treatment, and prevention of DKA and HHS in adult subjects. It is based on a previous technical review (4) and more recently published peer-reviewed articles since 2001, which should be consulted for further information.

EPIDEMIOLOGY — Recent epidemiological studies indicate that hospitalizations for DKA in the U.S. are increasing. In the decade from 1996 to 2006, there was a 35% increase in the number of cases, with a total of 136,510 cases with a primary diagnosis of DKA in 2006—a rate of increase perhaps more rapid than the overall increase in the diagnosis of diabetes (1). Most patients with DKA were between the ages of 18 and 44 years (56%) and 45 and 65 years (24%), with only 18% of patients <20 years of age. Two-thirds of DKA patients were considered to have type 1 diabetes and 34% to have type 2 diabetes; 50% were female, and 45% were nonwhite. DKA is the most common cause of death in children and adolescents with type 1 diabetes and accounts for half of all deaths in diabetic patients younger than 24 years of age (5,6). In adult subjects with DKA, the overall mortality is <1% (1); however, a mortality rate >5% has been reported in the elderly and in patients with concomitant life-threatening illnesses (7,8). Death in these conditions is rarely due to the metabolic complications of hyperglycemia or ketoacidosis but relates to the underlying precipitating illness (4,9). Mortality attributed to HHS is considerably higher than that attributed to DKA, with recent mortality rates of 5–20% (10,11). The prognosis of both conditions is substantially worsened at the extremes of age in the presence of coma, hypotension, and severe comorbidities (1,4,8, 12,13).

PATHOGENESIS — The events leading to hyperglycemia and ketoacidosis are depicted in Fig. 1 (13). In DKA, reduced effective insulin concentrations and increased concentrations of counterregulatory hormones (catecholamines, cortisol, glucagon, and growth hormone) lead to hyperglycemia and ketosis. Hyperglycemia develops as a result of three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues (12–17). This is magnified by transient insulin resistance due to the hormone imbalance itself as well as the elevated free fatty acid concentrations (4,18). The combination of insulin deficiency and increased counterregulatory hormones in DKA also leads to the release of free fatty acids into the circulation from adipose tissue (lipolysis) and to unrestrained hepatic fatty acid oxidation in the liver to ketone bodies (β-hydroxybutyrate and acetoacetate) (19), with resulting ketonemia and metabolic acidosis.

Increasing evidence indicates that the hyperglycemia in patients with hyperglycemic crises is associated with a severe inflammatory state characterized by an elevation of proinflammatory cytokines (tumor necrosis factor-α and interleukin-β, -6, and -8), C-reactive protein, reactive oxygen species, and lipid peroxidation, as well as cardiovascular risk factors, plasminogen activator inhibitor-1 and free fatty acids in the absence of obvious infection or cardiovascular pathology (20). All of these parameters return to near-normal values with insulin therapy and hydration within 24 h. The procoagulant and inflammatory states may be due to nonspecific phenomena of stress and may partially explain the association of hyperglycemic crises with a hypercoagulable state (21).

The pathogenesis of HHS is not as well understood as that of DKA, but a greater degree of dehydration (due to osmotic diuresis) and differences in insulin availability distinguish it from DKA (4,22). Although relative insulin deficiency is clearly present in HHS, endogenous insulin secretion (reflected by C-peptide levels) appears to be greater than in DKA, where it is negligible (Table 2). Insulin levels in HHS are inadequate to facilitate glucose utilization by insulin-sensitive tissues but adequate to prevent lipolysis and subsequent ketogenesis (12).

PRECIPITATING FACTORS — The most common precipitating factor in the development of DKA and HHS is infection (1,4,10). Other precipitating factors include discontinuation of or inadequate insulin therapy, pancreatitis, myocardial infarction, cerebrovascular accident, and

From the [1]Division of Endocrinology, Diabetes and Metabolism, the Department of Medicine, the University of Tennessee Health Science Center, Memphis, Tennessee; the [2]Emory University School of Medicine, Atlanta, Georgia; and [3]Mayo Clinic, Rochester, Minnesota.
Corresponding author: Abbas E. Kitabchi, akitabchi@utmem.edu.

DOI: 10.2337/dc09-9032

Table 1—*Diagnostic criteria for DKA and HHS*

	DKA			HHS
	Mild (plasma glucose >250 mg/dl)	Moderate (plasma glucose >250 mg/dl)	Severe (plasma glucose >250 mg/dl)	Plasma glucose >600 mg/dl
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00	>7.30
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10	>18
Urine ketone*	Positive	Positive	Positive	Small
Serum ketone*	Positive	Positive	Positive	Small
Effective serum osmolality†	Variable	Variable	Variable	>320 mOsm/kg
Anion gap‡	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Nitroprusside reaction method. †Effective serum osmolality: 2[measured Na^+ (mEq/l)] + glucose (mg/dl)/18. ‡Anion gap: $(Na^+) - [(Cl^- + HCO_3^-$ (mEq/l)]. (Data adapted from ref. 13.)

drugs (10,13,14). In addition, new-onset type 1 diabetes or discontinuation of insulin in established type 1 diabetes commonly leads to the development of DKA. In young patients with type 1 diabetes, psychological problems complicated by eating disorders may be a contributing factor in 20% of recurrent ketoacidosis. Factors that may lead to insulin omission in younger patients include fear of weight gain with improved metabolic control, fear of hypoglycemia, rebellion against authority, and stress of chronic disease.

Before 1993, the use of continuous subcutaneous insulin infusion devices had also been associated with an increased frequency of DKA (23); however, with improvement in technology and better education of patients, the incidence of DKA appears to have reduced in pump users. However, additional prospective studies are needed to document reduction of DKA incidence with the use of continuous subcutaneous insulin infusion devices (24).

Underlying medical illness that provokes the release of counterregulatory hormones or compromises the access to water is likely to result in severe dehydration and HHS. In most patients with HHS, restricted water intake is due to the patient being bedridden and is exacerbated by the altered thirst response of the elderly. Because 20% of these patients have no history of diabetes, delayed recognition of hyperglycemic symptoms may have led to severe dehydration. Elderly individuals with new-onset diabetes (particularly residents of chronic care facilities) or individuals with known diabetes who become hyperglycemic and are unaware of it or are unable to take fluids when necessary are at risk for HHS (10,25).

Drugs that affect carbohydrate metabolism, such as corticosteroids, thiazides, sympathomimetic agents, and pentamidine, may precipitate the development of HHS or DKA (4). Recently, a number of case reports indicate that the conventional antipsychotic as well as atypical antipsychotic drugs may cause hyperglycemia and even DKA or HHS (26,27). Possible mechanisms include the induction of peripheral insulin resistance and the direct influence on pancreatic β-cell function by 5-HT1A/2A/2C receptor antagonism, by inhibitory effects via α2-adrenergic receptors, or by toxic effects (28).

An increasing number of DKA cases without precipitating cause have been reported in children, adolescents, and adult subjects with type 2 diabetes. Observational and prospective studies indicate that over half of newly diagnosed adult African American and Hispanic subjects with unprovoked DKA have type 2 diabetes (28–32). The clinical presentation in such cases is acute (as in classical type 1 diabetes); however, after a short period of insulin therapy, prolonged remission is often possible, with eventual cessation of insulin treatment and maintenance of glycemic control with diet or oral antihyperglycemic agents. In such patients, clinical and metabolic features of type 2 diabetes include a high rate of obesity, a strong family history of diabetes, a measurable pancreatic insulin reserve, a low prevalence of autoimmune markers of β-cell destruction, and the ability to discontinue insulin therapy during follow-up (28, 31,32). This unique, transient insulin-requiring profile after DKA has been rec-

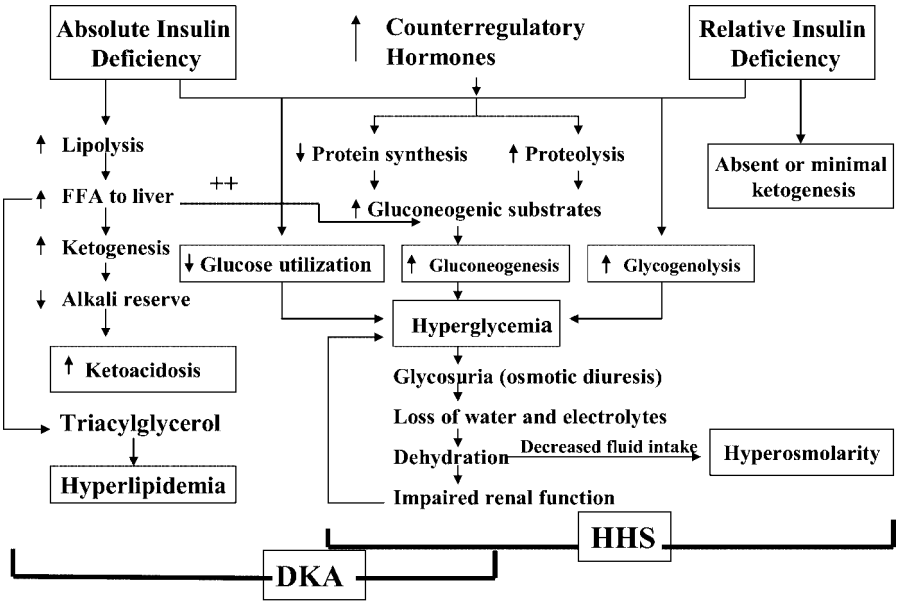


Figure 1—*Pathogenesis of DKA and HHS: stress, infection, or insufficient insulin. FFA, free fatty acid.*

Table 2—*Admission biochemical data in patients with HHS or DKA*

	HHS	DKA
Glucose (mg/dl)	930 ± 83	616 ± 36
Na^+ (mEq/l)	149 ± 3.2	134 ± 1.0
K^+ (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
Free fatty acids (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 (ng/ml)	689 ± 215	580 ± 147
Catacholamines (ng/ml)	0.28 ± 0.09	1.78 ± 0.4
Growth hormone (ng/ml)	1.1	7.9
ΔGap: anion gap − 12 (mEq/l)	11	17

*According to the formula 2(Na + K) + urea (mmol/l) + glucose (mmol/l). †Values following intravenous administration of tolbutamide. IRI, immunoreactive insulin. (Adapted from ref. 4.)

ognized mainly in blacks and Hispanics but has also been reported in Native American, Asian, and white populations (32). This variant of diabetes has been referred to in the literature as idiopathic type 1 diabetes, atypical diabetes, "Flatbush diabetes," type 1.5 diabetes, and more recently, ketosis-prone type 2 diabetes. Some experimental work has shed a mechanistic light on the pathogenesis of ketosis-prone type 2 diabetes. At presentation, they have markedly impaired insulin secretion and insulin action, but aggressive management with insulin improves insulin secretion and action to levels similar to those of patients with type 2 diabetes without DKA (28,31,32). Recently, it has been reported that the near-normoglycemic remission is associated with a greater recovery of basal and stimulated insulin secretion and that 10 years after diabetes onset, 40% of patients are still non–insulin dependent (31). Fasting C-peptide levels of >1.0 ng/dl (0.33 nmol/l) and stimulated C-peptide levels >1.5 ng/dl (0.5 nmol/l) are predictive of long-term normoglycemic remission in patients with a history of DKA (28,32).

DIAGNOSIS

History and physical examination

The process of HHS usually evolves over several days to weeks, whereas the evolution of the acute DKA episode in type 1 diabetes or even in type 2 diabetes tends to be much shorter. Although the symptoms of poorly controlled diabetes may be present for several days, the metabolic alterations typical of ketoacidosis usually evolve within a short time frame (typically <24 h). Occasionally, the entire symptomatic presentation may evolve or develop more acutely, and the patient may present with DKA with no prior clues or symptoms. For both DKA and HHS, the classical clinical picture includes a history of polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and mental status change. Physical findings may include poor skin turgor, Kussmaul respirations (in DKA), tachycardia, and hypotension. Mental status can vary from full alertness to profound lethargy or coma, with the latter more frequent in HHS. Focal neurologic signs (hemianopia and hemiparesis) and seizures (focal or generalized) may also be features of HHS (4,10). Although infection is a common precipitating factor for both DKA and HHS, patients can be normothermic or even hypothermic primarily because of peripheral vasodilation. Severe hypothermia, if present, is a poor prognostic sign (33). Nausea, vomiting, diffuse abdominal pain are frequent in patients with DKA (>50%) but are uncommon in HHS (33). Caution needs to be taken with patients who complain of abdominal pain on presentation because the symptoms could be either a result of the DKA or an indication of a precipitating cause of DKA, particularly in younger patients or in the absence of severe metabolic acidosis (34,35). Further evaluation is necessary if this complaint does not resolve with resolution of dehydration and metabolic acidosis.

Laboratory findings

The diagnostic criteria for DKA and HHS are shown in Table 1. The initial laboratory evaluation of patients include determination of plasma glucose, blood urea nitrogen, creatinine, electrolytes (with calculated anion gap), osmolality, serum and urinary ketones, and urinalysis, as well as initial arterial blood gases and a complete blood count with a differential. An electrocardiogram, chest X-ray, and urine, sputum, or blood cultures should also be obtained.

The severity of DKA is classified as mild, moderate, or severe based on the severity of metabolic acidosis (blood pH, bicarbonate, and ketones) and the presence of altered mental status (4). Significant overlap between DKA and HHS has been reported in more than one-third of patients (36). Although most patients with HHS have an admission pH >7.30 and a bicarbonate level >18 mEq/l, mild ketonemia may be present (4,10).

Severe hyperglycemia and dehydration with altered mental status in the absence of significant acidosis characterize HHS, which clinically presents with less ketosis and greater hyperglycemia than DKA. This may result from a plasma insulin concentration (as determined by baseline and stimulated C-peptide [Table 2]) adequate to prevent excessive lipolysis and subsequent ketogenesis but not hyperglycemia (4).

The key diagnostic feature in DKA is the elevation in circulating total blood ketone concentration. Assessment of augmented ketonemia is usually performed by the nitroprusside reaction, which provides a semiquantitative estimation of acetoacetate and acetone levels. Although the nitroprusside test (both in urine and in serum) is highly sensitive, it can underestimate the severity of ketoacidosis because this assay does not recognize the presence of β-hydroxybutyrate, the main metabolic product in ketoacidosis (4,12). If available, measurement of serum β-hydroxybutyrate may be useful for diagnosis (37). Accumulation of ketoacids results in an increased anion gap meta-

bolic acidosis. The anion gap is calculated by subtracting the sum of chloride and bicarbonate concentration from the sodium concentration: [Na − (Cl + HCO_3)]. A normal anion gap is between 7 and 9 mEq/l and an anion gap >10–12 mEq/l indicate the presence of increased anion gap metabolic acidosis (4).

Hyperglycemia is a key diagnostic criterion of DKA; however, a wide range of plasma glucose can be present on admission. Elegant studies on hepatic glucose production rates have reported rates ranging from normal or near normal (38) to elevated (12,15), possibly contributing to the wide range of plasma glucose levels in DKA that are independent of the severity of ketoacidosis (37). Approximately 10% of the DKA population presents with so-called "euglycemic DKA"—glucose levels ≤250 mg/dl (38). This could be due to a combination of factors, including exogenous insulin injection en route to the hospital, antecedent food restriction (39, 40), and inhibition of gluconeogenesis.

On admission, leukocytosis with cell counts in the 10,000–15,000 mm^3 range is the rule in DKA and may not be indicative of an infectious process. However, leukocytosis with cell counts >25,000 mm^3 may designate infection and require further evaluation (41). In ketoacidosis, leukocytosis is attributed to stress and maybe correlated to elevated levels of cortisol and norepinephrine (42). The admission serum sodium is usually low because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia. An increased or even normal serum sodium concentration in the presence of hyperglycemia indicates a rather profound degree of free water loss. To assess the severity of sodium and water deficit, serum sodium may be corrected by adding 1.6 mg/dl to the measured serum sodium for each 100 mg/dl of glucose above 100 mg/dl (4,12).

Studies on serum osmolality and mental alteration have established a positive linear relationship between osmolality and mental obtundation (9,36). The occurrence of stupor or coma in a diabetic patient in the absence of definitive elevation of effective osmolality (≥320 mOsm/kg) demands immediate consideration of other causes of mental status change. In the calculation of effective osmolality, [sodium ion (mEq/l) × 2 + glucose (mg/dl)/18], the urea concentration is not taken into account because it is freely permeable and its accumulation does not induce major changes in intracellular volume or osmotic gradient across the cell membrane (4).

Serum potassium concentration may be elevated because of an extracellular shift of potassium caused by insulin deficiency, hypertonicity, and acidemia (43). Patients with low normal or low serum potassium concentration on admission have severe total-body potassium deficiency and require careful cardiac monitoring and more vigorous potassium replacement because treatment lowers potassium further and can provoke cardiac dysrhythmia. Pseudonormoglycemia (44) and pseudohyponatremia (45) may occur in DKA in the presence of severe chylomicronemia.

The admission serum phosphate level in patients with DKA, like serum potassium, is usually elevated and does not reflect an actual body deficit that uniformly exists due to shifts of intracellular phosphate to the extracellular space (12, 46,47). Insulin deficiency, hypertonicity, and increased catabolism all contribute to the movement of phosphate out of cells.

Hyperamylasemia has been reported in 21–79% of patients with DKA (48); however, there is little correlation between the presence, degree, or isoenzyme type of hyperamylasemia and the presence of gastrointestinal symptoms (nausea, vomiting, and abdominal pain) or pancreatic imaging studies (48). A serum lipase determination may be beneficial in the differential diagnosis of pancreatitis; however, lipase could also be elevated in DKA in the absence of pancreatitis (48).

Differential diagnosis

Not all patients with ketoacidosis have DKA. Starvation ketosis and alcoholic ketoacidosis are distinguished by clinical history and by plasma glucose concentrations that range from mildly elevated (rarely >200 mg/dl) to hypoglycemia (49). In addition, although alcoholic ketoacidosis can result in profound acidosis, the serum bicarbonate concentration in starvation ketosis is usually not <18 mEq/l. DKA must also be distinguished from other causes of high–anion gap metabolic acidosis, including lactic acidosis; ingestion of drugs such as salicylate, methanol, ethylene glycol, and paraldehyde; and acute chronic renal failure (4). Because lactic acidosis is more common in patients with diabetes than in nondiabetic persons and because elevated lactic acid levels may occur in severely volume-contracted patients, plasma lactate should be measured on admission.

A clinical history of previous drug abuse should be sought. Measurement of serum salicylate and blood methanol level may be helpful. Ethylene glycol (antifreeze) is suggested by the presence of calcium oxalate and hippurate crystals in the urine. Paraldehyde ingestion is indicated by its characteristic strong odor on the breath. Because these intoxicants are low–molecular weight organic compounds, they can produce an osmolar gap in addition to the anion gap acidosis (14). A recent report states that active cocaine use is an independent risk factor for recurrent DKA (50).

Recently, one case report has shown that a patient with diagnosed acromegaly may present with DKA as the primary manifestation of the disease (51). In addition, an earlier report of pituitary gigantism was presented with two episodes of DKA with complete resolution of diabetes after pituitary apoplexy (52).

TREATMENT— Successful treatment of DKA and HHS requires correction of dehydration, hyperglycemia, and electrolyte imbalances; identification of comorbid precipitating events; and above all, frequent patient monitoring. Protocols for the management of patients with DKA and HHS are summarized in Fig. 2 (52).

Fluid therapy

Initial fluid therapy is directed toward expansion of the intravascular, interstitial, and intracellular volume, all of which are reduced in hyperglycemic crises (53) and restoration of renal perfusion. In the absence of cardiac compromise, isotonic saline (0.9% NaCl) is infused at a rate of 15–20 ml · kg body wt^{-1} · h^{-1} or 1–1.5 l during the first hour. Subsequent choice for fluid replacement depends on hemodynamics, the state of hydration, serum electrolyte levels, and urinary output. In general, 0.45% NaCl infused at 250–500 ml/h is appropriate if the corrected serum sodium is normal or elevated; 0.9% NaCl at a similar rate is appropriate if corrected serum sodium is low (Fig. 2). Successful progress with fluid replacement is judged by hemodynamic monitoring (improvement in blood pressure), measurement of fluid input/output, laboratory values, and clinical examination. Fluid replacement should correct estimated deficits within the first 24 h. In patients with renal or cardiac compromise, monitoring of serum osmolality and frequent assessment

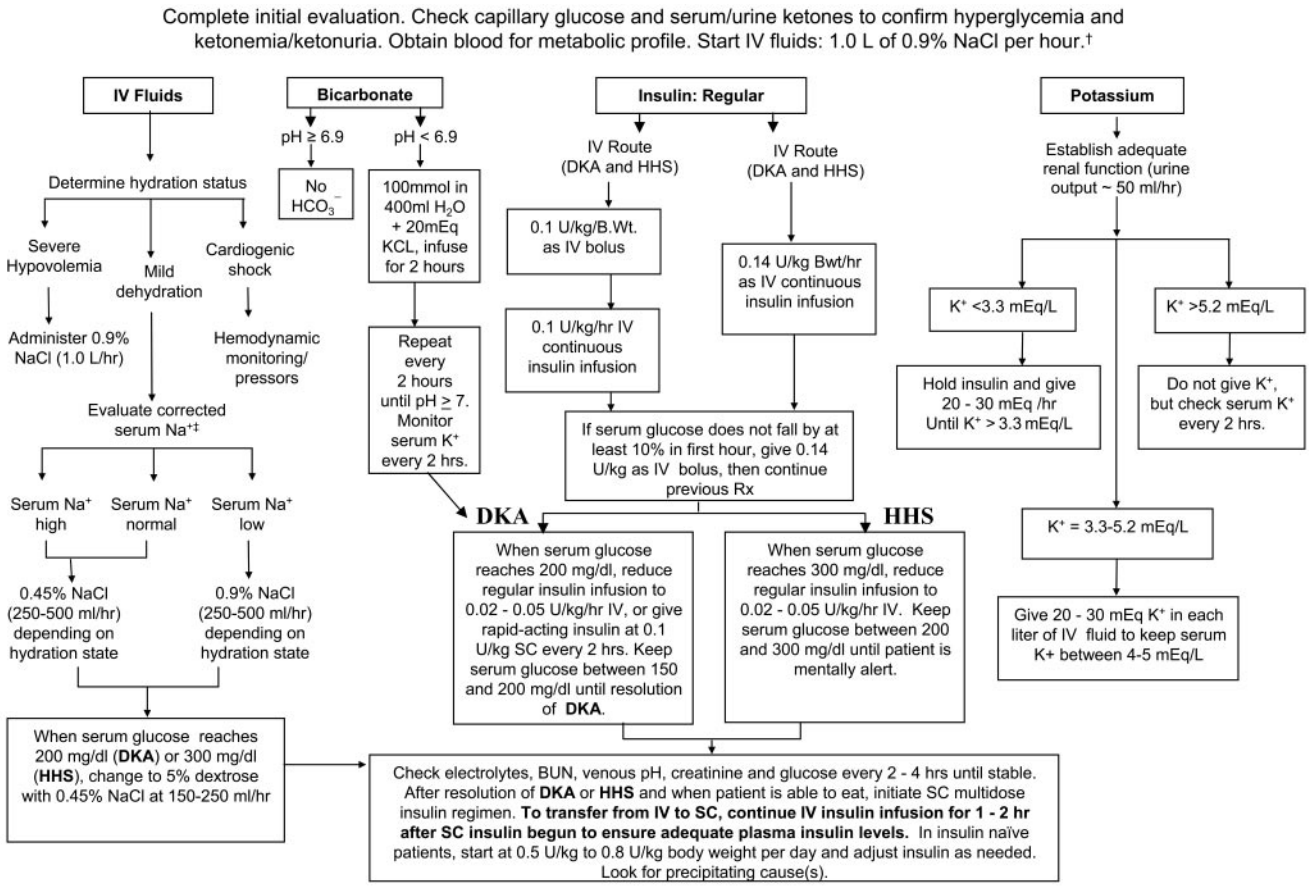


Figure 2—*Protocol for management of adult patients with DKA or HHS. DKA diagnostic criteria: blood glucose 250 mg/dl, arterial pH 7.3, bicarbonate 15 mEq/l, and moderate ketonuria or ketonemia. HHS diagnostic criteria: serum glucose >600 mg/dl, arterial pH >7.3, serum bicarbonate >15 mEq/l, and minimal ketonuria and ketonemia. †15–20 ml/kg/h; ‡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). (Adapted from ref. 13.) Bwt, body weight; IV, intravenous; SC, subcutaneous.*

of cardiac, renal, and mental status must be performed during fluid resuscitation to avoid iatrogenic fluid overload (4,10, 15,53). Aggressive rehydration with subsequent correction of the hyperosmolar state has been shown to result in a more robust response to low-dose insulin therapy (54).

During treatment of DKA, hyperglycemia is corrected faster than ketoacidosis. The mean duration of treatment until blood glucose is <250 mg/dl and ketoacidosis (pH >7.30; bicarbonate >18 mmol/l) is corrected is 6 and 12 h, respectively (9,55). Once the plasma glucose is ~ 200 mg/dl, 5% dextrose should be added to replacement fluids to allow continued insulin administration until ketonemia is controlled while at the same time avoiding hypoglycemia.

Insulin therapy

The mainstay in the treatment of DKA involves the administration of regular insulin via continuous intravenous infusion or by frequent subcutaneous or intramuscular injections (4,56,57). Randomized controlled studies in patients with DKA have shown that insulin therapy is effective regardless of the route of administration (47). The administration of continuous intravenous infusion of regular insulin is the preferred route because of its short half-life and easy titration and the delayed onset of action and prolonged half-life of subcutaneous regular insulin (36,47,58).

Numerous prospective randomized studies have demonstrated that use of low-dose regular insulin by intravenous infusion is sufficient for successful recovery of patients with DKA. Until recently, treatment algorithms recommended the administration of an initial intravenous dose of regular insulin (0.1 units/kg) followed by the infusion of 0.1 units $\cdot kg^{-1} \cdot h^{-1}$ insulin (Fig. 2). A recent prospective randomized study reported that a bolus dose of insulin is not necessary if patients receive an hourly insulin infusion of 0.14 units/kg body wt (equivalent to 10 units/h in a 70-kg patient) (59). In the absence of an initial bolus, however, doses <0.1 units $\cdot kg^{-1} \cdot h^{-1}$ resulted in a lower insulin concentration, which may not be adequate to suppress hepatic ketone body production without supplemental doses of insulin (15).

Low-dose insulin infusion protocols decrease plasma glucose concentration at a rate of 50–75 mg $\cdot dl^{-1} \cdot h^{-1}$. If plasma glucose does not decrease by 50–75 mg from the initial value in the first hour, the insulin infusion should be increased every hour until a steady glucose decline is achieved (Fig. 2). When the plasma glucose reaches 200 mg/dl in DKA or 300 mg/dl in HHS, it may be possible to decrease the insulin infusion rate to 0.02–0.05 units $\cdot kg^{-1} \cdot h^{-1}$, at which time dextrose may be added to the intravenous fluids (Fig. 2). Thereafter, the rate of in-

sulin administration or the concentration of dextrose may need to be adjusted to maintain glucose values between 150 and 200 mg/dl in DKA or 250 and 300 mg/dl in HHS until they are resolved.

Treatment with subcutaneous rapid-acting insulin analogs (lispro and aspart) has been shown to be an effective alternative to the use of intravenous regular insulin in the treatment of DKA. Treatment of patients with mild and moderate DKA with subcutaneous rapid-acting insulin analogs every 1 or 2 h in non–intensive care unit (ICU) settings has been shown to be as safe and effective as the treatment with intravenous regular insulin in the ICU (60,61). The rate of decline of blood glucose concentration and the mean duration of treatment until correction of ketoacidosis were similar among patients treated with subcutaneous insulin analogs every 1 or 2 h or with intravenous regular insulin. However, until these studies are confirmed outside the research arena, patients with severe DKA, hypotension, anasarca, or associated severe critical illness should be managed with intravenous regular insulin in the ICU.

Potassium

Despite total-body potassium depletion, mild-to-moderate hyperkalemia is common in patients with hyperglycemic crises. Insulin therapy, correction of acidosis, and volume expansion decrease serum potassium concentration. To prevent hypokalemia, potassium replacement is initiated after serum levels fall below the upper level of normal for the particular laboratory (5.0–5.2 mEq/l). The treatment goal is to maintain serum potassium levels within the normal range of 4–5 mEq/l. Generally, 20–30 mEq potassium in each liter of infusion fluid is sufficient to maintain a serum potassium concentration within the normal range. Rarely, DKA patients may present with significant hypokalemia. In such cases, potassium replacement should begin with fluid therapy, and insulin treatment should be delayed until potassium concentration is restored to >3.3 mEq/l to avoid life-threatening arrhythmias and respiratory muscle weakness (4,13).

Bicarbonate therapy

The use of bicarbonate in DKA is controversial (62) because most experts believe that during the treatment, as ketone bodies decrease there will be adequate bicarbonate except in severely acidotic patients. Severe metabolic acidosis can lead to impaired myocardial contractility, cerebral vasodilatation and coma, and several gastrointestinal complications (63). A prospective randomized study in 21 patients failed to show either beneficial or deleterious changes in morbidity or mortality with bicarbonate therapy in DKA patients with an admission arterial pH between 6.9 and 7.1 (64). Nine small studies in a total of 434 patients with diabetic ketoacidosis (217 treated with bicarbonate and 178 patients without alkali therapy [62]) support the notion that bicarbonate therapy for DKA offers no advantage in improving cardiac or neurologic functions or in the rate of recovery of hyperglycemia and ketoacidosis. Moreover, several deleterious effects of bicarbonate therapy have been reported, such as increased risk of hypokalemia, decreased tissue oxygen uptake (65), cerebral edema (65), and development of paradoxical central nervous system acidosis.

No prospective randomized studies concerning the use of bicarbonate in DKA with pH values <6.9 have been reported (66). Because severe acidosis may lead to a numerous adverse vascular effects (63), it is recommended that adult patients with a pH <6.9 should receive 100 mmol sodium bicarbonate (two ampules) in 400 ml sterile water (an isotonic solution) with 20 mEq KCl administered at a rate of 200 ml/h for 2 h until the venous pH is >7.0. If the pH is still <7.0 after this is infused, we recommend repeating infusion every 2 h until pH reaches >7.0 (Fig. 2).

Phosphate

Despite whole-body phosphate deficits in DKA that average 1.0 mmol/kg body wt, serum phosphate is often normal or increased at presentation. Phosphate concentration decreases with insulin therapy. Prospective randomized studies have failed to show any beneficial effect of phosphate replacement on the clinical outcome in DKA (46,67), and overzealous phosphate therapy can cause severe hypocalcemia (46,68). However, to avoid potential cardiac and skeletal muscle weakness and respiratory depression due to hypophosphatemia, careful phosphate replacement may sometimes be indicated in patients with cardiac dysfunction, anemia, or respiratory depression and in those with serum phosphate concentration <1.0 mg/dl (4,12). When needed, 20–30 mEq/l potassium phosphate can be added to replacement fluids. The maximal rate of phosphate replacement generally regarded as safe to treat severe hypophosphatemia is 4.5 mmol/h (1.5 ml/h of K_2PO_4) (69). No studies are available on the use of phosphate in the treatment of HHS.

Transition to subcutaneous insulin

Patients with DKA and HHS should be treated with continuous intravenous insulin until the hyperglycemic crisis is resolved. Criteria for resolution of ketoacidosis include a blood glucose <200 mg/dl and two of the following criteria: a serum bicarbonate level ≥15 mEq/l, a venous pH >7.3, and a calculated anion gap ≤12 mEq/l. Resolution of HHS is associated with normal osmolality and regain of normal mental status. When this occurs, subcutaneous insulin therapy can be started. To prevent recurrence of hyperglycemia or ketoacidosis during the transition period to subcutaneous insulin, it is important to allow an overlap of 1–2 h between discontinuation of intravenous insulin and the administration of subcutaneous insulin. If the patient is to remain fasting/nothing by mouth, it is preferable to continue the intravenous insulin infusion and fluid replacement. Patients with known diabetes may be given insulin at the dosage they were receiving before the onset of DKA so long as it was controlling glucose properly. In insulin-naïve patients, a multidose insulin regimen should be started at a dose of 0.5–0.8 units $\cdot kg^{-1} \cdot day^{-1}$ (13). Human insulin (NPH and regular) are usually given in two or three doses per day. More recently, basal-bolus regimens with basal (glargine and detemir) and rapid-acting insulin analogs (lispro, aspart, or glulisine) have been proposed as a more physiologic insulin regimen in patients with type 1 diabetes. A prospective randomized trial compared treatment with a basal-bolus regimen, including glargine once daily and glulisine before meals, with a split-mixed regimen of NPH plus regular insulin twice daily following the resolution of DKA. Transition to subcutaneous glargine and glulisine resulted in similar glycemic control compared with NPH and regular insulin; however, treatment with basal bolus was associated with a lower rate of hypoglycemic events (15%) than the rate in those treated with NPH and regular insulin (41%) (55).

Complications

Hypoglycemia and hypokalemia are two common complications with overzealous treatment of DKA with insulin and bicar-

bonate, respectively, but these complications have occurred less often with the low-dose insulin therapy (4,56,57). Frequent blood glucose monitoring (every 1–2 h) is mandatory to recognize hypoglycemia because many patients with DKA who develop hypoglycemia during treatment do not experience adrenergic manifestations of sweating, nervousness, fatigue, hunger, and tachycardia. Hyperchloremic non–anion gap acidosis, which is seen during the recovery phase of DKA, is self-limited with few clinical consequences (43). This may be caused by loss of ketoanions, which are metabolized to bicarbonate during the evolution of DKA and excess fluid infusion of chloride containing fluids during treatment (4).

Cerebral edema, which occurs in ~0.3–1.0% of DKA episodes in children, is extremely rare in adult patients during treatment of DKA. Cerebral edema is associated with a mortality rate of 20–40% (5) and accounts for 57–87% of all DKA deaths in children (70,71). Symptoms and signs of cerebral edema are variable and include onset of headache, gradual deterioration in level of consciousness, seizures, sphincter incontinence, pupillary changes, papilledema, bradycardia, elevation in blood pressure, and respiratory arrest (71). A number of mechanisms have been proposed, which include the role of cerebral ischemia/hypoxia, the generation of various inflammatory mediators (72), increased cerebral blood flow, disruption of cell membrane ion transport, and a rapid shift in extracellular and intracellular fluids resulting in changes in osmolality. Prevention might include avoidance of excessive hydration and rapid reduction of plasma osmolarity, a gradual decrease in serum glucose, and maintenance of serum glucose between 250–300 mg/dl until the patient's serum osmolality is normalized and mental status is improved. Manitol infusion and mechanical ventilation are suggested for treatment of cerebral edema (73).

PREVENTION — Many cases of DKA and HHS can be prevented by better access to medical care, proper patient education, and effective communication with a health care provider during an intercurrent illness. Paramount in this effort is improved education regarding sick day management, which includes the following:

1) Early contact with the health care provider.

2) Emphasizing the importance of insulin during an illness and the reasons never to discontinue without contacting the health care team.

3) Review of blood glucose goals and the use of supplemental short- or rapid-acting insulin.

4) Having medications available to suppress a fever and treat an infection.

5) Initiation of an easily digestible liquid diet containing carbohydrates and salt when nauseated.

6) Education of family members on sick day management and record keeping including assessing and documenting temperature, blood glucose, and urine/blood ketone testing; insulin administration; oral intake; and weight. Similarly, adequate supervision and staff education in long-term facilities may prevent many of the admissions for HHS due to dehydration among elderly individuals who are unable to recognize or treat this evolving condition.

The use of home glucose-ketone meters may allow early recognition of impending ketoacidosis, which may help to guide insulin therapy at home and, possibly, may prevent hospitalization for DKA. In addition, home blood ketone monitoring, which measures β-hydroxybutyrate levels on a fingerstick blood specimen, is now commercially available (37).

The observation that stopping insulin for economic reasons is a common precipitant of DKA (74,75) underscores the need for our health care delivery systems to address this problem, which is costly and clinically serious. The rate of insulin discontinuation and a history of poor compliance accounts for more than half of DKA admissions in inner-city and minority populations (9,74,75). Several cultural and socioeconomic barriers, such as low literacy rate, limited financial resources, and limited access to health care, in medically indigent patients may explain the lack of compliance and why DKA continues to occur in such high rates in inner-city patients. These findings suggest that the current mode of providing patient education and health care has significant limitations. Addressing health problems in the African American and other minority communities requires explicit recognition of the fact that these populations are probably quite diverse in their behavioral responses to diabetes (76).

Significant resources are spent on the cost of hospitalization. DKA episodes represent >1 of every 4 USD spent on direct medical care for adult patients with type 1 diabetes and 1 of every 2 USD in patients experiencing multiple episodes (77). Based on an annual average of 135,000 hospitalizations for DKA in the U.S., with an average cost of 17,500 USD per patient, the annual hospital cost for patients with DKA may exceed 2.4 billion USD per year (3). A recent study (2) reported that the cost burden resulting from avoidable hospitalizations due to short-term uncontrolled diabetes including DKA is substantial (2.8 billion USD). However, the long-term impact of uncontrolled diabetes and its economic burden could be more significant because it can contribute to various complications. Because most cases occur in patients with known diabetes and with previous DKA, resources need to be redirected toward prevention by funding better access to care and educational programs tailored to individual needs, including ethnic and personal health care beliefs. In addition, resources should be directed toward the education of primary care providers and school personnel so that they can identify signs and symptoms of uncontrolled diabetes and so that new-onset diabetes can be diagnosed at an earlier time. Recent studies suggest that any type of education for nutrition has resulted in reduced hospitalization (78). In fact, the guidelines for diabetes self-management education were developed by a recent task force to identify ten detailed standards for diabetes self-management education (79).

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

References

1. National Center for Health Statistics. National hospital discharge and ambulatory surgery data [article online]. Available from http://www.cdc.gov/nchs/about/major/hdasd/nhds.htm. Accessed 24 January 2009
2. Kim S. Burden of hospitalizations primarily due to uncontrolled diabetes: implications of inadequate primary health care in the United States. Diabetes Care 2007;30:1281–1282
3. Agency for Healthcare Research and Quality. Databases and related tools from the healthcare cost and utilization project (HCUP) [article online]. National Center for Health Statistics, Centers for Disease Control. Available from www.hcup-us.ahrq.gov/reports/statbriefs. Accessed 24 January 2009
4. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM. Management of hyperglycemic crises

in patients with diabetes. Diabetes Care 2001;24:131–153
5. Wolfsdorf J, Glaser N, Sperling MA. Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. Diabetes Care 2006;29:1150–2259
6. White NH. Diabetic ketoacidosis in children. Endocrinol Metab Clin North Am 2000;29:657–682
7. Graves EJ, Gillium BS, the National Center for Health Statistics. Detailed diagnoses and procedures: National Hospital Discharge Survey, 1995. Vital Health Stat 13 1997;(130):1–146
8. Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. J Am Geriatr Soc 1992;40:1100–1104
9. Umpierrez GE, Kelly JP, Navarrete JE, Casals MM, Kitabchi AE. Hyperglycemic crises in urban blacks. Arch Intern Med 1997;157:669–675
10. Ennis ED, Stahl EJVB, Kreisberg RA. The hyperosmolar hyperglycemic syndrome. Diabetes Rev 1994;2:115–126
11. Lorber D. Nonketotic hypertonicity in diabetes mellitus. Med Clin North Am 1995;79:39–52
12. Kitabchi AE, Fisher JN, Murphy MB, Rumbak MJ. Diabetic ketoacidosis and the hyperglycemic hyperosmolar nonketotic state. In *Joslin's Diabetes Mellitus*. 13th ed. Kahn CR, Weir GC, Eds. Philadelphia, Lea & Febiger, 1994, p. 738–770
13. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2006;29:2739–2748
14. DeFronzo RA, Matzuda M, Barret E. Diabetic ketoacidosis: a combined metabolic-nephrologic approach to therapy. Diabetes Rev 1994;2:209–238
15. Luzi L, Barrett EJ, Groop LC, Ferrannini E, DeFronzo RA. Metabolic effects of low-dose insulin therapy on glucose metabolism in diabetic ketoacidosis. Diabetes 1988;37:1470–1477
16. van de Werve G, Jeanrenaud B. Liver glycogen metabolism: an overview. Diabetes Metab Rev 1987;3:47–78
17. Felig P, Sherwin RS, Soman V, Wahren J, Hendler R, Sacca L, Eigler N, Goldberg D, Walesky M. Hormonal interactions in the regulation of blood glucose. Recent Prog Horm Res 1979;35:501–532
18. Barrett EJ, DeFronzo RA, Bevilacqua S, Ferrammi E. Insulin resistance in diabetic ketoacidosis. Diabetes 1982;31:923–928
19. Miles JM, Haymond MW, Nissen S, Gerich JE. Effects of free fatty acid availability, glucagon excess and insulin deficiency on ketone body production in postabsorptive man. J Clin Invest 1983; 71:1554–1561
20. Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. Diabetes 2004; 53:2079–2086
21. Buyukasik Y, Ileri NS, Haznedaroglu IC, Karaahmetoglu S, Muftuoglu O, Kirazli S, Dundar S. Enhanced subclinical coagulation activation during diabetic ketoacidosis. Diabetes Care 1998;21:868–870
22. Delaney MF, Zisman A, Kettyle WM. Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. Endocrinol Metab Clin North Am 2000;29: 683–705
23. Peden NR, Broatan JT, McKenry JB. Diabetic ketoacidosis during long-term treatment with continuous subcutaneous insulin infusion. Diabetes Care 1984;7:1–5
24. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. Diabetes Care 2003;26: 1079–1087
25. Wachtel TJ, Silliman RA, Laberton P. Predisposing factor for the diabetic hyperosmolar state. Arch Intern Med 1987;147: 499–501
26. Avella J, Wetli CV, Wilson JC, Katz M, Hahn T. Fatal olanzapine-induced hyerglycemic ketoacidosis. Am J Forensic Med Pathol 2004;25:172–175
27. Campanella LM, Lartey R, Shih R. Sever hyperglycemic hyperosmolar nonketotic coma in a nondiabetic patient receiving aripiprazole. Am Emerg Med 2009;53: 264–266
28. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. Ann Intern Med 2006; 144:350–357
29. Umpierrez GE, Woo W, Hagopian WA, Isaacs SD, Palmer JP, Gaur LK, Nepom GT, Clark WS, Mixon PS, Kitabchi AE. Immunogenetic analysis suggest different pathogenesis between obese and lean African-Americans with diabetic ketoacidosis. Diabetes Care 1999;22:1517–1523
30. Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, Bolgiano D, Rodriguez L, Rajan A, Lernmark A, Balasubramanyam A. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis, and clinical outcomes. J Clin Endocrinol Metab 2003;88:5090–5098
31. Mauvais-Jarvis F, Sobngwi E, Porcher R, Riveline JP, Kevorkian JP, Vaisse C, Charpentier G, Guillausseau PJ, Vexiau P, Gautier JF. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of β-cell dysfunction and insulin resistance. Diabetes 2004;53:645–653
32. Balasubramanyam A, Nalini R, Hampe CS, Maldonado M. Syndromes of ketosis-prone diabetes mellitus. Endocr Rev 2008; 29:292–302
33. Matz R. Hypothermia in diabetic acidosis. Hormones 1972;3:36–41
34. Umpierrez G, Freire AX. Abdominal pain in patients with hyperglycemic crises. J Crit Care 2002;17:63–67
35. Campbell IW, Duncan LJ, Innes JA, MacCuish AC, Munro JF. Abdominal pain in diabetic metabolic decompensation: clinical significance. JAMA 1975;233:166–168
36. Kitabchi AE, Fisher JN. Insulin therapy of diabetic ketoacidosis: physiologic versus pharmacologic doses of insulin and their routes of administration. In *Handbook of Diabetes Mellitus*. Brownlee M, Ed. New York, Garland ATPM Press, 1981, p. 95–149
37. Sheikh-Ali M, Karon BS, Basu A, Kudva YC, Muller LA, Xu J, Schwenk WF, Miles JM. Can serum β-hydroxybutyrate be used to diagnose diabetic ketoacidosis? Diabetes Care 2008;31:643–647
38. Miles JM, Gerich JE. Glucose and ketone body kinetics in diabetic ketoacidosis. Clin Endocrinol Metab 1983;12:303–319
39. Munro JF, Campbell IW, McCuish AC, Duncan LJ. Euglycaemic diabetic ketoacidosis. Br Med J 1973;2:578–580
40. Burge MR, Hardy KJ, Schade DS. Short-term fasting is a mechanism for the development of euglycemic ketoacidosis during periods of insulin deficiency. J Clin Endocrinol Metab 1993;76:1192–1198
41. Slovis CM, Mork VG, Slovis RJ, Bain RP. Diabetic ketoacidosis and infection: leukocyte count and differential as early predictors of serious infection. Am J Emerg Med 1987;5:1–5
42. Razavi L, Kitabchi AE, Stentz FB, Wan JY, Larijani BA, Tehrani M, Gozashti M, Midfar K, Taheri E. Proinflammatory cytokines in response to insulin-induced hypoglycemic stress in healthy subjects. Metab Clin Exp 2009;58:443–448
43. Adrogue HJ, Wilson H, Boyd AE 3rd, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med 1982;307:1603–1610
44. Rumbak MJ, Hughes TA, Kitabchi AE. Pseudonormoglycemia in diabetic ketoacidosis with elevated triglycerides. Am J Emerg Med 1991;9:61–63
45. Kaminska ES, Pourmotabbed G. Spurious laboratory values in diabetic ketoacidosis and hyperlipidemia. Am J Emerg Med 1993;11:77–80
46. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab 1983;57:177–180
47. Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low-dose insulin therapy by various routes. N Engl J Med 1977;297:238–241
48. Yadav D, Nair S, Norkus EP, Pitchumoni CS. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. Am J Gastroenterol

2000;95:3123–3128
49. Umpierrez GE, DiGirolamo M, Tuvlin JA, Isaacs SD, Bhoola SM, Kokko JP. Differences in metabolic and hormonal milieu in diabetic- and alcohol-induced ketoacidosis. J Crit Care 2000;15:52–59
50. Nyenwe E, Loganathan R, Blüm S, Ezuteh D, Erani D, Wan J, Palace MR, Kitabchi AE. Active use of cocaine: an independent risk factor for recurrent diabetic ketoacidosis in a city hospital. Endocr Pract 2007;13:22–29
51. Soveid M, Ranjbar-Omrani G. Ketoacidosis as the primary manifestation of acromegaly. Arch Iranian Med 2005;8:326–328
52. Kuzuya T, Matsuda A, Sakemoto Y, Yamamoto K, Saito T, Yoshida S. A case of pituitary gigantism who had two episodes of diabetic ketoacidosis followed by complete recovery of diabetes. Endocrinol Jpn 1983;30:323–334
53. Hillman K. Fluid resuscitation in diabetic emergencies: a reappraisal. Intensive Care Med 1987;13:4–8
54. Bratusch-Marrain PR, Komajati M, Waldhausal W. The effect of hyperosmolarity on glucose metabolism. Pract Cardiol 1985;11:153–163
55. Umpierrez GE, Jones S, Smiley D, Mulligan P, Keyler T, Temponi A, Semakula C, Umpierrez D, Peng L, Cerón M, Robalino G. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. Diabetes Care 2009;32:1164–1169
56. Alberti KGGM, Hockaday TDR, Turner RC. Small doses of intramuscular insulin in the treatment of diabetic 'coma.' Lancet 1973;5:515–522
57. Kitabchi AE, Ayyagari V, Guerra SNO, Medical House Staff. Efficacy of low dose vs conventional therapy of insulin for treatment of diabetic ketoacidosis. *Ann Intern Med* 1976;84:633–638
58. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty years of personal experience in hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. J Clin Endocrinol Metab 2008;93:1541–1552
59. Kitabchi AE, Murphy MB, Spencer J, Matteri R, Karas J. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? Diabetes Care 2008;31:2081–2085
60. Umpierrez GE, Latif K, Stoever J, Cuervo R, Park L, Freire AX, Kitabchi AE. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of diabetic ketoacidosis. Am J Med 2004;117:291–296
61. Umpierrez GE, Latif KA, Cuervo R, Karabell A, Freire AX, Kitabchi AE. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care 2004; 27:1873–1878
62. Viallon A, Zeni F, Lafond P, Venet C, Tardy B, Page Y, Bertrand JC. Does bicarbonate therapy improve the management of severe diabetic ketoacidosis? Crit Care Med 1999;27:2690–2693
63. Mitchell JH, Wildenthal K, Johnson RL Jr. The effects of acid-base disturbances on cardiovascular and pulmonary function. Kidney Int 1972;1:375–389
64. Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med 1986;105:836–840
65. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M, Malley R, Kuppermann N, the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med 2001;344:264–269
66. Latif KA, Freire AX, Kitabchi AE, Umpierrez GE, Qureshi N. The use of alkali therapy in severe diabetic ketoacidosis. Diabetes Care 2002;25:2113–2114
67. Winter RJ, Harris CJ, Phillips LS, Green OC. Diabetic ketoacidosis: induction of hypocalcemia and hypomagnesemia by phosphate therapy. Am J Med 1979;67: 897–900
68. Kreisberg RA. Phosphorus deficiency and hypophosphatemia. Hosp Pract 1977;12: 121–128
69. Miller DW, Slovis CM. Hypophosphatemia in the emergency department therapeutics. Am J Emerg Med 2000;18: 457–461
70. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990;13:22–33
71. Marcin JP, Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M, Malley R, Kuppermann N. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. J Pediatr 2002;141:793–797
72. Abbott NJ. Inflammatory mediators and modulation of blood-brain barrier permeability. Cell Mol Neurobiol 2000;20:131–147
73. Roberts MD, Slover RH, Chase HP. Diabetic ketoacidosis with intracerebral complications. Pediatr Diabetes 2001;2:109–114
74. Musey VC, Lee JK, Crawford R, Klatka MA, McAdams D, Phillips LS. Diabetes in urban African-Americans. I. Cessation of insulin therapy is the major precipitating cause of diabetic ketoacidosis. Diabetes Care 1995;18:483–489
75. Maldonado MR, Chong ER, Oehl MA, Balasubramanyam A. Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause. Diabetes Care 2003;26:1265–1269
76. Anderson RM, Herman WH, Davis JM, Freedman RP, Funnell MM, Neighbors HW. Barriers to improving diabetes care for blacks. Diabetes Care 1991;14:605–609
77. Javor KA, Kotsanos JG, McDonald RC, Baron AD, Kesterson JG, Tierney WM. Diabetic ketoacidosis charges relative to medical charges of adult patients with type I diabetes. Diabetes Care 1997;20: 349–354
78. Robbins JM, Thatcher GE, Webb DA, Valmanis VG. Nutritionist visits, diabetes classes, and hospitalization rates and charges: the Urban Diabetes Study. Diabetes Care 2008;31:655–660
79. Funnell MM, Brown TL, Childs BP, Haas LB, Hosey GM, Jensen B, Maryniuk M, Peyrot M, Piette JD, Reader D, Siminerio LM, Weinger K, Weiss MS. National Standards for Diabetes Self-Management Education. Diabetes Care 2009;32(Suppl. 1): S87–S94

Can J Diabetes 42 (2018) S109–S114

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

2018 Clinical Practice Guidelines

Hyperglycemic Emergencies in Adults

Diabetes Canada Clinical Practice Guidelines Expert Committee

Jeannette Goguen MD, MEd, FRCPC, Jeremy Gilbert MD, FRCPC

KEY MESSAGES

- Diabetic ketoacidosis and hyperosmolar hyperglycemic state should be suspected in people who have diabetes and are ill. If either diabetic ketoacidosis or hyperosmolar hyperglycemic state is diagnosed, precipitating factors must be sought and treated.
- Diabetic ketoacidosis and hyperosmolar hyperglycemic state are medical emergencies that require treatment and monitoring for multiple metabolic abnormalities and vigilance for complications.
- A normal or mildly elevated blood glucose level does not rule out diabetic ketoacidosis in certain conditions, such as pregnancy or with SGLT2 inhibitor use.
- Diabetic ketoacidosis requires intravenous insulin administration (0.1 units/kg/h) for resolution. Bicarbonate therapy may be considered only for extreme acidosis (pH ≤7.0).

KEY MESSAGES FOR PEOPLE WITH DIABETES

When you are sick, your blood glucose levels may fluctuate and be unpredictable:

- During these times, it is a good idea to check your blood glucose levels more often than usual (for example, every 2 to 4 hours).
- Drink plenty of sugar-free fluids or water.
- If you have type 1 diabetes with blood glucose levels remaining over 14 mmol/L before meals, or if you have symptoms of diabetic ketoacidosis (see Table 1), check for ketones by performing a urine ketone test or blood ketone test. Blood ketone testing is preferred over urine testing.
- Develop a sick-day plan with your diabetes health-care team. This should include information on:
  - Which diabetes medications you should continue and which ones you should temporarily stop
  - Guidelines for insulin adjustment if you are on insulin
  - Advice on when to contact your health-care provider or go to the emergency room.

Note: Although the diagnosis and treatment of diabetic ketoacidosis (DKA) in adults and in children share general principles, there are significant differences in their application, largely related to the increased risk of life-threatening cerebral edema with DKA in children and adolescents. The specific issues related to treatment of DKA in children and adolescents are addressed in the Type 1 Diabetes in Children and Adolescents chapter, p. S234.

Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are diabetes emergencies with overlapping features. With insulin deficiency, hyperglycemia causes urinary losses of water and electrolytes (sodium, potassium, chloride) and the resultant extracellular fluid volume (ECFV) depletion. Potassium is shifted out of cells, and ketoacidosis occurs as a result of elevated glucagon levels and insulin deficiency (in the case of type 1 diabetes). There may also be high catecholamine levels suppressing insulin release (in the case of type 2 diabetes). In DKA, ketoacidosis is prominent while, in HHS, the main features are ECFV depletion and hyperosmolarity. HHS is the preferred term to describe this condition as opposed to hyperosmolar nonketotic coma (HONKC) since less than one-third of people with HHS actually present with a coma (1).

Risk factors for DKA include new diagnosis of diabetes mellitus, insulin omission, infection, myocardial infarction (MI), abdominal crisis, trauma and, possibly, continuous subcutaneous insulin infusion (CSII) therapy, thyrotoxicosis, cocaine, atypical antipsychotics and, possibly, interferon. HHS is much less common than DKA (2,3). In addition to the precipitating factors noted above for DKA, HHS also has been reported following cardiac surgery and with the use of certain drugs, including diuretics, glucocorticoids, lithium and atypical antipsychotics. Infections are present in 40% to 60% of people with HHS (4). In up to 20% of cases of HHS, individuals had no prior history of diabetes (4).

The clinical presentation of DKA includes symptoms and signs of hyperglycemia, acidosis and the precipitating illness (Table 1). In HHS, there is often more profound ECFV contraction and decreased level of consciousness (proportional to the elevation in plasma osmolality). In addition, in HHS, there can be a variety of neurological presentations, including seizures and a stroke-like state that can resolve once osmolality returns to normal (3,5,6). In HHS, there also may be evidence of a precipitating condition similar to DKA.

In individuals with type 2 diabetes, the incidence of DKA is estimated to be in the range of 0.32 to 2.0 per 1,000 patient-years (7) while, in people with type 1 diabetes, the incidence is higher at 4.6

Table 1
Clinical presentation of DKA

	Symptoms	Signs
Hyperglycemia	Polyuria, polydipsia, weakness	ECFV contraction
Acidosis	Air hunger, nausea, vomiting and abdominal pain Altered sensorium	Kussmaul respiration, acetone-odoured breath Altered sensorium
Precipitating condition	See list of conditions in Table 2	

Conflict of interest statements can be found on page S113.

https://doi.org/10.1016/j.jcjd.2017.10.013

to 8.0 per 1000 patient-years (8). There is a group of individuals with diabetes that present with DKA but do not have the typical features of type 1 diabetes. There are various terms given to characterize this condition, such as flatbush diabetes, type 1.5 diabetes, atypical diabetes or type 1B diabetes, but it may be most useful to label this state as ketosis-prone diabetes (KPD). There are several classification systems used to describe KPD that take into account pathophysiology and prognosis. Individuals with KPD have very little beta cell function, may or may not have beta cell antibodies, and some may require temporary or lifelong insulin therapy (9).

Prevention

Sick-day management that includes capillary beta-hydroxybutyrate monitoring reduces emergency room visits and hospitalizations in young people (10).

SGLT2 Inhibitors and DKA

SGLT2 inhibitors may lower the threshold for developing DKA through a variety of different mechanisms (11–13). The presentation of the DKA is similar to those who develop DKA without SGLT2 inhibitor exposure, except that the blood glucose (BG) levels on presentation may not be as elevated as expected. In randomized controlled trials, the incidence of DKA associated with SGLT2 inhibitors is low (≤0.1% of treated people) (14,15). In most cases, there is usually a known precipitant as a contributing factor, such as insulin dose reduction or omission, bariatric surgery or other surgery, alcohol, exercise, or low carbohydrate or reduced food intake (16–20).

Diagnosis

DKA or HHS should be suspected whenever people have significant hyperglycemia, especially if they are ill or highly symptomatic (see above). As outlined in Figure 1, to make the diagnosis and determine the severity of DKA or HHS, the following should be assessed: plasma levels of electrolytes (and anion gap), plasma glucose (PG), creatinine, osmolality and beta-hydroxybutyric acid (beta-OHB) (if available), blood gases, serum and urine ketones, fluid balance, level of consciousness, precipitating factors and complications (1). Arterial blood gases may be required for more ill individuals, when knowing the adequacy of respiratory compensation and the A-a gradient is necessary. Otherwise, venous blood gases are usually adequate—the pH is typically 0.015 to 0.03 lower than arterial pH (21-23). Point-of-care capillary blood beta-OHB measurement in emergency is sensitive and specific for DKA and, as a screening tool, may allow more rapid identification of hyperglycemic persons at risk for DKA (24–29). This test is less accurate with hemoconcentration and/or when the beta-OHB level is >3 mmol/L (30).

There are no definitive criteria for the diagnosis of DKA. Typically, the arterial pH is ≤7.3, serum bicarbonate is ≤15 mmol/L and the anion gap is >12 mmol/L with positive serum and/or urine ketones (1,31–33). PG is usually ≥14.0 mmol/L but can be lower, especially with the use of SGLT2 inhibitors (34). DKA is more challenging to diagnose in the presence of the following conditions: 1) mixed acid-base disorders (e.g. associated vomiting, which will raise the bicarbonate level); 2) if there has been a shift in the redox potential, favouring the presence of beta-OHB (rendering serum ketone testing negative); or 3) if the loss of keto anions with sodium or potassium in osmotic diuresis has occurred, leading to a return of the plasma anion gap toward normal. It is, therefore, important to measure ketones in both the serum and urine. If there is an elevated anion gap and serum ketones are negative, beta-OHB levels should be measured. Negative urine ketones should not be used to rule out DKA (35).

Measurement of serum lactate should be considered in hypoxic states. In HHS, a more prolonged duration of relative insulin insufficiency and inadequate fluid intake (or high glucose intake) results in higher PG levels (typically ≥34.0 mmol/L), plasma osmolality >320 mOsm/kg and greater ECFV contraction, but minimal acid-base disturbance (1,31).

Pregnant women in DKA typically present with lower PG levels than nonpregnant women (36), and there are case reports of euglycemic DKA in pregnancy (37,38).

Management

Objectives of management include restoration of normal ECFV and tissue perfusion; resolution of ketoacidosis; correction of electrolyte imbalances and hyperglycemia; and the diagnosis and treatment of coexistent illness. The issues that must be addressed in the individual presenting with DKA or HHS are outlined in Table 2. A summary of fluid therapy is outlined in Table 3, and a management algorithm and formulas for calculating key measurements are provided in Figure 1.

People with DKA and HHS are best managed in an intensive care unit or step-down setting (1,31,32) with specialist care (39,40). Protocols and insulin management software systems (41) may be beneficial (42,43), but there can be challenges with achieving adherence (44,45). Volume status (including fluid intake and output), vital signs, neurological status, plasma concentrations of electrolytes, anion gap, osmolality and glucose need to be monitored closely, initially as often as every 2 hours (1,31,32). Capillary blood glucose (CBG) measurements are unreliable in the setting of severe acidosis (46). Precipitating factors must be diagnosed and treated (1,31,32).

Table 2
Priorities* to be addressed in the management of adults presenting with hyperglycemic emergencies

Metabolic	Precipitating cause of DKA/HHS	Other complications of DKA/HHS
• ECFV contraction • Potassium deficit and abnormal concentration • Metabolic acidosis • Hyperosmolality (water deficit leading to increased corrected sodium concentration plus hyperglycemia)	• New diagnosis of diabetes • Insulin omission • Infection • Myocardial infarction • Stroke • ECG changes may reflect hyperkalemia (78,79) • A small increase in troponin may occur without overt ischemia (80) • Thyrotoxicosis (81) • Trauma • Drugs	• Hyper/hypokalemia • ECFV overexpansion • Cerebral edema • Hypoglycemia • Pulmonary emboli • Aspiration • Hypocalcemia (if phosphate used) • Stroke • Acute renal failure • Deep vein thrombosis

DKA, diabetic ketoacidosis; *ECFV*, extracellular fluid volume; *HHS*, hyperosmolar hyperglycemic state.
* Severity of issue will dictate priority of action.

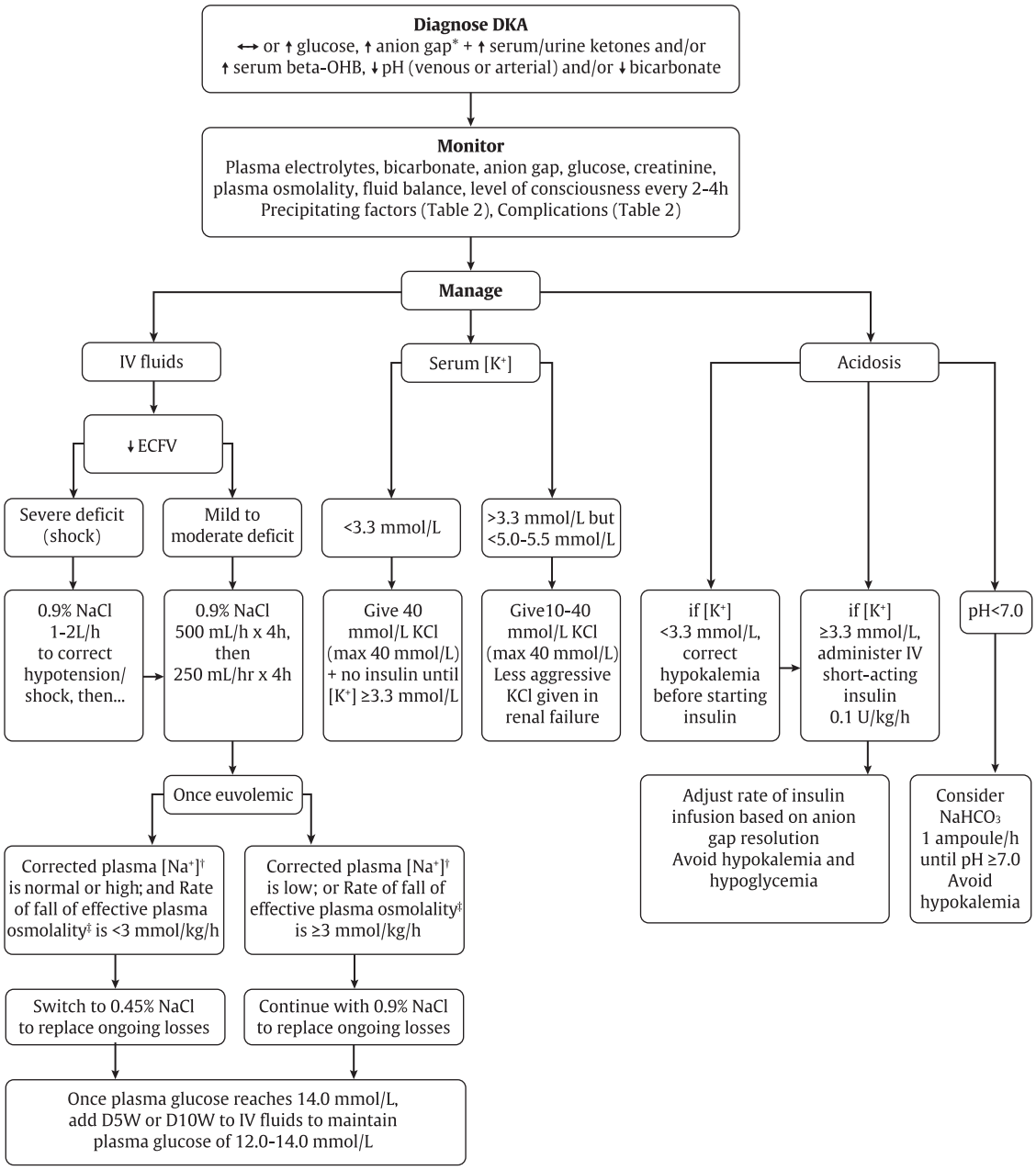


Figure 1. Management of diabetic ketoacidosis in adults.
Beta-OHB, beta-hydroxybutyric acid; *DKA*, diabetic ketoacidosis; *ECFV*, extracelluar fluid volume; *IV*, intravenous.
*Plasma glucose may be lower than expected in some settings.
**Anion gap = plasma [Na+] – plasma [Cl^-] – plasma [HCO_3^-].
†Corrected plasma [Na+] = measured [Na+] + 3/10 × ([plasma glucose (mmol/L)] – 5).
‡Effective plasma osmolality = [Na+] × 2 + [plasma glucose (mmol/L)], reported as mmol/kg.

Extracellular fluid volume contraction

The sodium deficit is typically 7 to 10 mmol/kg in DKA (47) and 5 to 13 mmol/kg in HHS, which, along with water losses (100 mL/kg and 100 to 200 mL/kg, respectively), results in decreased ECFV, usually with decreased intracellular fluid volume (47). Restoring ECFV improves tissue perfusion and reduces plasma glucose levels both by dilution and by increasing urinary glucose losses. ECFV re-expansion, using a rapid rate of initial fluid administration, was associated with an increased risk of cerebral edema in 1 study (48) but not in another (49). In adults, one should initially administer intravenous normal saline 1 to 2 L/h to correct shock, otherwise 500 mL/h for 4 hours, then 250 mL/h of intravenous fluids (50,51).

Potassium deficit

The typical potassium deficit range is 2 to 5 mmol/kg in DKA and 4 to 6 mmol/kg in HHS (48). There have been no randomized trials that have studied strategies for potassium replacement. Typical recommendations suggest that potassium supplementation should be started for plasma potassium <5.0 to 5.5 mmol/L once diuresis has been established, usually with the second litre of saline. If the individual at presentation is normo- or hypokalemic, potassium should be given immediately, at concentrations in the intravenous fluid between 10 to 40 mmol/L, at a maximum rate of 40 mmol/h.

In the case of frank hypokalemia (serum potassium <3.3 mmol/L), insulin should be withheld until potassium

Table 3
Summary of fluid therapy for DKA and HHS in adults

1. Administer IV 0.9% sodium chloride initially. If the person is in shock, give 1 to 2 L/hour initially to correct shock; otherwise, give 500 mL/hour for 4 h, then 250 mL/hour for 4 h, then as required.
2. Add potassium immediately if person is normo- or hypokalemic. Otherwise, if initially hyperkalemic, only add potassium once serum potassium falls to <5 to 5.5 mmol/L and person is diuresing.
3. Once plasma glucose reaches 14.0 mmol/L, add glucose to maintain plasma glucose at 12.0 to 14.0 mmol/L.
4. After hypotension has been corrected, switch 0.9% sodium chloride to 0.45% sodium chloride (with potassium chloride). However, if plasma osmolality is falling more rapidly than 3 mmol/kg/hour and/or the corrected plasma sodium is reduced, maintain intravenous fluids at higher osmolality (i.e. may need to maintain on normal saline).

DKA, diabetic ketoacidosis; *HHS*, hyperosmolar hyperglycemic state; *IV*, intravenous.

replacement at 40 mmol/h has restored plasma potassium to ≥3.3 mmol/L (1,31). It is reasonable to treat the potassium deficit of HHS in the same way.

Metabolic acidosis

Metabolic acidosis is a prominent component of DKA. People with HHS have minimal or no acidosis. Insulin is used to stop ketoacid production; intravenous fluid alone has no impact on parameters of ketoacidosis (52). Short-acting insulin (0.1 units/kg/h) is recommended (53–55). There is no conclusive evidence supporting the use of an initial insulin bolus in adults and it is not recommended in children. Although the use of an initial bolus of intravenous insulin is recommended in some reviews (1), there has been only 1 randomized controlled trial in adults examining the effectiveness of this step (56). In this study, there were 3 arms: a bolus arm (0.07 units/kg, then 0.07 units/kg/h), a low-dose infusion group (no bolus, 0.07 units/kg/h) and a double-dose infusion group (no bolus, 0.14 units/kg/h). Outcomes were identical in the 3 groups, except 5 of 12 participants needed extra insulin in the no-bolus/low-dose infusion group, and the double-dose group had the lowest potassium (nadir of 3.7 mmol/L on average). Unfortunately, this study did not examine the standard dose of insulin in DKA (0.1 units/kg/h). In children, using an initial bolus of intravenous insulin does not result in faster resolution of ketoacidosis (57,58) and increases the risk of cerebral edema (see Type 1 Diabetes in Children and Adolescents chapter, p. S234).

A systematic review based on low- to very-low-quality evidence, showed that subcutaneous hourly analogues provide neither advantages nor disadvantages compared to intravenous regular insulin when treating mild to moderate DKA (59). The dose of insulin should subsequently be adjusted based on ongoing acidosis (60), using the plasma anion gap or beta-OHB measurements.

Use of intravenous sodium bicarbonate to treat acidosis did not affect outcome in randomized controlled trials (61–63). Sodium bicarbonate therapy may be considered in adult individuals in shock or with arterial pH ≤7.0. For example, one can administer 1 ampoule (50 mmol) sodium bicarbonate added to 200 mL D5W (or sterile water, if available) over 1 hour, repeated every 1 to 2 hours, until pH is ≥7.0 (1,31). Potential risks associated with the use of sodium bicarbonate include hypokalemia (64) and delayed occurrence of metabolic alkalosis.

Hyperosmolality

Hyperosmolality is due to hyperglycemia and a water deficit. However, serum sodium concentration may be reduced due to shift of water out of cells. The concentration of sodium needs to be corrected for the level of glycemia to determine if there is also a water deficit (Figure 1). In people with DKA, plasma osmolality is usually ≤320 mmol/kg. In HHS, plasma osmolality is typically >320 mmol/kg. Because of the risk of cerebral edema with rapid reductions in osmolality (65), it has been recommended that the plasma osmolality be lowered no faster than 3 mmol/kg/h (1,31). This can be achieved by monitoring plasma osmolality, by adding glucose to the infusions when PG reaches 14.0 mmol/L to maintain it at that level and by selecting the correct concentration of intravenous saline. Typically, after volume re-expansion, intravenous fluid may be switched to half-normal saline because urinary losses of electrolytes in the setting of osmotic diuresis are usually hypotonic. The potassium in the infusion will also add to the osmolality. If osmolality falls too rapidly despite the administration of glucose, consideration should be given to increasing the sodium concentration of the infusing solution (1,31). Water imbalances can also be monitored using the corrected plasma sodium. Central pontine myelinolysis has been reported in association with overly rapid correction of hyponatremia in HHS (66).

PG levels will fall due to multiple mechanisms, including ECFV re-expansion (67), glucose losses via osmotic diuresis (52), insulin-mediated reduced glucose production and increased cellular uptake of glucose. Once PG reaches 14.0 mmol/L, intravenous glucose should be started to prevent hypoglycemia, targeting a plasma glucose of 12.0 to 14.0 mmol/L. Similar doses of intravenous insulin can be used to treat HHS, although these individuals are not acidemic, and the fall in PG concentration is predominantly due to re-expansion of ECFV and osmotic diuresis (67). Insulin has been withheld successfully in HHS (68), but generally its use is recommended to reduce PG levels (1,31).

Phosphate deficiency

There is currently no evidence to support the use of phosphate therapy for DKA (69–71), and there is no evidence that hypophosphatemia causes rhabdomyolysis in DKA (72). However, because hypophosphatemia has been associated with rhabdomyolysis in other states, administration of potassium phosphate in cases of severe hypophosphatemia may be considered for the purpose of trying to prevent rhabdomyolysis.

Complications

In Ontario, in-hospital mortality in people hospitalized for acute hyperglycemia ranged from <1% at ages 20 to 49 years to 16% in those over 75 years (73). Reported mortality in DKA ranges from 0.65% to 3.3% (3,39,74–76). In HHS, recent studies found mortality rates to be 12% to 17%, but included individuals with mixed DKA and hyperosmolality (2,5,77). About 50% of deaths occur in the first 48 to 72 hours. Mortality is usually due to the precipitating cause, electrolyte imbalances (especially hypo- and hyperkalemia) and cerebral edema.

RECOMMENDATIONS

1. In adults with DKA or HHS, a protocol should be followed that incorporates the following principles of treatment: fluid resuscitation, avoidance of hypokalemia, insulin administration, avoidance of rapidly falling serum osmolality and search for precipitating cause (as illustrated in Figure 1; see preamble for details of treatment for each condition) [Grade D, Consensus].

2. Point-of-care capillary beta-hydroxybutyrate may be measured in the hospital or outpatient setting [Grade D, Level 4 (33)] in adults with type 1 diabetes with CBG >14.0 mmol/L to screen for DKA, and a beta-hydroxybutyrate >1.5 mmol/L warrants further testing for DKA [Grade B, Level 2 (24–29)]. Negative urine ketones should not be used to rule out DKA [Grade D, Level 4 (35)].

3. In adults with DKA, intravenous 0.9% sodium chloride should be administered initially at 500 mL/h for 4 hours, then 250 mL/h for 4 hours [Grade B, Level 2 (50)] with consideration of a higher initial rate (1–2 L/h) in the presence of shock [Grade D, Consensus]. For adults with HHS, intravenous fluid administration should be individualized [Grade D, Consensus].

4. In adults with DKA, an infusion of short-acting intravenous insulin of 0.10 units/kg/h should be used [Grade B, Level 2 (54,55)]. The insulin infusion rate should be maintained until the resolution of ketosis [Grade B, Level 2 (60)] as measured by the normalization of the plasma anion gap [Grade D, Consensus]. Once the PG concentration falls to 14.0 mmol/L, intravenous dextrose should be started to avoid hypoglycemia [Grade D, Consensus].

5. Individuals treated with SGLT2 inhibitors with symptoms of DKA should be assessed for this condition even if BG is not elevated [Grade D, Consensus].

Abbreviations:
BG, blood glucose; *CBG*, capillary blood glucose; *DKA*, diabetic ketoacidosis; *ECFV*, extracellular fluid volume; *HHS*, hyperosmolar hyperglycemic state; *KPD*, ketosis-prone diabetes, *PG*, plasma glucose.

Other Relevant Guidelines

Glycemic Management in Adults With Type 1 Diabetes, p. S80
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Type 1 Diabetes in Children and Adolescents, p. S234

Relevant Appendix

Appendix 8: Sick-Day Medication List

Author Disclosures

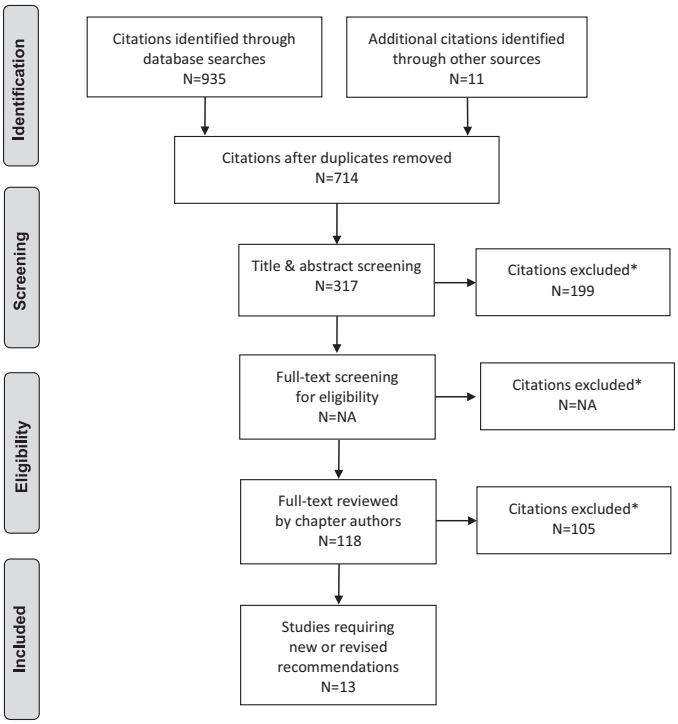
Dr. Gilbert reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi, outside the submitted work. Dr. Goguen does not have anything to disclose.

References

1. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. Diabetes Care 2001;24:131–53.
2. Hamblin PS, Topliss DJ, Chosich N, et al. Deaths associated with diabetic ketoacidosis and hyperosmolar coma. 1973–1988. Med J Aust 1989;151:41–2, 44.
3. Holman RC, Herron CA, Sinnock P. Epidemiologic characteristics of mortality from diabetes with acidosis or coma, United States, 1970–78. Am J Public Health 1983;73:1169–73.
4. Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: A historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care 2014;37:3124–31.
5. Wachtel TJ, Tetu-Mouradjian LM, Goldman DL, et al. Hyperosmolarity and acidosis in diabetes mellitus: A three-year experience in Rhode Island. J Gen Intern Med 1991;6:495–502.
6. Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. J Am Geriatr Soc 1992;40:1100–4.
7. Wang ZH, Kihl-Selstam E, Eriksson JW. Ketoacidosis occurs in both type 1 and type 2 diabetes–a population-based study from Northern Sweden. Diabet Med 2008;25:867–70.
8. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crises in adult patients with diabetes: A consensus statement from the American Diabetes Association. Diabetes Care 2006;29:2739–48.
9. Balasubramanyam A, Garza G, Rodriguez L, et al. Accuracy and predictive value of classification schemes for ketosis-prone diabetes. Diabetes Care 2006;29:2575–9.
10. Laffel LM, Wentzell K, Loughlin C, et al. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: A randomized clinical trial. Diabet Med 2006;23:278–84.
11. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: Possible mechanism and contributing factors. J Diabetes Investig 2016;7:135–8.
12. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: A predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care 2015;38:1638–42.
13. Singh AK. Sodium-glucose co-transporter-2 inhibitors and euglycemic ketoacidosis: Wisdom of hindsight. Indian J Endocrinol Metab 2015;19:722–30.
14. Erondu N, Desai M, Ways K, et al. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. Diabetes Care 2015;38:1680–6.
15. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
16. Hayami T, Kato Y, Kamiya H, et al. Case of ketoacidosis by a sodium-glucose cotransporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet. J Diabetes Investig 2015;6:587–90.
17. Peters AL, Buschur EO, Buse JB, et al. Euglycemic diabetic ketoacidosis: A potential complication of treatment with sodium-glucose cotransporter 2 inhibition. Diabetes Care 2015;38:1687–93.
18. Redford C, Doherty L, Smith J. SGLT2 inhibitors and the risk of diabetic ketoacidosis. Practical Diabetes 2015;32:263–4.
19. St Hilaire R, Costello H. Prescriber beware: Report of adverse effect of sodium-glucose cotransporter 2 inhibitor use in a patient with contraindication. Am J Emerg Med 2015;33:604, e3-.4.
20. Goldenberg RM, Berard LD, Cheng AYY, et al. SGLT2 inhibitor-associated diabetic ketoacidosis: Clinical review and recommendations for prevention and diagnosis. Clin Ther 2016;38:2654–64, e1.
21. Malatesha G, Singh NK, Bharija A, et al. Comparison of arterial and venous pH, bicarbonate, PCO2 and PO2 in initial emergency department assessment. Emerg Med J 2007;24:569–71.
22. Brandenburg MA, Dire DJ. Comparison of arterial and venous blood gas values in the initial emergency department evaluation of patients with diabetic ketoacidosis. Ann Emerg Med 1998;31:459–65.
23. Ma OJ, Rush MD, Godfrey MM, et al. Arterial blood gas results rarely influence emergency physician management of patients with suspected diabetic ketoacidosis. Acad Emerg Med 2003;10:836–41.
24. Charles RA, Bee YM, Eng PH, et al. Point-of-care blood ketone testing: Screening for diabetic ketoacidosis at the emergency department. Singapore Med J 2007;48:986–9.
25. Naunheim R, Jang TJ, Banet G, et al. Point-of-care test identifies diabetic ketoacidosis at triage. Acad Emerg Med 2006;13:683–5.
26. Sefedini E, Prašek M, Metelko Z, et al. Use of capillary beta-hydroxybutyrate for the diagnosis of diabetic ketoacidosis at emergency room: Our one-year experience. Diabetol Croat 2008;37:73–80.
27. Mackay L, Lyall MJ, Delaney S, et al. Are blood ketones a better predictor than urine ketones of acid base balance in diabetic ketoacidosis? Pract Diabetes Int 2010;27:396–9.
28. Bektas F, Eray O, Sari R, et al. Point of care blood ketone testing of diabetic patients in the emergency department. Endocr Res 2004;30:395–402.
29. Harris S, Ng R, Syed H, et al. Near patient blood ketone measurements and their utility in predicting diabetic ketoacidosis. Diabet Med 2005;22:221–4.
30. Misra S, Oliver NS. Utility of ketone measurement in the prevention, diagnosis and management of diabetic ketoacidosis. Diabet Med 2015;32:14–23.
31. Chiasson JL, Aris-Jilwan N, Belanger R, et al. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. CMAJ 2003;168:859–66.
32. Lebovitz HE. Diabetic ketoacidosis. Lancet 1995;345:767–72.
33. Cao X, Zhang X, Xian Y, et al. The diagnosis of diabetic acute complications using the glucose-ketone meter in outpatients at endocrinology department. Int J Clin Exp Med 2014;7:5701–5.
34. Munro JF, Campbell IW, McCuish AC, et al. Euglycaemic diabetic ketoacidosis. Br Med J 1973;2:578–80.
35. Kuru B, Sever M, Aksay E, et al. Comparing finger-stick beta-hydroxybutyrate with dipstick urine tests in the detection of ketone bodies. Turk J Emerg Med 2014;14:47–52.
36. Guo RX, Yang LZ, Li LX, et al. Diabetic ketoacidosis in pregnancy tends to occur at lower blood glucose levels: Case-control study and a case report of euglycemic diabetic ketoacidosis in pregnancy. J Obstet Gynaecol Res 2008;34:324–30.
37. Oliver R, Jagadeesan P, Howard RJ, et al. Euglycaemic diabetic ketoacidosis in pregnancy: An unusual presentation. J Obstet Gynaecol 2007;27:308.
38. Chico A, Saigi I, Garcia-Patterson A, et al. Glycemic control and perinatal outcomes of pregnancies complicated by type 1 diabetes: Influence of continuous subcutaneous insulin infusion and lispro insulin. Diabetes Technol Ther 2010;12:937–45.
39. May ME, Young C, King J. Resource utilization in treatment of diabetic ketoacidosis in adults. Am J Med Sci 1993;306:287–94.
40. Levetan CS, Passaro MD, Jablonski KA, et al. Effect of physician specialty on outcomes in diabetic ketoacidosis. Diabetes Care 1999;22:1790–5.
41. Ullal J, McFarland R, Bachand M, et al. Use of a computer-based insulin infusion algorithm to treat diabetic ketoacidosis in the emergency department. Diabetes Technol Ther 2016;18:100–3.
42. Bull SV, Douglas IS, Foster M, et al. Mandatory protocol for treating adult patients with diabetic ketoacidosis decreases intensive care unit and hospital lengths of stay: Results of a nonrandomized trial. Crit Care Med 2007;35:41–6.
43. Waller SL, Delaney S, Strachan MW. Does an integrated care pathway enhance the management of diabetic ketoacidosis? Diabet Med 2007;24:359–63.

44. Devalia B. Adherance to protocol during the acute management of diabetic ketoacidosis: Would specialist involvement lead to better outcomes? Int J Clin Pract 2010;64:1580–2.
45. Salahuddin M, Anwar MN. Study on effectiveness of guidelines and high dependency unit management on diabetic ketoacidosis patients. J Postgrad Med Inst 2009;23:120–3.
46. Corl DE, Yin TS, Mills ME, et al. Evaluation of point-of-care blood glucose measurements in patients with diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome admitted to a critical care unit. J Diabetes Sci Technol 2013;7:1265–74.
47. Kreisberg RA. Diabetic ketoacidosis: New concepts and trends in pathogenesis and treatment. Ann Intern Med 1978;88:681–95.
48. Mahoney CP, Vlcek BW, DelAguila M. Risk factors for developing brain herniation during diabetic ketoacidosis. Pediatr Neurol 1999;21:721–7.
49. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990;13:22–33.
50. Adrogue HJ, Barrero J, Eknoyan G. Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis. Use in patients without extreme volume deficit. JAMA 1989;262:2108–13.
51. Fein IA, Rachow EC, Sprung CL, et al. Relation of colloid osmotic pressure to arterial hypoxemia and cerebral edema during crystalloid volume loading of patients with diabetic ketoacidosis. Ann Intern Med 1982;96:570–5.
52. Owen OE, Licht JH, Sapir DG. Renal function and effects of partial rehydration during diabetic ketoacidosis. Diabetes 1981;30:510–18.
53. Kitabchi AE, Ayyagari V, Guerra SM. The efficacy of low-dose versus conventional therapy of insulin for treatment of diabetic ketoacidosis. Ann Intern Med 1976;84:633–8.
54. Heber D, Molitch ME, Sperling MA. Low-dose continuous insulin therapy for diabetic ketoacidosis. Prospective comparison with "conventional" insulin therapy. Arch Intern Med 1977;137:1377–80.
55. Butkiewicz EK, Leibson CL, O'Brien PC, et al. Insulin therapy for diabetic ketoacidosis. Bolus insulin injection versus continuous insulin infusion. Diabetes Care 1995;18:1187–90.
56. Kitabchi AE, Murphy MB, Spencer J, et al. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? Diabetes Care 2008;31:2081–5.
57. Fort P, Waters SM, Lifshitz F. Low-dose insulin infusion in the treatment of diabetic ketoacidosis: Bolus versus no bolus. J Pediatr 1980;96:36–40.
58. Lindsay R, Bolte RG. The use of an insulin bolus in low-dose insulin infusion for pediatric diabetic ketoacidosis. Pediatr Emerg Care 1989;5:77–9.
59. Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, et al. Subcutaneous rapid-acting insulin analogues for diabetic ketoacidosis. Cochrane Database Syst Rev 2016;(1):CD011281.
60. Wiggam MI, O'Kane MJ, Harper R, et al. Treatment of diabetic ketoacidosis using normalization of blood 3-hydroxybutyrate concentration as the endpoint of emergency management. A randomized controlled study. Diabetes Care 1997;20:1347–52.
61. Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med 1986;105:836–40.
62. Gamba G, Oseguera J, Castrejón M, et al. Bicarbonate therapy in severe diabetic ketoacidosis. A double blind, randomized, placebo controlled trial. Rev Invest Clin 1991;43:234–8.
63. Hale PJ, Crase J, Nattrass M. Metabolic effects of bicarbonate in the treatment of diabetic ketoacidosis. Br Med J (Clin Res Ed) 1984;289:1035–8.
64. Soler NG, Bennett MA, Dixon K, et al. Potassium balance during treatment of diabetic ketoacidosis with special reference to the use of bicarbonate. Lancet 1972;2:665–7.
65. Carlotti AP, Bohn D, Mallie JP, et al. Tonicity balance, and not electrolyte-free water calculations, more accurately guides therapy for acute changes in natremia. Intensive Care Med 2001;27:921–4.
66. O'Malley G, Moran C, Draman MS, et al. Central pontine myelinolysis complicating treatment of the hyperglycaemic hyperosmolar state. Ann Clin Biochem 2008;45:440–3.
67. Waldhausl W, Kleinberger G, Korn A, et al. Severe hyperglycemia: Effects of rehydration on endocrine derangements and blood glucose concentration. Diabetes 1979;28:577–84.
68. Gerich JE, Martin MM, Recant L. Clinical and metabolic characteristics of hyperosmolar nonketotic coma. Diabetes 1971;20:228–38.
69. Keller U, Berger W. Prevention of hypophosphatemia by phosphate infusion during treatment of diabetic ketoacidosis and hyperosmolar coma. Diabetes 1980;29:87–95.
70. Wilson HK, Keuer SP, Lea AS, et al. Phosphate therapy in diabetic ketoacidosis. Arch Intern Med 1982;142:517–20.
71. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab 1983;57:177–80.
72. Singhal PC, Abramovici M, Ayer S, et al. Determinants of rhabdomyolysis in the diabetic state. Am J Nephrol 1991;11:447–50.
73. Booth GL, Fang J. Acute complications of diabetes. In: Hux JE, Booth GL, Slaughter PM, et al., eds. Diabetes in Ontario: An iCES practice atlas. Toronto: Institute for Clinical Evaluative Science (ICES), 2003.
74. Bagg W, Sathu A, Streat S, et al. Diabetic ketoacidosis in adults at Auckland hospital, 1988–1996. Aust N Z J Med 1998;28:604–8.
75. Umpierrez GE, Kelly JP, Navarrete JE, et al. Hyperglycemic crises in urban blacks. Arch Intern Med 1997;157:669–75.
76. Musey VC, Lee JK, Crawford R, et al. Diabetes in urban African-Americans. I. Cessation of insulin therapy is the major precipitating cause of diabetic ketoacidosis. Diabetes Care 1995;18:483–9.
77. Wachtel TJ, Silliman RA, Lamberton P. Predisposing factors for the diabetic hyperosmolar state. Arch Intern Med 1987;147:499–501.
78. Bellazzini MA, Meyer T. Pseudo-myocardial infarction in diabetic ketoacidosis with hyperkalemia. J Emerg Med 2010;39:e139–41.
79. Petrov D, Petrov M. Widening of the QRS complex due to severe hyperkalemia as an acute complication of diabetic ketoacidosis. J Emerg Med 2008;34:459–61.
80. Geddes J, Deans KA, Cormack A, et al. Cardiac troponin I concentrations in people presenting with diabetic ketoacidosis. Ann Clin Biochem 2007;44:391–3.
81. Talapatra I, Tymms DJ. Diabetic ketoacidosis precipitated by subacute (De Quervain's) thyroiditis. Pract Diabetes Int 2006;23:76–7.
82. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.

Literature Review Flow Diagram for Chapter 15: Hyperglycemic Emergencies in Adults



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems *for Systematic Reviews and Meta-Analyses*: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (82).

For more information, visit www.prisma-statement.org**.**

Hyperglycemic Crises: Diabetic Ketoacidosis (DKA), And Hyperglycemic Hyperosmolar State (HHS)

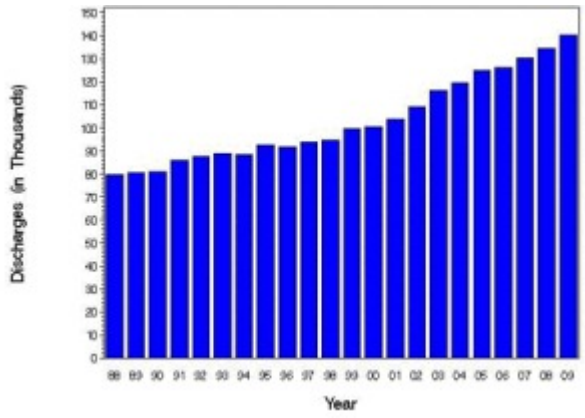
Gosmanov AR, Gosmanova EO, Kitabchi AE.

ABSTRACT

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute metabolic complications of diabetes mellitus that can occur in patients with both type 1 and 2 diabetes mellitus. Timely diagnosis, comprehensive clinical and biochemical evaluation, and effective management is key to the successful resolution of DKA and HHS. Critical components of the hyperglycemic crises management include coordinating fluid resuscitation, insulin therapy, and electrolyte replacement along with the continuous patient monitoring using available laboratory tools to predict the resolution of the hyperglycemic crisis. Understanding and prompt awareness of potential of special situations such as DKA or HHS presentation in comatose state, possibility of mixed acid-base disorders obscuring the diagnosis of DKA, and risk of brain edema during the therapy are important to reduce the risks of complications without affecting recovery from hyperglycemic crisis. Identification of factors that precipitated DKA or HHS during the index hospitalization should help prevent subsequent episode of hyperglycemic crisis. For complete coverage of all related areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) represent two extremes in the spectrum of decompensated diabetes. DKA and HHS remain important causes of morbidity and mortality among diabetic patients despite well-developed diagnostic criteria and treatment protocols (1). The annual incidence of DKA from population-based studies is estimated to range from 4 to 8 episodes per 1,000 patient admissions with diabetes (2). The incidence of DKA in the US continues to increase and it accounted for about 140,000 hospitalizations in 2009 (Figure 1a) and, most recently, in 2014 for 168,000 hospitalizations (3,4). The 2014 DKA hospitalization rates were the highest in persons aged <45 years (44.3 per 1,000) and lowest in persons aged ≥65 years (<2.0 per 1,000) (4). The rate of hospital admissions for HHS is lower than of DKA and is less than 1% of all diabetic-related admissions (5,6). In 2014, there were reported 207,000 emergency department visits with a diagnosis of hyperglycemic crisis (7). Decompensated diabetes imposes a heavy burden in terms of economics and patient outcomes. DKA is responsible for more than 500,000 hospital days per year at an estimated annual direct medical expense and indirect cost of 2.4 billion USD in 1997 (CDC) (8). The mortality rate for DKA and hyperglycemic crises has been falling over the years (Figure 1b) (3). In 2010, among adults aged 20 years or older, hyperglycemic crisis caused 2,361 deaths (9). There was a decline in mortality from 2000 to 2014 across all age groups and both sexes with largest absolute decrease among persons aged ≥75 years (4). The mortality rate of HHS is higher compared with DKA (10,11). Severe dehydration, older age, and the presence of comorbid conditions in patients with HHS account for the higher mortality in these patients (11).



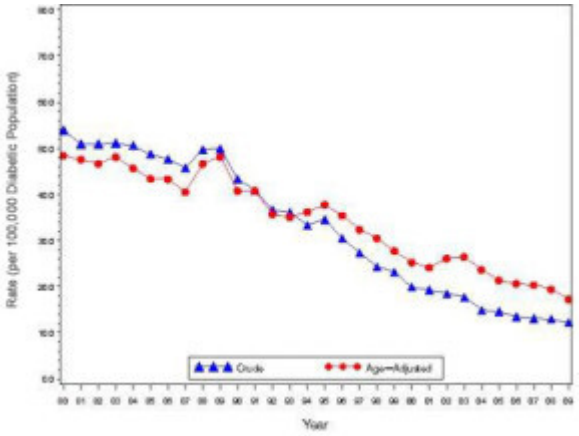


Figure 1a. Incidence of DKA 1980-2009 Figure 1b. Crude and Age-Adjusted Crises as Underlying Cause per 10 States, 1980-2009

Table

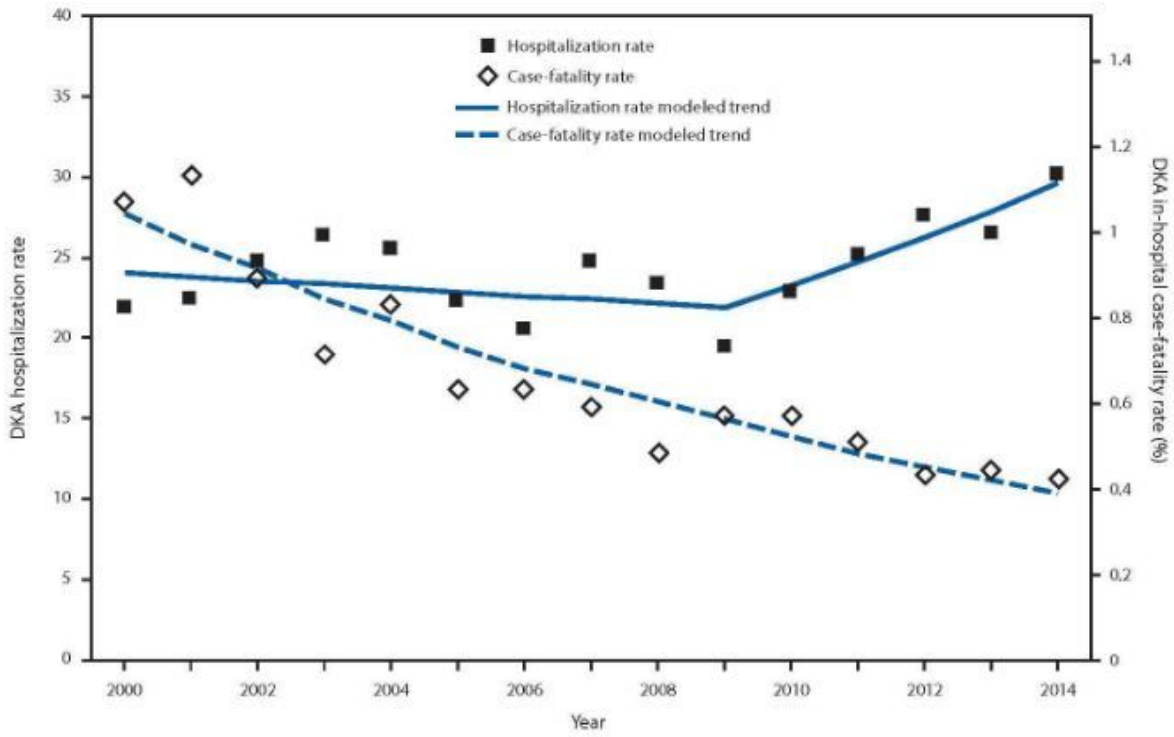
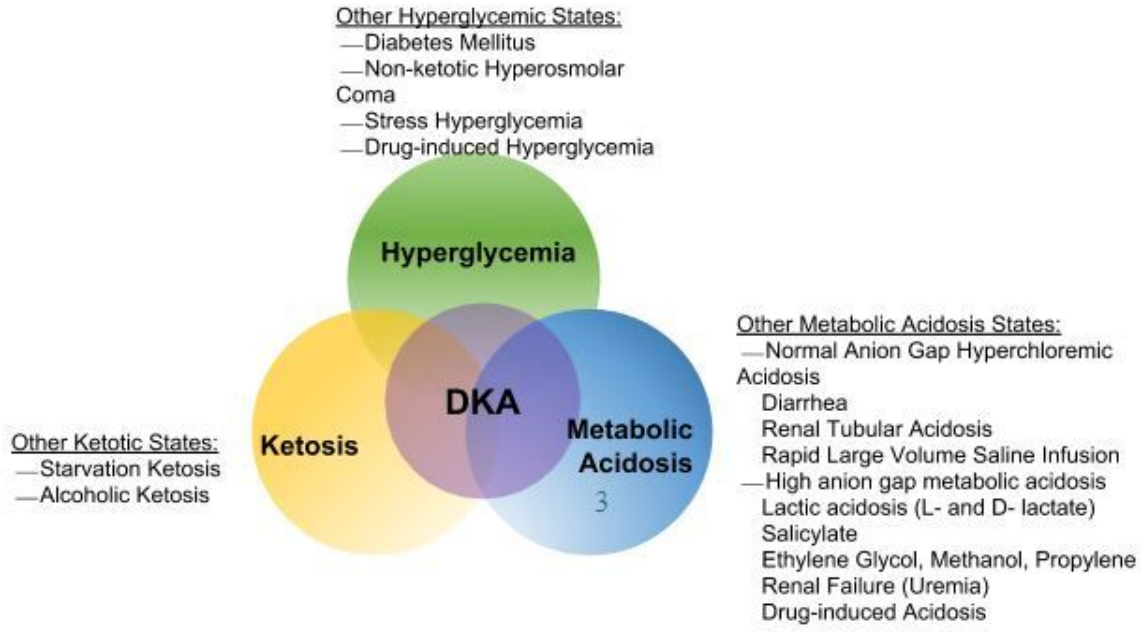


Figure 1c. Age-Adjusted DKA hospitalization rate per 1,000 persons with diabetes and in-hospital case-fatality rate, United States, 2000–2014 (4).

DEFINITIONS

DKA consists of the biochemical triad of hyperglycemia, ketonemia and high anion gap metabolic acidosis (12) (Figure 2). The terms “hyperglycemic hyperosmolar nonketotic state” and “hyperglycemic hyperosmolar nonketotic coma” have been replaced with the term “hyperglycemic hyperosmolar state” (HHS) to highlight that 1) the hyperglycemic hyperosmolar state may consist of moderate to variable degrees of clinical ketosis detected by nitroprusside method, and 2) alterations in consciousness may often be present without coma.

Figure 2. The triad of DKA (hyperglycemia, acidemia, and ketonemia) and other conditions with which the individual components are associated. From Kitabchi and Wall (12).



Both DKA and HHS are characterized by hyperglycemia and absolute or relative insulinopenia. Clinically, they differ by the severity of dehydration, ketosis and metabolic acidosis (11).

DKA most often occurs in patients with type 1 diabetes mellitus (T1DM). It also occurs in type 2 diabetes under conditions of extreme stress, such as serious infection, trauma, cardiovascular or other emergencies, and, less often, as a presenting manifestation of type 2 diabetes, a disorder called ketosis-prone type 2 diabetes (10). Similarly, whereas HHS occurs most commonly in T2DM, it can be seen in T1DM in conjunction with DKA.

PATHOGENESIS

The underlying defects in DKA and HHS are 1) reduced net effective action of circulating insulin as a result of decreased insulin secretion (DKA) or ineffective action of insulin in HHS (13-15), 2) elevated levels of counter regulatory hormones: glucagon (16,17), catecholamines (16,18), cortisol (16), and growth hormone (19,20), resulting in increased hepatic glucose production and impaired glucose utilization in peripheral tissues, and 3) dehydration and electrolyte abnormalities, mainly due to osmotic diuresis caused by glycosuria (21) (Figure 3). Diabetic ketoacidosis is also characterized by increased gluconeogenesis, lipolysis, ketogenesis, and decreased glycolysis (10).

DIABETIC KETOACIDOSIS

In DKA, there is a severe alteration of carbohydrate, protein, and lipid metabolism (5). In general, the body is shifted into a major catabolic state with breakdown of glycogen stores, hydrolysis of triglycerides from adipose tissues, and mobilization of amino acids from muscle (10). The released triglycerides and amino acids from the peripheral tissues become substrates for the production of glucose and ketone bodies by the liver (22). Hyperglycemia and ketone bodies production play central roles in developing this metabolic decompensation (23).

Hyperglycemia

The hyperglycemia in DKA is the result of three events: (a) increased gluconeogenesis; (b) increased glycogenolysis, and (c) decreased glucose utilization by liver, muscle and fat. Insulinopenia and elevated cortisol levels also lead to a shift from protein synthesis to proteolysis with resultant increase in production of amino acids (alanine and glutamine), which further serve as substrates for gluconeogenesis (5,24). Furthermore, muscle glycogen is catabolized to lactic acid via glycogenolysis. The lactic acid is transported to the liver in the Cori cycle where it serves as a carbon skeleton for gluconeogenesis (25). Increased levels of glucagon, catecholamines and cortisol with concurrent insulinopenia stimulate gluconeogenic enzymes, especially phosphoenol pyruvate carboxykinase (PEPCK) (19,26). Decreased glucose utilization is further exaggerated by increased levels of circulating catecholamines and FFA (27).

Ketogenesis

Excess catecholamines coupled with insulinopenia promote triglyceride breakdown (lipolysis) to free fatty acids (FFA) and glycerol. The latter provides a carbon skeleton for gluconeogenesis, while the former serves as a substrate for the formation of ketone bodies (28,29). The key regulatory site for fatty acid oxidation is known to be carnitine palmitoyltransferase 1(CPT1) which is inhibited by malonyl CoA in the normal non-fasted state

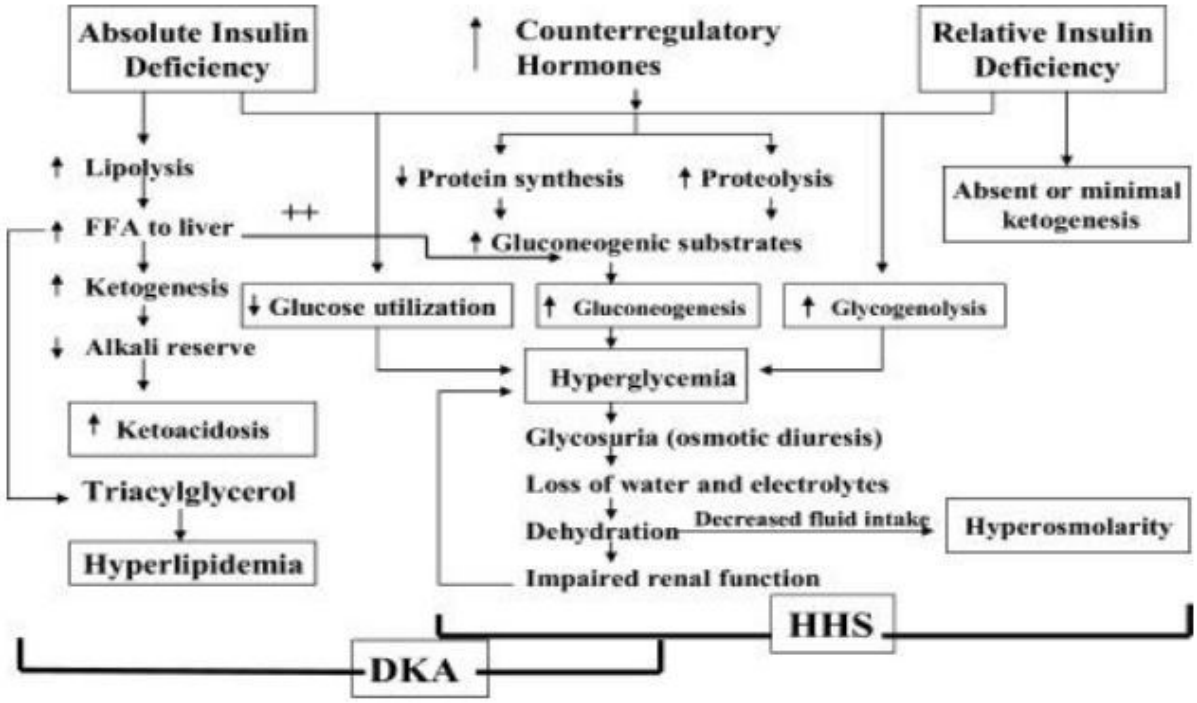
but the increased ratio of glucagon and other counter regulatory hormones to insulin disinhibit fatty acid oxidation and incoming fatty acids from fat tissue can be converted to ketone bodies (30,31). Increased production of ketone bodies (β-hydroxybutyrate and acetoacetate) leads to ketonemia (32). Ketonemia is further is maintained by the reduced liver clearance of ketone bodies in DKA. Extracellular and intracellular buffers neutralize hydrogen ions produced during hydrolysis of ketoacids. When overwhelming ketoacid production exceeds buffering capacity, a high anion gap metabolic acidosis develops. Studies in diabetic and pancreatectomized patients have demonstrated the cardinal role of hyperglucagonemia and insulinopenia in the genesis of DKA (33). In the absence of stressful situations, such as intravascular volume depletion or intercurrent illness, ketosis is usually mild (10,34).

Elevated levels of pro-inflammatory cytokines and lipid peroxidation markers, as well as procoagulant factors such as plasminogen activator inhibitor-1 (PAI-1) and C-reactive protein (CRP) have been demonstrated in DKA. The levels of these factors return to normal after insulin therapy and correction of hyperglycemia (35). This inflammatory and procoagulant state may explain the well-known association between hyperglycemic crisis and thrombotic state (36,37).

HYPERGLYCEMIC HYPEROSMOLAR STATE

While DKA is a state of near absolute insulinopenia, there is sufficient amount of insulin present in HHS to prevent lipolysis and ketogenesis but not adequate to cause glucose utilization (as it takes 1/10 as much insulin to suppress lipolysis as it does to stimulate glucose utilization) (26,27). In addition, in HHS there is a smaller increase in counter regulatory hormones (13,38).

Figure 3. Pathogenesis of DKA and HHS: stress, infection, or insufficient insulin. FFA, free fatty acid**.** Adapted from Kitabchi et al. (1).



PRECEPITATING FACTORS

The two most common precipitating factors in the development of DKA or HHS are inadequate insulin therapy (whether omitted or insufficient insulin regimen) or the presence of infection (39,40). Other provoking factors include myocardial infarction, cerebrovascular accidents, pulmonary embolism, pancreatitis, alcohol and illicit drug use (Table 1). In addition, numerous underlying medical illness and medications that cause the release of counter regulatory hormones and/or compromise the access to water can result in severe volume depletion and HHS (39). Drugs such as corticosteroids, thiazide diuretics, sympathomimetic agents (e.g., dobutamine and terbutaline), and second generation antipsychotic agents may precipitate DKA or HHS (11). Most recently, two new classes of medications have emerged as triggers for DKA. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) that are used for diabetes treatment have been implicated in the development of DKA in patients with both type 1 and type 2 diabetes (41). On the other hand, anti-cancer medications that belong to classes of immune checkpoint inhibitors such as Ipilimumab, Nivolumab, Pembrolizumab can cause DKA as the initial presentation of type 1 diabetes (42,43). In young patients

with type 1 diabetes, insulin omission due to fear of hypoglycemia or weight gain, the stress of chronic disease, and eating disorders, may contribute in 20% of recurrent DKA (44). Cocaine use also is associated with recurrent DKA (45,46). Mechanical problems with continuous subcutaneous insulin infusion (CSII) devices can precipitate DKA (47); however, with an improvement in technology and better education of patients, the incidence of DKA have been declining in insulin pump users (48). There are also case reports of patients with DKA as the primary manifestation of acromegaly (49-51).

Increasing numbers of DKA cases have been reported in patients with Type 2 DM. Available evidence shows that almost 50 % of newly diagnosed adult African American and Hispanic patients with DKA have type 2 diabetes (52). These ketosis-prone type 2 diabetic patients develop sudden-onset impairment in insulin secretion and action, resulting in profound insulinopenia (53). Clinical and metabolic features of these patients include high rates of obesity, a strong family history of diabetes, a measurable pancreatic insulin reserve, and a low prevalence of autoimmune markers of β-cell destruction (54-56). Aggressive management with insulin improves β-cell function, leading to discontinuance of insulin therapy within a few months of follow-up and 40% of these patients remain non-insulin dependent for 10 years after the initial episode of DKA (55). The etiology of acute transient failure of β-cells leading to DKA in these patients is not known, however, the suggested mechanisms include glucotoxicity, lipotoxicity, and genetic predisposition (57,58). A genetic disease, glucose-6-phosphate dehydrogenase deficiency, has been also linked with ketosis-prone diabetes (59).

Table 1 Common Precipitating Factors In DKA.

Table 1 Common Precipitating Factors In DKA.

Study location/dates	Number of cases	infection	Cardiovascular disease	Noncompliance	New onset	Other conditions	Unknown
Frankfurt, Germany Petzold et al 1971	472	19	6	38	+	+	+
Birmingham, UK Soler et al 1968-72	258	28	3	23	+	+	+
Erfurt, Germany Panzram 1970-71	133	35	4	21	+	+	+
Basel, Switzerland Faich et al 1975-79	163	56	5	31	+	+	+
Memphis, TN Kitabchi et al 1974-85	152	43	_	26	+	+	+
Atlanta, GA Umpierez et al 1993-94	202	38	_	28	22	10	4
Bronx,NY Nyenwe et al 2001-04	144	28	_	41	17	10	4
	219	25	3	44	25	12	15

Data are % of all cases except in Nyenwe et al, where new onset disease was not included in the percentage
+ complete data on these items were not given, therefore, the total is less than 100%.
Adapted with modification from ref 1.

CLINICAL FEATURES

DKA usually evolves rapidly within a few hours of the precipitating event(s). On the other hand, development of HHS is insidious and may occur over days to weeks (10). The common clinical presentation of DKA and HHS is due to hyperglycemia and include polyuria, polyphagia, polydipsia, weight loss, weakness, and physical signs of intravascular volume depletion, such as dry buccal mucosa, sunken eye balls, poor skin turgor, tachycardia, hypotension and shock in severe cases. Kussmaul respiration, acetone breath, nausea, vomiting and abdominal pain may also occur primarily in DKA and are due to ketosis and acidosis. Abdominal pain, which correlates with the severity of acidosis (60), may be severe enough to be confused with acute abdomen in 50-75% of cases (61). Therefore, in the presence of acidosis, DKA as an etiology of abdominal pain should be considered. Patients usually have normal body temperature or mild hypothermia regardless of presence of infection (62). Therefore, a careful search for a source of infection should be performed even in the absence of fever. Neurological status in patients with DKA may vary from full alertness to a profound

lethargy and coma, However, mental status changes in DKA are less frequent than HHS. The relationship of depressed consciousness and severity of hyperosmolality or DKA causes has been controversial (63,64). Some studies suggested that pH is the cause of mental status changes (65); while, others concluded that osmolality (66) is responsible for the comatose state. More recently, it has been proposed that consciousness level in adolescents with DKA was related to the severity of acidosis (pH) and not to a blood glucose levels (67). In our earlier studies of patients with DKA using low dose versus high dose insulin therapy, we evaluated the initial biochemical values of 48 patients with stupor/coma versus non comatose patients (68). Our study showed that glucose, bicarbonate, BUN and osmolality, and not pH were significantly different between non-comatose and comatose patients. Furthermore, in 3 separate studies in which 123 cases of DKA were evaluated, serum osmolality was also the most important determinant of mental status changes (12). However, in our recent retrospective study, it was shown that acidosis was independently associated with altered sensorium, but hyperosmolarity and serum “ketone” levels were not (69). In that study, a combination of acidosis and hyperosmolarity at presentation may identify a subset of patients with severe DKA (7% in this study) who may benefit from more aggressive treatment and monitoring. Identifying this class of patients, who are at a higher risk for poorer prognosis, may be helpful in triaging them, thus further improving the outcome (69). Furthermore, according to one study, ICU-admitted patients with DKA are less ill, and have lower disease severity scores, mortality, and shorter length of ICU and hospital stay, than non-DKA patients. Disease severity scores are not, but precipitating cause is, predictive of prolonged hospital stays in patients with DKA (70).

Table 2. Admission Clinical and Biochemical Profile in Comatose vs Non-Comatose Patients with DKA(69).

	Mental status		
	Alert	Altered	P
n	133	83	
Age (years)	37.1 ± 13.1	38.6 ± 11.5	0.41
Sex			0.05
Male	70	55	
Female	63	28	
Race			0.39
African American	116	71	
Caucasian	16	7	
Hispanic	2	1	
Others	3	0	
Type of diabetes			0.12
Type 1	94	45	
Type 2	24	21	
New-onset	24	8	
Systolic blood pressure	130 ± 21	122 ± 27	0.022*
Diastolic blood pressure	73 ± 18	70 ± 18	0.023*
Leucocytes	13.4 ± 6.7	17.1 ± 8.6	0.001*
Glucose	603 ± 236	747 ± 311	0.0004*
Serum ketones			0.06
Mild	46	20	
Moderate	68	43	
Large	16	19	
Blood pH	7.19 ± 0.10	7.05 ± 0.16	<0.0001*
Serum bicarbonate	11.8 ± 4.3	8.8 ± 4.7	<0.0001*
Anion gap	22.8 ± 6.7	29.8 ± 32.4	0.062
Serum osmolality	300.1 ± 18.0	310.8 ± 45.0	0.041*
Serum sodium	131.8 ± 6.2	131.2 ± 6.9	0.49
Serum potassium	5.1 ± 1.2	6.0 ± 5.5	0.14
Blood urea nitrogen	23.8 ± 16.8	33.8 ± 22.6	0.0007*
Serum creatinine	2.3 ± 1.1	3.1 ± 2.3	0.003*
pCO_2	50.0 ± 35.4	47.4 ± 38.5	0.61
pO_2	79.1 ± 52.8	88.3 ± 65.3	0.28

*Statistically significant.

In patients with HHS, neurological symptoms include clouding of sensorium which can progress to mental obtundation and coma (71). Occasionally, patients with HHS may present with focal neurological deficit and seizures (72,73). Most of the patients with HHS and an effective serum osmolality of >320 mOsm/kg are obtunded or comatose; on the other hand, the altered mental status rarely exists in patients with serum osmolality of <320 mOsm/kg (5). Therefore, severe alteration in the level of consciousness in patients with serum osmolality of <320 mOsm/kg requires evaluation for other causes including CVA and other catastrophic events like myocardial and bowel infarctions.

LABORATORY ABNORMALITIES AND DIAGNOSIS OF HYPERGLYCEMIC CRISES

The initial laboratory evaluation of patients with suspected DKA or HHS should include determination of plasma glucose, blood urea nitrogen, serum creatinine, serum ketones, electrolytes (with calculated anion gap), osmolality, urinalysis, urine ketones by dipstick, arterial blood gases, and complete blood count with differential. An electrocardiogram, blood, urine or sputum cultures and chest X-ray should also be performed, if indicated. HbA1c may be useful in differentiating chronic hyperglycemia of uncontrolled diabetes from acute metabolic decompensation in a previously well-controlled diabetic patient (11). Table 3 summarizes the biochemical criteria for DKA and HHS and electrolyte deficits in these two conditions. It also provides a simple method for calculating anion gap and serum osmolality.

Table 3. Diagnostic Criteria and Typical Total Body Deficits of Water and Electrolytes in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar Syndrome (HHS)

	DKA			HHS
	Mild (plasma glucose >250 mg/dl)	Moderate (plasma glucose >250 mg/dl)	Severe (plasma glucose >250 mg/dl)	Plasma glucose >600 mg/dl
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00	>7.30
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10	>18
Urine ketone*	Positive	Positive	Positive	Small
Serum ketone*	Positive	Positive	Positive	Small
Effective serum osmolality†	Variable	Variable	Variable	>320 mOsm/kg
Anion gap‡	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Nitroprusside reaction method. †Effective serum osmolality: 2[measured Na^+ (mEq/l)] + glucose (mg/dl)/18. ‡Anion gap: $(Na^+) - [(Cl^- + HCO_3^-$ (mEq/l)].

DKA can be classified as mild, moderate, or severe based on the severity of metabolic acidosis and the presence of altered mental status (11). Over 30% of patients have features of both DKA and HHS (10). Patients with HHS typically have pH >7.30, bicarbonate level >20 mEq/L, and negative ketone bodies in plasma and urine. However, some of them may have ketonemia. Several studies on serum osmolarity and mental alteration have established a positive linear relationship between osmolarity, pH and mental obtundation (68). Therefore, the occurrence of coma in the absence of definitive elevation of serum osmolality requires immediate consideration of other causes of mental status change. The levels of β-hydroxybutyrate (β-OHB) of ≥3.8mmol/L measured by a specific assay were shown to be highly sensitive and specific for DKA diagnosis (74). In patients with chronic kidney disease stage 4-5, the diagnosis of DKA could be challenging due to the presence of concomitant underlying chronic metabolic acidosis or mixed acid-base disorders. An anion gap of >20 mEq/L usually supports the diagnosis of DKA in these patients (75). Based on the 2009 American Diabetes Association publication, "euglycemic DKA" is characterized by metabolic acidosis, increased total body ketone concentration and blood glucose levels ≤250 mg/dL and is thought to occur in approximately 10% of patients with DKA and mostly associated with pregnancy and alcohol consumption (1). Since approval in 2013 and later of several SGLT-2 inhibitors for therapy of type 2 diabetes, multiple reports emerged demonstrating that the use of these medications can result in "euglycemic" DKA (41,76,77). Therefore, DKA must be excluded if high anion gap metabolic acidosis is present in a diabetic patient treated with SGLT-2 inhibitors irrespective if hyperglycemia is present or not.

The major cause of water deficit in DKA and HHS is glucose-mediated osmotic diuresis, which leads to loss of water in excess of electrolytes (78). Despite the excessive water loss, the admission serum sodium tends to be low. Because serum glucose in the presence of insulinopenia of DKA and HHS cannot penetrate to cells, in hyperglycemic crises, glucose becomes osmotically effective and causes water shifts from intracellular space to the extra cellular space resulting in dilution of sodium concentration – dilutional or hyperosmolar hyponatremia. Initially it has been thought that true sodium concentration (millimolar) can be obtained by multiplying excess glucose above 100 mg/dL by 1.6 /100 (79). It is, however, accepted now that true or corrected serum sodium concentration in patients experiencing hyperglycemic crisis should be calculated by adding 2.4 mmol/L to the measured serum sodium concentration for every 100 mg/dL incremental rise in serum glucose concentration above serum glucose concentration of 100 mg/dL (80). If the corrected sodium level remains low, hypertriglyceridemia (secondary to uncontrolled diabetes) should be also suspected. In this condition the plasma becomes milky and lipemia retinalis may be visible in physical examination (81). Osmotic diuresis and ketonuria also promote a total body sodium deficit via urinary losses, although concurrent conditions, such as diarrhea and vomiting, can further contribute to sodium losses. Total body sodium loss can result in contraction of extracellular fluid volume and signs of intravascular volume depletion. Serum potassium may be elevated on arrival due to insulin deficiency, volume depletion and a shift of potassium from intracellular to extra cellular compartments in response to acidosis (82). However, total body potassium deficit is usually present from urinary potassium losses due to osmotic diuresis and ketone excretion. More frequently, the initial serum potassium level is normal or low which is a danger sign. Initiation of insulin therapy, which leads to the transfer of potassium into cells, may cause fatal hypokalemia if potassium is not replaced early. Phosphate depletion in DKA is universal but on admission, like the potassium, it may be low, normal or high (83).

The differences and similarities in the admission biochemical data in patients with DKA or HHS are shown in Table 4.

Table 4. Biochemical Data in Patients with HHS and DKA (1).

	HHS	DKA
Glucose (mg/dl)	930 ± 83	616 ± 36
Na^+ (mEq/l)	149 ± 3.2	134 ± 1.0
K^+ (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
Free fatty acids (mmol/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 (ng/ml)	689 ± 215	580 ± 147
Catacholamines (ng/ml)	0.28 ± 0.09	1.78 ± 0.4
Growth hormone (ng/ml)	1.1	7.9
ΔGap: anion gap − 12 (mEq/l)	11	17

*According to the formula 2(Na + K) − urea (mmol/l) + glucose (mmol/l). †Values following intravenous administration of tolbutamide. IRI, immunoreactive insulin. (Adapted from ref. 4.)

Leukocytosis is a common finding in patients with DKA or HHS, but leukocytosis greater than 25,000 /μL suggests ongoing infection requiring further work up (84). The exact etiology of this non-specific leukocytosis is not known. One study also showed nonspecific leukocytosis in subjects with hypoglycemia induced by insulin injection and suggested that this phenomenon may be due to the increased levels of catecholamines, cortisol, and proinflammatory cytokines such as TNF-α during acute stress (85). Hypertriglyceridemia may be present in HHS (86) and is almost always seen in DKA (60). Hyperamylasemia, which correlates with pH and serum osmolality and elevated level of lipase, may occur in 16 - 25% of patients with DKA (87). The origin of amylase in DKA is usually non-pancreatic tissue such as the parotid gland (88).

Pitfalls of Laboratory Tests and Diagnostic Considerations for Interpreting Acid Base Status in DKA

False positive values for lipase may be seen if plasma glycerol levels are very high due to rapid breakdown of adipose tissue triglycerides (glycerol is the product measured in most assays for plasma lipase). Therefore, elevated pancreatic enzymes may not be reliable for the diagnosis of pancreatitis in the DKA setting. Other pitfalls include artificial elevation of serum creatinine due to interference from ketone bodies when a colorimetric method is used (89). Most of the laboratory tests for ketone bodies use the nitroprusside method, which detects acetoacetate, but not β-hydroxybutyrate (β-OHB). Additionally, since β-OHB is converted to acetoacetate during treatment (90), the serum ketone test may remain positive for a prolonged period suggesting erroneously that ketonemia is deteriorating; therefore, the follow up measurement of ketones during the treatment by nitroprusside method is not recommended (10). Newer glucose meters have the capability to measure β-OHB, which overcomes this problem (91,92). Furthermore drugs that have sulfhydryl groups can interact with the reagent in the nitroprusside reaction, giving a false positive result (93). Particularly important in this regard is captopril, an angiotensin converting enzyme inhibitor prescribed for the treatment of hypertension and diabetic nephropathy. Therefore, for the diagnosis of DKA, clinical judgment and consideration of other biochemical data are required to interpret the value of positive nitroprusside reactions in patients on captopril.

The classical presentation of acid-base disorders in DKA consists of increased anion gap metabolic acidosis where the relation of plasma anion gap change and bicarbonate change (Δ-Δ, ratio of AG change over change in bicarbonate) equals to 1 due to parallel reduction in plasma bicarbonate with the addition of ketoacids into the extravascular fluid space. With frequent additional bicarbonate losses in urine in the form of ketoanions during DKA, the initiation of intravenous volume resuscitation with chloride-containing solutions can further lower plasma bicarbonate and unmask non-anion gap metabolic acidosis when Δ-Δ becomes less than 1 due to changes in plasma bicarbonate that exceed the expected changes in AG. Respiratory compensation will accompany metabolic acidosis with reduction in PCO2 in arterial blood gas. The expected changes in PCO2 can be calculated using Winter's formula: PCO2 (mmHg) = 1.5 (Bicarbonate) + 8 ± 2 (94). Therefore, inappropriately high or low levels of PCO2, determined by ABG

will suggest the presence of a mixed acid-based disorder. For example, DKA patients with concomitant fever or sepsis may have additional respiratory alkalosis manifesting by lower than expected PCO2. In contrast, a higher than calculated PCO2 level signifies additional respiratory acidosis and can be seen in patients with underlying chronic lung disease. Vomiting is a common clinical manifestation in DKA and leads to a loss of hydrogen ions in gastric content and the development of metabolic alkalosis. Patients with DKA and vomiting may have relatively normal plasma bicarbonate levels and close to normal pH. However, AG will remain elevated and be an important clue for DKA. In addition, Δ-Δ ratio will be over 2 suggesting that there is less than expected reduction in bicarbonate as compared with increase in AG and confirm the presence of a mixed acid-base disorder (combination of metabolic acidosis and metabolic alkalosis). We recommend measurement of β-OHB in instances when a mixed acid-base disorder is present in patients with hyperglycemic crisis and DKA is suspected.

DIFFERENTIAL DIAGNOSIS

Patients may present with metabolic conditions resembling DKA or HHS. For example, in alcoholic ketoacidosis (AKA), total ketone bodies are much greater than in DKA with a higher β-OHB to acetoacetate ratio of 7:1 versus a ratio of 3:1 in DKA (5). The AKA patients seldom present with hyperglycemia (95). It is also possible that patients with a low food intake may present with mild ketoacidosis (starvation ketosis); however, serum bicarbonate concentration of less than 18 or hyperglycemia will be rarely present. Additionally, DKA has to be distinguished from other causes of high anion gap metabolic acidosis including lactic acidosis, advanced chronic renal failure, as well as ingestion of drugs such as salicylate, methanol and ethylene glycol. Isopropyl alcohol, which is commonly available as rubbing alcohol, can cause considerable ketosis and high serum osmolar gap without metabolic acidosis. Moreover, there is a tendency to hypoglycemia rather than hyperglycemia with isopropyl alcohol injection (96,97). Finally, patients with diabetes insipidus presenting with severe polyuria and dehydration, who are subsequently treated with free water in a form of intravenous dextrose water, can have hyperglycemia- a clinical picture that can be confused with HHS (98) (Table 5).

Table 5. Laboratory Evaluation of Metabolic Causes of Acidosis and Coma (10).

Table 5
Laboratory evaluation of metabolic causes of acidosis and coma

	Starvation or high fat intake	Diabetic ketoacidosis	Lactic acidosis	Uremic acidosis	Alcoholic ketosis (starvation)	Salicylate intoxication	Methanol or ethylene glycol intoxication	Hyperosmolar coma	Hypoglycemic coma	Rhabdomyolysis	Isopropyl alcohol
pH	Normal	↓	↓	Mild ↓	↓↑	↓↑[a]	↓	Normal	Normal	Mild ↓ may be ↓↓	Normal
Plasma glucose	Normal	↑	Normal	Normal	↓ or normal	Normal or ↓	Normal	↑↑> 500 mg/dL	↓↓ < 30 mg/dL	Normal	↓
Glycosuria Total plasma ketones[b]	Negative Slight ↑	++ ↑↑	Negative Normal	Negative Normal	Negative Slight to moderate ↑	Negative[c] Normal	Negative Normal	++ Normal or slight ↑	Negative Normal or slight ↑	Negative Normal	Negative ↑↑
Anion gap	Slight ↑	↑	↑	Slight ↑	↑	↑	↑	Normal	Normal or slight	↑↑	Normal
Osmolality	Normal	↑	Normal	↑	Normal	Normal	↑↑	↑↑>330 mOsm/kg	Normal	Normal or slight ↑	↑
Uric acid	Mild (starvation)	↑	Normal	Normal	↑	Normal	Normal	Normal	Normal	↑	Normal
Miscellaneous	False positive	May give lactate for ethylene glycol	Serum > 200 >7 mmol/L	SUN mg/dL	Salicylate	Serum levels positive	Serum positive		Hemoglobinuria	Myoglobinuria	

[a] Positive.
[b] Acetest and Ketostix measure acetoacetic acid only; thus, misleading low values may be obtained because the majority of "ketone bodies" are BOHB.
[c] Respiratory alkalosis/metabolic acidosis; may get false-positive or false-negative urinary glucose caused by the presence of salicylate or its metabolites.

TREATMENT OF DKA

The goals of therapy in patients with hyperglycemic crises include: 1) improvement of circulatory volume and tissue perfusion, 2) gradual reduction of serum glucose and osmolality, 3) correction of electrolyte imbalance, and 4) identification and prompt treatment of co-morbid precipitating causes (5). It must be emphasized that successful treatment of DKA and HHS requires frequent monitoring of patients regarding the above goals by clinical and laboratory parameters. Suggested approaches for the management of patients with DKA and HHS are illustrated in Figures 4 and 5.

Fluid Therapy

DKA and HHS are volume-depleted states with total body water deficit of approximately 6 L in DKA and 9 L in HHS (10,99,100). Therefore, the initial fluid therapy is directed toward expansion of intravascular volume and securing adequate urine flow. The initial fluid of choice is isotonic saline at the rate of 15–20 ml /kg body weight per hour or 1–1.5 L during the first hour. The choice of fluid for further repletion depends on the hydration status, serum electrolyte levels, and urinary output. In patients who are hypernatremic or eunatremic, 0.45% NaCl infused at 4–14 ml/kg/hour is appropriate, and 0.9% NaCl at a similar rate is preferred in patients with hyponatremia. The goal is to replace half of the estimated water and sodium deficit over a period of 12-24 hours [161]. In patients with hypotension, aggressive fluid therapy with isotonic saline should continue until blood pressure is stabilized. The administration of insulin without fluid replacement in such patients may further aggravate hypotension (10). Furthermore, the use of hydrating fluid in the first hour of therapy before insulin administration provides time to obtain serum potassium value before insulin administration, prevents possible deterioration of hypotensive patients with the use of insulin without adequate hydration, and decreases serum osmolality (11). Hydration alone may also reduce the level of counter-regulatory hormones and hyperglycemia (21). Intravascular volume expansion reduces serum blood glucose, BUN, and potassium levels without significant changes in pH or HCO3.The mechanism for lowering glucose is believed to be due to osmotic diuresis and modulation of counter-regulatory hormone release (16,101). We recommend avoiding too rapid correction of hyperglycemia (which may be associated with cerebral edema especially in children) and also inhibiting hypoglycemia (16,101). In HHS, the reduction in insulin infusion rate and/or use of D5 ½ NS should be started when blood glucose reaches 300 mg/dL, because overzealous use of hypotonic fluids has been associated with the development of cerebral edema (102). In one recent review, authors suggested gradual reduction in osmolality not exceeding 3 mOsm/kg H2O per hour and a fall of serum sodium at a rate of less than 0.5 mmol/L per hour in order to prevent significant osmotic shifts of water to intracellular compartment during the management of hyperglycemic crises (103). It should be emphasized that urinary losses of water and electrolytes are also need to be considered.

Insulin Therapy

The cornerstone of DKA and HHS therapy is insulin in physiologic doses. Insulin should only be started after serum potassium value is > 3.3 mmol/L (5). In DKA, we recommend using intravenous (IV) bolus of regular insulin (0.1 u/kg body weight) followed by a continuous infusion of regular insulin at the dose of 0.1u/kg/hr. The insulin infusion rate ion HHS should be lower as major pathophysiological process in these patients is severe dehydration. The optimal rate of glucose reduction is between 50-70 mg/hr. If desirable glucose reduction is not achieved in the first hour, an additional insulin bolus at 0.1 u/kg can be given. As mentioned earlier, when plasma glucose reaches 200-250 mg/dL in DKA or 300 in HHS, insulin rate should be decreased to 0.05 U/kg/hr, followed, as indicated, by the change in hydration fluid to D5 ½ NS. The rate of insulin infusion should be adjusted to maintain blood glucose between 150-200 mg/dL in DKA until it is resolved, and 250-300 mg/dL in HHS until mental obtundation and hyperosmolar state are corrected.

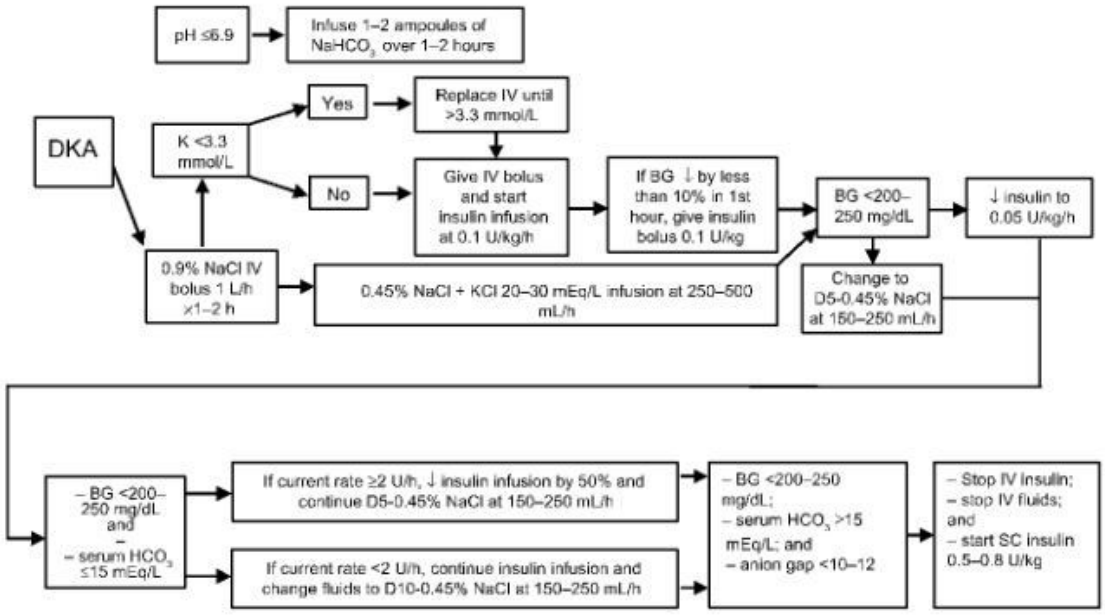
A study that investigated the optimum route of insulin therapy in DKA demonstrated that the time for resolution of DKA was identical in patients who received regular insulin via intravenous, intramuscular, or subcutaneous routes (104). However, patients who received intravenous insulin showed a more rapid decline in blood glucose and ketone bodies in the first 2 hours of treatment. Patients who received intravenous insulin attained an immediate pharmacologic level of insulin concentration. Thus, it was established that an intravenous loading dose of insulin would be beneficial regardless of the subsequent route of insulin administration during treatment. A follow up study demonstrated that a priming or loading dose given as one half by IV route and another half by intramuscular route was as effective as one dose given intravenously in lowering the level of ketone bodies in the first hour (105). A bolus or priming dose of insulin has been used in a number of studies. The need of such a method, when using intravenous infusion of insulin, is not clear, as there is no prospective randomized study to establish efficacy of bolus or priming dose before infusion of insulin. However, our study in children demonstrated the effectiveness of intravenous injection of insulin without a bolus dose (106). Therefore, it would appear that if intravenous insulin is used, priming or bolus dose insulin might not be necessary.

Several clinical studies have shown the potency and cost effectiveness of subcutaneous rapid-acting insulin analogs (lispro or aspart) in the management of patients with uncomplicated mild to moderate DKA (107,108). The patients received subcutaneous rapid-acting insulin doses of 0.2 U/kg initially, followed by 0.1 U/kg every 1 hour or an initial dose of 0.3 U/kg followed by 0.2 U/kg every 2 hours until blood glucose was < 250 mg/dL. Then the insulin dose was decreased by half to 0.05, or 0.1 U/kg respectively, and administered every 1 or 2 hours until resolution of DKA. There were no differences in length of hospital stay, total amount of insulin needed for resolution of hyperglycemia or ketoacidosis, or in the incidence of hypoglycemia among treatment groups. The use of insulin analogs allowed treatment of DKA in general wards or the emergency department and so reduced cost of hospitalization by 30% without any significant changes in hypoglycemic events (107). Similar results have been reported recently in pediatric patients with DKA (109). The administration of continuous IV infusion of regular insulin is the preferred route because of its short half-life and easy titration and the delayed onset of action and prolonged half-life of subcutaneous regular insulin. It is important to point out that the IV use of fast-acting insulin analogs is not recommended for patients with severe DKA or HHS, as there are no studies to support their use. Again, these agents may not be effective in patients with severe fluid depletion since they are given subcutaneously.

Potassium Therapy

Although total-body potassium is depleted (110,111), mild to moderate hyperkalemia frequently seen in patients with DKA is due to acidosis and insulinopenia. Insulin therapy, correction of acidosis, and volume expansion decrease serum potassium concentrations. To prevent hypokalemia, potassium replacement is initiated after serum levels fall below 5.3 mmol/L in patients with adequate urine output (50 ml/h). Adding 20–30 mmol potassium to each liter of infused fluid is sufficient to maintain a serum potassium concentration within the normal range of 4–5 mmol/L (5). Patients with DKA who had severe vomiting or had been on diuretics may present with significant hypokalemia. In such cases, potassium replacement should begin with fluid therapy, and insulin treatment should be postponed until potassium concentration becomes > 3.3 mmol/L in order to prevent arrhythmias and respiratory muscle weakness (112).

Figure 4. Protocol for the Management of Adult Patients with DKA. Adapted from (75).



Bicarbonate Therapy

The use of bicarbonate in treatment of DKA remains controversial. In patients with pH >7.0, insulin therapy inhibits lipolysis and also corrects ketoacidosis without use of bicarbonate. Bicarbonate therapy has been associated with some adverse effects, such as hypokalemia (113), decreased tissue oxygen uptake and cerebral edema (114,115) and delay in the resolution of ketosis (116). However, patients with severe DKA (low bicarbonate <10 mEq/L, or PCo2 < 12) may experience deterioration of pH if not treated with bicarbonate. A prospective randomized study in patients with pH between 6.9 and 7.1 showed that bicarbonate therapy had no risk or benefit in DKA (117). Therefore, in patients with pH between 6.9 and 7.0, it may be beneficial to give 50 mmol of bicarbonate in 200 ml of sterile water with 10 mmol KCL over two hours to maintain the pH at > 7.0 (5,118,119). Considering the adverse effects of severe acidosis such as impaired myocardial contractility, adult patients with pH < 6.9 should be given 100 mmol sodium bicarbonate in 400 ml sterile water (an isotonic solution) with 20 mmol KCl administered at a rate of 200 ml/h for two hours until the venous pH becomes greater than 7.0. Venous pH should be assessed every 2 hours until the pH rises to 7.0; treatment can be repeated every 2 hours if necessary.

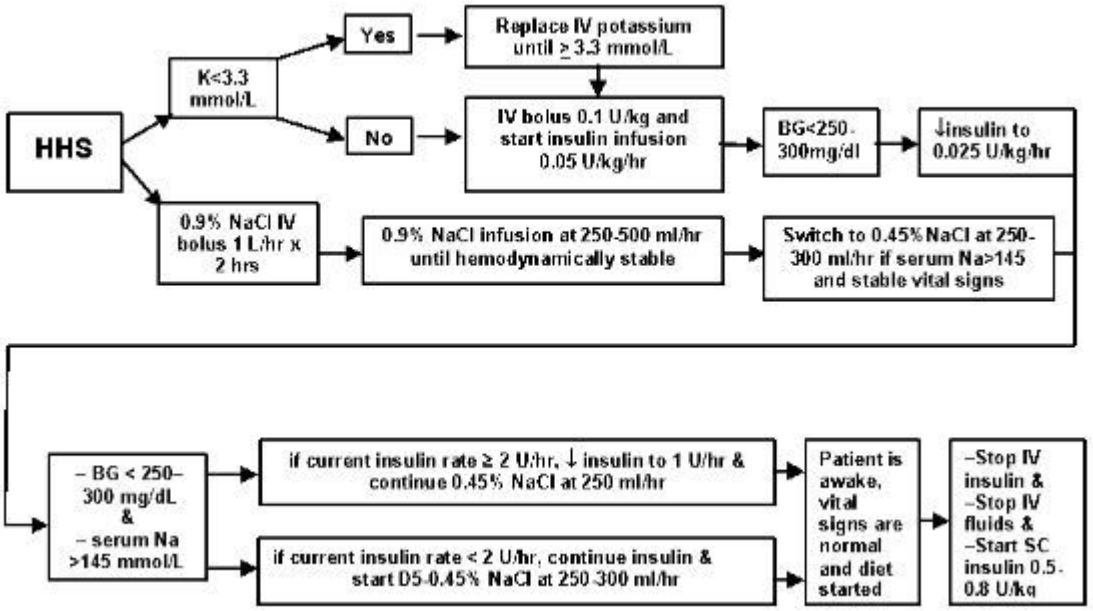
Phosphate Therapy

There is no evidence that phosphate therapy is necessary in treatment for better outcome of DKA (120-123). However, in patients with potential complications of hypophosphatemia, including cardiac and skeletal muscle weakness, the use of phosphate may be considered (124). Phosphate administration may result in hypocalcemia when used in high dose (120,123).

TREATMENT OF HHS

A similar therapeutic approach can be also recommended for treatment of HHS, but no bicarbonate therapy is needed for HHS, and changing to glucose-containing fluid is done when blood glucose reaches 300 mg/dL.

Figure 5. Protocol for the Management of Adult Patients with HHS.



Severe hyperosmolarity and dehydration associated with insulin resistance and presence of detectable plasma insulin level are the hallmarks of HHS pathophysiology. The main emphasis in the management of HHS is effective volume repletion and normalization of serum osmolality. There are no randomized controlled studies that evaluated safe and effective strategies in the treatment of HHS (102). It is important to start HHS therapy with the infusion of normal saline and monitor corrected serum sodium in order to determine appropriate timing of the change to hypotonic fluids. Insulin substitution approach should be very conservative as it is expected that insulin resistance will improve with rehydration. We recommend against rapid decreases in serum glucose and correction of serum sodium in order to avoid untoward effects of shifts in osmolarity on brain volume. This notion should particularly apply in the management of HHS in elderly and patients with multiple medical problems in whom it may not be clear how long these subjects experienced severe hyperglycemia prior to the admission to the hospital.

RESOLUTION OF DKA AND HHS

During follow up, blood should be drawn every 2-4 h for determination of serum electrolytes, glucose, blood urea nitrogen, creatinine, osmolality, and venous pH. After the initial arterial pH is drawn, venous pH can be used to assess the acid/base status. An equivalent arterial pH value is calculated by adding 0.03 to the venous pH value (125). The resolution of DKA is reached when the blood glucose is < 200 mg/dl, serum bicarbonate is ≥15 mEq/L, pH is >7.30 and anion gap is ≤12 mEq/L (11). HHS is resolved when serum osmolality is < 320 mOsm/kg with a gradual recovery to mental alertness. The latter may take twice as long as to achieve blood glucose control. Ketonemia typically takes longer to clear than hyperglycemia.

The proposed ADA criteria for DKA resolution include serum glucose level <200 mg/dL and two of the following: serum bicarbonate level ≥15 mEq/L, pH >7.3, and anion gap ≤12 mEq/L (1). Therefore, the treatment goal of DKA is to improve hyperglycemia and to stop ketosis with subsequent resolution of acidosis. In this regard, it is important to distinguish ketosis and acidosis, as the two terms are not always synonymous in DKA. Ketoacid production in DKA results in reduction in plasma bicarbonate (HCO3-) levels due to neutralization of hydrogen ion produced during dissociation of ketoacids in the extravascular fluid space. Concomitantly, ketoacid anion is added into extravascular space resulting in anion gap (AG) increase. The change in HCO3- concentration (Δ HCO3-/normal serum HCO3- – observed serum HCO3-) usually corresponds to equal changes in serum anion gap (Δ AG/observed AG – normal AG, both corrected for decreases and increases in plasma albumin concentration). Therefore, the ratio of AG excess to HCO3- deficit (delta-delta, or Δ-Δ) is close to 1 (124,126,127). In most patients with DKA bicarbonate deficit exceeds the addition of ketoanions, even though Δ-Δ ratio remains close to 1 (128). This is observed due to several reasons. First, hyperglycemia-induced osmotic diuresis leads to excretion of large amounts of sodium and potassium ions that is accompanied by the excretion of ketoanions. Ultimately, the amount of excreted ketoanions depends on degree of kidney function preservation with the largest amount of ketoanion loss in patients with relatively preserved glomerular filtration rate (126). Each ketoanion can be converted back to HCO3- during resolution of DKA and, therefore, ketoanion loss results in the loss of HCO3-. Additionally, extravascular fluid space contraction during DKA, leads to elevation of plasma HCO3-. Therefore, intravenous administration of sodium and chloride-containing fluids leads to further HCO3- reduction and hyperchloremic metabolic acidosis (124,126). This is an important point as persistent decrease in plasma HCO3- concentration should not be interpreted as a sign of continuous DKA if ketosis and hyperglycemia are resolving. Although not evaluated in prospective studies, measurement of serial levels of blood beta-hydroxybutyrate (β-OHB) can be useful adjunct to monitor the resolution of DKA (129). The expected fall in β-OHB with the adequate insulin dosing is 1mmol/L/hr; a lower decrease in blood β-OHB may suggest inadequate insulin provision.

Once DKA has resolved, patients who are able to eat can be started on a multiple dose insulin regimen with long acting insulin and short/rapid acting insulin given before meals as needed to control plasma glucose. Intravenous insulin infusion should be continued for 2 hours after giving the subcutaneous insulin to maintain adequate plasma insulin levels. Immediate discontinuation of intravenous insulin may lead to hyperglycemia or recurrence of ketoacidosis. If the patient is unable to eat, it is preferable to continue the intravenous insulin infusion and fluid replacement. Patients with known diabetes may be given insulin at the dose they were receiving before the onset of hyperglycemic crises. In patients with new onset diabetes, a multi-dose insulin regimen should be started at a dose of 0.5-0.8 U/kg per day, including regular or rapid-acting and basal insulin until an optimal dose is established (11).

COMPLICATIONS

The most common complications of DKA and HHS include hypoglycemia and hypokalemia due to overzealous treatment with insulin and bicarbonate (hypokalemia), but these complications occur infrequently with current low dose insulin regimens. During the recovery phase of DKA, patients commonly develop a short-lived hyperchloremic non-anion gap acidosis, which usually has few clinical consequences (130). Hyperchloremic acidosis is caused by the loss of large amounts of ketoanions, which are usually metabolized to bicarbonate during the evolution of DKA, and excess infusion of chloride containing fluids during treatment (131).

Cerebral edema, a frequently fatal complication of DKA, occurs in 0.7–1.0% of children, particularly those with newly diagnosed diabetes (101). It may also occur in patients with known diabetes and in very young adults usually under 20 years of age (132,133). Cerebral edema has also been reported in patients with HHS, with some cases of mortality (71). Clinically, cerebral edema is characterized by deterioration in the level of consciousness, lethargy, decreased arousal, and headache. Headache is the earliest clinical manifestation of cerebral edema. This is followed by altered level of consciousness and lethargy. Neurological deterioration may lead to seizures, incontinence, pupillary changes, bradycardia, and respiratory arrest. It may be so rapid in onset due to brain stem herniation that no papilledema is found. If deteriorating clinical symptoms occur, the mortality rate may become higher than 70%, with only 7–14% of patients recovering without permanent neurological deficit. Mannitol infusion and mechanical ventilation are used to combat cerebral edema. The cause of cerebral edema is not known with certainty. It may result from osmotically driven movement of water into the central nervous system when plasma osmolality declines too rapidly during treatment of DKA or HHS. As glucose concentration improves following insulin infusion and administration of the intravenous fluids, serum osmotic gradient previously contributed by hyperglycemia reduces which limits water shifts from the intracellular compartment. However, hyperglycemia treatment is associated with “recovery” in serum sodium that restores water transfer between extracellular and intracellular compartments and prevents water accumulation in cells (80). In cases when the serum glucose concentration improves to a greater extent than the serum sodium concentration rises, serum effective osmolality will decrease and may precipitate brain edema (134,135). Although the osmotically mediated mechanism seems most plausible, one study using magnetic resonance imaging (MRI) showed that cerebral edema was due to increased cerebral perfusion (116). Another postulated mechanism for cerebral edema in patients with DKA involves the cell membrane Na+/H+ exchangers, which are activated in DKA. The high H+ level allows more influx of Na+ thus increasing more influx of water to the cell with consequent edema (136). β-hydroxybutyrate and acetoacetate may also play a role in the pathogenesis of cerebral edema. These ketone bodies have been shown to affect vascular integrity and permeability, leading to edema formation (137). In summary, reasonable precautionary measures to decrease the risk of cerebral edema in high-risk patients include 1) avoidance of overenthusiastic hydration and rapid reduction of plasma osmolality and 2) closed hemodynamic monitoring (138).

Hypoxemia and rarely non-cardiogenic pulmonary edema may complicate the treatment of DKA [242]. Hypoxemia may be related to the reduction in colloid osmotic pressure that leads to accumulation of water in lungs and decreased lung compliance. The pathogenesis of pulmonary edema may be similar to that of cerebral edema suggesting that the sequestration of fluid in the tissues may be more widespread than is thought. Thrombotic conditions and disseminated intravascular coagulation may contribute to the morbidity and mortality of hyperglycemic emergencies (139-141). Prophylactic use of heparin, if there is no gastrointestinal hemorrhage, should be considered.

PREVENTION

Several studies suggested that the omission of insulin is one of the most common precipitating factors of DKA, sometimes because patients are socio-economically underprivileged, and may not have access to or afford medical care (142-144). In addition, they may have a propensity to use illicit drugs such as cocaine, which has been associated with recurrent DKA (45), or live in areas with higher food deprivation risk (145). Therefore, it is important to continuously re-assess socio-economic status of patients who had at least one episode of DKA. The most recent data demonstrating a significant increase in DKA hospitalization rates in diabetic persons aged 45 years and younger (4) suggests that this group of patients may require particular attention to understand why they are more vulnerable than others to develop hyperglycemic crisis. Education of the patient about sick day management is very vital to prevent DKA and should include information on when to contact the health care provider, blood glucose goals, use of insulin and initiation of appropriate nutrition during illness and should be reviewed with patients periodically. Patients must be advised to continue insulin and to seek professional advice early in the course of the illness. Close follow up is very important, as it has been shown that three-monthly visits to the endocrine clinic will reduce the number of ER admission for DKA (146). Close observation, early detection of symptoms and appropriate medical care would be helpful in preventing HHS in the elderly.

A study in adolescents with type 1 diabetes suggests that some of the risk factors for DKA include higher HbA1c, uninsured children and psychological problems (147). In other studies, education of primary care providers and school personnel in identifying the signs and symptoms of DKA has been shown to be effective in decreasing the incidence of DKA at the onset of diabetes (148). In another study outcome data of 556 patients with diabetes under continuing care over a 7-year period were examined. The hospitalization rates for DKA and amputation were decreased by 69 % due to continuing care and education (149). Considering DKA and HHS as potentially fatal and economically burdensome complications of diabetes, every effort for diminishing the possible risk factors is worthwhile.

REFERENCES

1. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes care 2009; 32:1335-1343
2. Johnson DD, Palumbo PJ, Chu CP. Diabetic ketoacidosis in a community-based population. Mayo Clin Proc 1980; 55:83-88
3. CDC. 2014 national diabetes fact sheet (http://www.cdc.gov/diabetes/statistics/dkafirst/index.htm) accessed 04.07.15;
4. Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in Diabetic Ketoacidosis Hospitalizations and In-Hospital Mortality - United States, 2000-2014. MMWR Morb Mortal Wkly Rep 2018; 67:362-365
5. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM. Management of hyperglycemic crises in patients with diabetes. Diabetes care 2001; 24:131-153
6. Matz R. Management of the hyperosmolar hyperglycemic syndrome. Am Fam Physician 1999; 60:1468-1476
7. CDC. 2017 national diabetes statistics (https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf) accessed 05.05.18;
8. Javor KA, Kotsanos JG, McDonald RC, Baron AD, Kesterson JG, Tierney WM. Diabetic ketoacidosis charges relative to medical charges of adult patients with type I diabetes. Diabetes care 1997; 20:349-354
9. Prevention. CfDCa. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014.
10. Kitabchi AE, Nyenwe EA. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endocrinol Metab Clin North Am 2006; 35:725-751, viii
11. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes care 2006; 29:2739-2748
12. Kitabchi AE, Wall BM. Diabetic ketoacidosis. Med Clin North Am 1995; 79:9-37
13. Chupin M, Charbonnel B, Chupin F. C-peptide blood levels in keto-acidosis and in hyperosmolar non-ketotic diabetic coma. Acta Diabetol Lat 1981; 18:123-128
14. Kipnis DM. Insulin secretion in diabetes mellitus. Annals of internal medicine 1968; 69:891-901
15. Kitabchi AE, Ayyagari V, Guerra SM. The efficacy of low-dose versus conventional therapy of insulin for treatment of diabetic ketoacidosis. Annals of internal medicine 1976; 84:633-638
16. Kitabchi AE, Young R, Sacks H, Morris L. Diabetic ketoacidosis: reappraisal of therapeutic approach. Annu Rev Med 1979; 30:339-357
17. Muller WA, Faloona GR, Unger RH. Hyperglucagonemia in diabetic ketoacidosis. Its prevalence and significance. Am J Med 1973; 54:52-57
18. Christensen NJ. Plasma norepinephrine and epinephrine in untreated diabetics, during fasting and after insulin administration. Diabetes 1974; 23:1-8
19. Alberti KG. Role of glucagon and other hormones in development of diabetic ketoacidosis. Lancet 1975; 1:1307-1311
20. Unger RH. High Growth-Hormone Levels in Diabetic Ketoacidosis: A Possible Cause of Insulin Resistance. JAMA 1965; 191:945-947
21. Waldhausl W, Kleinberger G, Korn A, Dudczak R, Bratusch-Marrain P, Nowotny P. Severe hyperglycemia: effects of rehydration on endocrine derangements and blood glucose concentration. Diabetes 1979; 28:577-584
22. Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. N Engl J Med 1983; 309:159-169
23. Miles JM, Rizza RA, Haymond MW, Gerich JE. Effects of acute insulin deficiency on glucose and ketone body turnover in man: evidence for the primacy of overproduction of glucose and ketone bodies in the genesis of diabetic ketoacidosis. Diabetes 1980; 29:926-930
24. Felig P, Wahren J. Influence of endogenous insulin secretion on splanchnic glucose and amino acid metabolism in man. The Journal of clinical investigation 1971; 50:1702-1711
25. Hue L. Gluconeogenesis and its regulation. Diabetes Metab Rev 1987; 3:111-126
26. Schade DS, Eaton RP. The temporal relationship between endogenously secreted stress hormones and metabolic decompensation in diabetic man. J Clin Endocrinol Metab 1980; 50:131-136
27. McGarry JD, Dobbins RL. Fatty acids, lipotoxicity and insulin secretion. Diabetologia 1999; 42:128-138
28. McGarry JD. Lilly Lecture 1978. New perspectives in the regulation of ketogenesis. Diabetes 1979; 28:517-523
29. Nurjhan N, Consoli A, Gerich J. Increased lipolysis and its consequences on gluconeogenesis in non-insulin-dependent diabetes mellitus. The Journal of clinical investigation 1992; 89:169-175

30. Balasse EO, Fery F. Ketone body production and disposal: effects of fasting, diabetes, and exercise. Diabetes Metab Rev 1989; 5:247-270
31. McGarry JD, Woeltje KF, Kuwajima M, Foster DW. Regulation of ketogenesis and the renaissance of carnitine palmitoyltransferase. Diabetes Metab Rev 1989; 5:271-284
32. Reichard GA, Jr., Skutches CL, Hoeldtke RD, Owen OE. Acetone metabolism in humans during diabetic ketoacidosis. Diabetes 1986; 35:668-674
33. Barnes AJ, Bloom SR, Goerge K, Alberti GM, Smythe P, Alford FP, Chisholm DJ. Ketoacidosis in pancreatectomized man. N Engl J Med 1977; 296:1250-1253
34. Cahill GF, Jr. Starvation in man. N Engl J Med 1970; 282:668-675
35. Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. Diabetes 2004; 53:2079-2086
36. Cherian SV, Khara L, Das S, Hamarneh WA, Garcha AS, Frechette V. Diabetic ketoacidosis complicated by generalized venous thrombosis: a case report and review. Blood Coagul Fibrinolysis 2012; 23:238-240
37. Wakabayashi S, Tsujimoto T, Kishimoto M, Ikeda N, Inoue K, Ihana N, Hamasaki H, Noto H, Yamamoto-Honda R, Kajio H, Noda M. Acute Multiple Arteriovenous Thromboses in a Patient with Diabetic Ketoacidosis. Intern Med 2015; 54:2025-2028
38. Gerich JE, Martin MM, Recant L. Clinical and metabolic characteristics of hyperosmolar nonketotic coma. Diabetes 1971; 20:228-238
39. Wachtel TJ, Silliman RA, Lamberton P. Predisposing factors for the diabetic hyperosmolar state. Arch Intern Med 1987; 147:499-501
40. Wachtel TJ, Tetu-Mouradjian LM, Goldman DL, Ellis SE, O'Sullivan PS. Hyperosmolarity and acidosis in diabetes mellitus: a three-year experience in Rhode Island. J Gen Intern Med 1991; 6:495-502
41. Fadini GP, Bonora BM, Avogaro A. SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA Adverse Event Reporting System. Diabetologia 2017; 60:1385-1389
42. Miyoshi Y, Ogawa O, Oyama Y. Nivolumab, an Anti-Programmed Cell Death-1 Antibody, Induces Fulminant Type 1 Diabetes. Tohoku J Exp Med 2016; 239:155-158
43. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A, investigators K-. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015; 372:2521-2532
44. Polonsky WH, Anderson BJ, Lohrer PA, Aponte JE, Jacobson AM, Cole CF. Insulin omission in women with IDDM. Diabetes care 1994; 17:1178-1185
45. Nyenwe EA, Loganathan RS, Blum S, Ezuteh DO, Erani DM, Wan JY, Palace MR, Kitabchi AE. Active use of cocaine: an independent risk factor for recurrent diabetic ketoacidosis in a city hospital. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2007; 13:22-29
46. Warner EA, Greene GS, Buchsbaum MS, Cooper DS, Robinson BE. Diabetic ketoacidosis associated with cocaine use. Arch Intern Med 1998; 158:1799-1802
47. Peden NR, Braaten JT, McKendry JB. Diabetic ketoacidosis during long-term treatment with continuous subcutaneous insulin infusion. Diabetes care 1984; 7:1-5
48. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. Diabetes care 2003; 26:1079-1087
49. Katz JR, Edwards R, Khan M, Conway GS. Acromegaly presenting with diabetic ketoacidosis. Postgrad Med J 1996; 72:682-683
50. Szeto CC, Li KY, Ko GT, Chow CC, Yeung VT, Chan JC, Cockram CS. Acromegaly in a woman presenting with diabetic ketoacidosis and insulin resistance. Int J Clin Pract 1997; 51:476-477
51. Vidal Cortada J, Conget Donlo JI, Navarro Tellez MP, Halperin Rabinovic I, Vilardell Latorre E. [Diabetic ketoacidosis as the first manifestation of acromegaly]. An Med Interna 1995; 12:76-78
52. Umpierrez GE, Casals MM, Gebhart SP, Mixon PS, Clark WS, Phillips LS. Diabetic ketoacidosis in obese African-Americans. Diabetes 1995; 44:790-795
53. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. Annals of internal medicine 2006; 144:350-357
54. Kitabchi AE. Ketosis-prone diabetes--a new subgroup of patients with atypical type 1 and type 2 diabetes? J Clin Endocrinol Metab 2003; 88:5087-5089
55. Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, Bolgiano D, Rodriguez L, Rajan A, Lernmark A, Balasubramanyam A. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis, and clinical outcomes. J Clin Endocrinol Metab 2003; 88:5090-5098
56. Mauvais-Jarvis F, Sobngwi E, Porcher R, Riveline JP, Kevorkian JP, Vaisse C, Charpentier G, Guillausseau PJ, Vexiau P, Gautier JF. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. Diabetes 2004; 53:645-653
57. Banerji MA, Chaiken RL, Huey H, Tuomi T, Norin AJ, Mackay IR, Rowley MJ, Zimmet PZ, Lebovitz HE. GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. Flatbush diabetes.

Diabetes 1994; 43:741-745

58. Umpierrez GE, Woo W, Hagopian WA, Isaacs SD, Palmer JP, Gaur LK, Nepom GT, Clark WS, Mixon PS, Kitabchi AE. Immunogenetic analysis suggests different pathogenesis for obese and lean African-Americans with diabetic ketoacidosis. Diabetes care 1999; 22:1517-1523
59. Sobngwi E, Gautier JF, Kevorkian JP, Villette JM, Riveline JP, Zhang S, Vexiau P, Leal SM, Vaisse C, Mauvais-Jarvis F. High prevalence of glucose-6-phosphate dehydrogenase deficiency without gene mutation suggests a novel genetic mechanism predisposing to ketosis-prone diabetes. J Clin Endocrinol Metab 2005; 90:4446-4451
60. Umpierrez G, Freire AX. Abdominal pain in patients with hyperglycemic crises. Journal of critical care 2002; 17:63-67
61. Campbell IW, Duncan LJ, Innes JA, MacCuish AC, Munro JF. Abdominal pain in diabetic metabolic decompensation. Clinical significance. JAMA 1975; 233:166-168
62. Matz R. Hypothermia in diabetic acidosis. Hormones 1972; 3:36-41
63. Alberti KG, Nattrass M. Severe diabetic ketoacidosis. Med Clin North Am 1978; 62:799-814
64. Ruderman NB, Goodman MN. Brain metabolism in diabetes. Horm Metab Res Suppl 1980; 9:1-8
65. Rosival V. The influence of blood hydrogen ion concentration on the level of consciousness in diabetic ketoacidosis. Ann Clin Res 1987; 19:23-25
66. Fulop M, Rosenblatt A, Kreitzer SM, Gerstenhaber B. Hyperosmolar nature of diabetic coma. Diabetes 1975; 24:594-599
67. Edge JA, Roy Y, Bergomi A, Murphy NP, Ford-Adams ME, Ong KK, Dunger DB. Conscious level in children with diabetic ketoacidosis is related to severity of acidosis and not to blood glucose concentration. Pediatr Diabetes 2006; 7:11-15
68. Morris LR, Kitabchi AE. Efficacy of low-dose insulin therapy for severely obtunded patients in diabetic ketoacidosis. Diabetes care 1980; 3:53-56
69. Nyenwe EA, Razavi LN, Kitabchi AE, Khan AN, Wan JY. Acidosis: the prime determinant of depressed sensorium in diabetic ketoacidosis. Diabetes care 2010; 33:1837-1839
70. Freire AX, Umpierrez GE, Afessa B, Latif KA, Bridges L, Kitabchi AE. Predictors of intensive care unit and hospital length of stay in diabetic ketoacidosis. Journal of critical care 2002; 17:207-211
71. Arieff AI. Cerebral edema complicating nonketotic hyperosmolar coma. Miner Electrolyte Metab 1986; 12:383-389
72. Guisado R, Arieff AI. Neurologic manifestations of diabetic comas: correlation with biochemical alterations in the brain. Metabolism: clinical and experimental 1975; 24:665-679
73. Harden CL, Rosenbaum DH, Daras M. Hyperglycemia presenting with occipital seizures. Epilepsia 1991; 32:215-220
74. Sheikh-Ali M, Karon BS, Basu A, Kudva YC, Muller LA, Xu J, Schwenk WF, Miles JM. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? Diabetes care 2008; 31:643-647
75. Gosmanov AR, Gosmanova EO, Dillard-Cannon E. Management of adult diabetic ketoacidosis. Diabetes Metab Syndr Obes 2014; 7:255-264
76. Handelsman Y, Henry RR, Bloomgarden ZT, Dagogo-Jack S, DeFronzo RA, Einhorn D, Ferrannini E, Fonseca VA, Garber AJ, Grunberger G, LeRoith D, Umpierrez GE, Weir MR. American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on the Association of Sglt-2 Inhibitors and Diabetic Ketoacidosis. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2016; 22:753-762
77. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes care 2015; 38:1687-1693
78. Umpierrez GE, Khajavi M, Kitabchi AE. Review: diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. Am J Med Sci 1996; 311:225-233
79. Robin AP, Ing TS, Lancaster GA, Soung LS, Sparagana M, Geis WP, Hano JE. Hyperglycemia-induced hyponatremia: a fresh look. Clin Chem 1979; 25:496-497
80. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E, Hyponatraemia Guideline Development G. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dial Transplant 2014; 29 Suppl 2:i1-i39
81. Kaminska ES, Pourmotabbed G. Spurious laboratory values in diabetic ketoacidosis and hyperlipidemia. The American journal of emergency medicine 1993; 11:77-80
82. Adrogue HJ, Lederer ED, Suki WN, Eknoyan G. Determinants of plasma potassium levels in diabetic ketoacidosis. Medicine (Baltimore) 1986; 65:163-172
83. Wilson HK, Keuer SP, Lea AS, Boyd AE, 3rd, Eknoyan G. Phosphate therapy in diabetic ketoacidosis. Arch Intern Med 1982; 142:517-520
84. Slovis CM, Mork VG, Slovis RJ, Bain RP. Diabetic ketoacidosis and infection: leukocyte count and differential as early predictors of serious infection. The American journal of emergency medicine 1987; 5:1-5
85. Razavi Nematollahi L, Kitabchi AE, Stentz FB, Wan JY, Larijani BA, Tehrani MM, Gozashti MH, Omidfar K, Taheri E. Proinflammatory cytokines in response to insulin-induced hypoglycemic stress in healthy subjects. Metabolism: clinical and experimental 2009; 58:443-448
86. Bewsher PD, Petrie JC, Worth HG. Serum lipid levels in hyperosmolar non-ketotic diabetic coma. Br Med J 1970; 3:82-84

87. Vinicor F, Lehrner LM, Karn RC, Merritt AD. Hyperamylasemia in diabetic ketoacidosis: sources and significance. Annals of internal medicine 1979; 91:200-204
88. Yadav D, Nair S, Norkus EP, Pitchumoni CS. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. Am J Gastroenterol 2000; 95:3123-3128
89. Gerard SK, Khayam-Bashi H. Characterization of creatinine error in ketotic patients. A prospective comparison of alkaline picrate methods with an enzymatic method. Am J Clin Pathol 1985; 84:659-664
90. Stephens JM, Sulway MJ, Watkins PJ. Relationship of blood acetoacetate and 3-hydroxybutyrate in diabetes. Diabetes 1971; 20:485-489
91. Fulop M, Murthy V, Michilli A, Nalamati J, Qian Q, Saitowitz A. Serum beta-hydroxybutyrate measurement in patients with uncontrolled diabetes mellitus. Arch Intern Med 1999; 159:381-384
92. Porter WH, Yao HH, Karounos DG. Laboratory and clinical evaluation of assays for beta-hydroxybutyrate. Am J Clin Pathol 1997; 107:353-358
93. Csako G, Elin RJ. Unrecognized false-positive ketones from drugs containing free-sulfhydryl group(s). JAMA 1993; 269:1634
94. Albert MS, Dell RB, Winters RW. Quantitative displacement of acid-base equilibrium in metabolic acidosis. Annals of internal medicine 1967; 66:312-322
95. Halperin ML, Hammeke M, Josse RG, Jungas RL. Metabolic acidosis in the alcoholic: a pathophysiologic approach. Metabolism: clinical and experimental 1983; 32:308-315
96. Bjellerup P, Kallner A, Kollind M. GLC determination of serum-ethylene glycol, interferences in ketotic patients. J Toxicol Clin Toxicol 1994; 32:85-87
97. Paulson WD, Gadallah MF. Diagnosis of mixed acid-base disorders in diabetic ketoacidosis. Am J Med Sci 1993; 306:295-300
98. Freidenberg GR, Kosnik EJ, Sotos JF. Hyperglycemic coma after suprasellar surgery. N Engl J Med 1980; 303:863-865
99. Hillman K. Fluid resuscitation in diabetic emergencies--a reappraisal. Intensive Care Med 1987; 13:4-8
100. Diabetes Canada Clinical Practice Guidelines Expert C, Goguen J, Gilbert J. Hyperglycemic Emergencies in Adults. Can J Diabetes 2018; 42 Suppl 1:S109-S114
101. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes care 1990; 13:22-33
102. Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. Diabetes care 2014; 37:3124-3131
103. Cardoso L, Vicente N, Rodrigues D, Gomes L, Carrilho F. Controversies in the management of hyperglycaemic emergencies in adults with diabetes. Metabolism: clinical and experimental 2017; 68:43-54
104. Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low-dose insulin therapy by various routes. N Engl J Med 1977; 297:238-241
105. Sacks HS, Shahshahani M, Kitabchi AE, Fisher JN, Young RT. Similar responsiveness of diabetic ketoacidosis to low-dose insulin by intramuscular injection and albumin-free infusion. Annals of internal medicine 1979; 90:36-42
106. Burghen GA, Etteldorf JN, Fisher JN, Kitabchi AQ. Comparison of high-dose and low-dose insulin by continuous intravenous infusion in the treatment of diabetic ketoacidosis in children. Diabetes care 1980; 3:15-20
107. Umpierrez GE, Cuervo R, Karabell A, Latif K, Freire AX, Kitabchi AE. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes care 2004; 27:1873-1878
108. Umpierrez GE, Latif K, Stoever J, Cuervo R, Park L, Freire AX, A EK. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med 2004; 117:291-296
109. Della Manna T, Steinmetz L, Campos PR, Farhat SC, Schvartsman C, Kuperman H, Setian N, Damiani D. Subcutaneous use of a fast-acting insulin analog: an alternative treatment for pediatric patients with diabetic ketoacidosis. Diabetes care 2005; 28:1856-1861
110. Atchley DW, Loeb RF, Richards DW, Benedict EM, Driscoll ME. ON DIABETIC ACIDOSIS: A Detailed Study of Electrolyte Balances Following the Withdrawal and Reestablishment of Insulin Therapy. The Journal of clinical investigation 1933; 12:297-326
111. Beigelman PM. Potassium in severe diabetic ketoacidosis. Am J Med 1973; 54:419-420
112. Abramson E, Arky R. Diabetic acidosis with initial hypokalemia. Therapeutic implications. JAMA 1966; 196:401-403
113. Viallon A, Zeni F, Lafond P, Venet C, Tardy B, Page Y, Bertrand JC. Does bicarbonate therapy improve the management of severe diabetic ketoacidosis? Crit Care Med 1999; 27:2690-2693
114. Glaser NS, Wootton-Gorges SL, Marcin JP, Buonocore MH, Dicarlo J, Neely EK, Barnes P, Bottomly J, Kuppermann N. Mechanism of cerebral edema in children with diabetic ketoacidosis. J Pediatr 2004; 145:164-171
115. Krane EJ, Rockoff MA, Wallman JK, Wolfsdorf JI. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. N Engl J Med 1985; 312:1147-1151
116. Okuda Y, Adrogue HJ, Field JB, Nohara H, Yamashita K. Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. J Clin Endocrinol Metab 1996; 81:314-320
117. Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. Annals of internal medicine 1986; 105:836-840

118. Green SM, Rothrock SG, Ho JD, Gallant RD, Borger R, Thomas TL, Zimmerman GJ. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. Ann Emerg Med 1998; 31:41-48
119. Lever E, Jaspan JB. Sodium bicarbonate therapy in severe diabetic ketoacidosis. Am J Med 1983; 75:263-268
120. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab 1983; 57:177-180
121. Keller U, Berger W. Prevention of hypophosphatemia by phosphate infusion during treatment of diabetic ketoacidosis and hyperosmolar coma. Diabetes 1980; 29:87-95
122. Kreisberg RA. Phosphorus deficiency and hypophosphatemia. Hosp Pract 1977; 12:121-128
123. Winter RJ, Harris CJ, Phillips LS, Green OC. Diabetic ketoacidosis. Induction of hypocalcemia and hypomagnesemia by phosphate therapy. Am J Med 1979; 67:897-900
124. Adrogue HJ, Wilson H, Boyd AE, 3rd, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med 1982; 307:1603-1610
125. Kelly AM. The case for venous rather than arterial blood gases in diabetic ketoacidosis. Emerg Med Australas 2006; 18:64-67
126. Adrogue HJ, Eknoyan G, Suki WK. Diabetic ketoacidosis: role of the kidney in the acid-base homeostasis re-evaluated. Kidney Int 1984; 25:591-598
127. Oster JR, Epstein M. Acid-base aspects of ketoacidosis. Am J Nephrol 1984; 4:137-151
128. Kamel KS, Halperin ML. Acid-base problems in diabetic ketoacidosis. N Engl J Med 2015; 372:546-554
129. Wallace TM, Matthews DR. Recent advances in the monitoring and management of diabetic ketoacidosis. QJM 2004; 97:773-780
130. Fleckman AM. Diabetic ketoacidosis. Endocrinol Metab Clin North Am 1993; 22:181-207
131. Oh MS, Carroll HJ, Goldstein DA, Fein IA. Hyperchloremic acidosis during the recovery phase of diabetic ketosis. Annals of internal medicine 1978; 89:925-927
132. Duck SC, Wyatt DT. Factors associated with brain herniation in the treatment of diabetic ketoacidosis. J Pediatr 1988; 113:10-14
133. Silver SM, Clark EC, Schroeder BM, Sterns RH. Pathogenesis of cerebral edema after treatment of diabetic ketoacidosis. Kidney Int 1997; 51:1237-1244
134. Haringhuizen A, Tjan DH, Grool A, van Vugt R, van Zante AR. Fatal cerebral oedema in adult diabetic ketoacidosis. The Netherlands journal of medicine 2010; 68:35-37
135. Hoorn EJ, Carlotti AP, Costa LA, MacMahon B, Bohn G, Zietse R, Halperin ML, Bohn D. Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. The Journal of pediatrics 2007; 150:467-473
136. Smedman L, Escobar R, Hesser U, Persson B. Sub-clinical cerebral oedema does not occur regularly during treatment for diabetic ketoacidosis. Acta Paediatr 1997; 86:1172-1176
137. Isales CM, Min L, Hoffman WH. Acetoacetate and beta-hydroxybutyrate differentially regulate endothelin-1 and vascular endothelial growth factor in mouse brain microvascular endothelial cells. Journal of diabetes and its complications 1999; 13:91-97
138. Edge JA. Cerebral oedema during treatment of diabetic ketoacidosis: are we any nearer finding a cause? Diabetes Metab Res Rev 2000; 16:316-324
139. Buyukasik Y, Ileri NS, Haznedaroglu IC, Karaahmetoglu S, Muftuoglu O, Kirazli S, Dundar S. Enhanced subclinical coagulation activation during diabetic ketoacidosis. Diabetes care 1998; 21:868-870
140. McLaren EH, Cullen DR, Brown MJ. Coagulation abnormalities in diabetic coma before and 24 hours after treatment. Diabetologia 1979; 17:345-349
141. Timperley WR, Preston FE, Ward JD. Cerebral intravascular coagulation in diabetic ketoacidosis. Lancet 1974; 1:952-956
142. Maldonado MR, Chong ER, Oehl MA, Balasubramanyam A. Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause. Diabetes care 2003; 26:1265-1269
143. Musey VC, Lee JK, Crawford R, Klatka MA, McAdams D, Phillips LS. Diabetes in urban African-Americans. I. Cessation of insulin therapy is the major precipitating cause of diabetic ketoacidosis. Diabetes care 1995; 18:483-489
144. Randall L, Begovic J, Hudson M, Smiley D, Peng L, Pitre N, Umpierrez D, Umpierrez G. Recurrent diabetic ketoacidosis in inner-city minority patients: behavioral, socioeconomic, and psychosocial factors. Diabetes care 2011; 34:1891-1896
145. Lindner LME, Rathmann W, Rosenbauer J. Inequalities in glycaemic control, hypoglycaemia and diabetic ketoacidosis according to socio-economic status and area-level deprivation in Type 1 diabetes mellitus: a systematic review. Diabet Med 2018; 35:12-32
146. Laffel LM, Brackett J, Ho J, Anderson BJ. Changing the process of diabetes care improves metabolic outcomes and reduces hospitalizations. Qual Manag Health Care 1998; 6:53-62
147. Rewers A, Chase HP, Mackenzie T, Walravens P, Roback M, Rewers M, Hamman RF, Klingensmith G. Predictors of acute complications in children with type 1 diabetes. JAMA 2002; 287:2511-2518
148. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. Diabetes care 1999; 22:7-9

149. Runyan JW, Jr., Zwaag RV, Joyner MB, Miller ST. The Memphis diabetes continuing care program. Diabetes care 1980; 3:382-386

Publication Details

Author Information

Adair R Gosmanov, M.D., Ph.D., F.A.C.E.

Associate Professor of Medicine, Division of Endocrinology, Department of Medicine, Albany Medical College, Albany, NY and Endocrinology Section, Stratton VAMC, Albany, NY. agosmanov@gmail.com

Elvira O Gosmanova, M.D., F.A.S.N.

Associate Professor of Medicine, Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN

Abbas E Kitabchi, M.D., Ph.D., M.A.C.E.

Professor of Medicine and Molecular Sciences Emeritus, Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN

Publication History

Last Update: May 17, 2018.

Copyright

Publisher

MDText.com, Inc., South Dartmouth (MA)

NLM Citation

Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic Crises: Diabetic Ketoacidosis (DKA), And Hyperglycemic Hyperosmolar State (HHS) [Updated 2018 May 17]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-.