Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

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

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

Most patients with DKA have type 1 diabetes; however, patients with type 2 diabetes are also at risk during the catabolic stress of acute illness. Contrary to popular belief, DKA is more common in adults than in children. In community-based studies, more than 40% of African-American patients with DKA were >40 years of age and more than 20% were >55 years of age. Many of these adult patients with DKA were classified as having type 2 diabetes because 29% of patients were obese, had measurable insulin secretion, and had a low prevalence of autoimmune markers of β-cell destruction.

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

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

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

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

DKA is characterized by hyperglycemia, metabolic acidosis, and increased circulating total body ketone concentration. Ketoadsosis results from the lack of, or ineffective-ness of, insulin with concomitant eleva-tion of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone).2,3 The association of insulin deficiency and increased counterregulatory hormones leads to altered glucose production and disposal and to increased lipolysis and production of ketone bodies. 

Hyperglycemia results from increased hepatic and renal glucose production (gluconeogenesis and glycolysis) and impaired glucose utilization in peripheral tissues.7 Increased gluco-neogenesis results from the high avail-ability of noncarbohydrate substrates (alanine, lactate, and glycerol in the liver and glutamine in the kidney)9 and from the increased activity of glu-coneogenic enzymes (phosphoenol pyruvate carboxykinase [PEPCK], fructose-1,6-bisphosphatase, and pyruvate carboxylase). From a quanti-tative standpoint, increased hepatic glucose production represents the major pathogenic disturbance responsi-ble for hyperglycemia in patients with DKA.3 In addition, both hyper-glycemia and high ketone levels cause osmotic diuresis that leads to hypo-volemia and decreased glomerular fil- tration rate. The latter further aggra-vates hyperglycemia.

The mechanisms that underlie the increased production of ketones have recently been reviewed.6 The combina-tion of insulin deficiency and increased concentration of counterregulatory hormones causes the activation of hor-mone-sensitive lipase in adipose tissue. The increased activity of tissue lipase causes breakdown of triglyceride into glycerol and free fatty acids (FFA). While glycerol becomes an important substrate for gluconeogenesis in the liver, the massive release of FFA assumes pathophysiological predomi-nance, as they are the hepatic precursors of the ketoacids. In the liver, FFA are oxidized to ketone bodies, a process predominantly stimulated by glucagon. Increased concentration of glucagon lowers the hepatic levels of malonyl coenzyme A (CoA) by block-ing the conversion of pyruvate to acetyl CoA through inhibition of acetyl CoA carboxylase, the first rate-limiting enzyme in de novo fatty acid synthesis. Malonyl CoA inhibits carni-tine palmitoyl-transferase I (CPT I), the rate-limiting enzyme for transester-fi-fication of fatty acyl CoA to fatty acyl carni-tine, allowing oxidation of fatty acids to ketone bodies. CPT I is re-quired for movement of FFA into the mitochondria where fatty acid oxidation takes place. The increased activity of fatty acyl CoA and CPT I in DKA leads to accelerated ketogenesis.6

Studies in animals and humans with diabetes have shown that lower insulin levels are needed for antilipoly-sis than for peripheral glucose uptake.10,11 HHS is characterized by a relative deficiency of insulin concentra-tion to maintain normoglycemia but adequate levels to prevent lipolysis and ketogenesis.11 To date, very few studies have been performed compar-ing differences in counterregulatory response in DKA versus HHS. Patients with HHS have been reported to have higher insulin concentration (demonstrated by basal and stimulat-ed C-peptide levels),12 and reduced concentra-tions of FFA, cortisol, growth hormone, and glucagon com-pared to patients with DKA.12–14 However, one study reported similar levels of FFA in patients with DKA and HHS,12 indicating that further studies are needed to characterize metabolic responses in such patients.

PRECIPITATING CAUSES

DKA is the initial manifestation of diabetes in 20% of adult patients3 and 30–40% of children15,16 with type 1 diabetes. In patients with established diabetes, precipitating factors for DKA include infections, intercurrent illness-es, psychological stress, and poor com-pliance with therapy. Infection is the most common precipitating factor for DKA, occurring in 30–50% of cases. Urinary tract infection and pneumonia account for the majority of infections. Other acute conditions that may precip-itate DKA include cerebrovascular accident, alcohol/drug abuse, pancre-atitis, pulmonary embolism, myocard-ial infarction, and trauma. Drugs that affect carbohydrate metabolism, such as corticosteroids, thiazides, sympath-omimetic agents, and pentamidine, may also precipitate the development of DKA.

Recent studies have emphasized the importance of noncompliance and psychological factors in the incidence of DKA. In a survey of 341 female patients with type 1 diabetes,17 it was reported that psychological problems complicated by eating disorders were a contributing factor in 20% of recur-ent ketoacidosis in young women. M ore recently, it was reported that up to one-third of young women with type 1 diabetes have eating distur-bances,18 which affect the manage-ment of diabetes and increase the risk of microvascular complications. Factors that may lead to insulin omission in young subjects included fear of gaining weight with good metabolic control, fear of hypoglycemia, rebellion from authority, and diabetes-related stress. Noncompliance with therapy has also been reported to be a major precipitating cause for DKA in urban black and medically indigent patients. A recent study reported that in urban black patients, poor compli ance with insulin accounted for more than 50% of DKA cases admitted to a major urban hospital.3

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

DIAGNOSIS

Symptoms and Signs

The clinical presentation of DKA usu-ally develops rapidly, over a period of <24 hours. Polyuria, polydipsia, and weight loss may be present for several days before the development of ketoacidosis, and vomiting and abdominal pain are frequently the presenting symptoms. Abdominal pain, sometimes mimicking an acute abdomen, is reported in 40–75% of cases of DKA.20 In our institution, we have observed that the presence of abdominal pain is associated with a more severe metabolic acidosis and
with a history of alcohol or cocaine abuse, but not with the severity of hyperglycemia or dehydration. Although the potential of an acute abdominal problem requiring surgical intervention should not be overlooked, in the majority of patients, the abdominal pain spontaneously resolves after correction of the metabolic disturbance.

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

Typical patients with HHS have undiagnosed diabetes, are between 55 and 70 years of age, and frequently are nursing home residents. Most patients who develop HHS do so over days to weeks during which they experience polyuria, polydipsia, and progressive decline in the level of consciousness. The most common clinical presentation for patients with HHS is altered sensorium. Physical examination reveals signs of volume depletion. Fever due to underlying infection is common, and signs of acidosis (Kussmaul respiration, acetone breath) are usually absent. Gastrointestinal manifestations (abdominal pain, vomiting) are frequently reported in patients with DKA and are altered sensorium.

Laboratory Findings

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

The diagnostic criteria for HHS include a plasma glucose concentration >600 mg/dl, a serum osmolality >320 mOsm/kg of water, and the absence of significant ketoacidosis. Although by definition patients with HHS have a serum pH >7.3, a serum bicarbonate >18 mEq/l, and negative ketone bodies in urine and plasma, mild ketonemia may be present. Approximately 50% of patients with HHS have an increased anion gap metabolic acidosis as the result of concomitant ketoacidosis and/or an increase in serum lactate levels. The assessment of ketonemia, the key diagnostic feature of ketoacidosis, is usually performed by the nitroprusside reaction. However, clinicians should be aware that the nitroprusside reaction provides a semiquantitative estimation of acetoacetate and acetone levels but does not recognize the presence of β-hydroxybutyrate, which is the main ketacid in DKA. Therefore, this test may underestimate the level of ketosis. Direct measurement of β-hydroxybutyrate is now available by fingerstick method, which is a more accurate indicator of ketoacidosis.

Common Laboratory Pitfalls

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

Table 1. Diagnostic Criteria for DKA and HHS

<table>
<thead>
<tr>
<th>Diagnostic Criteria and Classification</th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td><strong>Moderate</strong></td>
<td><strong>Severe</strong></td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>&gt;250</td>
<td>&gt;250</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25–7.30</td>
<td>7.00–7.24</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/L)</td>
<td>15–18</td>
<td>10–&lt;15</td>
</tr>
<tr>
<td>Urine ketone*</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Serum ketone*</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Effective serum osmolality**</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Anion gap***</td>
<td>&gt;10</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Alteration in sensorium or mental obtundation</td>
<td>A</td>
<td>A/D</td>
</tr>
</tbody>
</table>

*Nitroprusside reaction method
**Calculation: Effective serum osmolality: 2(measured Na [mEq/L]) + glucose (mg/dl)/18
***Calculation: Anion gap: (Na⁺) – [(Cl⁻ + HCO₃⁻) (mEq/L)]. See text for details.
A, alert; D, drowsy; S, stuporous, C, comatose.
The admission serum potassium concentration is usually elevated in patients with DKA. In a recent series, the mean serum potassium in patients with DKA and those with HHS was 5.6 and 5.7 mEq/l, respectively. These high levels occur because of a shift of potassium from the intracellular to the extracellular space due to acidemia, insulin deficiency, and hypertonicity. Similarly, the admission serum phosphate level may be normal or elevated because of metabolic acidosis. Dehydration also can lead to increases in total serum protein, albumin, amylase, and creatine phosphokinase concentration in patients with acute diabetic decompensation. Finally, serum creatinine, which is measured by a colorimetric method, may be falsely elevated as a result of interference by blood acetoacetate levels.

Clinicians should remember that not all patients who present with ketoacidosis have DKA. Patients with chronic ethanol abuse with a recent binge culminating in nausea, vomiting, and acute starvation may present with alcoholic ketoacidosis. The key diagnostic feature that differentiates diabetic and alcohol-induced ketoacidosis is the concentration of blood glucose. While DKA is characterized by severe hyperglycemia, the presence of ketoacidosis without hyperglycemia in an alcoholic patient is virtually diagnostic of alcoholic ketoacidosis. In addition, some patients with decreased food intake (<500 kcal/day) for several days may present with starvation ketosis. However, a healthy subject is able to adapt to prolonged fasting by increasing ketone clearance by peripheral tissue (brain and muscle) and by enhancing the kidney’s ability to excrete ammonia to compensate for the increased acid production. Therefore, a patient with starvation ketosis rarely presents with a serum bicarbonate concentration <18 mEq/l.

**TREATMENT**

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

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**PROTOCOL FOR MANAGEMENT OF ADULT PATIENTS WITH DKA**

**Initial evaluation:** After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, plasma glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT as well as an ECG. Chest X-ray and cultures as needed. Start IV fluid, 1.0 L of 0.9% NaCl per hour initially (15-20 ml/kg/hour).

**Diagnostic criteria:** DKA: blood glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15 mEq/l, moderate ketonuria or ketonemia.

**IV Fluids**

- **Hypovolemic shock:** Administer 0.9% NaCl (1.0 L/hr) and/or plasma expander.
- **Hemodynamic monitoring:** Evaluate corrected serum Na*.
- **Serum Na high:** 0.45% NaCl (4-14 ml/kg/h) depending on hydration state.
- **Serum Na normal:** 0.9% NaCl (4-14 ml/kg/h) depending on hydration state.
- **Serum Na low:** Double insulin infusion hourly until glucose falls by 50-70 mg/dl in first hour.

**Insulin**

- **Intravenous Route:** 0.1 U/kg/hr Regular Insulin SC or IM.
- **Insulin:** 0.4 U/kg B. Wt. as IV bolus.
- **SCI/IM Route:** 0.1 U/kg/hr Regular Insulin SC or IM.
- **Insulin:** 0.4 U/kg B. Wt. 1/2 IV bolus, 1/2 IM or SC.

**Assess need for bicarbonate**

- **pH <6.9:** No HCO3-
- **pH 6.9-7.0:** NaHCO3 (100 mmol) Dilute in 400 ml H2O. Infuse at 200 ml/h.
- **pH 7.0:** NaHCO3 (50 mmol) Dilute in 200 ml H2O. Infuse at 200 ml/h.

**Check electrolytes, BUN, creatinine and glucose every 2 - 4 h until stable. After resolution of DKA, if the patient is NPO, continue IV insulin and supplement with SC regular insulin as needed. When the patient can eat, initiate a multidose insulin regimen and adjust as needed. Continue IV insulin infusion for 1 - 2 h after SC insulin is begun to ensure adequate plasma insulin levels. Continue to look for precipitating cause(s).**

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

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

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

Adapted with permission from reference 27.
and, in patients with DKA, venous pH, bicarbonate, and anion gap values until resolution of hyperglycemia and metabolic acidosis.

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

After intravascular volume depletion has been corrected, the rate of normal saline infusion should be reduced to 250 ml/h or changed to 0.45% saline (250–500 ml/h) depending on the serum sodium concentration and state of hydration. The goal is to replace half of the estimated water deficit over a period of 12–24 h. See Table 2 for typical total body deficits of water and electrolytes in DKA and HHS.

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

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

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

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**Figure 2. Management of Adult Patients with Hyperglycemic Hyperosmolar State (HHS)**

<table>
<thead>
<tr>
<th>IV Fluids</th>
<th>Insulin</th>
<th>Potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine hydration status</td>
<td>Regular, 0.15 U/kg as IV bolus</td>
<td>If serum K &lt; 3.3 mEq/L, hold insulin and give 40 mEq KCl and 1/2 as [(PO4)3] as KPO4 until</td>
</tr>
<tr>
<td>Hypovolemic shock</td>
<td>0.1 U/kg/h IV insulin infusion</td>
<td>5 mEq/L, do not give K but check potassium 2 h</td>
</tr>
<tr>
<td>Mild hypotension</td>
<td></td>
<td>If serum K ≥ 5.0 mEq/L, give 20-30 mEq K in each liter of IV fluid (1/3 as KCl and 2/3 as KPO4) to keep</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td></td>
<td>serum K at 4-5 mEq/L</td>
</tr>
<tr>
<td>Administer 0.9% NaCl (1.0 L/hr) and/or plasma expanders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluate Corrected Serum Na***</td>
<td>Check serum glucose hourly. If serum glucose does not fall by at least 50 mg/dl in first hour, double insulin dose hourly until glucose falls at a steady hourly rate of 50-70 mg/dl.</td>
<td></td>
</tr>
<tr>
<td>Serum Na high</td>
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<tr>
<td>Serum Na normal</td>
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<td>Serum Na low</td>
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</tr>
<tr>
<td>0.45% NaCl (4-14 ml/kg/h) depending on state of hydration</td>
<td>Change to 5% dextrose with 0.45% NaCl and decrease insulin to 0.05 - 0.1 U/kg/hour to maintain serum glucose between 250-300 mg/dl until plasma osmolality is ≤315 mOsm/Kg and patient is mentally alert.</td>
<td></td>
</tr>
<tr>
<td>0.9% NaCl (4-14 ml/kg/h) depending on state of hydration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When serum glucose reaches 300 mg/dl</td>
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<td></td>
</tr>
<tr>
<td>Change to 5% dextrose with 0.45% NaCl and decrease insulin to 0.05 - 0.1 U/kg/hour to maintain serum glucose between 250-300 mg/dl until plasma osmolality is ≤315 mOsm/Kg and patient is mentally alert.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check Chem 7 every 2-4 h until stable. After resolution of HHS, if the patient is NPO, continue IV insulin and supplement with sc insulin as needed. When the patient can eat, initiate sc insulin or previous treatment regimen and assess metabolic control. Continue IV insulin 1-2 h to ensure control after initiating daily regimen. Continue to look for precipitating cause(s).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Adapted with permission from reference 27.**

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

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

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

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

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

A conscious patient with mild DKA could be admitted to a general hospital ward. In such patients, the administration of regular insulin every 1–2 h by subcutaneous or intramuscular route has been shown to be as effective in lowering blood glucose and ketone bodies concentration as giving the entire insulin dose by intravenous infusion.33,34 Furthermore, it has been shown that the addition of albumin in the infusate was not necessary to prevent adsorption of insulin to the IV tubing or bag.33 Such patients should receive the recommended hydrating solution and an initial “priming” dose of regular insulin of 0.4 unit/kg of body weight, given half as intravenous bolus and half as a subcutaneous or intramuscular injection (Figures 1 and 2). The effectiveness of intramuscular or subcutaneous administration has been shown to be similar; however, subcutaneous injections are easier and less painful.

**Potassium**

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

In some hyperglycemic patients with severe potassium deficiency, insulin administration may precipitate profound hypokalemia,44 which can induce life-threatening arrhythmias and respiratory muscle weakness. Thus, if the initial serum potassium is lower than 3.3 mEq/L, potassium replacement should begin immediately by an infusion of KCl at a rate of 40 mEq/h, and insulin therapy should be delayed until serum potassium is ≥3.3 mEq/L (Figure 1).

**Phosphate**

Total body phosphate deficiency is universally present in patients with DKA, but its clinical relevance and benefits of replacement therapy remain uncertain. Several studies have failed to show any beneficial effect of phosphate replacement on clinical outcome.35 Furthermore, aggressive phosphate therapy is potentially hazardous, as indicated in case reports of children with DKA who developed hypocalcemia and tetany secondary to intravenous phosphate administration.37 Theoretical advantages of phosphate therapy include prevention of respiratory depression and generation of erythrocyte 2,3-diphosphoglycerate.

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

**Transition to Subcutaneous Insulin**

Patients with moderate to severe DKA should be treated with continuous intravenous insulin until ketoacidosis is resolved. Criteria for resolution of ketoacidosis include a blood glucose concentration of 5.0 mEq/L.
Hypoglycemia unawareness (loss of perception of warning symptoms of developing hypoglycemia), which may complicate diabetes management after resolution of hyperglycemic crises.

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

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

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

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

It has been hypothesized that cerebral edema in children with DKA may be caused by the rapid shift in extracellular and intracellular fluids and changes in osmolality due to accumulation of osmolytes in brain cells exposed to hyperosmolar conditions. A rapid decrease in extracellular osmolality during treatment would then result in osmotically mediated swelling of the brain. Although osmotic factors and other mechanisms may play a part in the development of cerebral edema, recent data suggest that cerebral edema in children with DKA is related to brain ischemia.

In children with DKA, both hypoponagia (which causes cerebral vasoconstriction) and extreme dehydration (as determined by a high initial serum urea nitrogen concentration) were associated with increased risk for cerebral edema. Hyperglycemia superimposed on an ischemic insult increases the extent of neurological damage, blood-brain barrier dysfunction, and edema formation.

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

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

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

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

PREVENTION

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

Paramount in this effort is improved education regarding sickday management. Education on sickday management should review:

- the importance of early contact with the health care provider
- the importance of insulin during an illness and the reasons never to discontinue insulin without contacting the health care team
• blood glucose goals and the use of supplemental short- or rapid-acting insulin
• availability of medications to suppress a fever and treat an infection
• initiation of an easily digestible liquid diet containing carbohydrates and salt when nauseated
• information for family members on sick-day management and record keeping, including assessing and documenting temperature, respiration and pulse, blood glucose and urine/blood ketones, insulin taken, oral intake, and weight
• information for primary care providers and school personnel on the signs and symptoms of new-onset and decompensated diabetes.

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

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

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

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

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

**References**


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