INTRODUCTION

Disordered glucose metabolism is a significant medical problem in the outpatient, emergency room, ward, and intensive care settings. Diabetes mellitus (DM), the most important group of medical conditions resulting from disordered glucose metabolism, results in a significant short-term and chronic morbidity, with growing prevalence around the globe. In the United States alone, nearly 9.3% of the population (29.1 million people) is estimated to have this disease (1). Additionally, approximately 8.1 million are undiagnosed (27.8%), which can further negatively impact their health. In 2014, the global prevalence of diabetes was estimated to be 9% of adults over 18 years old, but the incidence has been unchanged in the United States from 2006 to 2011 (2,3).

Because of a combination of the sheer volume of patients with DM and the associated chronic health conditions, the disease is important for physicians, nurses, health care administrators, insurers, and public health advocates. More than 5.3 million hospitalizations per year are associated with diabetes, a number that has increased over the past 20 years (4). The average length of stay was 5.0 days for these hospitalizations. Undeniably, these facts alone place an enormous economic and workforce burden on the entire health care system.

In addition to the many associated chronic health conditions developed by patients with DM, there are several acute and life-threatening conditions that also develop in these patients. Hyperglycemic emergencies, such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic nonketotic syndrome (HHS), are important causes of morbidity and mortality in patients with DM, who are admitted to the intensive care unit (ICU). In 2011, about 175,000 people of all ages presented to the emergency room with hyperglycemic emergencies with the number steadily increasing yearly since 1988 (1).

DIABETIC KETOACIDOSIS

Since the discovery of insulin by Frederick Banting in 1921, outcomes for patients with DKA have steadily improved. Nevertheless, DKA remains a serious and potentially fatal complication of DM. Hospital and ICU admissions for DKA and related conditions are increasing, and cause a significant burden on current health care delivery systems (5). Epidemiologic data show a U-shape relationship between age and mortality in DKA. With an annual incidence of 4.6 to 8 episodes per 1,000 patients with diabetes, DKA is the initial presentation of DM in up to 30% of patients overall, with approximately 40% of children and 17% of adults presenting in DKA without prior diagnosis of DM (5,6). In addition, DKA is the most common cause of death in children/adolescents with type 1 diabetes, with estimated 5% mortality with DKA in patients with advanced age (7–9). Although most patients presenting with DKA have type 1 DM, those with type 2 DM can also develop DKA during times of significant physiologic stress. Furthermore, eating disorder–related psychological disease contributes to the majority of recurrent DKA (10). Although, in most instances, there is a clear precipitating cause for DKA, half of the African-American and Hispanic patients with DKA may be unprovoked with undiagnosed type 2 DM (Ketosis–Prone Type 2 Diabetes) (11).

Pathophysiology

DKA results from a serious dysregulation of normal glucose homeostasis, leading to hyperglycemia and ketone body formation. The excess of glucose and ketones launch unrelenting systemic sequelae complicated by deficiency, either relative or absolute, in insulin production. In addition, an excess production of certain insulin counterregulatory hormones (CRH)—glucagon, catecholamines, cortisol, and growth hormone—is responsible for further worsening of serum glucose control. Most patients with type 1 DM who develop DKA have an absolute or near-absolute insulin deficiency; whereas, most patients with type 2 DM have either normal or elevated insulin levels (7,12). Because of the aberrant hormonal milieu, protein, lipid, and carbohydrate metabolism are all disrupted and culminate with the production of proinflammatory cytokines, such as interleukin-6, interleukin-1β, interleukin-8, tumor necrosis factor-α, free fatty acids, and plasminogen activator inhibitor-1, despite the absence of infection or cardiovascular pathology to cause significant morbidity and mortality (13).

Normal glucose metabolism is typically tightly regulated to maintain a serum glucose concentration between 3.9 and 6.4 mMol/L (1 mMol/L of glucose is equal to 18 mg/dL) by carefully balancing glucose production in the liver and glucose utilization in peripheral tissues (14). Insulin, a 51-amino-acid peptide, is mainly responsible for this tight glucose control by stimulating hepatic glucose uptake and storage (glycogen synthesis) and suppressing hepatic gluconeogenesis and glycogenolysis. Insulin also affects peripheral muscle tissue by promoting peripheral glucose uptake, promoting glycogen synthesis, and inhibiting peripheral glycogenolysis.

In DKA, either relative or absolute insulin deficiency combined with increased CRH promotes metabolic pathways opposite to insulin in both hepatic and peripheral tissues (15–17). These changes are typically the result of a precipitating event in patients with severely imbalanced DM (Table 137.1). Infection accounts for 30% to 50% of precipitating causes of DKA, with urinary tract and pulmonary infections making up the vast majority (18). Myocardial infarction, cerebrovascular accident, pulmonary embolism, pancreatitis, trauma, alcohol abuse, and drugs that affect carbohydrate metabolism—corticosteroids, thiazides, sympathomimetic agents, antipsychotics, and pentamidine—can also precipitate DKA (5,19).
for the clinical picture as the depletion of the intravascular space produces the life-threatening signs and symptoms. The body’s response is a further increase in CRH, and the cycle is perpetuated.

### Presentation and Diagnosis

The presentation and diagnosis of DKA relies on a thorough patient history, focused physical examination, and appropriate laboratory analysis. Patients typically report a history of poor glucose control and symptoms associated with hyperglycemia, such as polyuria, polydipsia, dehydration, weakness, weight loss, and lethargy that may progress over the course of days to weeks. Nausea, vomiting, and abdominal pain are also common presenting complaints and frequently signify the progression from symptomatic hyperglycemia to overt DKA. Interestingly, there is a strong correlation between severity of metabolic acidosis (HCO₃⁻ <8 mMol/L and pH <7.12) and the presence of abdominal pain (20). In absent of such, abdominal pain secondary to intra-abdominal pathology should be investigated instead of attributing it to hyperglycemic-induced abdominal pain (20). The physical examination may reveal evidence of dehydration—for example, tachycardia, hypotension, prolonged capillary refill time, poor skin turgor, dry mucous membranes, and weight loss. In the setting of infection, the patient could be normothermic or hypothermic due to peripheral vasodilation. Additionally, Kussmaul respiration—very deep, gasping breaths taken in response to severe metabolic acidosis—an acetone or fruity breath odor, depressed mental status, and even focal neurologic deficits or coma may also be seen.

Laboratory analysis is usually confirmatory of DKA in these patients (Table 137.2). A complete blood count with differential, blood glucose, serum electrolytes, serum osmolality, serum lactate, blood urea nitrogen, serum creatinine, arterial or venous blood gas, serum, and urinary ketones should be ordered in patients with suspected DKA. In addition, an electrocardiogram and cardiac enzymes should be requested, with a workup for infection if infectious triggers of DKA are suspected. Caution should be exercised when using the serum sodium levels in patients with DKA, as the reported laboratory value can be artificially low, normal, or elevated, depending upon the spurious effects of glucose and triglycerides in these patients and the relative loss of water compared to sodium. In the presence of hyperglycemia, serum sodium measurement can be corrected by adding 1.6 mg/dL to the measured serum sodium for each 100 mg/dL increase in glucose above 100 mg/dL (21). Other tests, such as serum lactate, β-human chorionic gonadotropin (β-hCG), chest radiography, and computed tomography may be indicated, depending on the clinical scenario. Potassium is frequently faulty elevated secondary to the extracellular shift caused by academia while hypokalemia may indicate severe total-body potassium deficit that might contribute to arrhythmia.

Elevated plasma anion gap–associated metabolic acidosis (AGMA) is typically seen in laboratory analysis of patients with DKA, as ketosis and ketone body accumulation are responsible for an increase in the anion gap. Although the degree of plasma glucose levels in DKA has no correlation with degree of acidosis, in up to 11% of patients a nongap hyperchloremic metabolic acidosis may ensue (22, 23). Typically, the normal anion gap is between 7 and 9 mEq/L and reflects unmeasured ions in the serum. In patients with DKA, an elevated anion

<table>
<thead>
<tr>
<th>TABLE 137.1 Precipitating Factors in Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic Nonketotic Syndrome</th>
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<tbody>
<tr>
<td><strong>INFECTION</strong></td>
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<tr>
<td>Urinary tract infection</td>
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<tr>
<td>Pneumonia</td>
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<tr>
<td>Dental infection</td>
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<tr>
<td>Cellulitis</td>
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<tr>
<td><strong>COEXISTING CONDITIONS</strong></td>
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<tr>
<td>Acute myocardial infarction</td>
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<tr>
<td>Cerebral vascular accident</td>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Pulmonary embolism</td>
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<tr>
<td>Hyperthermia</td>
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<tr>
<td>Hypothermia</td>
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<tr>
<td>Renal failure/dialysis</td>
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<tr>
<td>Severe thermal injury</td>
</tr>
<tr>
<td>Thryotoxicosis</td>
</tr>
<tr>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Mesenteric thrombosis</td>
</tr>
<tr>
<td><strong>MEDICATIONS</strong></td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
</tr>
<tr>
<td>β-Blockers</td>
</tr>
<tr>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Cimetidine</td>
</tr>
<tr>
<td>Diazoxide</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
</tr>
<tr>
<td>Phenytoin</td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Total parental nutrition</td>
</tr>
<tr>
<td><strong>SUBSTANCE ABUSE</strong></td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Cocaine</td>
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<tr>
<td><strong>UNDIAGNOSED DIABETES MELLITUS</strong></td>
</tr>
</tbody>
</table>

The result of these changes is a substantial increase in serum glucose—through increased hepatic gluconeogenesis, glycolysis, and lipolysis—with inappropriately decreased peripheral glucose uptake (Fig. 137.1). DKA is also associated with ketosis, an additional product of worsening glucose homeostatic decompensation, which occurs as a result of increased lipolysis from increased action of hormone-sensitive lipase, an enzyme that causes increased triglyceride breakdown and free fatty acid release into the systemic circulation. Hormone-sensitive lipase is highly upregulated during periods of insulin deficiency and elevations in CRH. Hepatic oxidation of free fatty acids induced by hormone-sensitive lipase produces ketone bodies, mainly β-hydroxybutyrate (β-OHB) and acetoacetate acid, strong acids that present a significant hydrogen ion load to the body; the normal buffering systems are rapidly overwhelmed by the ongoing hydrogen burden, and an anion gap acidosis develops.

Hyperglycemia and ketonemia produce a hypertonic intravascular environment, resulting in an intracellular water shift into the intravascular and interstitial compartments. The ensuing cellular dehydration is accompanied by electrolyte shifts as well. When the renal glucose reabsorption rate is exceeded, an osmotic diuresis of water and electrolytes occurs. Sodium, potassium, magnesium, calcium, chloride, and phosphate are all lost during this osmotic diuresis. Commonly, water and electrolyte deficits are compounded by poor oral intake and protracted vomiting. Effects of hypovolemia are responsible...
A gap—more than 10 to 12 mEq/L—occurs because of the high ketone concentration. Other causes of AGMA, which must be excluded during DKA evaluation, include alcoholic ketoacidosis, starvation ketoacidosis, lactic acidosis, and renal failure. In patients with possible DKA, these other causes of AGMA should be excluded through further history and laboratory analysis. For example, alcoholic ketoacidosis may present with profound metabolic acidosis, but typically has a characteristic history, an elevated blood alcohol content, and only mildly elevated serum glucose concentration. Likewise, starvation ketosis is accompanied by a significant history and only mild acidosis (serum bicarbonate is usually >18 mMol/L). Furthermore, AGMA secondary to salicylate ingestion, paraldehyde, methanol, and ethylene glycol should be considered. Ingesting of these alcohol derivatives results in an increased osmolar gap in addition to elevated anion gap; this may be a clue to the diagnosis.

Ketoneemia and ketonuria can both be assessed semiquantitatively with the nitroprusside reaction test. This test estimates the relative levels of acetoacetate and acetone in the blood, but does not detect the presence of the main metabolic product in ketoacidosis, β-hydroxybutyrate (β-OHB), which could contribute to underestimating the degree of ketosis. Because the ratio of β-OHB to acetoacetate may increase from 1:1 to as much as 5:1 during the development of DKA, an increase in β-OHB may represent the predominant ketone during that illness (24). Of note, β-OHB monitoring may significantly improve the diagnostic specificity in DKA patients with euglycemia or only mild hyperglycemia—as with prolonged vomiting, starvation, pregnancy, hepatic insufficiency, or following insulin administration—where blood glucose levels can be

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**TABLE 137.2 Diagnostic Criteria for Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic Nonketotic Syndrome**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mMol/L)</td>
<td>&lt;6.7</td>
<td>13.9</td>
<td>&gt;33</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.35–7.45</td>
<td>&lt;7.30</td>
<td>&gt;7.30</td>
</tr>
<tr>
<td>Serum bicarbonate (mMol/L)</td>
<td>22–28</td>
<td>&lt;15</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Anion gap</td>
<td>&lt;10</td>
<td>12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Serum osmolality (mOsm/kg)</td>
<td>Variable</td>
<td>Variable</td>
<td>&gt;320</td>
</tr>
<tr>
<td>Serum ketones</td>
<td>Negative</td>
<td>Moderate to high</td>
<td>None</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>Negative</td>
<td>Moderate to high</td>
<td>None</td>
</tr>
</tbody>
</table>

misleading (25). Leukocytosis may be explained by the stress response from DKA; however, a WBC greater than 25,000 cells/µL is unlikely and warrants a further workup (26). Elevation of pancreatic enzymes does not correlate with the degree of gastrointestinal symptoms or the presence of pancreatitis (27).

Management

Management of DKA includes initial resuscitation, correction of hyperglycemia and resolution of ketosis, and treatment of any precipitating causes (Figs. 137.2 and 137.3). Following these phases, it is essential also to provide chronic therapy to prevent repeated episodes and secondary sequelae of DM.

DKA can cause loss of protective airway reflexes, hypoxia, and hyperventilation. In patients with a severely depressed mental status, appropriate care should be taken to protect the airway so that pulmonary aspiration of gastric contents does not occur. If the patient’s Glasgow Coma Scale is 8 or less, or in situations that require sedation and transport away from the acute care environment for further evaluation, tracheal intubation may be necessary to ensure adequate airway protection and ventilation. Because these patients have a high incidence of gastroparesis, the placement of a decompressive gastric tube may also be warranted in the presence of an altered level of consciousness, and elevation of the head of bed to 30 and 40 degrees may serve to prevent passive regurgitation. Mechanical ventilation, if utilized, should be set to maintain respiratory compensation of the accompanying severe metabolic acidosis initially and adjusted appropriately as the acidosis corrects.

Following airway and respiratory care, initial therapy should be directed at restoring adequate blood volume and organ perfusion with intravascular volume resuscitation. In addition to correcting the hemodynamic insults associated with severe hypovolemia, appropriate volume administration can also decrease CRH levels and plasma glucose concentration (28,29). The goal during this phase is to replace the fluid deficit over the first 24 hours, half of which should be replaced in the first 6 to 8 hours. Estimation of fluid deficit can be based on body weight or general guidelines and response characteristics. Typically, 1 to 2 L (15 to 20 mL/kg body weight) of

![Figure 137.2](https://example.com/figure1372.png)

isotonic saline in the first 1 to 2 hours is sufficient for initial resuscitation; however, in more severe cases the resuscitation may require larger volumes, and some prefer to add colloids. The following clinical estimations of volume deficit using orthostatic blood pressure and heart rate may also be used to guide initial fluid replacement, although these criteria may be less reliable in patients with neuropathy and/or impaired cardiovascular reflexes (18).

- An increase in pulse without change in blood pressure with orthostatic position change indicates approximately a 10% decrease in extracellular volume (i.e., 2 L).
- A decline in blood pressure (>15/10 mmHg) with position change indicates approximately a 15% to 20% decrease in extracellular volume (i.e., 3 to 4 L).
- Supine hypotension indicates a decrease of more than 20% in extracellular fluid volume (i.e., >4 L).

After the initial resuscitation phase, both the rate of infusion and type of intravenous fluid must be adjusted. Current recommendations are to decrease the infusion rate to 250 mL/hr or to 4 to 14 mL/kg/hr, depending on the patient’s hydration status and to maintain adequate urine output of approximately 0.5 mL/kg/hr or, in a normal adult about 50 mL/hr. Depending on the patient’s corrected serum sodium, isotonic saline is continued or changed to hypotonic saline. If the patient’s corrected serum sodium is low, 0.9% saline solution should be continued as the replacement fluid; however, if the patient’s corrected serum sodium is normal or elevated, the fluid should be changed to 0.45% saline solution in order to continue free water deficit replacement. In general, resolution of hyperglycemia is faster than ketoacidosis (30). Additionally, once plasma glucose levels reach 250 mg/dL, 5% or even 10% dextrose solution should be added to the replacement fluids to maintain serum glucose levels between 150 and 200 mg/dL and allow the insulin infusion to continue until ketosis is reversed, defined as closing the anion gap and negative ketonemia, and to prevent the too rapid correction of serum glucose levels.

Concomitant with aggressive fluid resuscitation, insulin therapy should be instituted to decrease glucose production and increase glucose utilization with subsequent improvements in ketosis, acidosis, and hyperglycemia. Most experts recommend low-dose insulin infusion in all but the mildest cases of DKA over intermittent intravenous or subcutaneous administration, as the former is more physiologic, more therapeutically reliable, and decreases the risk of hypoglycemia and hypokalemia (31–35).

For continuous insulin infusion, many experts recommend an initial bolus of regular insulin 0.1 U/kg followed by an infusion at 0.1 U/kg/hr, with a goal of decreasing plasma glucose levels by 10% in the first hour. If the plasma glucose level does not respond appropriately after the first hour, and if the intravascular volume status is adequate, additional bolus of 0.14 unit/kg and the infusion rate may be doubled every hour until a constant decline in plasma glucose level is achieved. As previously mentioned, once the plasma glucose concentration reaches 11.1 mMol/L (200 mg/dL), the insulin infusion rate should be decreased to 0.02 to 0.05 U/kg/hr and dextrose should be added to the replacement fluid to maintain the
plasma glucose level between 8.3 and 11.1 mMol/L (150 and 200 mg/dL) until anion gap acidosis is resolved.

In addition to serum glucose and bicarbonate levels, the American Diabetic Association recommends evaluation of \( ^\beta-OHB \) levels as the preferred method for rapid diagnosis and monitoring of DKA. Typically, \( ^\beta-OHB \) concentrations are less than 1 mMol/L; however, in patients with DKA, plasma \( ^\beta-OHB \) concentration can be elevated to concentrations in excess of 4 to 12 mMol/L (mean, 7 mMol/L). Adequate DKA treatment should allow \( ^\beta-OHB \) concentration to decrease by approximately 1 mMol/L/hr and eventually return to baseline \((<1 \text{ mMol/L})\) (24,36–39). As has been documented, serum bicarbonate levels are slower to correct while \( ^\beta-OHB \) is a more appropriate measure of therapy. Notably, as adequate treatment progresses, \( ^\beta-OHB \) is oxidized to acetoacetate, which can be detected by the nitroprusside reaction test leading to incorrect conclusions. Hence, it is recommended to measure directly \( ^\beta-OHB \) for diagnosis and monitoring treatment of DKA (19,40).

Despite massive potassium losses (3 to 5 mEq/kg) in patients presenting with DKA, the serum potassium concentration may be normal due to intravascular volume contraction and intracellular electrolyte shifts, and should not be used as an indicator of potassium homeostasis in the early phases of treatment. As insulin is provided, and acidosis is corrected, potassium may quickly shift back into the intracellular compartment. Additionally, initial resuscitation with normal saline may lower the serum potassium concentration. Severe hypokalemia may potentially cause life-threatening cardiac dysrhythmias and respiratory muscle weakness (41–43). Particular attention should be directed to help prevent hypokalemia during DKA treatment. If serum potassium is less than 3.3 mMol/L (3.3 mEq/L), it is recommended not start insulin because the reduction in plasma glucose levels and acidosis can cause significant intracellular fluid and potassium shifts that may worsen cardiovascular function to the point of collapse (18,44). Potassium replacement should begin once the serum potassium concentration is less than 3.3 mMol/L (3.3 mEq/L), assuming adequate urine output, using the following guidelines:

- If the serum potassium is less than 3.3 mMol/L (3.3 mEq/L), 40 to 60 mEq of potassium should be added to each liter of IV fluid. Initiate replacement at 10 mEq/hr through a peripheral venous access or, preferably, 20 to 30 mEq/hr through a CIVL, until the serum potassium level is more than 3.3 mMol/L.
- If the serum potassium is 3.3 to 4 mMol/L, 30 to 40 mEq of potassium should be added to each liter of IV fluid.
- If the serum potassium is 4 to 5 mMol/L, 20 to 30 mEq of potassium should be added to each liter of IV fluid.
- If serum potassium level is above 5.5 mMol/L, insulin and intravenous fluids should be initiated, and potassium chloride infusion held with serum potassium level evaluated every 2 hours.

In addition to potassium, other electrolytes such as magnesium, phosphate, and calcium are also depleted in patients with DKA. Inadequate serum concentrations of these electrolytes may cause respiratory depression, cardiac dysfunction, and alteration of tissue oxygenation that can be avoided by diligent monitoring and appropriate replacement. Measurement of these electrolytes should be done at presentation to identify significant abnormalities in order to facilitate appropriate early correction as clinically indicated. They should be repeated as necessary, depending on the clinical scenario. Although several studies have failed to show an outcome benefit to phosphate replacement, some experts continue to recommend replacement of phosphate in those with serum phosphate concentration less than 1.0 mMol/L (0.323 mg/dL) by using potassium phosphate as a portion of the total phosphate replacement (18,45,46). Of note, hypocalcemia may become problematic in the face of overaggressive phosphate replacement.

Adequate treatment of DKA—intravascular volume replacement with reversal of hyperglycemia and ketosis—is generally associated with improvements in both physiologic and laboratory parameters. Criteria for resolution of DKA include plasma glucose less than 11.1 mMol/L (200 mg/dL) and two of following parameters: serum bicarbonate concentration 15 mEq/L or more, venous pH greater than 7.3, anion gap 12 mEq/L or less, and, recently, \( ^\beta-OHB \) less than 1 mMol/L (25). After resolution of the DKA episode, when the patient is able to tolerate enteral nutrition, a multidose subcutaneous insulin regimen that includes a combination of short- and intermediate- or long-acting insulin should be instituted. To allow for sufficient insulin plasma level, intravenous insulin should be continued for 1 to 2 hours following the first dose of subcutaneous insulin. Patients with previously diagnosed diabetes may restart their previous insulin schedule with additional adjustment and coverage as needed. If the patient is not ready for oral intake, intravenous insulin should be continued as well as fluid resuscitation. Bicarbonate offers no benefit in improving cardiac or neurologic functions in DKA (47). However, the American Diabetic Association suggests selectively use in severe acidosis with pH less than 6.9 (10).

Treatments of DKA should ideally be provided in an environment that has adequate nursing care and monitoring capabilities, as well as a rapid turnaround of laboratory tests. Invasive monitoring should be provided as necessary; patients with mild-to-moderate DKA may require only noninvasive blood pressure monitoring, continuous electrocardiography, pulse oximetry, and a urinary catheter, whereas patients with the most severe disease states and comorbidities may, in addition, require arterial and central venous catheterization. Additionally, patients with oliguria or hypotension refractory to initial rehydration, mental obtundation, sepsis, respiratory insufficiency, pregnancy, or significant comorbidities or precipitating events such as myocardial infarction or decompensated congestive heart failure should be managed in a critical care environment (18,42).

**Complications**

Common complications encountered during DKA treatment include hypoglycemia and hyperglycemia, various electrolyte disturbances, lactic acidosis, intravascular volume overload, cerebral edema, acute respiratory distress syndrome (ARDS), coagulopathy, rhabdomyolysis, and thromboembolism (Table 137.3).

Hypoglycemia and hyperglycemia are common complications of DKA treatment. Because intensive intravenous insulin therapy intentionally decreases blood glucose levels, reverses ketone body formation, and improves insulin sensitivity, it also places the patient at significant risk for hypoglycemia. The latter is associated with serious complications, including significant cognitive dysfunction, coma, and death. The incidence of serious hypoglycemic episodes associated with DKA treatment...
may occur at any time during the process of DKA. The disorder cerebral edema.

is largely supportive, and may be improved with the use of mannitol as an osmotic diuretic to decrease the amount of water deficits should be slowly corrected while avoiding rapid changes in the level of consciousness, the development of papilledema, or the onset of seizures. Additionally, sodium and transient cardiac and renal compromise, serum osmolality should be monitored every 4 to 6 hours, depending upon the severity of the episode of DKA and underlying disease (29,48–51).

With worsening cerebral edema, intracranial pressure may significantly increase—occasionally to the point of brainstem herniation with associated respiratory arrest and cardiovascular derangements. For this reason, careful monitoring should be done during DKA treatment for signs of cerebral edema and brainstem herniation such as the acute onset of headache, changes in the level of consciousness, the development of papilledema, or the onset of seizures. Additionally, sodium and water deficits should be slowly corrected while avoiding rapid decreases in blood glucose levels. Treatment of this condition is largely supportive, and may be improved with the use of mannitol as an osmotic diuretic to decrease the amount of cerebral edema.

ARDS is also a rare, but potentially fatal, complication that may occur at any time during the process of DKA. The disorder may be linked to the underlying cause of DKA, for example, a source of infection, or the treatment phase with associated fluid resuscitation, fluid shifts, and changing osmotic gradients. Pulmonary aspiration of gastric secretions may also be responsible for the respiratory involvement. Patients with hypoxemia, widened alveolar to arterial oxygen gradients, or other pre-existing cardiorespiratory conditions warrant close monitoring and possibly more judicious fluid resuscitation (18,52).

**HYPEROSMOLAR HYPERGLYCEMIC NONKETOTIC SYNDROME**

HHS is a medical emergency that develops in response to one of many precipitating conditions (Table 137.1) in patients with type 2 DM. Among adults in the United States, the incidence of HHS is approximately 17.5 cases/100,000 persons per year and contributes to higher mortality than DKA (53). In addition, HHS can be the initial presentation in 20% of type 2 diabetes patients (53). Unfortunately, the diagnosis is usually made after a significant delay that is made more challenging by the fact that HHS can coexist with DKA in approximately 30% of patients (54). The mortality rate from HHS is related directly to patient age with of mortality less than 10% in patients less than 75 years of age compared with 35% in those older than 84 years of age (54,55).

**Pathophysiology**

The basic pathophysiologic abnormality in HHS is a relative insulin deficiency caused by both an increase in peripheral insulin resistance and an increase in blood levels of CRH (see Fig. 137.1) (54,56,57). These hormones—glucagon, cortisol, growth hormone—and various catecholamines increase hepatic and renal glucose production and further worsen peripheral tissue glucose utilization (54,56). Together, these effects cause an insidious but dramatic rise in serum glucose concentration, typically over days to weeks (56).

With increasing serum glucose concentration, an osmotic gradient develops between the intravascular and extravascular compartment (58). As water moves from the extravascular compartment down this osmotic gradient, it leads to intracellular dehydration and a transient increase in the intravascular volume with relative serum hyponatremia. As the serum glucose concentration continues to rise, osmotic diuresis causes profound decreases in intravascular volume, coupled with losses of vital electrolytes such as sodium, potassium, phosphate, and magnesium (55). This massive intravascular volume loss can result in life-threatening end-organ hypoperfusion and nonketotic metabolic acidosis. Compared to DKA, ketones are minimally produced in patients with HHS likely due to the ability of the pancreas to secrete insulin. The amount of insulin, while not sufficient to prevent hyperglycemia in these patients, does prevent fatty acid lipolysis and the formation of ketone bodies and development of ketoacidosis.

**Presentation and Diagnosis**

Typically the time from onset to diagnosis and initiation of treatment can be significantly longer than in patients with
DKA (56). The clinical diagnosis of these patients, therefore, requires a high clinical suspicion to recognize promptly the signs and symptoms of HHS and institute appropriate diagnostic and treatment modalities. The key diagnostic of HHS is hyperglycemia and dehydration in absence of acidosis.

Patients with suspected HHS may initially exhibit nausea/vomiting, visual disturbances, muscle weakness, and leg cramps (59). Left untreated, these patients eventually develop confusion, lethargy, hemiparesis, seizures, and coma (60). Physical examination may reveal both signs of profound dehydration—such as decreased skin turgor and dry mucous membranes—as well as abdominal distension from gastroparesis (61).

Initial laboratory evaluation in patients with suspected HHS should include serum glucose, ketones, electrolytes, and creatinine concentration; serum measured and calculated osmolality; urinalysis; and appropriate empiric bacterial and fungal cultures (Table 137.2) (56). Since these patients can have significantly elevated serum glucose concentrations ($\geq 1,000 \text{ mg/dL}$), the serum osmolality can be quite high and seems to correlate with neurologic symptoms (62).

Management

The treatment goals for HHS include aggressive intravascular fluid replacement, insulin administration to correct hyperglycemia, appropriate electrolyte replacement, and if indicated, respiratory system support (Fig. 137.4). Ultimately, effective patient education and long-term patient support are also essential.

HHS treatment is typically undertaken in two phases. The first is an emergency-phase and consists of rapid restoration of circulatory volume and electrolyte deficits with concomitant insulin administration to correct serum hyperglycemia and hyperosmolality. Additionally, treatment of the triggering disorder should be started. This phase ends with near-correction of hyperglycemia. The second phase is a transitional phase centered on changing insulin replacement to appropriate chronic diabetes therapy (i.e., subcutaneous or oral hypoglycemic regimens), as well as patient education and support.

In patients with HHS, the total-body water deficit can be as high as 100 to 200 mL/kg in adults; thus, fluid replacement is


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**Complete initial evaluation. Start IV fluids: 1.0 L of 0.9% NaCl per hour initially.**

**IV Fluids**

- Determine hydration status
  - Hypovolemic shock
  - Mild hypotension
  - Cardiogenic shock
  - Administer 0.9% NaCl (1.0 L/h) and/or plasma expander
  - Evaluate corrected serum Na$^+$
    - Serum Na$^+$ high
    - Serum Na$^+$ normal
    - Serum Na$^+$ low
  - 0.45% NaCl (4–14 mL/kg/hr) depending on hydration state
  - 0.9% NaCl (4–14 mL/kg/hr) depending on hydration state
  - When serum glucose reaches 300 mg/dL
    - Change to 5% dextrose with 0.45% NaCl and decrease insulin to 0.05–0.1 U/kg/hr to maintain serum glucose between 250 and 300 mg/dL until plasma osmolality is $\geq 315 \text{ mOsm/kg}$ and patient is mentally alert

**Insulin**

- Regular, 0.15 U/kg as IV bolus
- 0.1 U/kg/hr IV insulin infusion
- Check serum glucose hourly, if serum glucose does not fall by at least 50 mg/dL in first hour then, double insulin dose hourly until glucose falls at a steady hourly rate of 50–70 mg/dL
- After resolution of HHS, follow blood glucose(DG) every 4 hr and give sliding scale regular insulin SC in 5-unit increments for every 50 mg/dL increase in DG above 150 mg/dL for up to 20 units for DG $\geq 300 \text{ mg/dL}$

**Potassium**

- If serum K$^+$ is $< 3.3 \text{ mEq/L}$ hold insulin and give 40 mEq K$^+$ (2/3 as KCl and 1/3 KPO$_4$) until K$^+$ $\geq 3.3 \text{ mEq/L}$
- If serum K$^+$ is $\geq 5.0 \text{ mEq/L}$ Do not give K$^+$ but check potassium every 2 hr
- If serum K$^+$ $\geq 3.3$ but $< 5.5 \text{ mEq/L}$, give 20–30 mEq K$^+$ in each liter of IV fluid (2/3 as KCl and 1/3 as KPO$_4$) to keep serum K$^+$ at 4–5 mEq/L
- Check Chem 7 every 2–4 hr until stable. Look for precipitating causes.
the mainstay therapy for intravascular collapse and poor organ perfusion. Such intervention may lower glucose concentration independent of insulin administration. Initially, 0.9% saline solution should be infused at 15 to 20 mL/kg total body weight per hour to restore extracellular fluid volume deficit. Normal saline infusion should continue until blood pressure, and end-organ perfusion have been normalized. The intravenous solution should then be changed to 0.45% saline solution at a reduced rate to restore the intracellular fluid deficit. The overall fluid resuscitation goal should be the replacement of one-half of the estimated fluid deficit over the first 8 hours and the other half of the estimated fluid deficit over the next 16 hours. Care should be taken to ensure that the serum osmolality does not decrease more than 3 mOsm/kg/hr to reduce the risk of acute cerebral edema.

The cornerstone of therapy for HHS is intravenous insulin given to restore normal peripheral glucose uptake, suppress lipolysis, and decrease hepatic gluconeogenesis. Complications of insulin therapy include hypoglycemia, hypokalemia—hence insulin infusion should not begin with serum potassium less than 3.5 mMol/L, or hypophosphatemia. Insulin should be initially given as an intravenous bolus of 0.15 unit/kg, followed by a continuous infusion of 0.1 unit/kg/hr with a goal of decreasing plasma glucose levels by 10% in the first hour. Although the patient is receiving intravenous insulin, the glucose should be monitored every 1 to 2 hours via either capillary or serum samples. Once the serum glucose decreases to 16.7 mMol/L (300 mg/dL), dextrose should be added to the intravenous fluid administration, and the insulin infusion should be decreased by 0.05 to 0.1 unit/kg/hr.

Electrolyte replacement is also an important component of the management of HHS. Hypokalemia can develop during HHS treatment because insulin administration causes an intracellular shift of potassium ions from the extracellular compartment. Additionally, the ongoing osmotic diuresis can cause a dramatic depletion of total-body potassium stores; this loss can exceed 400 mMol in severe HHS. For this reason, electrocardiographic monitoring should be utilized during this phase of therapy, and aggressive potassium replacement—with up to 40 mMol/hr—may be necessary. Hypophosphatemia may also develop secondary to the ongoing osmotic diuresis. Replacement of phosphate during HHS treatment seems prudent; however, several prospective randomized studies have failed to show a definitive benefit to phosphate replacement in the absence of decreased cardiac or respiratory function and anemia (45,46). If phosphate replacement is necessary, potassium phosphate may be an ideal replacement infusion to correct both hypokalemia and hypophosphatemia. Criteria for resolution of HHS include normalization of osmolality and regain of normal mental status.

Complications

In addition to the electrolyte abnormalities discussed above, complications from HHS include pancreatitis, rhabdomyolysis, hyperchloremic metabolic acidosis, cerebral edema, acute gastric dilatation, and ARDS (Table 137.3). Patients with HHS are at increased risk for thromboembolism, and thus, subcutaneous heparin administration may be warranted to prevent thromboembolic complications (55,63). Complications of HHS treatment include intravascular fluid overload and acute cerebral edema from overaggressive intravenous fluid administration. Intravascular volume overload is seen as a hypoxic respiratory failure—often with pulmonary edema—and lower extremity pitting edema. Acute cerebral edema is manifested by headache, lethargy, and depressed levels of consciousness that can rapidly progress to brainstem herniation. Treatment of this potentially devastating complication is with an osmotic diuretic such as mannitol and supportive care.

GLYCEMIC CONTROL AND INSULIN THERAPY IN THE INTENSIVE CARE UNIT

Numerous studies documented the role of hyperglycemia as independent factor for inpatient mortality (64–66). Stress-induced hyperglycemia is defined as the transient increase in blood sugar above normal range during acute illness in non-diabetics (66). It may be found in up to 40% of critically ill patients and is associated with higher mortality, longer ICU length of stay (67), infectious complications, and organ failure (66,68,69).

Hyperglycemia contributes to several metabolic derangements and may predispose to bacterial infection (70). The latter can be attributed to hyperglycemia-induced immune dysfunction by impeding neutrophil adherence (71) in addition to hampering chemotaxis, phagocytosis (72), and bactericidal activity (73). Additionally, inflammatory mediator release in response to illness and injuries (74) compromises insulin secretion while, at the same time, releasing insulin CRH which leads to worsening hyperglycemia.

Multiple studies had suggested that intensified glycemic control of the ICU patients by using intravenous insulin infusion results in improved outcomes, including decreased mortality rate (64,67,75). The recommendation that glucose levels be maintained no higher than 4.4 to 6.1 mMol/L has its origins in a key study conducted in Leuven, Belgium, and published in 2001 by Van den Berghe et al. (64). In this large randomized single-center trial of predominantly cardiac surgery ICU patients, there was a reduction in ICU mortality with intensive intravenous insulin protocol targeting blood glucose to 4.4 to 6.1 mMol/L; for all patients, a relative 43% and absolute 3.4% mortality reduction, while for those with more than 5 days in the ICU, a 48% relative and 9.6% absolute mortality reduction. Additionally, it demonstrated a reduction in organ dysfunction and ICU length of stay (64,69) in the subset with ICU length of stay of more than 5 days. Several studies that followed supported the proposition that mortality directly correlated with increasing glucose level in a combined ICU, in stroke populations and postcardiac surgery populations (75–77). Although there were significant differences in the designs of these studies as regards patient populations and the blood glucose levels achieved, the results were for the most part fairly similar. Intensive therapy with intravenous insulin produced a consistent decrease in mortality rate in a variety of patient populations. Such findings led to the 2004 recommendation from American College of Endocrinology (69) and the American Association of Clinical Endocrinologists (AACE) that the ICU glycemic target should be less than 6.1 mMol/L (78).

However, subsequent implementation of the identical protocol by Van den Berghe et al. in a medical ICU did not
demonstrate similar mortality benefit (67). Furthermore, this study’s secondary analysis suggested reduced mortality only in a subgroup of patients who stayed longer than 3 days in ICU, but with risk of hypoglycemic events increased by sixfold. These data added to general uncertainties regarding aggressive glycemic control and its contribution to overall improved ICU outcome.

To deal with the above controversies, a large international multicenter randomized of tight glucose control in both medical and surgical ICU patients published its results in 2009 (79). The investigators concluded that target blood glucose of 10 mMol/L or less resulted in a lower mortality than a goal of 4.5 to 6 mMol/L (79). Most interestingly, the mortality from cardiovascular causes and hypoglycemia were higher in the tight blood glucose control group. Several “post-intensive insulin therapy era” data demonstrated the lack of survival benefit and an increased incidence of hypoglycemia (80–82). Additionally, two large randomized multicenter trials of intensive insulin therapy in Europe (Glucose control study and VISEP—Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) were prematurely stopped owing to failure to demonstrate improvement in mortality and a higher rate of hypoglycemia and morbidity (83,84). This finding is particularly important for the ICU patients who are commonly sedated and mechanically ventilated, since aggressive lowering of serum glucose levels may carry the risk of hypoglycemia that is potentially much difficult to detect (85). The findings of the previous studies were reflected in the 2012 Surviving Sepsis Campaign Guideline which sets the ICU patients’ blood glucose goal of less than 10 mMol/L, rather than the 8.3 mMol/L, as was originally recommended in the 2008 update (Table 137.4) (64,86).

### Point-of-Care Glucometer Use in Critically Ill Patients

In 2014, a draft guidance document was issued by U.S. Food and Drug Administration that required improved accuracy for new point-of-care (POC) glucometers for professional use (91). This guidance reemphasizes that glucose measurement with glucometers in critically ill patients is being used in a population beyond the intended use described in the package insert.

POC glucometers analyze glucose concentrations using enzymatic reaction through glucose oxidase, glucose dehydrogenase, or hexokinase to produce results that are spectrophotometrically or electrically detectable. Such results can be quantified based on a reference standard (92,93). Although the literature is not consistent, recent data suggest that POC glucometers may provide inaccurate results. Such inaccuracy is for the most part observable in patients who are on vasopressors, have anemia, and particularly those on an insulin infusion (92–94). Compounding this risk, glucometers also appear to be less accurate in the hypoglycemic range (95), and, in general, to overestimate blood glucose concentrations compared to a reference standard (93,96,97). More variable associations are reported with arterial hypotension (98) and the existence of edema (93,99). The potential inaccuracy creates risk of iatrogenic hypoglycemia, an adverse event associated with increased mortality in ICU patients (79). However, no inaccuracy has been reported with increasing severity of illness, change in pH, and the use of mechanical ventilation (93). None-the-less, severe hyperoxia does affect meters employing a glucose oxidase reagent (100).

Considering these findings, identification of those critically ill patients at greatest risk of hypoglycemia is a first priority. One such definition might include patients with hypotension who are receiving vasopressor support to maintain mean arterial blood pressure more than 60 mmHg, a hematocrit of less than 24%, unless using a multichannel POC glucometer with built-in hematocrit correction or if utilizing a mathematical correction for hematocrit (101), and continuous insulin infusion for tight glycemic control when the minimum of the target glucose range is 5.5 mMol/L or less, or the measured glucose level approaches 8.3 mMol/L.

Some sort of corrective measures are needed to maintain the accuracy of bedside glucometry in critically ill patients. Short-term measures may include glucose measurement for these patients meeting the above criteria in either the clinical chemistry laboratory or on a portable gas analyzer, iSTAT (102) or a small chemistry analyzer like the Piccolo (103). Nonetheless, results from portable machines should be routinely validated in a central laboratory. Additionally, we strongly recommended against very strict glycemic control. Finally, a longer-term approach will require the utilization of a glucose monitoring system that has been adequately validated in critically ill patients, though no such devices exist at this time.

### Conclusion

Although glucose control is widely accepted as part of routine care in the ICU, questions remain as to the optimal target of blood glucose while avoiding complications. Intensive insulin therapy with blood sugar target less than 5.5 mMol/L was strongly associated with high rate of serious hypoglycemia without survival benefit. Hence, current professional guidelines

<table>
<thead>
<tr>
<th>Year</th>
<th>Organization</th>
<th>Patient Population</th>
<th>Treatment Threshold (mMol/L)</th>
<th>Target Glucose Level (mMol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>American Diabetes Association (87)</td>
<td>ICU patients</td>
<td>10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>2014</td>
<td>American Heart Association (88)</td>
<td>ICU patients</td>
<td>10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>2013</td>
<td>American Heart Association (89)</td>
<td>ICU patients with NSTEMI</td>
<td>10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>2012</td>
<td>Surviving Sepsis Campaign (86)</td>
<td>ICU patients</td>
<td>&gt;10 on two consecutive blood glucose</td>
<td>&lt;10</td>
</tr>
<tr>
<td>2012</td>
<td>American College of Critical Care Medicine (90)</td>
<td>ICU patients&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.3</td>
<td>5.5–8.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Medical, postoperative cardiac surgery, trauma, and neurology.  
NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction.
recommend blood sugar target less than 10 mMol/L, irrespec-
tive of the type of diabetes. However, it might be beneficial
to consider a glucose control target taking into account the
patient’s pre-morbid state, and considering chronic hyperglyce-
mia versus stress hyperglycemia differently. To date, there is no
specific recommendation for this subgroup of the population
and its impact on ICU patients.

Finally, glucose measurement with glucometers in critically ill
patients is being used in a population beyond the device’s
original intended use. The use of these devices in such a manner
carries the risk of iatrogenic hypoglycemia, an adverse event
associated with increased mortality in ICU patients. Active
measures are needed to identify those critically ill patients at
least risk of hypoglycemia. Glucose measurement for such
patients is recommended through the clinical chemistry labo-
ratory or via portable devices that have been adequately vali-
dated in critically ill patients.

Key Points

• DKA and HHS result from dysregulation of normal
glucose homeostasis caused by one of many precipitating
conditions in patients with DM.

• DKA (minimal intrinsic insulin secretion) is associated
with hyperglycemia and ketone body formation, whereas
HHS (intrinsic insulin secretion) is associated with
hyperglycemia without ketone body formation.

• Both DKA and HHS may present with various and vague
complaints, and progress to severe shock with cardiovas-
cular collapse, severe metabolic acidosis, and death.

• The clinical features of HHS and DKA commonly over-
lap and may observed simultaneously (overlapping cases);
this suggests that these two states of uncontrolled DM
differ only with respect to the magnitude of dehydra-
tion and the severity of acidosis.

• The treatment of DKA and HHS involves intravascular
fluid resuscitation and insulin replacement with addi-
tional electrolyte supplementation.

• Patients should be closely monitored during treatment
of DKA and HHS for evidence of hypoglycemia, hyper-
glycemia, electrolyte disturbances, worsening lactic
acidosis, and intravascular volume overload. In addi-
tion, they should be observed closely for signs of cere-
bral edema, acute respiratory distress syndrome, severe
coumadopathy, rhabdomyolysis, and thromboembolism.

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CHAPTER 137  Disordered Glucose Metabolism


