

# Hyperosmolar Hyperglycemic State

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Hyperosmolar hyperglycemic state is a life-threatening emergency manifested by marked elevation of blood glucose and hyperosmolarity with little or no ketosis. Although there are multiple precipitating causes, underlying infections are the most common. Other causes include certain medications, nonadherence to therapy, undiagnosed diabetes mellitus, substance abuse, and coexisting disease. In children and adolescents, hyperosmolar hyperglycemic state is often present when type 2 diabetes is diagnosed. Physical findings include profound dehydration and neurologic symptoms ranging from lethargy to coma. Treatment begins with intensive monitoring of the patient and laboratory values, especially glucose, sodium, and potassium levels. Vigorous correction of dehydration is critical, requiring an average of 9 L of 0.9% saline over 48 hours in adults. After urine output is established, potassium replacement should begin. Once dehydration is partially corrected, adults should receive an initial bolus of 0.1 units of intravenous insulin per kg of body weight, followed by a continuous infusion of 0.1 units per kg per hour (or a continuous infusion of 0.14 units per kg per hour without an initial bolus) until the blood glucose level decreases below 300 mg per dL. In children and adolescents, dehydration should be corrected at a rate of no more than 3 mOsm per hour to avoid cerebral edema. Identification and treatment of underlying and precipitating causes are necessary. (*Am Fam Physician.* 2017;96(11):729-736. Copyright © 2017 American Academy of Family Physicians.)

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**H**yperosmolar hyperglycemic state (HHS) is a life-threatening endocrine emergency that most commonly affects adults with type 2 diabetes mellitus.<sup>1,2</sup> However, the incidence increased by 52.4% among children from 1997 to 2009.<sup>3</sup> HHS occurs in patients with type 2 diabetes who can still produce insulin (as opposed to diabetic ketoacidosis [DKA], which occurs in persons with type 1 diabetes and some with type 2 diabetes). The hallmarks of HHS include profound dehydration, marked hyperglycemia, variable degrees of neurologic impairment, and mild or no ketosis. Although DKA and HHS have been described as distinct entities, one-third of patients exhibit findings of both.<sup>2</sup> They may represent opposite ends of the decompensated diabetes spectrum, differing in time of onset, degree of dehydration, and severity of ketosis<sup>4</sup> (depending on the degree of insulinopenia<sup>5</sup>). *Table 1* compares laboratory findings of mild to severe DKA with those of HHS.<sup>6</sup>

The mortality rate from HHS ranges from 10% to 50%, which is considerably higher than that of DKA (1.2% to 9%).<sup>2,7-13</sup> In children, the mortality rate from HHS may be as high as 60%.<sup>14</sup> Mortality predictors include age, degree of dehydration, hemodynamic instability (hypotension, absence of reflex

tachycardia), degree of consciousness, infection, and a history of cancer.<sup>2,15-17</sup>

## Pathophysiology

Elevated levels of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) initiate HHS by stimulating hepatic glucose production through glycogenolysis and gluconeogenesis, leading to hyperglycemia, intracellular water depletion, and subsequent osmotic diuresis.<sup>5,12,18</sup> High levels of catecholamines combined with low levels of insulin reduce peripheral glucose uptake. Glycosuria causes greater loss of water than of sodium, resulting in hyperosmolarity and dehydration. Decreased intravascular volume, often combined with underlying renal disease, decreases the glomerular filtration rate, thereby decreasing glucose clearance and further increasing blood glucose levels.

Although the insulin level is not adequate to control blood glucose,<sup>19,20</sup> it can suppress lipolysis and ketogenesis.<sup>5</sup> Proinflammatory cytokines (e.g., tumor necrosis factor  $\alpha$ , interleukin  $\beta$ , interleukin-6, interleukin-8), plasminogen activator inhibitor-1, reactive oxygen species, and lipid peroxidation increase two- to threefold during the acute crisis, but return to normal within 24 hours.<sup>21</sup> These increases create a temporary

**Table 1. Comparison of Diabetic Ketoacidosis with Hyperosmolar Hyperglycemic State**

Variables	Diabetic ketoacidosis			Hyperosmolar hyperglycemic state
	Mild	Moderate	Severe	
Alternative sensoria in mental obtundation	Alert	Alert, drowsy	Stupor, coma	Stupor, coma
Anion gap	> 10	> 12	> 12	Variable
Arterial pH level	7.25 to 7.30	7.00 to 7.24	< 7.00	> 7.30
Effective serum osmolality (mOsm per kg)	Variable	Variable	Variable	> 320
Plasma glucose level (mg per dL [mmol per L])	> 250 (13.9)	> 250	> 250	> 600 (33.3)
Serum bicarbonate level (mEq per L)	15 to 18	10 to < 15	< 10	> 15
Urine or serum ketones	Positive	Positive	Positive	Trace or negative

Adapted with permission from Kitabchi AE, Umpierrez GE, Murphy MB, et al.; American Diabetes Association. Hyperglycemic crises in diabetes. *Diabetes Care*. 2004;27(suppl 1):S95.

prothrombotic environment that increases the risk of vascular occlusion, mesenteric artery thrombosis, myocardial infarction, low-flow syndrome, disseminated intravascular coagulopathy, cerebrovascular accident, and bilateral femoral artery thrombosis.<sup>22-26</sup>

### Causes and Risk Factors

HHS can be precipitated by infections, medications, non-adherence to therapy, undiagnosed diabetes, substance abuse, and coexisting diseases<sup>20,27-32</sup> (Table 2<sup>25</sup>). Infections are the leading cause (57% of cases)<sup>17</sup>; pneumonia, often gram-negative, is the most common infection, followed by urinary tract infection and sepsis.<sup>28</sup> Poor adherence to diabetes medication causes 21% of HHS cases.<sup>17</sup> Other causes include myocardial infarction, cerebrovascular accident, pulmonary embolism, and mesenteric artery thrombosis.<sup>22,24,28,33</sup> Psychoactive medications, especially second-generation antipsychotics, cause glucose elevations, insulin resistance, and diabetes independent of weight gain.<sup>34-40</sup> Older adults with type 2 diabetes (sometimes undiagnosed) are at higher risk of HHS because they often take dehydrating medications (e.g., diuretics) and may be unable to adequately communicate their symptoms if they live alone or in a nursing home.<sup>41</sup>

Risk factors for HHS in children include morbid obesity (body mass index of 39 kg per m<sup>2</sup> or greater), long-term steroid use, gastroenteritis, black race, acanthosis nigricans, and a family history of diabetes.<sup>9,12,41-44</sup> Undiagnosed diabetes can result in HHS when early symptoms are unrecognized, particularly in children.<sup>12</sup>

### Clinical Presentation

Physical findings in patients with HHS include profound dehydration with poor tissue turgor; dry buccal mucosa; soft, sunken eyeballs; cool extremities; and a rapid,

**Table 2. Precipitating Factors in Hyperosmolar Hyperglycemic State**

Coexisting diseases	Medications
Acute myocardial infarction	Aripiprazole (Abilify)
Adrenocorticotrophic hormone–producing tumors	Calcium channel blockers
Cerebrovascular accident	Chemotherapeutic agents
Cushing syndrome	Chlorpromazine
Hyperthermia	Cimetidine (Tagamet)
Hypothermia	Diazoxide (Proglycem)
Mesenteric thrombosis	Glucocorticoids
Neuroleptic malignant syndrome	Haloperidol
Pancreatitis	Loop diuretics
Pulmonary embolus	Methadone
Renal failure	Olanzapine (Zyprexa)
Severe burns	Phenytoin (Dilantin)
Thyrototoxicosis	Propranolol
<b>Infections</b>	Quetiapine (Seroquel)
Cellulitis	Risperidone (Risperdal)
Dental infections	Thiazide diuretics
Pneumonia	Ziprasidone (Geodon)
Sepsis	
Urinary tract infection	

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thready pulse.<sup>19</sup> Adults often present with a low-grade fever. Children may present with nonspecific symptoms such as headache, weakness, and vomiting with or without abdominal pain.<sup>42</sup> Abdominal distention may occur secondary to gastroparesis induced by hypertonicity.<sup>45</sup> Abdominal distention that persists after rehydration

**Table 3. Typical Water and Electrolyte Losses in Hyperosmolar Hyperglycemic State**

Electrolyte/water	Typical loss
Calcium	50 to 100 mEq per kg
Chloride	3 to 7 mEq per kg
Magnesium	50 to 100 mEq per kg
Phosphate	70 to 140 mEq per kg
Potassium	5 to 15 mEq per kg
Sodium	7 to 13 mEq per kg
Water	100 to 200 mL per kg

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may have another underlying cause and requires further investigation.

Depending on effective serum osmolarity, mental status can range from complete lucidity to disorientation and lethargy to coma.<sup>30,46</sup> Coma often occurs once the serum osmolarity is greater than 340 mOsm per kg.<sup>22</sup> Seizures occur in up to 25% of patients and may be generalized, focal, myoclonic jerking, or movement induced.<sup>45</sup> Hemiparesis may occur but should resolve when the fluid deficit is corrected.<sup>28,47</sup>

#### COMPLICATIONS

Rhabdomyolysis, which is diagnosed by a serum creatine phosphokinase level more than 10 times the upper limit of normal, may increase the risk of acute renal failure. Children may experience a malignant hyperthermia-like syndrome that presents with high fever (often higher than 104°F [40°C]<sup>48</sup>) and an elevated creatine kinase level. This syndrome may be caused by a reaction to m-cresol (a preservative in all preparations of regular insulin produced in the United States) and is treated with dantrolene (Dantrium).<sup>42</sup>

#### Diagnostic Testing

Initial laboratory findings in patients with HHS include marked elevations in blood glucose levels (greater than 600 mg per dL [33.3 mmol per L]) and in serum osmolarity (greater than 320 mOsm per L of water [normal = 290 ± 5]), with a pH level greater than 7.30 and mild or absent ketosis. One-half of patients will have a mild anion-gap metabolic acidosis (i.e., 10 to 12). If the anion gap is greater than 12, the differential diagnosis should include lactic acidosis or, if the lactic acid level is not elevated, a combination of DKA and HHS or other entities unrelated to HHS. Vomiting and thiazide diuretics may cause a metabolic alkalosis that could mask

the severity of acidosis.<sup>28</sup> Serum potassium levels may be elevated or normal.<sup>28</sup> Creatinine, blood urea nitrogen, and hematocrit levels are almost always elevated.<sup>49</sup> HHS also produces significant total body losses of many electrolytes<sup>19</sup> (Table 3<sup>25</sup>).

The reported sodium level should be corrected when the patient's glucose level is markedly elevated. The types of fluids administered depend on the corrected serum sodium level<sup>50</sup> and the effective serum osmolality, which are calculated using the formulas in Figure 1.<sup>25</sup>

#### Treatment

Treatment of HHS requires a four-pronged approach: (1) vigorous intravenous rehydration, (2) electrolyte management, (3) intravenous insulin, and (4) diagnosis and management of precipitating and coexisting problems.<sup>49</sup> Figure 2 outlines the American Diabetes Association's algorithm for managing DKA and HHS in adults.<sup>51</sup> Patients require intensive care if they have cardiovascular instability, cannot maintain an airway, are obtunded, report acute abdominal symptoms, or cannot be monitored adequately on the general medical ward.<sup>52</sup> Management of HHS in children is similar to that in adults.<sup>44</sup>

#### FLUID REPLACEMENT

Aggressively replacing fluids is the first and most important step in treating HHS. It should begin by estimating the fluid deficit (usually 100 to 200 mL per kg, or an average of 9 L in adults).<sup>6,28</sup> In children, the degree of dehydration ranges from 12% to 15%.<sup>8</sup> Isotonic fluids may cause fluid overload, and hypertonic fluids may correct sodium deficits too rapidly, increasing the risk of diffuse myelinolysis and death.<sup>28</sup> Therefore, fluid replacement in adults should begin with 1 L of 0.9% saline per hour. Hemodynamic status should

$$\text{Corrected serum sodium} = \frac{\text{sodium (mEq per L)}}{\text{mEq per L}} + \frac{1.65 \times (\text{glucose [mg per dL]} - 100)}{100}$$

$$\text{Effective serum osmolality} = (2 \times \text{corrected sodium}) + \frac{\text{glucose}}{18}$$

**Example:**

$$\text{Corrected serum sodium} = 145 + \frac{1.65 \times (1,100 - 100)}{100} = 162$$

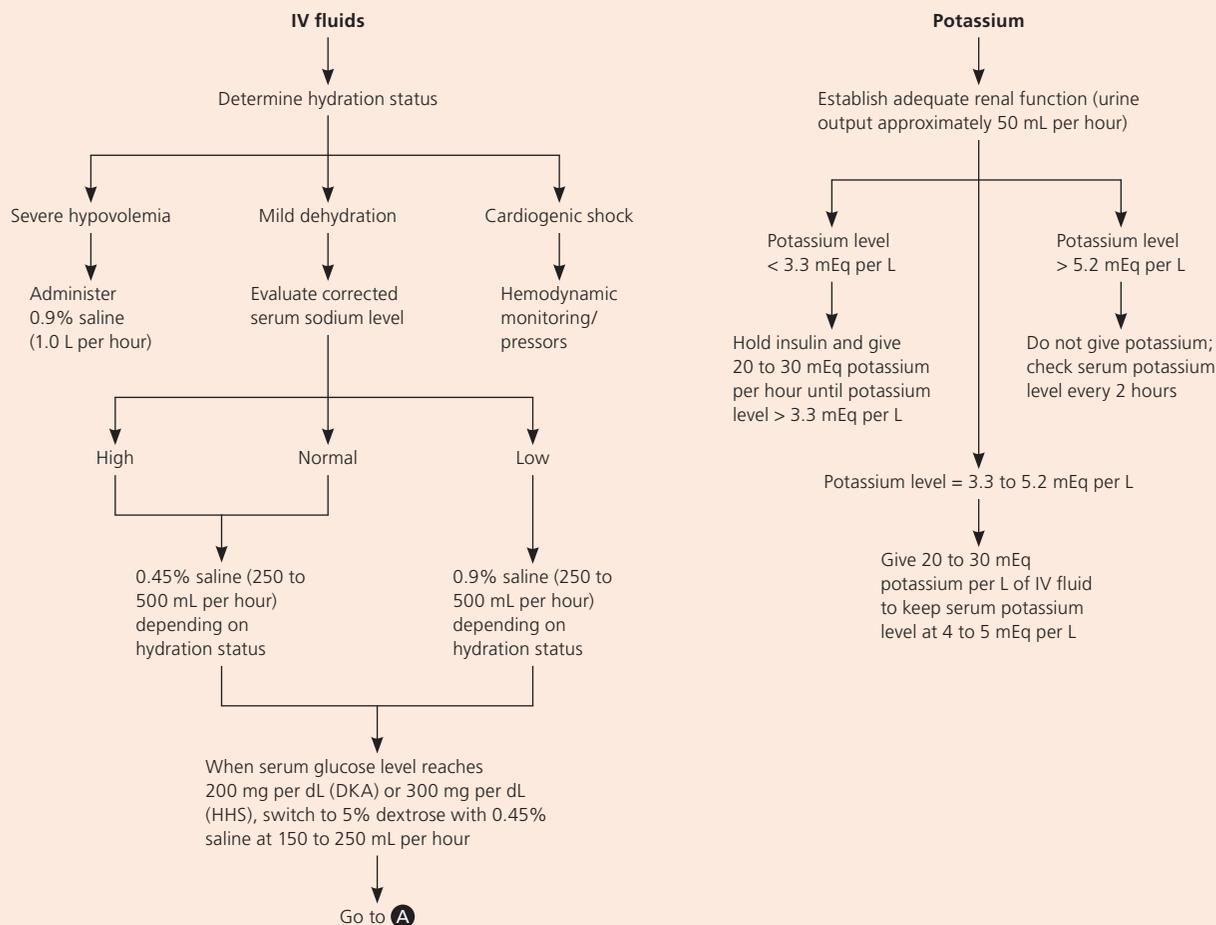
$$\text{Effective serum osmolality} = (2 \times 152) + \frac{1,100}{18} = 365$$

**Figure 1.** Calculating corrected serum sodium and effective serum osmolality.

Information from reference 25.

## Management of DKA and HHS

Complete initial evaluation. Check capillary glucose level and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain blood for metabolic profile. Start IV fluids: 1.0 L of 0.9% saline per hour.



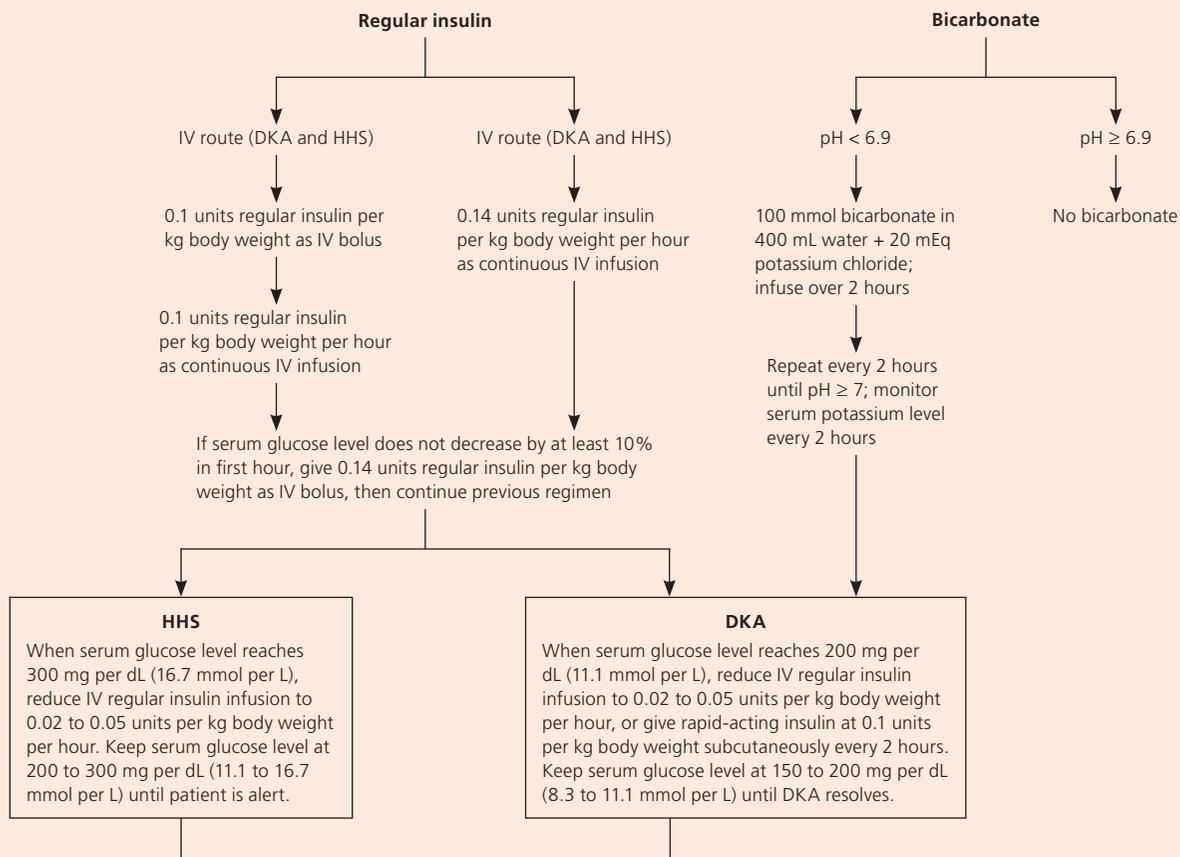
**Figure 2.** Algorithm for management of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) in adults. Diagnostic criteria for DKA include blood glucose level of 250 mg per dL (13.9 mmol per L), arterial pH of 7.3, bicarbonate level of 15 mEq per L, and moderate ketonuria or ketonemia. (IV = intravenous.)

be monitored in patients with shock. Fluid resuscitation should be guided by vital signs, urine output, and improvement in sensorium.

Once hypotension improves, the corrected serum sodium level is calculated. If it is high (greater than 145 mEq per L [145 mmol per L]) or normal (135 to 145 mEq per L [135 to 145 mmol per L]), 0.45% saline should be given at a rate of 4 to 14 mL per kg per hour, depending on the hydration state. If the corrected serum sodium level is low (less than 135 mEq per L), 0.9% saline should be infused at the same rate. When the serum glu-

cose level reaches 300 mg per dL (16.7 mmol per L), the fluid should be switched to 5% dextrose solution with 0.45% saline.<sup>28,50</sup> At least one-half of the calculated deficit should be given in the first 18 to 24 hours, with the remainder given over the next 24 hours.

Fluid administration alone will cause the plasma glucose level to decrease without insulin administration, a sign of adequate fluid replacement.<sup>19</sup> A plasma glucose level that does not decrease by 75 to 100 mg per dL (4.2 to 5.6 mmol per L) per hour implies inadequate fluid volume or renal impairment.<sup>19</sup>



**A** Check venous pH and electrolyte, blood urea nitrogen, creatinine, and glucose levels every 2 to 4 hours until stable. When DKA or HHS resolves and patient is able to eat, initiate subcutaneous multidose insulin regimen. To transfer from IV to subcutaneous insulin, continue IV infusion for 1 to 2 hours after beginning subcutaneous insulin to ensure adequate plasma insulin levels. In insulin-naïve patients, start at 0.5 to 0.8 units per kg body weight per day, then adjust as needed. Look for precipitating cause

Adapted with permission from Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32(7):1339.

Children are at greater risk of developing potentially fatal cerebral edema during treatment. For this reason, the rate at which serum tonicity is returned to normal is slower than in adults, and it should not exceed 3 mOsm per hour.<sup>53</sup>

### ELECTROLYTE MANAGEMENT

Total body potassium depletion is often unrecognized because the initial potassium level may be normal or high.<sup>19,28</sup> However, it may plummet when insulin is administered because insulin forces potassium into cells. Therefore, once urine output is established, potas-

sium replacement should begin. Electrolytes should be checked every one to two hours until stable, and the cardiac rhythm should be monitored continuously.

If the patient's initial serum potassium level is less than 3.3 mEq per L (3.3 mmol per L), insulin should be held and saline and potassium chloride given until the potassium level reaches at least 3.3 mEq per L. If the serum potassium level is greater than 5.2 mEq per L (5.2 mmol per L), potassium should be held until the level falls below 5.2 mEq per L, with monitoring every two hours. If the initial serum potassium level is 3.3 to 5.2 mEq per L, 20 to 30 mEq of potassium chloride should be added to each

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### SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Fluid and electrolyte replacement should be initiated in patients with HHS based on recommendations from the American Diabetes Association (Figure 2).	C	6
Phosphate replacement should be considered in patients with HHS only if hypophosphatemia is severe (less than 1.0 mEq per L [1.0 mmol per L]) or if respiratory depression, anemia, or cardiac dysfunction is present.	C	6
Insulin therapy should be initiated in patients with HHS once fluid replacement has been started.	C	6
Patients should be assessed and treated for underlying causes of HHS.	C	6

HHS = hyperosmolar hyperglycemic state.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

liter of intravenous fluid to maintain the level between 4.0 and 5.0 mEq per L (4.0 and 5.0 mmol per L).<sup>50</sup>

The evidence for monitoring and replacing phosphate, calcium, or magnesium is inconclusive.<sup>41</sup> Most studies that examined the need for phosphate replacement involved patients with acute-onset DKA.<sup>1,6,54</sup> Because HHS develops over days to weeks, these patients are more likely to become phosphate depleted. However, no controlled studies have shown improved outcomes with phosphate replacement.<sup>19</sup> It may be reasonable when the patient's serum phosphate level is less than 1.0 mEq per L (1.0 mmol per L) and when muscle weakness is a concern, such as in patients with respiratory impairment, anemia, and cardiac dysfunction.<sup>6</sup> Because phosphate replacement can cause severe hypocalcemia, serum calcium levels should be monitored closely.<sup>50</sup>

Hypomagnesemia can cause arrhythmias, muscle weakness, convulsions, stupor, and agitation. It may be present in as many as 90% of patients with uncontrolled diabetes.<sup>19</sup> However, there is no clear evidence that magnesium should be replaced initially. Unless the patient has renal failure, administering magnesium is safe and physiologic.<sup>19</sup>

### INSULIN THERAPY

Adequate fluid replacement must begin before insulin is administered.<sup>6</sup> Giving insulin before fluids moves intravascular water into the cells, exacerbating hypotension and potentially causing vascular collapse or death.

In adults, insulin should be started with an initial intravenous bolus of 0.1 units per kg, followed by a continuous infusion of 0.1 units per kg per hour until the blood glucose level falls to 250 to 300 mg per dL (13.9 to 16.7 mmol per L).<sup>55</sup> Another option is to give a continuous infusion of 0.14 units of insulin per kg per hour without

a loading dose. If the glucose level does not decrease by 10% in the first hour, a bolus of 0.14 units of insulin per kg should be given, followed by continuous infusion of 0.1 units per kg per hour.<sup>56</sup> Children should not receive an initial bolus of insulin because it may increase the risk of cerebral edema. Instead, a continuous infusion of 0.1 units per kg per hour should be started. Once the serum glucose level falls below 300 mg per dL, 5% dextrose should be added to the intravenous fluid and the insulin dosage reduced to 0.02 to 0.05 units per kg per hour, maintaining serum glucose between 200 and 300 mg per dL until mental obtundation and hyperosmolarity resolve. When the patient can eat, subcutaneous insulin should be started or the previous treatment regimen restarted.

### IDENTIFY AND TREAT THE CAUSE

Routine antibiotics are not recommended for all patients with suspected infection. However, they are warranted while awaiting culture results in older patients or in those with hypotension. An elevated C-reactive protein level is an early indicator of sepsis in patients with HHS.<sup>57</sup>

Medications should be reviewed to identify any that may precipitate or aggravate HHS; these medications should be discontinued or reduced. Investigation for other causes may be indicated after reviewing the precipitating factors<sup>6</sup> (Table 2<sup>25</sup>).

### TREATMENT COMPLICATIONS

Complications from inadequate treatment include vascular occlusion (e.g., mesenteric artery thrombosis, myocardial infarction, low-flow syndrome, disseminated intravascular coagulopathy) and rhabdomyolysis.<sup>19,20,49,52,58</sup> Although there is a temporary prothrombotic environment during the treatment of HHS,

evidence is not available to recommend anticoagulation for all patients. Overhydration may lead to respiratory distress syndrome in adults and induced cerebral edema, which is rare in adults but often fatal in children. Cerebral edema should be treated with 1 to 2 g per kg of intravenous mannitol over 30 minutes.

This article updates previous articles on this topic by the author<sup>25</sup> and by Matz.<sup>19</sup>

**Data Sources:** Searches were performed in PubMed using the key words hyperosmolar hyperglycemic state. Other sources included Essential Evidence Plus, the Cochrane Database of Systematic Reviews, and the National Institute for Health and Care Excellence. Search dates: February 6 and 12, 2016.

The author thanks Dr. John Halvorsen and Mary Annen for their assistance in the preparation of the manuscript.

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