

# Hyperosmolar Hyperglycemic State

Bruce W. Nugent, MD\*

*Division of Emergency Medicine, Spectrum Health-Butterworth,  
100 Monroe NW, MC-49,  
Grand Rapids, MI 49503, USA*

As the prevalence of diabetes mellitus escalates, emergency medicine practitioners will continue to see increasing numbers of patients with complications of uncontrolled hyperglycemia. Hyperosmolar hyperglycemic state (HHS) represents one of the two most serious acute metabolic complications of diabetes mellitus and is a life-threatening emergency. HHS is the end result of a sustained osmotic diuresis, and is characterized by severe hyperglycemia, hyperosmolarity, and dehydration, but without significant ketoacidosis. Less common than the other critical hyperglycemic diabetic emergency, diabetic ketoacidosis (DKA), HHS carries a higher mortality rate, associated with serious concurrent illness. It is usually seen in older type 2 diabetics, but can present at any age, and in patients with type 1 diabetes mellitus.

Hyperosmolar hyperglycemic state first was described in 1957, and the literature since has referred to this syndrome by many terms, including hyperosmolar nonketotic state, hyperosmolar coma, hyperglycemic hyperosmolar syndrome, or nonketotic hyperosmolar syndrome [1]. Hyperosmolar hyperglycemic state is the nomenclature recommended by the American Diabetes Association (ADA), used here to emphasize that varying alterations in sensorium less than coma are usually present and that HHS may occur with some degree of ketosis and acidosis [1–3]. Diagnostic features of HHS include the following [2]:

- Plasma glucose level of 600 mg/dL or greater
- Effective serum osmolality of 320 mOsm/kg or greater
- Profound dehydration (typically 8 to 12 L) with elevated serum urea nitrogen (BUN):creatinine ratio
- Small ketonuria, absent to low ketonemia
- Bicarbonate greater than 15 mEq/L
- Some alteration in consciousness

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\* 1792 Tahoe Pine Drive Southwest, Grand Rapids, MI 49509, USA.

E-mail address: [nugentbw@cs.com](mailto:nugentbw@cs.com)

Hyperosmolar hyperglycemic state often is reviewed together with DKA because of similarities in pathogenesis and treatment approach. Many experts view these as two extremes on the spectrum of decompensated diabetes, differing from each other by the magnitude of hyperglycemia, the severity of acidosis/ketonemia, and the degree of dehydration [4–7]. Both disorders can occur in type 1 and type 2 diabetes mellitus, and up to one third of patients with decompensated diabetes share features of both DKA and HHS [4,5]. Important distinctions, however, exist in pathogenesis, clinical presentation, and treatment between these disease states. This article focuses on the emergency department (ED) evaluation and management of HHS.

### **Emergency department presentation**

#### *Epidemiology*

In 2002, an estimated 6.3% of the US population (about 18.2 million people) had diabetes. Type 2 diabetes mellitus accounts for 90% to 95% of cases, and people 65 years or older make up almost 40% of all persons with diabetes [8]. The prevalence of type 2 diabetes mellitus is increasing dramatically and parallels the epidemic of obesity. Blacks, Hispanics, and Native Americans are affected disproportionately. Type 2 diabetes mellitus now accounts for as much as half of newly diagnosed diabetes in children ages 10 to 21 years, depending on the socioeconomic and ethnic composition of the population [9,10].

Hyperosmolar hyperglycemic state occurs primarily in patients with type 2 diabetes mellitus, although that diagnosis may not have been known previously. In 30% to 40% of cases, HHS is the initial presentation of a patient's diabetes [11,12]. HHS is significantly less common than DKA. The incidence of HHS is less than 1 case per 1000 person-years, compared with DKA, which occurs at a rate of 4.6 to 8 cases per 1000 person-years [13]. The mean age of patients with HHS is 60 years, yet cases in pediatric patients are reported [14]. Elderly people, especially those dependent on others for their daily care, are at greatest risk, and many patients are direct admissions from nursing homes [15]. There is a small female predominance [1,16].

Mortality rates continue to be high, even with proper treatment, and are higher than those associated with DKA. Precise mortality rates are not available because of the prevalence of comorbid illnesses that may be listed as the main cause of death, rather than HHS [12]. HHS historically has had reported mortality rates reaching as high as 50%; however, the most recently quoted average mortality is 15% [2,12,15]. In contrast, the mortality rate for DKA is usually less than 2% to 5% [2]. Mortality in HHS increases with increasing age and increases with higher levels of serum osmolality [1,16,17]. Patients with HHS usually do not die because of the hypertonicity, but rather succumb to a comorbid illness that may have precipitated or developed during the treatment of HHS [16]. Prognosis is worsened substantially in the presence

of a coma or hypotension [2,16,18]. Higher mortality also may be associated with a delay in diagnosis and failure to aggressively treat HHS [19,20]. Mortality may occur as a complication of treatment.

Despite the increasing incidence of type 2 diabetes mellitus, HHS is rare in childhood. Recent reports, however, highlight a disturbing trend in the epidemiology of pediatric-type 2 diabetes mellitus, including complications (eg, DKA and HHS). Although DKA is most common in type 1 diabetes mellitus and may be its initial presentation in children, DKA also may occur at the time of diagnosis in up to 25% of pediatric patients presenting with type 2 diabetes mellitus [14]. In contrast, it is estimated that 4% of newly diagnosed type 2 diabetes mellitus cases in children are associated with HHS, and that 12% of these cases will be fatal, often caused by cerebral edema and dehydration [14]. Before 2002, HHS had been reported in only 12 children, 10 of whom were 9 months to 7 years old, two 12 and 13 years old; none were overweight [14]. A more recent report, however, describes six male adolescent patients with HHS complicated by malignant hyperthermia and rhabdomyolysis [21]. Another report documents seven obese African American youths who were considered to have died from DKA caused by type 1 diabetes mellitus, but actually met the criteria for HHS and not DKA, and who had previously unrecognized type 2 diabetes mellitus [14]. Common findings in these patients include disease onset in early adolescence, positive family history of type 2 diabetes mellitus, and physical findings of insulin resistance including obesity, and acanthosis nigricans, a velvety hyperpigmented thickened skin patch most prominent in intertriginous areas (eg, neck and groin) [14,21]. More timely diagnosis and treatment could have prevented some of these complications and deaths. Physicians need to have a high index of suspicion for type 2 diabetes mellitus in children. When discovered, this diagnosis should be considered as much an emergency as recognition of type 1 diabetes mellitus, and appropriate referral for urgent initiation of diabetic education and treatment should take place [10].

### *Predisposing and precipitating factors*

Patients with known or unknown diabetes progress from poor glucose control to overt HHS typically over a period of days to weeks, and the process may be initiated or sustained by serious underlying illness and other factors. Infection (eg, pneumonia, urinary tract infection, and sepsis) is the most common precipitating illness, occurring in up to 60% of cases [4,11,22]. Other acute conditions that may provoke release of counter regulatory hormones and precipitate HHS include silent myocardial infarction, cerebrovascular accident, pulmonary embolism, and mesenteric thrombosis [13]. Acute pancreatitis, gastrointestinal (GI) bleeding, heat illness, and procedures with glucose loading (eg, peritoneal dialysis and recent surgical operation) have been identified as precipitants [4,12,22]. Patients with underlying renal insufficiency and congestive heart failure (CHF) are at greater risk. Many

different medications have been identified that may contribute to the development of HHS by their affect on carbohydrate metabolism. These include glucocorticoids, thiazide diuretics, phenytoin, and beta blockers [4]. More recently, the antipsychotic drugs clozapine and olanzapine have been associated with the development of hyperglycemia, and cases of DKA and HHS have been reported [23,24]. Use of alcohol and cocaine also has been implicated in the development of HHS [11,25].

In general, any medical illness that predisposes to dehydration may contribute to development of HHS. Disorders that affect mental function, impair means of communication, or limit mobility, and therefore create dependence on others for providing access to and ensuring adequate fluid intake can precipitate HHS [12]. One of the most common predisposing factors is under-recognition of the signs and symptoms of uncontrolled diabetes, especially when the patient is not known to be diabetic, and underestimation of fluid needs by caregivers in nursing homes and other settings [6]. Replacement with high glucose containing fluids, poor diabetic education, not monitoring blood sugars, and noncompliance with insulin or oral therapy also may contribute [2].

For the emergency medicine practitioner, identification of any underlying acute illness precipitating HHS is critical, and treatment must be initiated concurrent with that of HHS. The search for hidden precipitants should continue even in the presence of one or more obvious causes. **Box 1** summarizes common precipitating factors.

### *Clinical presentation*

Despite the profound metabolic abnormalities that are present, HHS may not be clinically obvious. The classical picture of HHS includes a history of first the signs and symptoms of uncontrolled hyperglycemia (eg, polyuria, polydipsia, fatigue, and visual disturbances), and then subsequent dehydration (including weakness, anorexia, weight loss, leg cramps, dizziness, confusion, and lethargy). The average duration of symptoms is 12 days in HHS versus less than 1 to 2 days in DKA [20]. In some cases, however, the clinical presentation of HHS is similar to DKA, and a definite diagnosis must be confirmed through laboratory investigation [13]. Because significant acidosis is absent, abdominal pain is much less common in HHS than in DKA, and nausea and vomiting may not be present [26]. When abdominal pain is a prominent symptom, it should be investigated as either a precipitating cause or complication (eg, mesenteric ischemia) of the HHS.

The most common reason caretakers seek medical attention for the patient is concern related to a change in level of cognition [20]. Despite the previous nomenclature, less than 20% of patients with HHS present in coma [6,27]. Some patients may present alert with a near normal mental status, but a gradual clouding of consciousness is typical [6]. The degree of alteration in mental status tends to correlate with the degree of hyperosmolarity, and

## **Box 1. Precipitating factors to development of hyperosmolar hyperglycemic state**

### *Infection*

Pneumonia  
Sepsis (particularly gram-negative)  
Urinary Tract Infection

### *Concurrent medical illness*

#### Vascular occlusive illness

- Cerebral vascular accident
- Mesenteric thrombosis
- Myocardial infarction
- Pulmonary embolus

#### Metabolic illness

- Acute pancreatitis
- Heat illness
- Hypothermia
- Intestinal obstruction
- Renal failure

#### Endocrine causes

- Acromegaly
- Cushing's syndrome
- Previously undiagnosed diabetes mellitus
- Thyrotoxicosis

#### Other

- Alcohol abuse
- Burns
- Cocaine abuse
- GI bleeding
- Neuroleptic malignant syndrome
- Peritoneal or hemodialysis
- Rhabdomyolysis
- Trauma

### *Medications*

Beta-blockers  
Calcium channel blockers  
Carbamazepine  
Chlorpromazine  
Cimetidine  
Corticosteroids  
Didanosine  
Glucocorticoids  
Immunosuppressants  
Lithium  
Mannitol  
Neuroleptics  
Olanzapine  
Pentamidine  
Phenytoin  
Thiazide and loop diuretics  
Total parenteral nutrition or enteral nutrition  
Noncompliance with diabetes mellitus therapy

### *Postoperative*

Coronary artery bypass graft  
Neurosurgery  
Orthopedic surgery  
Renal transplant

### *Sociodemographic factors*

Dependent on others for self-care (unable to meet fluid needs)  
Elderly  
Female

### *Reference*

1,2,4-7,10,11,13,15,16

serious alteration in consciousness is uncommon with osmolarities less than 340 mOsm/L [22]. Coma is associated with severe hypertonicity, with serum osmolarity at 350 mOsm/L or greater, and usually more significant hypernatremia than hyperglycemia [12,28]. The absence of hyperosmolarity or hypoglycemia in an obtunded patient with diabetes mellitus suggests an etiology other than a direct complication of diabetes [6,22,29].

Many neurologic changes can occur in HHS, including unilateral or bilateral focal motor or sensory deficits, aphasia, myoclonic jerks, chorea, nystagmus, and Babinski's signs [27]. Seizures occur in 15% of cases, and are often focal seizures, either intermittent or continuous (epilepsia partialis continua) [5,12,27]. It is important to note that the neurologic changes seen as a result of HHS typically reverse completely with appropriate treatment and correction of the metabolic abnormalities [22]. Focus solely on the neurologic deficits (eg, seizures, hemiparesis, and coma) can delay diagnosis and appropriate treatment unless a glucose level is obtained early in the presentation. Especially in the era of thrombolytic reperfusion therapy for acute ischemic stroke, evaluation of new focal neurologic deficits always must include a glucose level to exclude a stroke mimic from either hypoglycemia or, in the case of HHS, extreme hyperglycemia [30,31]. Hyperglycemia is common in patients with acute stroke, and it is associated with a worse outcome in reperfused and non-reperfused stroke patients. The level, however, will not be to the extremes seen with HHS [32].

Patients with HHS typically present with a debilitated weakened general appearance and show physical signs of dehydration including dry mucous membranes, poor skin turgor, and sunken eyes, although these changes can often be subtle in the elderly. Tachycardia and tachypnea (not Kussmaul respirations) are common, as are hypotension and signs of decreased perfusion in advanced cases. Although some authors suggest that patients may have a low-grade fever because of dehydration and lack of sweating, in general any degree of fever suggests infection [33]. Signs of localized infection (eg, pneumonia or cellulitis) may be present. Finally, the physical exam may show evidence of insulin resistance, including obesity, acanthosis nigricans, and diabetic dermatopathy.

### **Pathophysiology**

In a diabetic patient with pre-existing insulin lack or resistance, a physiologic stress (eg, an acute illness) can cause further net reduction in the effectiveness of circulating insulin. Concomitant elevations in counter regulatory hormones (eg, glucagon, catecholamines, cortisol, and growth hormone) contribute to impaired glucose use in the peripheral tissues. Hypercortisolemia increases proteolysis, which leads to the production of amino acid precursors for gluconeogenesis, and glucagon induces glycogenolysis. As in DKA, the combination of hepatic glucose production and

decreased peripheral glucose use is the main pathogenic etiology for hyperglycemia associated with HHS [2,13,22].

Hyperglycemia leads to glycosuria, hypotonic osmotic diuresis, and dehydration. Glucose is osmotically active and creates an osmotic gradient drawing water from the intracellular to extracellular compartments. As serum concentrations of glucose exceed 180 mg/dL, the kidney's capacity to reabsorb glucose is exceeded [19]. The presence of glucose in the urine impairs the concentrating capacity of the kidney, therefore exacerbating water losses [2]. If fluid intake is adequate, renal excretion of glucose may be sufficient to prevent marked serum hyperglycemia. If the patient is unable to maintain adequate fluid intake (eg, due to acute illness, decreased thirst mechanism, immobility, or other ongoing fluid losses), however, these water losses further decrease kidney perfusion, which markedly exacerbates the hyperglycemia [6]. It is this renal insufficiency in HHS that allows for the extremely high levels of glucose seen with this disorder, much higher than in DKA, resulting in the severe hyperosmolality and intracellular dehydration [34]. The alteration in consciousness seen in HHS directly corresponds to the elevation in effective osmolarity and may be related to intracellular cerebral dehydration, changes in neurotransmitter levels, and microischemia [12].

In the osmotic diuresis, free water is lost in excess of electrolytes, but there is a large loss of sodium, potassium, magnesium, and phosphate in the urine. Losses of electrolytes are more profound than those seen in DKA (Table 1) [13]. Initial measured serum levels of electrolytes may not reflect the actual deficits accurately. The full development of HHS occurs over several days, and the total body water deficit averages 8 to 12 L in HHS, compared with 5 to 7 L in DKA [13]. In its severe form, this prolonged osmotic diuresis results in hypotension and impaired tissue perfusion.

In addition to the degree of fluid loss and dehydration, another key difference between DKA and HHS is the absence of significant ketosis. The reason for this absence of ketosis in HHS is not known, but it is proposed that insulin levels may be adequate to prevent lipolysis and subsequent ketogenesis, yet inadequate to facilitate peripheral glucose uptake and to prevent hepatic

Table 1

Water and electrolyte loss at presentation of hyperosmolar hyperglycemic state and diabetic ketoacidosis [2-4,13]

| Electrolyte         | HHS*             | DKA*           |
|---------------------|------------------|----------------|
| Water (mL/kg)       | 100-200 (10.5 L) | 100 (7 L)      |
| Sodium (mEq/kg)     | 5-13 (350-910)   | 7-10 (490-700) |
| Potassium (mEq/kg)  | 5-15 (350-1050)  | 3-5 (210-300)  |
| Chloride (mEq/kg)   | 3-7 (210-490)    | 3-5 (210-350)  |
| Phosphate (mmol/kg) | 1-2 (70-140)     | 1-1.5 (70-105) |
| Magnesium (mEq/kg)  | 1-2 (70-140)     | 1-2 (70-140)   |
| Calcium (mEq/kg)    | 2 (140)          | 1-2 (70-140)   |

\* Values in parentheses represent total body deficits for a 70 kg patient.

gluconeogenesis [22]. Also, lower levels of counter-regulatory hormones compared with patients with DKA have been found in some studies, and the insulin to glucagon ratio is higher [7]. Finally, hyperosmolality itself may act to decrease lipolysis (the release of free fatty acids) and subsequent ketogenesis [22]. The absence of clinically significant ketoacidosis is a factor in the progression of the pathogenesis of HHS. Lack of physical discomforts associated with ketosis may result in a delay in seeking treatment, and this delay can sustain the osmotic diuresis.

### Differential diagnosis

The differential diagnosis of HHS includes any cause of altered level of consciousness, including hypoglycemia, hyponatremia, severe dehydration, uremia, hyperammonemia, drug overdose, and sepsis [20]. Seizures and acute stroke-like syndromes are common presentations. Early measurement of a blood glucose level in any patient with impaired consciousness is imperative. In the unlikely event a level cannot be obtained rapidly, administration of dextrose is indicated to treat possible hypoglycemia, and will only minimally worsen HHS if it is present.

Hyperosmolar hyperglycemic state can be differentiated from DKA by the presentation and laboratory features (Table 2). Mixed syndromes of HHS and DKA can exist. There are essentially no disorders other than uncontrolled diabetes mellitus that produce the marked hyperglycemia seen in HHS [35].

### Emergency department evaluation

#### Laboratory

The initial laboratory evaluation of patients with suspected HHS should consider the frequency of precipitating causes and underlying comorbidities

Table 2

Typical presenting laboratory values associated with hyperosmolar hyperglycemic state compared with diabetic ketoacidosis [2,4,13]

|                                | HHS                | DKA               |
|--------------------------------|--------------------|-------------------|
| <b>Diagnostic</b>              |                    |                   |
| Serum glucose (mg/dL)          | > 600 (mean: 1166) | > 250 (mean: 475) |
| Serum osmolality (mOsm/kg)     | > 320              | < 320             |
| Arterial pH value              | > 7.3              | < 7.2             |
| Sodium bicarbonate (mEq/L)     | > 15               | < 15              |
| Serum ketones                  | Absent or low      | Moderate to high  |
| <b>Variable, mean (and SD)</b> |                    |                   |
| Serum sodium (mEq/L)           | 149 (3.2)          | 134 (1)           |
| Serum potassium (mEq/L)        | 3.9 (0.2)          | 4.5 (0.13)        |
| BUN (mg/dL)                    | 61 (10.9)          | 32 (3.1)          |
| Serum creatinine (mg/dL)       | 1.4 (0.01)         | 1.1 (0.01)        |

associated with HHS. Baseline laboratory assessment includes measurement of serum glucose, serum urea nitrogen (BUN), creatinine, electrolytes, serum ketones, osmolality, urinalysis, complete blood count with differential, and arterial blood glasses if respiratory compromise or acidosis is suspected. Bacterial cultures of urine and blood almost always are indicated. Typical laboratory values in HHS compared with DKA are noted in Table 2.

### *Glucose*

Extreme hyperglycemia defines HHS, and the degree of hyperglycemia is usually proportional to the degree of dehydration and osmolality. Serum glucose levels greater than 600 mg/dL, and often well over 1000 mg/dL, are present. When levels are this high, laboratory determinations, rather than finger-stick bedside measurements, are needed for accurate assessment [16].

### *Osmolality*

The second diagnostic criterion is hyperosmolality. Osmolality is measured directly in the laboratory by determining the freezing point of the serum. This can be approximated by the formula:

$$\text{Osmolarity} = [2 \times \text{Na (mEq/L)}] + \frac{\text{glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}$$

Because the density of water is 1 kg/L, osmolarity (in osm/L) is roughly equivalent to osmolality (in osm/kg) in water based systems with minimal temperature variation (eg, the human body) and they are often used interchangeably [36]. This calculated value can be compared with the measured value to determine any osmolar gap. This calculation of osmolarity, however, includes urea, which is freely diffusible across cell membranes, is therefore not osmotically active, and is not important in the pathogenesis of HHS. A more useful calculation is the effective osmolarity, which reflects actual tonicity, the osmotic pressure of a solution. The effective osmolarity can be calculated by the formula:

$$\text{Effective osmolarity (mOsm/L)} = 2 \times [(\text{Na}) + (\text{K}^+)] + \text{glucose}/18$$

Measuring the effective osmolarity is important to help guide the optimal choice of fluid for replacement therapy, as elevated BUN and azotemia may mask an actual hypotonicity of the extracellular fluid and can lead to inappropriate administration of hypotonic fluids [6]. The normal serum osmolarity ranges from 275 to 295 mOsm/L. Levels above 320 mOsm/L may involve some alteration in cognitive function, and patients with coma caused by HHS almost always have values of 340 mOsm/L or greater. Rarely, serum osmolarity may be greater than 400 mOsm/L. As reflected in the formula, serum sodium actually contributes more to effective osmolarity than glucose, and most cases of coma are associated with a high serum sodium [28].

### *Sodium*

The measured sodium may be low, normal, or elevated, despite the patient being total body sodium depleted. Because glucose osmotically shifts water into the extracellular space, sodium is diluted, and the measured value is decreased falsely. The measured sodium value should be corrected to a true sodium value that accounts for hyperglycemia by using the formula:

$$\text{Corrected (Na)} = 1.6 \times (\text{glucose} - 100)/100$$

This reflects that the measured serum sodium value is decreased by approximately 1.6 mEq for every 100 mg/dL increase in glucose above 100 [36]. The formula listed is the traditional formula used, although one study has suggested the relationship between glucose and sodium is nonlinear, and that a more accurate correction factor in extreme hyperglycemic states is 2.4 mEq/L for each 100 mg/dL [37]. The dilutional effect of hyperglycemia is counteracted by the glucosuria-induced diuresis, as water is lost more than sodium and potassium. A mild hyponatremia or a normal sodium level usually suggests moderate dehydration. If the serum sodium concentration is high despite severe hyperglycemia, significant water loss has occurred, and extreme volume contraction and dehydration are present [27]. Corrected sodium levels more accurately reflect the state of dehydration and are useful in monitoring treatment [38].

### *Potassium*

Total body potassium depletion is even more profound in HHS than in DKA. The presenting serum potassium concentration, however, is often high because of volume contraction, insulin deficiency, shift of potassium from intracellular to extracellular fluid compartments, and some degree of acidosis. In some instances, this initial serum potassium can be symptomatic [39]. Potassium deficits are common in uncontrolled diabetes and may be especially high in patients who are on diuretics. The presence of normal or low potassium at presentation suggests a profound deficit. Initiation of treatment with volume replacement and insulin will result in a further decrease in the serum potassium concentration. Hypokalemia is a significant risk in the initial treatment phase and should be anticipated.

### *Other laboratory measurements*

Body stores of phosphate and magnesium will be decreased comparable to those of potassium, although serum levels may high or normal. The clinical consequences of magnesium or phosphate deficiency are not as significant as those of potassium in the immediate treatment setting of the ED. Levels tend to normalize during treatment, and there is no evidence that replacement is necessary unless levels are extremely low [4].

Dehydration may cause a rise in the plasma levels of routine chemistries including calcium, protein, amylase, lactate dehydrogenase, transaminases, and creatinine kinase. Underlying disease states associated with these levels need to be excluded, however. Patients present with prerenal azotemia, and the initial BUN to creatinine ratio may exceed 30:1. Leukocytosis is often present secondary to stress, demarginalization, and hemoconcentration [7]. Infection, however, should be ruled out as the cause of any marked elevation in white blood cell count. Hemoglobin and hematocrit concentrations may be elevated falsely because of hemoconcentration, and anemia should be suspected in a patient with a normal hematocrit on examination [20].

A mild high anion gap metabolic acidosis, characterized by an arterial pH above 7.3 and bicarbonate level greater than 15 is common in HHS [22,33]. This acidosis can be multifactorial, contributed to by dehydration, renal failure, starvation, or mild lactic acidosis. Vomiting or the use of thiazide diuretics can cause a metabolic alkalosis that can mask the degree of acidosis [4,12,22]. If acidosis is severe, lactic acidosis caused by hypovolemia and decreased perfusion, underlying infection, or other concurrent severe illness (eg, ischemic bowel) should be considered [4]. Arterial blood gas measurements can help clarify what is sometimes a complicated mixed acid base picture, and indicate other cardiac or pulmonary comorbidities. Although HHS is described as a nonketotic hyperosmolar state, there is often some elevation of serum ketones, including  $\beta$ -hydroxybutyrate, which are related mostly to the starvation ketosis or to dehydration [2,19]. Urinalysis always is indicated and may demonstrate some degree of ketonuria also. Gross proteinuria suggests the presence of underlying renal disease.

### **Other studies**

Other diagnostic studies are obtained routinely in the ED evaluation to look for precipitating or underlying illnesses. The initial chest radiograph may be falsely negative for pneumonitis in light of the state of dehydration, and cardiomegaly in this setting suggests likely cardiomyopathy [19]. An electrocardiogram always is indicated to look for signs of ischemia and infarction, and acute changes related to electrolyte deficiencies. CT of the brain to exclude intracranial pathology is indicated because of the frequent presence of altered cognition. Lumbar puncture and toxicologic studies should be performed if indicated.

### **Emergency department management**

Management in the ED begins with a rapid clinical assessment focused on the elements of history and physical, and with appropriate evaluation and monitoring of respiratory, cardiovascular, and central nervous system function. The diagnosis of the extreme decompensated diabetic state can be

made immediately with an early glucose measurement, and a potassium level should follow quickly. The goals of therapy include [7,16]:

- Restoration of hemodynamic stability and correction of hypovolemia
- Maintenance of electrolyte homeostasis
- Gradual correction of hyperglycemia and hyperosmolality
- Detection and treatment of underlying disease states and precipitating causes
- Avoidance of complications

The most rapid therapy is directed toward hypovolemic shock and life-threatening electrolyte abnormalities.

When faced with such extreme elevations of glucose and abnormalities of osmolality and sodium as seen in HHS, there is a tendency to think that initial interventions can be gross and inaccurate without consequence. The severity of the disease, however, demands a rational and systematic approach to therapy from the beginning. The initial treatment in the ED can make a difference in the frequency of complications and outcome. Although adherence to protocols and standard treatment algorithms have improved outcomes, therapy must be individualized based on the degree of dehydration and underlying disease states (eg, sepsis, renal failure, and left ventricular dysfunction). Close monitoring in the first hours of treatment is essential. Central venous and urinary catheterization may be required to guide fluid administration. A flow sheet to frequently assess therapy is useful and should be maintained diligently. With prolonged ED stays and EDs serving as holding area for admitted patients, the most critical period for these patients may occur during their ED course. The ED becomes the critical care unit, and patients cannot be forgotten after a few initial interventions. The key is continuing and careful monitoring and therapeutic adjustments.

### *Fluid therapy*

Fluid replacement to expand intravascular volume and restore renal and tissue perfusion is the first priority in managing HHS and is the cornerstone of therapy. Patients invariably are volume depleted, and the approximate fluid deficit can be calculated to help guide therapy. Total body weight is 50% to 60% of usual body weight, and the fluid deficit averages 20% to 25% of total body water, or approximately 12% to 15% of body weight [12]. A range of typical fluid deficits is 8 to 12 L, with the average being 9 L [6,12]. Another way to approximate this deficit is simply 150 mL/kg of body weight or to compare normal recent weight with current weight: every liter of body fluids lost results in 1 kg loss in body weight [6]. The goal is to replace one half of the fluid deficit in the first 12 hours and the remainder in the next 12 to 24 hours [2,12,16,22]. There is general agreement that initial replacement should be with isotonic crystalloid (eg, 0.9% sodium chloride). Sodium chloride will restore intravascular volume effectively but is still hypotonic to the patient's serum

osmolality [12]. If the patient is hypotensive and in shock, immediate fluid resuscitation with 0.9% sodium chloride is indicated, and 1 to 2 L are given rapidly until the blood pressure increases, and urine output is established. For most adult patients who are not hypotensive, 0.9% sodium chloride is administered at rates of 15 to 20 mL/kg per hour (average of 1 to 1.5 L) during the first hour [2].

The type of fluid and rate of administration after this should be individualized and adjusted depending upon vital signs, serum electrolyte levels, and urinary output. In general, once circulating volumes have been restored, replacement will be slower, and the solution changed to 0.45% sodium chloride to avoid further osmotic loads. The ADA guidelines recommend looking to the corrected serum sodium. If it is normal or elevated, 0.45% sodium chloride is infused at 4 to 14 mL/kg per hour (approx 300 to 1200 mL) depending on hydration state, and if low, 0.9% sodium chloride is continued at the same rate [2]. Another approach would be to look at the effective osmolality. Some authors suggest that 0.9% sodium chloride be used if the serum osmolality is less than 320 to 330 mOsm/L and 0.45% sodium chloride if it is above this level [6]. Sodium chloride will continue to expand the intravascular volume and slows the decrease in osmolality, but it can be associated with a persistent hypernatremia and runs greater risk of fluid overload. Hypotonic fluids (eg, 0.45% sodium chloride) are more effective in replacing free water loss and prevent hypernatremia, but they may be associated with a more rapid decrease in extracellular osmolality and sodium [12]. To avoid the risk of cerebral edema, especially in younger patients, the goal is not to exceed a change in serum osmolality greater than 3 mOsm/kg per hour [2]. Early in treatment, a decrease in the plasma glucose level also serves as an index of the adequacy rehydration and restoration of renal perfusion. Failure of the plasma glucose to decrease by 75 to 100 mg/dL per hour usually implies impairment of renal function or inadequate volume administration [6]. Potassium is added to fluids early on, and glucose-containing fluids are begun when the glucose level reaches 300 mg/dL [2]. Carefully monitored, rapid restoration of plasma volume in adult patients with HHS usually is tolerated well. An average fluid administration would be 3 to 4 L in the first 4 hours of therapy.

Underlying disease states (eg, left ventricular dysfunction or renal disease) may modify a patient's ability to handle large volumes of fluid and therefore determine the rate of fluid replacement [27]. Patients with chronic renal insufficiency are especially challenging, and knowledge of a patient's previous renal function can be helpful. In these patients, the glucose can exceed over 1000 mg/dL or even 1500 mg/dL, but because of renal insufficiency, the patient may not establish an osmotic diuresis and may effectively present with hyponatremia and hypochloremia because of the extracellular fluid shift induced by the elevated glucose. The rise in plasma osmolality is limited, as is the likelihood therefore of neurologic symptoms. Overhydration in this subgroup of patients quickly can result in CHF and pulmonary edema. In

long-established renal failure or with anuria, the role of fluid therapy in the treatment of HHS is limited, and treatment consists primarily of providing insulin to decrease glucose levels, shift fluid back into the intracellular space, and decrease potassium levels. Patients with underlying renal disease, cardiac disease, or other complicating states are more likely to require invasive monitoring to guide fluid therapy [12].

In pediatric patients (younger than 20 years), fluid replacement objectives are similar to adults. Because of the risk of cerebral edema associated with fluid resuscitation in pediatric patients, however, the rate of administration of 0.9% sodium chloride should be less than that in adults, and should not exceed 50 mL/kg over the first 4 hours of therapy. Continued fluid therapy is calculated to replace the fluid deficit over 48 hours in pediatric patients, compared with 24 hours in adults [2].

### *Potassium and other electrolytes*

Although the potassium level may be initially normal or even high, all patients with HHS are potassium depleted. Losses average 5 to 6 mEq/kg, range as high as 10 to 15 mEq/kg, and are often greater than those seen in DKA [16,27]. After hypovolemic shock, acute hypokalemia is the most serious immediate risk to patients with HHS, and monitoring and replacement of potassium are critical. Treatment of HHS with rehydration and insulin usually results in a rapid decline in the serum concentration of potassium, particularly during the first few hours of therapy. Other factors contributing to this decline include correction of any acidosis and continued potassium loss because of osmotic diuresis [13,40]. Knowledge of the serum potassium level at the beginning of treatment is essential. Patients whose potassium is low initially in the presence of HHS are at the greatest risk of complications including cardiac dysrhythmias, cardiac arrest, and respiratory muscle weakness. If the initial serum potassium level is less than 3.3 mEq/L, potassium replacement should begin immediately with initial fluid therapy at a rate of up to 40 mEq/L per hour until levels are above 3.3 mEq/L. Otherwise, potassium replacement should be initiated as soon urinary output is assured and levels reach 5 mEq/L or below. Routinely, 20 mEq/L potassium chloride can be added to each 1 L of intravenous fluid with the goal being to maintain a serum concentration of potassium within the normal range of 4 to 5 mEq/L [2,12,16]. Initially, the serum concentration of potassium should be measured every 1 to 2 hours, because the most rapid change occurs during the first 5 hours of treatment. Electrocardiogram monitoring is recommended in patients presenting with hypokalemia and receiving replacement therapy. Because insulin facilitates potassium re-entry in to the intracellular compartment, insulin therapy should be delayed until the potassium level is at least 3.3 mEq/L.

Some authorities recommend administering one-third of potassium replacement as potassium phosphate to avoid excess chloride administration and to prevent hypophosphatemia [2]. The rationale for this recommendation

has been questioned [4]. Despite the presence of hypophosphatemia, most controlled trials, focused on DKA management, have not demonstrated benefit of phosphate replacement [12]. Although phosphate levels should be measured and treatment initiated when levels are below 1 mg/dL, routine administration of phosphate in the ED setting is not indicated. More gradual replacement, to avoid the complications of hypocalcemia or in the face of renal failure, may be physiologically appropriate in selected patients and can be pursued during inpatient treatment. Likewise, despite total body depletion, replacement of magnesium need only be initiated in the ED when the magnesium level is below normal [29,41]. A total dose of 2 to 3 g of 10% solution can be added to intravenous fluid if renal failure is not present. Because potassium and magnesium regulations are related closely, correction of hypokalemia may be contingent on magnesium replacement [41].

### *Insulin*

Insulin plays a secondary role in the ED management of HHS, and fluid therapy always should precede insulin administration. The osmotic pressure that glucose exerts within the vascular space contributes to maintenance of circulating volume in these severely dehydrated patients. Insulin drives glucose, potassium, and water into cells, and administration of insulin alone could lead to circulatory collapse, shock, and even thromboembolism if fluid has not been replaced first [12,19,27]. Insulin therapy in the ED may not be required at all with appropriate fluid therapy [20]. Once hemodynamic stability is achieved and the kidneys are well perfused, low-dose insulin therapy may be initiated. Also, as noted previously, insulin administration should await measurement of serum potassium and should be delayed if the serum potassium is less than 3.3 mEq/L.

Although glucose initially can drop as much as 80 to 200 mg/dL per hour because of adequate fluid therapy alone, insulin likely will be required [16]. The recommended dose of insulin in HHS is 0.1 U/kg per hour of regular insulin by continuous intravenous infusion with or without an initial bolus of 0.15 U/kg [2]. Steady-state insulin levels can be achieved within 25 minutes of an insulin infusion. No proven benefit of a bolus has been demonstrated, and it specifically is not recommended in pediatric patients [2]. Insulin should be infused separate from other fluids, and the infusion should not be interrupted or suspended once begun [19]. Serum glucose levels should be determined every hour and followed by adjustment of the insulin infusion. In the presence of adequate hydration, this dose of insulin usually decreases plasma glucose concentration at a rate of 50 to 75 mg/dL per hour [2]. The goal is to decrease glucose by no more than 100 mg/dL per hour, and the target is to lower it only to 300 mg/dL [19]. Once the serum concentration of glucose reaches 300 mg/dL or less, dextrose 5% water should be added to the intravenous fluids, and the insulin infusion rate can be decreased by half to 0.05 U/kg per hour [2]. Conversely, if the glucose level does not improve after an hour of insulin

infusion, the infusion rate can be doubled until a response is noted; however, the adequacy of fluid therapy should be questioned. Although insulin resistance is present, patients usually respond well to exogenously administered insulin, and less insulin may be required in HHS than in DKA, where insulin also is required to reverse the ketoacidosis.

### *Underlying illness*

Detection and treatment of any underlying predisposing illness is a crucial part of the management of HHS. Antibiotics should be administered early, after appropriate cultures, in patients in whom infection is known or suspected as a precipitant to HHS. Treatment for seizures should avoid phenytoin, which inhibits the release of endogenous insulin and has been associated with HHS [12,20]. A high index of suspicion should be maintained for underlying pancreatitis, GI bleeding, renal failure, and thromboembolic events, especially acute myocardial infarction.

### **Complications**

Complications can occur secondary to the pathophysiology of HHS itself or as a result of treatment. The most common lethal problems of initial treatment include failure to manage the airway and inadequate fluid resuscitation. Hypoglycemia as a consequence of insulin infusion is seen less often than with DKA, and would not be expected during the ED time course. Hypokalemia can occur related to therapy as described previously. Some treatment-related complications of HHS are not typically apparent during the ED course, but ED management could impact their incidence. Serious complications of HHS include thromboembolic events, cerebral edema, adult respiratory distress syndrome, and rhabdomyolysis.

Severe dehydration and elevated serum osmolality in HHS can result in hypotension, low cardiac output, and hyperviscosity of the blood. This and other factors, such as various prothrombotic elements of the diabetic state and frequent presence of underlying atherosclerosis, may predispose the patient to complications such cerebral infarct, myocardial infarction, pulmonary embolism, mesenteric vessel thrombosis, and disseminated intravascular coagulation [13,19]. Such vascular complications may be prevented with aggressive fluid therapy at the onset of treatment to correct the hyperosmolality and restore perfusion [22]. Because large-vessel thromboembolic events are a cause of late mortality, use of low-dose heparin for prophylaxis is recommended, but full heparinization with either low molecular weight or unfractionated heparin is reserved for clinical evidence of thrombosis [42].

Cerebral edema is a devastating complication that is extremely rare in adults with HHS despite the typically rapid fluid resuscitation. Children with HHS, however, should be assumed to be at similar risk for developing cerebral edema as those with DKA [14]. In the study by Glaser et al, those

children who had more severe dehydration at presentation with higher BUN concentrations were at increased risk for cerebral edema [43]. Neurologic deterioration may not occur for an average of 7 hours after initiation of therapy. ED treatment could impact the incidence of this complication, and, in younger patients particularly, gradual correction of the sodium and water deficits and avoidance of rapid decline in plasma glucose concentration are important. The guidelines for slower rehydration should be adhered to meticulously for patients up to 20 years of age [2].

Rhabdomyolysis detected by increasing levels of creatinine kinase is a recognized complication of adult patients with HHS. Related complications occurring at the initial diagnosis of type 2 diabetes mellitus in teenaged children have been reported. Hollander et al described a case series of six adolescent males presenting with HHS complicated by a malignant hyperthermia-like picture with fever, rhabdomyolysis, and severe cardiovascular instability. Four of the six patients died, and all had increased temperature after administration of insulin. Although the etiology of the state is unclear, the authors suggested empiric treatment with dantrolene in this setting [21]. Morales and Rosenbloom reported on seven African-American youth with unrecognized type 2 diabetes mellitus who died from HHS complicated by delayed diagnosis and treatment. One of these patients died from cerebral edema, and one had fever and rhabdomyolysis [14].

## **Disposition**

All patients diagnosed with HHS require hospitalization. Because of the close monitoring and dynamic therapy necessary in these patients, most will require admission to an intensive care setting. Some patients with less severe degrees of metabolic derangement and alteration in consciousness may be considered for step down units if response to initial therapy in the ED is adequate [27]. Careful monitoring of vital signs, fluid balance, and frequent clinical re-evaluation usually obviates the need for invasive monitoring and its associated infection risk [12,28].

## **Summary**

This article has discussed the ED presentation, evaluation, and treatment of HHS. Aggressive volume replacement to restore renal perfusion is the first priority and cornerstone of therapy, with attention on electrolyte balance, especially treatment of hypokalemia. Calculation of the effective osmolarity and corrected sodium values can help guide treatment, and fluid replacement should be more judicious in younger patients. Identification and treatment of any precipitating illness are essential. HHS is usually the result of decompensated type 2 diabetes, and prevention centers on early

diagnosis and identification of patients at risk, education of patients and caregivers on the early signs of uncontrolled hyperglycemia, and ensuring proper hydration and consistent monitoring. Finally, maintaining a high index of suspicion for type 2 diabetes mellitus in selected children and especially adolescents, will help prevent presentations of HHS in this age group.

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