Diagnosis and Acute Management of Hyperglycemic Hyperosmolar Syndrome in Children and Adolescents

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Abstract: Hyperglycemic hyperosmolar syndrome (HHS) is an indolent process characterized by significantly increased levels of serum glucose, high osmolality, and electrolyte abnormalities. The incidence of HHS has steadily risen in the pediatric population over the past several years. Patients with HHS often present with profound dehydration, fatigue, and early mental status changes. Primary emergency management of HHS involves fluid replacement, hemodynamic support, correcting electrolyte derangements, and addressing complications and underlying illnesses. Insulin is not an initial therapy in HHS and should be considered only after the patient's fluids and electrolytes have been repleted. Unlike in diabetic ketoacidosis, HHS patients are not acidotic, although children may present with mixed HHS/diabetic ketoacidosis syndromes. Complications of HHS include thrombosis, rhabdomyolysis, and, rarely, malignant hyperthermia.

Key Words: diabetic ketoacidosis, DKA, endocrinology, HHS, hyperglycemic hyperosmolar syndrome

TARGET AUDIENCE
This article is for pediatric emergency physicians, emergency physicians, pediatricians, and other health care providers who care for acutely ill children with hyperglycemia in emergency departments and urgent care settings.

LEARNING OBJECTIVES
1. Identify the signs and symptoms of hyperglycemic hyperosmolar syndrome (HHS) in children.
2. Differentiate the pathophysiology of HHS from diabetic ketoacidosis.
3. Explain the management of HHS.
4. Describe the complications associated with HSS.

INTRODUCTION AND EPIDEMIOLOGY OF HYPERGLYCEMIC HYPEROSMOLAR SYNDROME IN CHILDREN

Hyperglycemic hyperosmolar syndrome (HHS) is an endocrinologic emergency characterized by significantly increased levels of serum glucose and high osmolality. Previously thought to primarily affect adults with type 2 diabetes (T2D), HHS has been increasingly reported in children and adolescents with both T2D and type 1 diabetes (T1D). Historically, 2% of pediatric patients with T2D presented with HHS, although the incidence of pediatric HHS presentations and hospitalizations is rising by as much as 4% to 5% annually in the United States. This increase is thought to be closely linked to increasing rates of childhood obesity and T2D, the prevalent consumption of sugar-rich beverages, and a spreading awareness of HHS presentations in children. The increased incidence is also likely due to a renewed understanding that HHS can also affect T1D pediatric patients both with and without diabetic ketoacidosis (DKA).

Emergency medicine clinicians should be aware that HHS may be present in hyperglycemic children with varying body mass indices, racial and ethnic backgrounds, and known and undiagnosed T1D and T2D. Hyperglycemic hyperosmolar syndrome can also occur following recent trauma, burns, dialysis, or the initiation of certain medications, even in children who do not have underlying diabetes. The syndrome's indolent course, vague symptoms, and its potential to affect different types of children have led to many delayed or missed HHS diagnoses, resulting in worsened dehydration, hemodynamic derangements, and electrolyte abnormalities. Prompt HHS recognition and treatment are crucial, given that it has a 10% to 30% pediatric mortality rate, nearly 10 times higher than the mortality rate of DKA.

Signs and Symptoms of HHS
Hyperglycemic hyperosmolar syndrome presents with severe dehydration, fatigue, weakness, anorexia, early mental status changes, and electrolyte abnormalities. Unlike DKA, which is usually accompanied by abdominal pain, vomiting, and relatively rapid progression, the dehydration and electrolyte changes of HHS develop slowly, over days to weeks, because of gradual onset of polyuria, accompanying inadequate fluid intake, and ability of most children to hemodynamically compensate before deterioration. As a result, compared with DKA, children with HHS tend to present later in their course and with more severe symptoms of dehydration. Prognosis is often dependent on the degree of dehydration and hyperosmolality, timing of treatment, and presence of comorbid conditions. Refractory hypovolemic shock, sizable electrolyte derangements, and multiorgan failure are the complications most likely to lead to death in HHS.

The most common precipitating cause of HHS is infection, particularly urinary tract infections and pneumonias, although any stressor that leads to hypovolema and hyperglycemia (eg, trauma, stroke, myocardial infarction) has the potential to induce HHS. Further contributors to hypovolema, such as poor oral intake from developmental delay or feeding intolerance, will worsen the syndrome. As T2D is the primary risk factor of HHS in children, medication and insulin noncompliance are also precipitators. Some studies have reported increased HHS risk in children on atypical antipsychotic medications. However, it is important to recognize that many patients present with HHS as an initial manifestation of new-onset diabetes or without an identifiable precipitating cause.

HHS Pathophysiology
The profound dehydration and electrolyte disturbances of HHS are due to the underlying pathophysiology of the disease. In HHS, hyperglycemia results from an initial precipitating insult

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coupled to increased insulin resistance (in T2D) or absolute lack of insulin (in T1D).1,2 Hyperglycemia is worsened by a surge of counterregulatory hormones (eg, glucagon, cortisol, catecholamines), which induces glycogenolysis (breakdown of glycogen) and gluconeogenesis (glucose generation by noncarbohydrate sources), with catecholamine circulation also reducing glucose uptake by peripheral tissues.1,3 This hyperglycemia results in extracellular hyperosmolality, which in turn creates an osmolar gradient that pulls water from cells.2,7 Otherwise, healthy children can initially compensate for the hyperglycemia and fluid shifts through glucosuria, slowing the rise in serum glucose but leading to dehydration.1,2 Renal compensation and maintenance of intra-vascular volume can occur for days to weeks. Eventually, hypovolemia becomes so severe that renal function decreases, and patients can no longer excrete excess glucose, leading to life-threatening hyperosmolality.1,3,10,13 Dehydration further spurs the release of counterregulatory hormones, creating a feedback process that worsens hyperglycemia and leads to hemodynamic collapse.9,12 The total body water loss in HHS is considerable, with some studies estimating that patients lose 15% to 20% of their total body water, compared with only 5% to 10% in DKA.5,13,16 The same process that leads to dehydration also results in electrolyte abnormalities, with extracellular fluid shifts from hyperosmolality initially inducing pseudohyponatremia.7 Osmotic diuresis additionally causes the loss of potassium, sodium, magnesium, and phosphate. As dehydration progresses, renal function worsens and hypernatremia develops.2

The pathophysiology of HHS and that of DKA are similar, with an initial insult causing hyperglycemia and counterregulatory hormone release. However, in HHS patients with T2D or without any form of diabetes, the presence of circulating insulin and lower hormone release. However, in HHS patients with T2D or without any form of diabetes, the presence of circulating insulin and lower insulin induces ketogenesis, ketoacidosis, and osmotic diuresis from ketonuria and glucosuria.2,3 Patients with T1D can also exhibit mixed DKA and HHS presentations, depending on the initial insult, presence of exogenous insulin, and serum osmolality.3,14

Approach to Diagnosis of HHS

HHS Diagnostic Criteria

All patients with HHS will have increased serum glucose and osmolality. Other electrolyte derangements and an anion-gap acidosis will depend on the severity of dehydration and if there is a co-occurring DKA process.1,2 Table 1 reviews the diagnostic and clinical features of HHS, DKA, and mixed presentations. Figure 1 provides helpful formulas to aid in diagnosis and management.

Commonly accepted HHS diagnostic criteria include blood glucose levels greater than 600 mg/dL and serum osmolality greater than 320 mOsm/kg.2 In HHS without DKA, venous pH is greater than 7.25, serum bicarbonate is greater than 15 mEq/L, and ketonuria is small or absent.2 In patients with HHS and venous pH levels less than 7.25, providers should measure the metabolic anion gap. Causes of an anion-gap acidosis with HHS include a superimposed DKA, elevated lactic acid from organ dysfunction in the setting of shock, and renal failure.12

HHS Versus DKA Presentations

The symptoms exhibited with HHS and DKA are similar, and up to one-third of HHS and DKA children have mixed presentations.2,9 Both diseases cause osmotic diuresis and dehydration; however, the ketone formation and acidosis of DKA lead to gastrointestinal symptoms, hyperventilation, and general ill feelings, which cause DKA patient to present relatively earlier in their course of illness.2,7,10,13 Without acidosis, HHS patients can compensate for weeks and ultimately present with more severe clinical dehydration and electrolyte losses.1,13,14 Approximately half of HHS patients also have altered mental status (AMS) (eg, lethargy, behavioral changes, seizures).2,6 The severity of AMS is dependent on the degree of hyperosmolality and dehydration.13,16 Altered mental status is also seen in DKA, primarily in severe cases with pH <7.10,2,6

**Approach to Emergency Management of HHS**

Because of its high mortality rate and severe clinical presentation, treatment for HHS in the emergency department should begin as soon as the diagnosis is suspected. Emergency management of HHS encompasses (1) fluid replacement and hemodynamic support, (2) correcting electrolyte derangements, (3) insulin administration, and (4) addressing complications and underlying illnesses.

**Fluid and Hemodynamic Management**

Immediate and continued fluid replacement is the mainstay of therapy in children, adolescents, and adults with HHS.2,10 Pediatric patients with HHS present with approximately 10% to 20% or more total body water loss (100–200 mL/kg); replacing this fluid is crucial to expanding vascular volume and restoring renal perfusion.2,5,16 An initial isotonic fluid bolus of 20 mL/kg should be given over 30 to 60 minutes or even more rapidly depending on the patient’s hemodynamic state.2 Additional 10 to 20 mL/kg isotonic fluid boluses should be given until perfusion and hemodynamics have improved.2,10 Patients should then be administered hypotonic fluids (0.45% or 0.75% NaCl) at a rate that replaces the patient’s water deficit over 24 to 48 hours in addition to the weight-based hourly maintenance rate.2,10 As osmotic diuresis tends to continue as osmolality and serum glucose decline, urinary losses should be replaced 1:1 with additional maintenance fluids, beginning as soon as the patient urinates.2,10 Measuring strict fluid input and urinary output is key to fluid management.

After initial resuscitation with isotonic fluids, the choice of maintenance fluid should reflect the patient’s corrected serum sodium with a goal of gradually decreasing sodium and osmolality.1,2 Most HHS patients have hypernatremic dehydration, and hypotonic fluids are appropriate to target a corrected serum sodium that is high (>145 mEq/L) or normal (135–145 mEq/L); a low corrected serum sodium (<135 mEq/L) should be treated with isotonic fluid at the same maintenance rate.2,9 In patients with normal or high corrected serum sodium, the transition from isotonic to hypotonic fluids is necessary to prevent further hypernatremia, which can propagate the hyperosmolar state.2,10 However, serum sodium and osmolality need to be gradually lowered to avoid cerebral edema and other complications.7 A decline in serum sodium of approximately 0.5 mmol/L per hour should be targeted through frequent electrolyte monitoring (approximately every 2–3 hours).2,10 Similarly, serum osmolality should be corrected by an average of 3 mOsm/h to avoid potential cerebral edema.1,2

Apart from sodium, maintenance fluid should be adjusted with falling glucose levels. Fluid resuscitation and isotonic maintenance fluid will decrease serum glucose substantially (75–150 mg/dL per hour) without insulin administration.2,5,10,18 After initial resuscitation and several hours of maintenance fluid, dextrose (2.5% or 5%) should be added to fluid if serum glucose declines too rapidly or falls less than 200 to 300 mg/dL.2,8 Serum glucose levels should be monitored hourly to ensure appropriate decreases. In patients where glucose levels fail to decline, clinicians should evaluate renal function and other underlying comorbidities.10 (Fig. 2).

Even with initial resuscitation and maintenance fluid, the risk of refractory shock and hemodynamic collapse remains high.2
Intravenous hydration lowers serum osmolality, inducing intracellular shifts and reduced intravascular volume. Despite initial fluid resuscitation, intravascular volume can decline to life-threatening levels. Clinicians should prioritize frequent hemodynamic monitoring and administer the correct amount of maintenance fluids for HHS. As DKA treatment guidelines call for less fluid replacement, patients with HHS who are mistakenly diagnosed with exclusively DKA are often given insufficient fluids. Providers trying to avoid rapid corrections in serum osmolality and cerebral edema might also reduce maintenance fluids to insufficient amounts. With HHS, clinicians should err on the side of aggressive fluid replacement, which has demonstrated the most optimal outcomes in children and adolescents.

**Electrolyte Management**

Patients with HHS will often have other electrolyte abnormalities in addition to hyperglycemia and hypernatremia. Although serum potassium may be high or normal on initial laboratory tests, patients with HHS tend to have low total body potassium due to dehydration, urinary losses, and extracellular shifts. As a result, in addition to frequent electrolyte monitoring, patients with HHS should receive periodic electrocardiograms to evaluate for arrhythmias. Once the patient urinates (to ensure renal function is intact), 40 mEq/L of potassium should be added to maintenance fluids, as long as measured potassium is less than 5.0 mEq/L. If insulin is administered, additional potassium may be needed. Hypophosphatemia is also commonly seen with HHS and can lead to rhabdomyolysis, hemolytic uremic syndrome, and muscle weakness. Adding a mixture of potassium phosphate to fluids is recommended; this can be achieved through a combination of potassium phosphate and either potassium chloride or potassium acetate. Phosphate administration may also worsen hypocalcemia, so electrolytes should be checked frequently. In addition, although hypomagnesemia occurs with HHS, studies are mixed on magnesium replacement. If patients experience concomitant hypokalemia, hypocalcemia, or cardiac arrhythmias, magnesium replacement at 25 to 50 mg/kg per

**TABLE 1. Comparison of Common Laboratory Values and Clinical Presentations of HHS, DKA, and a Mixed Syndrome**

<table>
<thead>
<tr>
<th>Electrolyte abnormalities</th>
<th>HHS</th>
<th>DKA</th>
<th>Mixed HHS/DKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose, mg/dL</td>
<td>&gt;600</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Serum osmolality, mOsm/kg</td>
<td>&gt;320</td>
<td>&lt;320</td>
<td>&lt;320</td>
</tr>
<tr>
<td>Venous pH</td>
<td>&gt;7.25</td>
<td>7.10–7.25</td>
<td>&lt;7.10</td>
</tr>
<tr>
<td>Serum bicarbonate, mEq/L</td>
<td>&gt;15</td>
<td>17–5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Anion gap</td>
<td>Variable, usually &lt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>Trace or negative</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Onset</th>
<th>Mental status</th>
<th>Dehydration, %</th>
<th>Gastrointestinal symptoms</th>
<th>Populations affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days to weeks</td>
<td>Alert</td>
<td>Variable</td>
<td>Typically present</td>
<td>T2D &gt; T1D</td>
</tr>
<tr>
<td></td>
<td>Hours to days</td>
<td>Hour</td>
<td>Hour</td>
<td>Typically present</td>
<td>T1D</td>
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<tr>
<td></td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>T1D</td>
</tr>
</tbody>
</table>

**Total Body Water Deficit (L):**

\[
\text{Water Deficit} = \text{Total Body Water}^* \times \text{Weight} [\text{kg}] \times \left( \frac{\text{Sodium}}{140} - 1 \right)
\]

* YBW Infants (< 1 year) = 0.4
  YBW Children (1–12 years old) = 0.6
  YBW Teenagers/Adults (> 12 years old) = 0.4

**Effective Serum Osmolality (mOsm/kg):**

\[
\text{Effective Osm} = 2 \times \text{Sodium} + \frac{\text{Glucose} [\text{mg/dL}]}{18}
\]

**Corrected Sodium (mEq/L):**

\[
\text{Corrected Sodium} = \frac{1.6 \times (\text{glucose} [\text{mg/dL}] - 100)}{106}
\]

**Anion Gap (mEq/L):**

\[
\text{Anion Gap} = \text{Sodium} - (\text{Chloride} + \text{Bicarbonate})
\]

**FIGURE 1.** Commonly used formulas in the diagnosis of HHS.
Every Hour:
- Point-of-care blood glucose

Every 2 to 4 Hours:
- Serum electrolytes
- Serum calcium, magnesium, and phosphate
- Serum creatinine kinase

Additional Tests:
- ECG: upon arrival and then every four hours (based on electrolytes and clinical changes)
- Urinalysis: upon arrival and repeated every void if mixed HHS/DKA presentation

FIGURE 2. Suggested laboratory monitoring for pediatric patients with HHS.

dose (every 4–6 hours; maximum 2 g/h and 3–4 doses total) can be considered. Of note, bicarbonate replacement is contraindicated in HHS because of the risk of attenuating hypokalemia and worsening oxygen delivery.

Insulin Management

Unlike in DKA, insulin administration is usually not necessary with HHS, given the lack of ketosis and ability of fluid to correct hyperglycemia. Even with severe hyperglycemia, early insulin administration is contraindicated in HHS as the excess glucose is responsible for maintaining vascular osmotic pressure. Driving glucose out of vasculature too quickly could induce circulatory collapse. Early insulin administration can also adversely affect potassium levels and cause arrhythmias. Once HHS patients receive sufficient fluid resuscitation, if the rate of glucose decline drops less than 50 mg/dL per hour, the addition of low-dose insulin can be considered. Rates of 0.025 to 0.05 U/kg per hour should be utilized with goal decreases in glucose by approximately 75 to 100 mg/dL per hour. Insulin should be stopped if glucose begins falling more than 100 mg/dL per hour. Insulin boluses are contraindicated in HHS.

Treating Mixed DKA/HHS Patients

Patients with HHS can also present with DKA, and providers should be aware of the management differences between the 2 syndromes and how to approach patients with mixed presentations. Unlike HHS, where aggressive and early fluid therapy is needed to avoid circulatory collapse, for DKA patients not in hypovolemic shock, treatment guidelines typically suggest a single initial fluid bolus (usually 0.9% saline over 30 minutes) before beginning insulin and maintenance fluids. In addition, urinary losses are not typically replaced in DKA. These recommendations are partially due to DKA patients presenting with more mild dehydration than in HHS. They also represent the theoretically increased risk of cerebral edema in DKA from rapid and excessive fluid replacement, although recent studies demonstrated equivocal neurocognitive outcomes with more rapid fluid administration. As a result, children with mixed presentations should be treated with higher rates of fluid than in DKA alone, yet undergo frequent neurologic and electrolyte checks to assess for complications. If in doubt, clinicians should err on the side of less, fluid administration, because inadequate fluid resuscitation in HHS and mixed HHS/DKA presentations has been shown to lead to increased morbidity and mortality.

In mixed HHS/DKA pictures, electrolyte replacements will likely exceed what is required in DKA alone. In patients with HHS/DKA where the acidosis is primarily due to ketosis and not lactic acidosis, clinicians should give insulin earlier than in HHS. However, insulin should still be administered only after initial fluid boluses are given and hemodynamics stabilized. In mixed presentations, exact insulin rates and glucose targets should be carefully determined, and consultation with a pediatric endocrinologist considered.

HHS Complications

Apart from the dehydration, impaired hemodynamics, and electrolyte abnormalities, providers should be aware of several other complications that may arise from HHS. Although HHS patients often present with AMS due to high serum osmolality, prior studies have shown that their risk of cerebral edema is actually lower than in DKA, where cerebral edema is the main cause of morbidity and mortality. Nonetheless, HHS patients remain at theoretical risk of cerebral edema if serum osmolality and corrected sodium decline too rapidly. Osmolality decreases of 3 mOsm/h and sodium decreases of 0.5 mEq/L per hour should be targeted. Given the relative rarity of cerebral edema with HHS, and the overwhelming tendency for AMS and other complications resulting from severe dehydration, fluid repletion should not be delayed because of fear of worsening cerebral edema. In children with HHS or mixed HHS/DKA with concern for cerebral edema, mannitol and hypertonic saline can be considered, with the caveat that hypertonic saline administration will likely worsen osmolality corrections.

“Hyperglycemic hyperosmolar syndrome places children at far greater risk for thrombosis than DKA. This is primarily due to hyperosmolar damage to endothelial cells and dehydration directly upregulating coagulation factors. Although multiple types of venous occlusions are possible, sinus venous thromboses are a particular concern and can distort the mental status assessment. Neuroimaging should be considered in children with acute changes in mental status despite slow electrolyte corrections, or in children whose mental status fails to improve. Pulmonary embolisms are also frequently seen in adults with HHS. As a result, prophylactic anticoagulation with low-molecular-weight heparin can be considered in children with HHS (especially if older than 12 years and have other thrombotic risk factors); we advise consultation with a pediatric hematologist if thromboses are identified and/or heparin is being considered.

Rhabdomyolysis can also be observed with HHS and may lead to additional renal damage and electrolyte abnormalities, including hyperkalemia and hypocalcemia. Frequent monitoring of creatine kinase levels is recommended along with other electrolytes, especially in children with muscle pain, swelling, or hypophosphatemia (which can directly induce rhabdomyolysis). Finally, malignant hyperthermia has been reported in multiple pediatric HHS patients, although the pathophysiologic connection to HHS remains unknown. This complication has a very high mortality rate, and patients with fevers, rigors, and elevated creatine kinase should be treated with dantrolene.

Emergency Department Disposition and Consultations

Given the required fluid and electrolyte replacements, as well as the need for frequent monitoring of fluid balance, urine output,
electrolytes, and neurologic status of patients with HSS, most patients will require admission to a pediatric intensive care unit. Consultations with a pediatric endocrinologist and/or other subspecialists may assist with management decisions.

**SUMMARY**

Hyperglycemic hyperosmolar syndrome is an indolent process that results in significant dehydration, elevated serum glucose, increase in serum osmolality, and electrolyte derangements. Unlike DKA, there is minimal ketosis, and unless the picture is mixed, the patient will not be acidic. Patients often present with AMS and are at high risk for complications including thrombosis, rhabdomyolysis, and death. As HHS rates are rising in the pediatric population, it is important for providers to recognize the pathophysiologic and management difference between HHS, DKA, and mixed HHS/DKA. Management of HHS centers around hydration and electrolyte replacement and monitoring. Insulin is not an initial therapy in HHS and should be considered only after the patient’s fluids and electrolytes have been repleted. Patients should be admitted to the intensive care unit for close monitoring.

**REFERENCES**