IN BRIEF

Hyperosmolar Nonketotic Hyperglycemia

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OVERVIEW/WHY SHOULD PEDIATRICIANS CARE

Hyperosmolar nonketotic hyperglycemic state or hyperosmolar hyperglycemic state (HHS) is an acute emergency characterized by significant hyperglycemia and hyperosmolarity without ketosis. HHS was first described in the 1880s in adult patients with type 2 diabetes by von Frerichs and Dreschfeld as a diabetic coma without dyspnea and the acetone smell of the breath. As the obesity epidemic has led to the earlier age at onset of type 2 diabetes, HHS has been increasing in prevalence in the pediatric population. In addition to clear cases of HHS, patients can present with a mixed picture of both diabetic ketoacidosis (DKA) and HHS symptoms, accounting for 28% of pediatric cases and a mortality rate 10-fold higher than that of pure DKA (Table). The increased mortality associated with HHS is potentially due to the severity of dehydration on presentation because patients are often in a hypovolemic state for a longer period in HHS than in DKA before diagnosis. Infection and the intake of high-carbohydrate beverages are common precipitating causes of HHS in pediatric patients. Multiorgan involvement is usually seen in patients with HHS (pancreatitis, cerebrovascular accidents, myocardial infarction, pulmonary embolism, acute kidney injury), although which is the true inciting factor remains an area of further study.

PATHOPHYSIOLOGY

The pathophysiology between DKA and HHS is similar, ultimately leading to a hyperglycemic hypovolemic state. Both diseases revolve around 2 main risk factors. The first is insulin deficiency, which leads to inadequate uptake of glucose by muscles and peripheral tissues. The degree of insulin deficiency is different between the 2 processes, with HHS having a relative insulin deficiency compared with the absolute insulin deficiency in those with DKA. Lipolysis and ketogenesis, usually seen with DKA, are absent in HHS secondary to the increased ratio of insulin to glucagon.

The second risk factor is a physiologic stress state that causes increased glucose production via gluconeogenesis and glycogenolysis in HHS. The increased glucose in the extracellular space draws water out of the intracellular space into the extracellular space, leading to an osmotic diuresis. The osmotic diuresis causes the removal of glucose from the bloodstream, initially masking the hyperglycemic state. As the osmotic diuresis continues, it often exceeds intake, leading to hypovolemia. The resulting volume depletion leads to decreased renal excretion of glucose, perpetuating the hyperglycemic state. The severe hypovolemia also contributes to the altered mental status seen with progression of HHS.

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Hyperglycemic Hyperosmolar State: An Emerging Pediatric Problem. Rosenbloom AL. *J Pediatr.* 2010;156(2):180–184

Diabetic Emergencies: Ketoacidosis, Hyperglycaemic Hyperosmolar State and Hypoglycaemia. Umpierrez G, Korytkowski M. *Nat Rev Endocrinol.* 2016;12(4):222–232

Hyperglycemic Hyperosmolar Syndrome in Children: Pathophysiological Considerations and Suggested Guidelines for Treatment. Zeitler P, Haqq A, Rosenbloom A, Glaser N; Drugs and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. *J Pediatr.* 2011;158(1):9–14, 14.e1–14.e2

ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic Ketoacidosis and the Hyperglycemic Hyperosmolar State. Wolfsdorf JI, Glaser N, Agus M, et al. *Pediatr Diabetes.* 2018;19(suppl 27):155–177

Table. Diagnostic Laboratory Criteria for HHS Compared with DKA and a Mixed HHS-DKA Presentation

	DKA	HHS	HHS-DKA
Blood glucose, mg/dL (mmol/L)	>250 (>13.88)	>600 (>33.30)	>600 (>33.30)
pH	<7.3	>7.3	<7.3
Bicarbonate, mEq/L (mmol/L)	<15 (<15)	>15 (>15)	<15 (<15)
Osmolarity, mOsm/kg (mmol/kg)	Variable	>320 (>320)	>320 (>320)
Ketones	Moderate or large	Absent or small	Present

DKA=diabetic ketoacidosis, HHS=hyperosmolar hyperglycemic state.

There are 3 main distinguishing factors when comparing HHS and DKA: in HHS, the absence of ketones, less severe metabolic acidosis, and increased severity of the hypovolemia.

CLINICAL PRESENTATION/DIAGNOSTIC CRITERIA

HHS is diagnosed through clinical criteria as well as laboratory testing defined by a plasma glucose level greater than 600 mg/dL (>33 mmol/L), increased effective plasma osmolality greater than 320 mOsm/kg (>320 mmol/kg), and serum bicarbonate level greater than 15 mEq/L (>15 mmol/L), with minimal or absent ketosis. The Table shows the diagnostic laboratory criteria for HHS compared with DKA and a mixed HHS-DKA presentation. Patients with DKA and HHS clinically present with polydipsia, polyuria, weakness, altered mental status, dry mucous membranes, decreased skin turgor, and tachycardia. Patients with DKA will have ketoacidosis, which causes the additional symptoms of Kussmaul respirations, fruity breath, nausea, and abdominal pain, leading patients to present within 24 hours of onset. The time course of HHS is more insidious compared with that of DKA owing to the higher ratio of insulin to glucagon, which leads to the prolongation and worsening of the hyperosmotic state. After several days, when the insulin is no longer sufficient and the inciting factors remain unaddressed, patients in HHS will present with severe hyperglycemia and hypovolemia. Symptoms in HHS can progress to coma and death. Severe complications specific to HHS are malignant hyperthermia, pancreatitis, rhabdomyolysis, and thrombosis. Similar to DKA, HHS can present with severe electrolyte imbalance and acute renal injury, although the degree is usually more severe. Although more common in DKA, cerebral edema can occur, specifically if the hyperosmolarity is corrected rapidly.

TREATMENT

HHS, a hyperglycemic hypovolemic state with little to no ketones, should be recognized in a timely manner to initiate urgent treatment, which involves aggressive fluid resuscitation, correcting the hyperglycemia; electrolyte monitoring; and addressing the inciting factor. Given that infectious etiologies are the most common inciting factor, a thorough infectious evaluation including inflammatory markers, blood cultures, a respiratory viral panel, and clinically indicated imaging should be performed, and patients should be treated with the appropriate antimicrobial or supportive care. In both DKA and HHS, fluid resuscitation is the first step in management; however, in those with HHS, the degree of dehydration is much more profound and often a cause for many of the complications seen in HHS. The estimated water deficit in a patient with HHS is approximately 100 to 200 mL/kg, or approximately 12% to 15% of body weight. Therefore, the first step in management should address the profound state of hypovolemia with an isotonic intravenous fluid infusion to replace the intracellular and extracellular fluid losses. Isotonic fluid will rapidly increase the patient's volume status, restoring circulatory volume and increasing tissue perfusion. After the initial repletion with isotonic fluid, hypotonic fluid should be initiated to mediate hypernatremia, which can perpetuate the hyperosmolar state. The decrease in hypernatremia with fluids should be corrected gradually. In addition, urinary losses should be replaced with 0.45% saline, which differs from DKA management. Most patients will have an improvement in mental status on correction of the fluid deficit as well as improvement of the hyperglycemia.

In HHS, an insulin infusion should be initiated when, despite fluid administration, serum glucose concentration is not declining at a minimum rate of 54 mg/dL (3 mmol/L) per hour. This differs from treatment of a mixed HHS and DKA, when the insulin infusion should be initiated immediately after the initial fluid bolus. When an insulin infusion is started, it should be at a lower rate than used for DKA management. The insulin infusion will help correct the hyperglycemia via use of glucose and decreasing hepatic gluconeogenesis. Frequent monitoring of electrolytes, with close attention to sodium, potassium, calcium, magnesium, and phosphorus derangements, needs to occur during the stabilization process as total body electrolytes are depleted. As with both HHS and DKA, bicarbonate therapy does not have a role in treatment. Mortality is related to the inciting factor, severity of dehydration, and comorbid conditions. Given the overall increase in

mortality with HHS, these patients should be cared for in an ICU setting with the ability to perform frequent monitoring of fluids, glucose levels, and electrolytes. Malignant hyperthermia, if present, can be managed with dantrolene therapy. Due to the risk of thrombosis in patients with HHS with intravenous indwelling catheters, heparin infusion can be considered for prophylaxis. Patients are also at risk for rhabdomyolysis due to the potential for severe hypophosphatemia and should have frequent creatine kinase monitoring. Resolution of symptoms is marked by a serum osmolality less than 310 mOsm/kg (<310 mmol/kg), a glucose level less than 250 mg/dL (<13.88 mmol/L), and improvement in mental status.

As HHS is becoming more common in the pediatric population, it is imperative to consider it in the differential diagnosis for a patient presenting with hyperglycemia and multiorgan system involvement. Identification of HHS is important because treatment is marked by aggressive fluid resuscitation, which differs from DKA management. The line between these 2 entities is blurred, and further investigation into the pathophysiology of HHS needs to be conducted.

Comments: I learned a great deal in reviewing this In Brief. Because the presentation and treatment approaches differ among DKA, HHS, and mixed picture, it is critical to initiate and continue the appropriate management while observing for associated morbidities for the different entities. One article that I read from the authors' suggested readings mentioned that HHS may be the initial presentation of diabetes in 7% to 17% of patients. This finding emphasized to me the insidious presentation and the need for providers to be knowledgeable in making the correct diagnosis in patients presenting with hyperglycemia. In reference to the marked increase in the prevalence of obesity with resulting increased risks of both HHS and DKA, prevention in pediatrics remains key. We must continue to counsel our patients to eat a healthy diet, incorporate appropriate portion sizes, and exercise to enhance the health of our future generations.

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