

Hyperglycemic Hyperosmolar Syndrome in Children: Pathophysiological Considerations and Suggested Guidelines for Treatment

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Hyperglycemic hyperosmolar syndrome (HHS), characterized by extreme elevations in serum glucose concentrations and hyperosmolality without significant ketosis, has historically been infrequent in children. However, recent case reports and series describing HHS in children suggests that the incidence of this disorder may be increasing.¹⁻⁵ The epidemiology of HHS in children and adolescents has been reviewed recently.⁶ HHS has a high mortality rate, and an understanding of the unique pathophysiology (Figure 1) of this condition is important to guide clinical decision-making. However, although treatment of diabetic ketoacidosis (DKA) in children is familiar to most clinicians, the management of HHS in youth presents a unique set of clinical challenges for which little guidance is currently available. The aim of this review is to discuss the pathophysiology of HHS and to provide broad treatment recommendations on the basis of the available literature and known physiological principles.

Criteria for the diagnosis of HHS are listed in Table I. Although HHS is distinct from DKA (Table II; available at www.jpeds.com), patients may present with features of both conditions. HHS occurs less frequently in children than DKA, and some children with DKA can have severe hyperosmolality, complicating the recognition of HHS as a distinct entity. As a result, children with HHS are often treated with DKA protocols. However, the pathophysiology of HHS differs from DKA, and these differences should be considered in planning a rational therapeutic approach.

Unlike the usual symptoms of DKA (hyperventilation, vomiting, and abdominal pain), which typically bring children to medical attention, the gradually increasing polyuria and polydipsia of HHS may go unrecognized.⁷ As a result, both dehydration and electrolyte loss are profound in HHS; in adults, fluid losses in HHS have been estimated to be twice those of DKA. Furthermore, obesity and hyperosmolality can make the clinical assessment of dehydration unreliable.⁹⁻¹⁴ It has been suggested on the basis of information from small case series that intake of copious quantities of carbonated sugar-enriched drinks before presentation may be a common feature of patients presenting with severe hyperglycemia. Because these case series lack control data, however, it is unclear whether this finding is specific to these patients.⁸

Despite severe electrolyte losses and total body volume depletion, hypertonicity leads to preservation of intravascular volume, and signs of dehydration may be less evident (Figure 2, A and B; available at www.jpeds.com). During therapy, however, declining serum osmolality (a consequence of urinary glucose excretion and insulin-mediated glucose uptake) results in movement of water out of the intravascular space, with a decline in intravascular volume (Figure 2, C).¹⁵ In addition, osmotic diuresis may persist for hours as markedly elevated glucose concentrations slowly decrease. Therefore ongoing urinary fluid losses early in treatment may be considerable. Because of the greater dehydration in HHS, the substantial ongoing urinary fluid losses, and the potential for rapid decline in intravascular volume during treatment (Figure 2, D), children with HHS require more aggressive replacement of intravascular volume during treatment than do children with DKA to avoid the vascular collapse that contributes to the high mortality rate.^{10,16}

The effect of HHS on the brain may differ from that seen in DKA. Studies of chronic hypertonicity suggest that brain cells produce “idiogenic osmoles,” osmotically active substances that preserve intracellular volume by increasing intracellular osmolality.^{5,17-19} Patients are believed to be at risk for cerebral edema (CE) if the rate of decline in serum osmolality exceeds the rate at which brain cells can eliminate osmotically active particles. Therefore, in theory, children with HHS who experience prolonged, persistent hypertonicity should be at greater risk for CE than those with DKA. However, in one case report of a patient with severe hyperglycemia and hyperosmolality (435 mosm/Kg) who had intracranial pressure monitoring during treatment, no increase in intracranial pressure occurred during fluid resuscitation.²⁰ Furthermore, demise typical of CE has been recorded in only one

CE	Cerebral edema
DKA	Diabetes ketoacidosis
HHS	Hyperglycemic hyperosmolar syndrome

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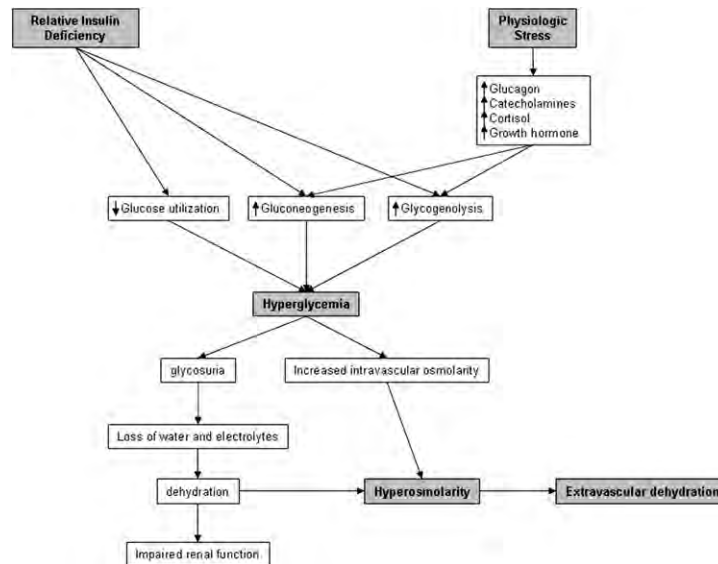


Figure 1. Pathophysiology of HHS.

adolescent with HHS and an abnormal magnetic resonance imaging result, whereas all other reported brain imaging study results have been normal.^{4,21-23} Cerebral vasoconstriction caused by hypocapnia may be important in the pathogenesis of DKA-related CE.²⁴⁻²⁶ Diminished circulatory volume combined with cerebral vasoconstriction may lead to cerebral hypoperfusion, with edema occurring during reperfusion. The absence of hypocapnia in children with HHS may therefore account for the decreased incidence of CE in HHS.

Although both DKA and HHS are associated with an increased risk of thrombosis, the risk is far greater in HHS.^{27,28} Hypertonicity may directly result in osmotic disruption of endothelial cells, leading to release of tissue thromboplastins and elevated vasopressin caused by the fluid status may also contribute to enhanced coagulation.²⁹

Treatment of HHS

There are no prospective data to guide treatment of children and adolescents with HHS. Nonetheless, experience with adults and awareness of the physiological differences between HHS and DKA suggest a rational approach for children and adolescents (**Figure 3**). All patients with HHS, as well as patients with hyperosmolality with DKA, should be admitted to an intensive care unit or equivalent setting in

which expert medical, nursing, and laboratory services are available.

Fluid Therapy

The goal of initial fluid therapy is expansion of the intravascular and extravascular volume and restoration of normal renal perfusion. Vigorous fluid replacement is recommended for adults with HHS and rates of fluid replacement in children should be more rapid than those recommended for DKA. A minimum initial bolus of 20 mL/kg of isotonic saline solution (0.9% NaCl) should be administered and fluid deficits of approximately 12% to 15% of body weight should be assumed.^{9,12-14,16} Additional fluid boluses should be given to restore peripheral perfusion. Subsequently, 0.45% to 0.75% NaCl should be administered to replace the deficit over 24 to 48 hours, with a goal of promoting a gradual decline in serum sodium and osmolality. The specific choice for subsequent fluid replacement is dependent on serum electrolyte and glucose concentrations, urinary output, and clinical hydration status.

Adult studies suggest that administration of isotonic fluids (0.9% saline solution) during ongoing osmotic diuresis may increase serum sodium concentration because the urine sodium concentration is typically hypotonic to that of serum^{9,30,31} and elevated aldosterone concentrations, secondary to hypoperfusion, promote sodium retention and potassium loss. A rise in serum sodium concentration is undesirable as it may perpetuate the hyperosmolar state. However, isotonic fluids are more effective in maintaining circulatory volume. Therefore isotonic fluids are recommended initially to restore perfusion, followed by more hypotonic (0.45%-0.75% saline solution) fluids. Isotonic fluids should be restarted if perfusion and hemodynamic status become problematic as osmolality declines. Serum sodium

Table I. Diagnostic feature of HHS

Serum glucose concentration >600 mg/dL (33 mmol/L)
Serum osmolality >330 mOsm/Kg
Absence of significant ketosis and acidosis (serum bicarbonate concentration >15 mEq/L, urine ketone (acetoacetate) concentration < 15 mg/dL (1.5 mmol/L; negative or "trace" on urine dipstick)

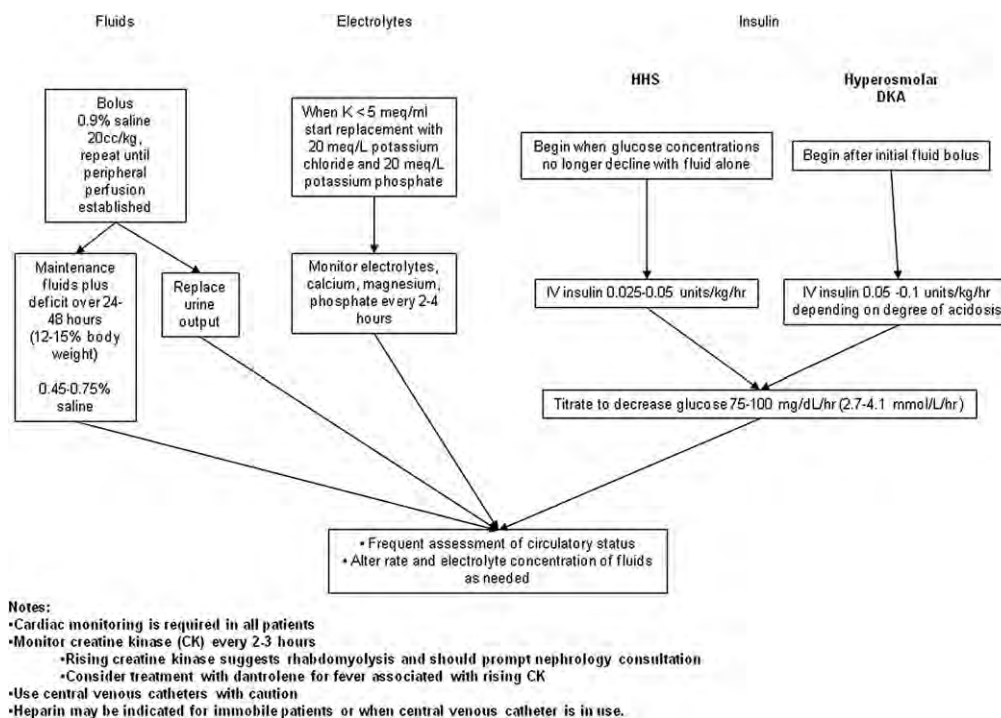


Figure 3. Treatment of HHS in pediatric patients.

concentrations should be frequently monitored, and the concentration of sodium in fluids adjusted to promote a gradual decline in corrected serum sodium. Although there are no data to indicate an optimal rate of decline in serum sodium, a rate of 0.5 mEq/L per hour has been recommended for hypernatremic dehydration.³² With adequate rehydration, serum glucose concentrations should decline by 75 to 100 mg/dL/hr (4.1-5.5 mmol/L).^{9,10} A more rapid decline in serum glucose concentration is typical during the first few hours of treatment, when renal perfusion is improved by expansion of vascular volume. Lack of appropriate decline in serum glucose should prompt reassessment and evaluation of renal function. It has also been suggested that the presence of large quantities of sugar-containing liquids in the stomach at presentation may contribute to changes in both water and glucose as stomach contents are absorbed and should be considered in monitoring and ongoing evaluation.³³ Recommended laboratory monitoring frequency is provided in **Table III**.

Patients may be more dehydrated than assumed and frequent reassessment of fluid balance and peripheral perfusion is necessary. Central venous pressure monitoring may be helpful; however, the benefits should be balanced against the risks of thrombosis (see below). Replacement of urinary losses is recommended;¹² 0.45% saline solution approximates the typical urine sodium concentration during osmotic diuresis. Fluid with higher sodium content may be acceptable for replacement of urinary losses in situations where there is ongoing concern over adequate circulatory volume.

Insulin Therapy

Ketosis in HHS is usually minimal and, although mild acidosis is common, it is typically the result of hypoperfusion (lactic acidosis). Therefore early insulin administration is unnecessary in non-ketotic HHS and may increase the risk of death.² Fluid administration alone results in a substantial decline in serum glucose as a result of dilution, improved renal perfusion, and increased tissue glucose uptake with improved circulation.³⁴ Furthermore, the osmotic pressure that glucose exerts within the vascular space contributes to maintenance of blood volume in these profoundly dehydrated patients. Therefore more rapid declines in serum glucose concentration and osmolality after insulin administration might lead to circulatory compromise and thromboembolism unless there is adequate fluid replacement.^{10,31} Additionally, patients with HHS have extreme deficits of potassium (see below), and the rapid insulin-induced shift of potassium from the circulation to intracellular space can result in arrhythmia.

In general, insulin administration should be considered when serum glucose concentrations are no longer declining adequately (< 50 mg/dL/h [<2.7 mmol/L/h]) with fluid administration alone. Insulin should be considered earlier in children with more severe ketosis and acidosis. When insulin treatment is begun, continuous administration at 0.025 to 0.05 units/kg/h can be used initially, with the dosage titrated to achieve a decrease in glucose concentration of 50 to 75 mg/dL/h (2.7-4.1 mmol/L/h).⁹ Insulin boluses are not recommended for pediatric patients. Unlike in DKA, insulin

Table III. Monitoring of children and adolescents with HHS

Hourly: serum glucose, vital signs, clinical assessment of hydration status
Every 2-3 hours: serum electrolytes, blood urea nitrogen, creatinine, osmolality, creatine kinase, determination of intake/output balance
Every 3-4 hours: serum calcium, phosphate, magnesium
Continuous cardiac monitor

therapy is not usually necessary for resolution of ketosis in HHS and should be suspended if the glucose concentration drops more than 100 mg/dL/hr (5.5 mmol/L/h).

Electrolyte Imbalances (Potassium, Phosphate, and Magnesium)

Electrolyte deficits, particularly potassium, phosphate, and magnesium, are more extreme in HHS than DKA.^{4,9,12-14,16,31} Potassium replacement should begin as soon as potassium concentrations are within the normal range and adequate renal function has been established. Potassium replacement should be initiated at 40 mEq/L of replacement fluid, but higher rates of administration may be needed after insulin infusion is started. Serum potassium concentration should be monitored at least every 2 to 3 hours during insulin administration and the rate of potassium administration adjusted; hourly monitoring may be required, and cardiac monitoring is recommended. Bicarbonate therapy is contraindicated because of the increased risk of hypokalemia, the possible effect of decreased tissue oxygen uptake,^{12,35} and the absence of a therapeutic rationale for its use.

Replacement of phosphate in DKA has been controversial. Severe hypophosphatemia may lead to rhabdomyolysis, hemolytic anemia, or paralysis.^{36,37} Conversely, phosphate treatment may contribute to hypocalcemia.³⁸ In HHS, however, phosphate deficits are more severe, increasing the risk for severe hypophosphatemia during treatment.⁴ Use of intravenous solutions containing a 50:50 mixture of potassium phosphate and potassium chloride generally permits adequate phosphate replacement and avoids deleterious hypocalcemia. Phosphate concentrations should be monitored at least every 3 to 4 hours.

Patients with HHS frequently have large deficits of magnesium, but there are no data to determine whether replacement of magnesium is beneficial. Hypomagnesemia may occasionally contribute to hypocalcemia during therapy, and replacement should be considered in patients with hypocalcemia and a low magnesium concentrations. The recommended dose for magnesium replacement is 25 to 50 mg/kg/dose for 3 to 4 doses given every 4 to 6 hours, with a maximum infusion rate of 150 mg/min and 2 g/h.

Complications (Thrombosis, Rhabdomyolysis, Malignant Hyperthermia, and CE)

Thromboembolic complications occur commonly in HHS, and central venous catheters appear to be particularly prone

to thrombosis.²⁷ Prophylaxis with low-dose heparin has been suggested in adults,³⁹ but there are no data that indicate benefit. On the other hand, low-dose heparin administration may cause gastrointestinal hemorrhage in the presence of hypertonicity-induced gastroparesis.⁴⁰ Heparin treatment therefore should generally be reserved for children who require central venous catheters for monitoring or venous access and are immobile for >24 to 48 hours. The use of compression stockings in children in this setting has not been specifically evaluated but should be considered.

Rhabdomyolysis may occur in children with HHS, and monitoring of creatine kinase concentration every 2 to 3 hours is recommended for early detection.⁴¹⁻⁴⁶ Rhabdomyolysis is potentially life-threatening; it may result in acute kidney failure, severe hyperkalemia, and hypocalcemia leading to cardiac arrest, and muscle swelling causing compartment syndrome.⁴⁷ If rhabdomyolysis is suspected, consultation with a nephrologist should be obtained promptly.

A malignant hyperthermialike syndrome of unclear cause has been reported in several children with HHS.^{3,4,23,48} Treatment with dantrolene, which is believed to reduce the release of calcium from the sarcoplasmic reticulum and stabilize calcium metabolism within muscle cells, should be initiated early for children who have fever associated with a rise in creatine kinase concentration.⁴⁸

Adult reports suggest that altered mental status is common with osmolality greater than 330 mOsm/Kg and therefore is not unexpected at presentation of HHS. Whether central nervous system imaging is necessary for children with altered mental status at presentation of HHS is unclear, given the evidence that CE is rare. However, declines in mental status after improvement in the hyperosmolar state are unusual and such declines should prompt further investigation. Patients should be monitored closely for headache and changes in level of consciousness. Severe dehydration, electrolyte disturbance, and hypertonicity are far more frequent causes of death in HHS than is CE, however, and concerns about possible CE should not deter the clinician from administering necessary amounts of fluid for adequate hydration.

Mixed HHS and DKA

Some children have severe hypertonicity in combination with substantial ketosis and acidosis, and treatment must take into account potential complications of both DKA and HHS. Frequent reassessment of circulatory status and fluid balance is necessary to guide therapy. To maintain adequate circulatory volume, the rate of fluid administration will generally exceed that used for treatment of typical DKA. The rate of electrolyte administration required to maintain normal electrolyte concentrations is also likely to exceed that used for DKA. Insulin treatment is necessary to resolve ketosis in these patients and continuous insulin infusion should be started after the initial fluid bolus(es). It should be recognized, however, that insulin administration may result in a more rapid decline in glucose concentration, and therefore a potential decrease in intravascular volume.

Insulin therapy also dictates a need for close attention to potassium and phosphate concentrations. In children with mixed DKA and HHS, guidelines for adjusting insulin and dextrose infusions should be similar to those generally recommended for DKA,⁴⁹ but frequent reassessment of circulatory status, and readjustment of fluid administration rates, as dictated by clinical status, is necessary. In these patients, the risk of CE is higher than in those with a classical presentation of HHS. Fluid treatment should therefore be aimed at ensuring adequate circulatory volume and cerebral perfusion while avoiding excess fluid administration. Frequent monitoring of mental status is also essential.

Conclusions

HHS may be occurring with increased frequency in children and adolescents. Although population-based data are lacking, a review of available literature suggests that pediatric HHS may differ from HHS in adults in several ways. Unlike adult HHS, where comorbid conditions frequently play a role, pediatric HHS appears to occur most often in otherwise healthy children and adolescents with type 2 DM, particularly in obese African American males. In addition, both rhabdomyolysis and a malignant hyperthermia-like syndrome may occur as complications of HHS in children. Finally, mixed features of DKA and HHS may be more common in children than in adults.⁵⁰ Because of the perceived rarity of HHS in children and the familiarity of recommendations for conservative fluid management in children with DKA, there may be a tendency toward inadequate rehydration in children with HHS. Increased awareness of the occurrence of HHS in children and the differences in management strategy between DKA and HHS are needed to improve outcomes in this life-threatening disorder. ■

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Table II. Features of HHS and DKA

	HHS	DKA
Hyperglycemia	+++	+ to +++
Ketosis/Acidosis	-/+	++ to +++
Dehydration	+++	+ to +++
Osmolality	+++ (> 330 mosm/kg)	+ to +++
Electrolyte Deficits	+++	+ to +++

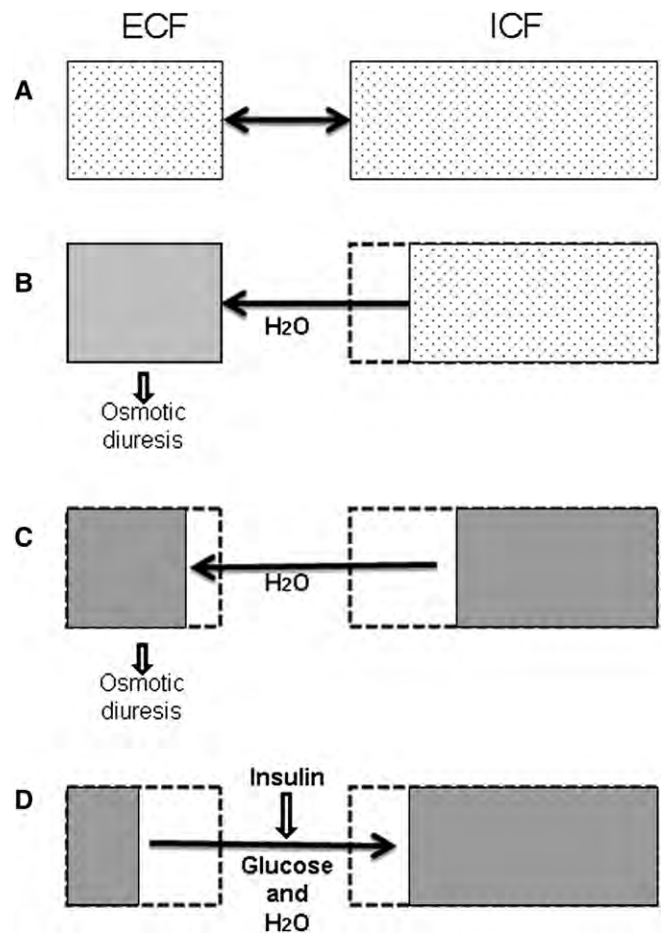


Figure 2. Fluid balance in diabetic hyperosmolarity. **A**, Normoglycemia and hydration. **B**, Early: Extracellular fluid (ECF) is hyperosmolar, causing water to shift from intracellular (ICF) into ECF. **C**, Late: Continued osmotic diuresis causes dehydration, volume loss, and hyperosmolarity in both ECF and ICF. **D**, Insulin therapy without adequate fluid replacement shifts glucose and water from ECF into ICF causing vascular collapse, shock, and death.