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Hyperglycemic Hyperosmolar Syndrome (HHS) Care Process Model Synopsis

Background

Hyperglycemic Hyperosmolar Syndrome (HHS) is an acute diabetic emergency that exists in a continuum with Diabetic Ketoacidosis (DKA). In general, HHS is associated with type 2 diabetes and thus is relatively rare in pediatrics with most of the literature focused on individual case reports or case series. However, it is notably becoming more common as the prevalence of type 2 diabetes in the pediatric population increases. One series identified HHS in 3.7% of patients with newly diagnosed type 2 diabetes.[1] HHS has been diagnosed in patients with antibody negative diabetes as young as age 5.[2] However, it has also been reported in patients with type 1 diabetes.[3] Approximately 25-30% of cases presenting with combined features of DKA and HHS.[4] Treatment for HHS is distinct from DKA, though, and there have been reports of poorer outcomes in those managed on a standard DKA protocol.[5] HHS often has a delayed diagnosis compared to DKA due to the lack of significant abdominal symptoms.[6,7]

There is minimal guidance in the literature particularly for management of pediatric patients. Here, we provide a summary of case reports and case series with recommendations for management by organ system.

Definitions

The exact definition of HHS varies in the literature. Historically called Hyperglycemic Hyperosmolar Non-Ketotic Coma, obtundation was one of the required features of the disorder. Now it is characterized by significant hyperglycemia (≥600 mg/dL) and dehydration with hyperosmolality (typically >320 mOsm/kg), without evidence of ketoacidosis (classically a CO2 >15 and negative to small urine ketones). Though altered mental status is a common finding in these patients, it is not necessary for significant alterations to be present.

The Osmolality cut-off is the most variable criteria in the literature. Not only does the value vary from 300 mOsm/kg to 350 mOsm/kg,[5,8] but the technique for determining osmolality also varies. Some authors use measured serum osmolality, some using calculated osmolality, and some use effective osmolality (which removes Urea from consideration of the calculated value, as it moves freely across the cell membrane)[9].

Based on discussions within Children's Mercy, we have chosen to classify HHS as a blood glucose ≥600 mg/dL and a calculated serum osmolality ≥320 mOsm/kg. As the prevalence of mixed DKA/HHS is relatively high at our hospital, based on currently available data, we will not use ketone measurements or serum bicarbonate to exclude patients from the diagnosis of HHS but recognize that management may need to be individualized based on degree of ketoacidosis.

Initial ED Management

The goal of the initial management is to recognize HHS early during treatment. If new onset diabetes or DKA/HHS is suspected, initial labs should include a POC glucose and ketones, BMP with osmolality, and lactate level (as elevated lactate can also cause a high anion gap metabolic acidosis[7]). If no previous history of diabetes and POC glucose suggests diagnosis, new onset labs should also be obtained. If febrile, blood cultures, and other infectious workup should be obtained as clinically indicated.

New onset diabetes with hyperosmolality should be suspected in patients who are hypertensive with signs of dehydration,[9] those with dehydration with continued brisk urine output,[7] or in those with dehydration and altered mental status.

If POC glucose is greater than 500 mg/dL (or reads 'HI'), the patient should receive an initial fluid bolus of 10-20 mL/kg, instead of the usual 10 mL/kg in the DKA protocol (max 1000 mL). If there is evidence of hemodynamic instability (such as hypotension), this bolus should be administered faster and boluses continued until the patient is normotensive. Additional blood pressure support may be needed to achieve this goal.

Patients with HHS should not receive Lantus (or other long-acting insulins) initially so that the fall in blood glucose levels can be managed more closely.

If initial BMP confirms the diagnosis of HHS and the blood glucose levels remains above 550 mg/dL, hourly plasma/serum glucose checks will need to be performed, along with BMP with Osm every 2 hours to monitor changes in electrolyte concentrations.

Admission to the ICU

PICU admission or transfer should be considered in any patient with:

1. Altered mentation
2. Calculated osmolality >350 mOsm/kg
3. Persistent glucose >550 mg/dL (unable to read on POC glucose monitor)
4. Significant hyperkalemia (>6 mmol/L)
5. Hemodynamic instability (hypotension, significant tachycardia, etc)
6. Bicarbonate level <5 mmol/L or ≤ 10 mmol/L if under 5 years of age
7. Excessive urine output suggesting need for urine output replacement

Fluid Management

The degree of dehydration in patients with HHS is often masked due to hypertonicity. Initially, there is often poor renal perfusion resulting in a low urine output. As renal perfusion improves with fluid therapy, a profound osmotic diuresis occurs as the kidneys work to excrete excess glucose. This diuresis, combined with a decrease in serum osmolality, results in movement of water out of the intravascular spaces (either into the urine or into intracellular spaces during rehydration), resulting in hypovolemic shock.[8]

There are no prospective data to guide management of children and adolescents with HHS. These guidelines are derived from recommendations for management of HHS in adults with the recognition that children may be at a higher or lower risk of complications (cerebral edema, etc.) based on additional factors.

1. Goal of initial fluid therapy is to expand intra- and extra- vascular volume and restore normal renal perfusion.
2. Initial bolus should be 20 ml/kg of isotonic saline. Additional boluses may be necessary to restore perfusion and maintain normal blood pressure.
3. Fluid deficit should be assumed to be 12-15% of body weight and replaced over 24-48 hours

4. Fluids should be adjusted to ensure sodium level declines slowly (0.5 mmol/L/hr)
5. Dextrose should be added to fluids earlier than in DKA, to maintain glucose drop 75-100 mg/dL/hr and stabilize at 250-300 mg/dL until rehydration occurs (i.e. serum sodium level normalizes).
6. Consider replacing urine output 1:1 with ½ NS to reduce ongoing fluid losses. One study suggested starting urine replacement once UOP exceeded 40 mL/m2/hr, which approximates 1.5 ml/kg/hr.[9]

Caution should be used in those with mixed DKA/HHS, as fluid administration in excess of 4 L/m2/day has been associated with the development of cerebral edema.

Cardiovascular Status

As above, there is often a period of refractory hypovolemic shock following initial rehydration. Early initiation of vasopressor support (epinephrine, norepinephrine, dopamine) should be considered. An echocardiogram should be obtained if inotropes are needed.

Electrolyte abnormalities are not uncommon (see Electrolytes section) and can result in arrhythmias. Therefore, cardiac lead monitoring is recommended in any patient with HHS during the initial phases of treatment.

Insulin

Insulin is generally not recommended in the initial management of HHS. Rather, recommendations are to continue aggressive fluid management and start an insulin drip once the drop in blood glucose levels falls below 50 mg/dL/hr.

However, in cases of mixed DKA and HHS, insulin may be needed to stop ketosis. In these cases, starting an insulin drip at 0.025 to 0.05 u/kg/hr may be reasonable, along with titration of the insulin drip and fluid rate to achieve a decline in blood glucose no more than 75-100 mg/dL/hr.[8]

Lantus (or other long-acting insulin analogs) should not be administered until blood glucose levels are <400 mg/dL to reduce the risk of a rapid drop in glucose levels.

Electrolytes

HHS is associated with risk of multiple electrolyte abnormalities, particularly with potassium. Frequent monitoring of potassium and phosphorus (recommendation for BMP every 2-3 hours and phos every 3-4 hours) should be included in management, with replacement as needed.

Hypokalemia is the most worrisome of the electrolyte abnormalities, as these patients tend to have very high potassium losses (more significant than in DKA). There are reports of pediatric patients having cardiac rhythm abnormalities, including ventricular tachycardia,[10] as a result of hypokalemia. Therefore, it is recommended to start replacement of potassium at 40 mEq/L once levels are in the normal range and adequate renal function has been established. Higher rates of potassium may be needed once insulin therapy is initiated.[8]

Bicarbonate **should not** be administered, as it increases the risk of hypokalemia.

Hypophosphatemia has been associated with HHS.[11,12] Severe hypophosphatemia may lead to rhabdomyolysis (see Rhabdomyolysis section). Therefore, phosphate should be administered in a 50:50 mixture of potassium phosphate and another potassium salt (such as potassium chloride or potassium acetate) to reduce the risk of severe hypophosphatemia or hypocalcemia from phosphate replacement.[8]

Ionized calcium should also be monitored frequently. In cases of hemodynamic instability calcium acts as an inotrope. The goal should be to maintain ionized calcium in the normal range. In addition, calcium levels can be very low in the oliguric phase of rhabdomyolysis and acute renal injury, requiring frequent replacement. Levels can also be high in the diuretic phase of recovery from acute renal injury.[13]

There is no guidance on whether or not *magnesium* replacement is beneficial in the treatment of HHS. However, it should be repleted in the setting of hypocalcemia to allow improvement in calcium levels.[8]

Kidney Injury

The significant dehydration that defined HHS results in acute kidney injury. There is often significant elevation in the BUN and Creatinine with initial labs, which often improves with rehydration. However, other features of HHS (especially rhabdomyolysis, detailed in the following section) may result in additional injury after the initial hypoperfusion is corrected. Therefore consideration for CRRT or hemodialysis, should be ongoing based on the clinical status of the patient, particularly if urine output decreases during treatment.

Rhabdomyolysis

Rhabdomyolysis is a frequently cited complication of HHS and is occasionally seen in DKA.[14] It may be induced by hypophosphatemia.[5] It has been seen in association with a malignant hyperthermia-like syndrome as well (see Fever/Hyperthermia section).[15]

It is recommended to trend Creatine Kinase (CK) levels every 2-3 hours for early detection.[8] If previously normal, but a rise in creatinine is noted, CK levels should be repeated.

Fever/Hyperthermia

In adults, infection is often a trigger for the development of HHS, and thus fevers are relatively common. However, infection has not been identified as a common cause of HHS in pediatrics.[1] There has been an association of a malignant hyperthermia-like syndrome that occurs with HHS.[15] It has been proposed to be a reaction to a preservative in IV insulin,[16] but not all cases have been associated with insulin initiation.[15]

It is recommended that in instances of fever or hyperthermia, an infectious workup should be completed, and any underlying infection treated. If no infectious etiology is found, dantrolene may be considered for treatment of hyperthermia.

Hematology

Thrombosis has been identified as a complication of HHS.[1] This is thought to be due to the dehydration and hemoconcentration that results, though elevated vasopressin levels may also promote clotting tendencies.[5] Current recommendations are to reserve anticoagulant therapy for those who have central lines or are expected to be immobile for longer than 24-48 hours.[8]

DKA[17–19] and HHS have also been associated with thrombocytopenia-associated multi-organ failure.[20] This condition is defined by new onset thrombocytopenia (<100K) or drop of 50% from baseline over less than 30 hours, and overt disseminated intravascular coagulopathy (DIC). If suspected, an LDH level can be drawn and is typically high in this condition. Those with multi-organ dysfunction may benefit from plasma exchange.[21]

Mental Status and Cerebral Edema

It is not uncommon to have altered mental status associated with HHS. In general, mental status improves during treatment. A complication not infrequently seen in DKA is cerebral edema. There have been few reported cases of cerebral edema in the setting of HHS,[1,11] indicating that the incidence is significantly less than DKA. However, if there is a deterioration of mental status during treatment, this should be promptly investigated and consideration for treatment of cerebral edema should be made.[8] Of note, less is known about the incidence of cerebral edema in cases of mixed DKA/HHS, so particular care should be taken in this population.

Deteriorating mental status should also raise concern for cerebral thrombosis, as cerebral thromboses have been noted in patients with HHS.[22,23] Anecdotally, there have been instances of CNS venous thrombosis in patients with severe dehydration secondary to HHS, though this is not widely reported in the literature. In these cases, a head CT should be obtained urgently.

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