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Clinical Reviews

Diagnosis and Management of the Critically Ill Adult Patient with Hyperglycemic Hyperosmolar State

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□ **Abstract—Background: Hyperglycemic hyperosmolar state is a life-threatening complication of diabetes mellitus. Therefore, it is important for emergency physicians to be aware of this unique diagnosis and treatment considerations. Objective: This manuscript reviews the emergency department evaluation and management of the adult patient with hyperglycemic hyperosmolar state. Discussion: Hyperglycemic hyperosmolar state is diagnosed by an elevated glucose, elevated serum osmolality, minimal or absent ketones, and a neurologic abnormality, most commonly altered mental status. Treatment involves fluid resuscitation and correction of electrolyte abnormalities. It is important to monitor these patients closely to avoid overcorrection of osmolality, sodium, and other electrolytes. These patients are critically ill and generally require admission to an intensive care unit. Conclusions: Hyperglycemic hyperosmolar state is associated with significant morbidity and mortality. It is important for clinicians to be aware of the current evidence regarding the diagnosis, management, and disposition of these patients. Published by Elsevier Inc.**

□ **Keywords—hyperglycemia; hyperosmolar; hyperglycemic hyperosmolar state; hyperosmotic hyperglycemic nonketotic state; endocrine; diabetes**

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Introduction

Hyperglycemic emergencies are life-threatening complications of diabetes mellitus and include both diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS), previously known as hyperosmotic hyperglycemic nonketotic state. These emergencies may occur in both insulin-dependent and non-insulin-dependent diabetics, though DKA is more common in those with insulin-dependent diabetes, whereas HHS is more common in patients with non-insulin-dependent diabetes (1,2). Importantly, 20% of HHS cases may not possess a prior history of diabetes (3). Whereas DKA and HHS exist along a spectrum with similar pathophysiology, HHS has unique management components that differ from DKA (1,4–6). This review will specifically focus on HHS.

Determining the epidemiology of HHS is challenging. It is less common than DKA, accounting for fewer than 1% of diabetic admissions (3,7). HHS most commonly occurs in older patients, but it may affect younger adults as the initial presentation of type 2 diabetes (8–10). With

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Table 1. List of Potential Triggers for HHS

- Alcohol or other substance use
- Dehydration/reduced oral intake
- Environmental exposures
- Gastrointestinal hemorrhage
- Infection (most common)
- Medication nonadherence (i.e., insulin, other diabetic medications)
- Medications (steroids, thiazide diuretics, beta-blockers, antipsychotics, protease inhibitors, and chemotherapeutic agents)
- Myocardial infarction
- Pancreatitis
- Pulmonary embolism
- Renal injury or failure
- Seizure
- Stroke (ischemic or hemorrhagic)
- Toxic ingestion

HHS = hyperglycemic hyperosmolar state.

the increase in childhood obesity and consequent diagnosis of type 2 diabetes mellitus in the pediatric population in recent years, there are case reports and studies showing HHS occurring in the pediatric population as well (11,12). Mortality rates range from 5–20%, which is 10 times greater than that observed with DKA (7,13–18). This significant mortality rate is often due to a combination of the precipitating cause, dehydration, comorbidities, and advanced age in patients with HHS (3,7,19,20).

There is a variety of potential triggers for HHS (Table 1) (13,21–23). The most common precipitating etiology is infection, accounting for 40–60% of cases, with the most common infection being pneumonia in up to 60% and urinary tract infection in up to 16% (21,24–26). Diabetic medication nonadherence is the second most common cause, accounting for 21% of cases (27). Nondiabetic medications can also lead to HHS by altering the metabolism of carbohydrates (3,22,28–41). Another major contributor is restricted water intake in elderly patients and patients with chronic health conditions, which may be compounded by mobility issues that further limit access to water, leading to worsened dehydration.

Methods

The authors searched PubMed and Google Scholar for articles using a combination of the keywords "hyperglycemic hyperosmolar state," "HHS," "hyperosmolar hyperglycemic non-ketotic state," "HONC," OR "hyperglycemic emergency." The search was conducted from the database's inception to December 1, 2019. PubMed yielded 1118 articles. Authors evaluated case reports and series, retrospective and prospective studies, randomized controlled trials, systematic reviews and meta-analyses, and other narrative reviews. Authors also reviewed guidelines and supporting citations of included articles. The literature search was restricted to studies published in English, with a focus on the emergency medicine and critical care literature. Authors decided which studies to include for the review by consensus. When available, systematic reviews and meta-analyses were preferentially selected. These were followed sequentially by randomized controlled trials, prospective studies, retrospective studies, case reports, and other narrative reviews when alternate data were not available. A total of 85 resources were selected for inclusion in this narrative review. Of these, there were four randomized controlled trials, 12 prospective studies, 22 retrospective studies, seven case reports or case series, and 40 narrative reviews or expert consensus documents.

Discussion

Pathophysiology

The underlying physiologic changes of HHS generally occur over many days, leading to severe metabolic disturbances and dehydration (1,20,21). The hallmark features of HHS include severe hyperglycemia, hyperosmolality, and dehydration, with minimal to no ketosis (Figure 1)

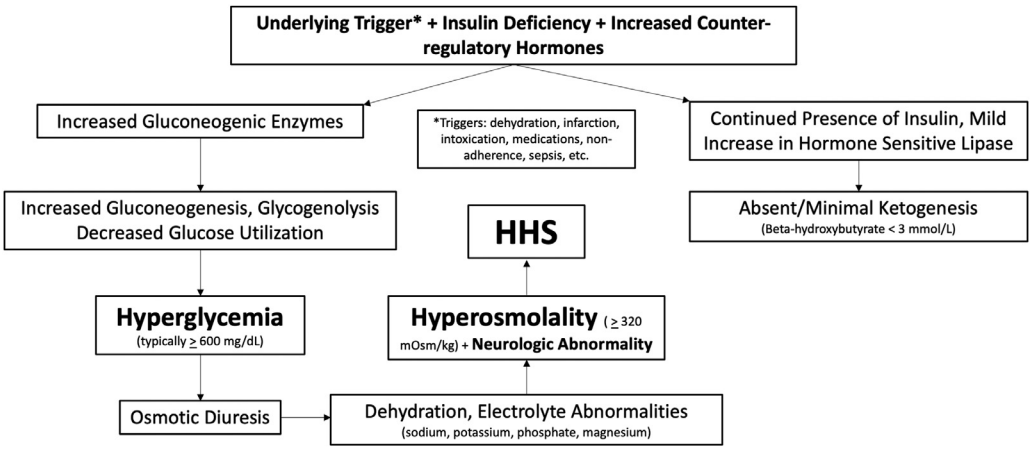

Figure 1. HHS Pathophysiology.

(1,4,7). The underlying pathophysiology includes a physiologic stressor (e.g., infection, ischemia) that results in insulin resistance and increased serum glucose levels (2). As opposed to the insulin deficiency seen in DKA, HHS is not associated with significant ketone body production because sufficient insulin is present to prevent lipolysis and the subsequent development of ketosis (7,13). However, significantly greater levels of insulin are needed to control the hyperglycemia in HHS when compared with DKA (1,4,7). The cells have difficulty utilizing glucose due to the insulin resistance, whereas counter-regulatory hormones such as catecholamines, glucagon, cortisol, and growth hormone increase, further worsening the insulin resistance, which allows serum glucose to continue increasing (7,42–45). Moreover, increased levels of glucagon in HHS cause gluconeogenesis and glycogenolysis, further increasing serum glucose. Initially, this contributes to increased glomerular filtration with glucosuria and osmotic diuresis of largely electrolyte-free urine, leading to greater degrees of dehydration and increased effective osmolality compared with DKA (25,46,47). Patients typically fail to compensate for this water loss with oral intake, often due to baseline debility or an insensitive drive to maintain normal serum tonicity (48). As the water loss worsens over days, fluid deficits in HHS approximate 10–22 L in a 100-kg person (1,19). Once this hypovolemia occurs, hyperglycemia worsens. Osmotic diuresis further increases serum osmolality and tonicity, most notably from alterations in sodium, which can cause significant alterations in mental status. The hyperglycemia also induces a proinflammatory state with elevated cytokines, reactive oxygen species, and oxidative stress (49–51). Other electrolyte abnormalities may occur, particularly with regard to potassium. Increased serum concentrations in the setting of osmotic diuresis causes hyperkalemia, though the total body potassium stores are low due to increased diuresis (Table 2).

Presentation

The onset of symptoms is often difficult to ascertain, as HHS more commonly develops over days to weeks, compared with DKA, which presents over hours (1,2,6). Although patients with HHS may present with nonspecific symptoms, one of the hallmarks of the disease is a neurologic abnormality (4,22,52). The most common neurologic abnormality in HHS is altered mental status, though coma, seizures, or focal neurologic deficits may occur (1,4,6,7). The presence of altered mental status is associated with dehydration and the severity of the hyperosmolality, occurring most commonly in patients with a serum osmolality > 330 mOsm/kg (1,6,25). Most patients with HHS present with polyuria, polydipsia, weakness, and blurred vision caused by the osmotic diuresis and dehydration (22,52). Patients with significant dehydration can present with dry mucous membranes, poor skin turgor, sunken eyes, tachycardia, and hypotension (53–55). Determining the level of dehydration on examination alone can be challenging, as patients may not appear as volume depleted as expected because the hypertonicity preserves their intravascular volume (56–58). Whereas patients with DKA may present with abdominal pain and vomiting, these symptoms are less common in patients with HHS because ketosis is minimally present (59). The patient should also be closely examined to evaluate for an underlying precipitant (e.g., infection, ischemia).

Diagnosis

There are two main definitions for HHS, though they vary slightly in their specific criteria (Table 3). Importantly, the combination of hyperglycemia and hyperosmolality should not be used in isolation for the diagnosis. Prior definitions included serum glucose ≥ 600 mg/dL, serum osmolality ≥ 320 mOsm/kg, pH > 7.3, serum bi-

Table 2. Comparison of Pathophysiology of HHS and DKA

Consideration	HHS	DKA
Pathophysiology	Insulin resistance with relative deficiency	Absolute insulin deficiency
Serum glucose	> 600 mg/dL	> 250 mg/dL
pH	> 7.3	< 7.3
Serum bicarbonate	> 15 mmol/L	< 15 mmol/L
Serum osmolality	> 320 mOsm/kg	< 320 mOsm/kg
Ketones	Absent to minimal	Large
Glucose intolerance	Insidious	Acute
Insulin sensitivity	Reduced	Normal
Serum insulin	Variable	Low or absent
Dehydration	Severe	Moderate or severe

HHS = hyperglycemic hyperosmolar state; DKA = diabetic ketoacidosis; mg/dL = milligrams per deciliter; mmol/L = millimoles per liter; mOsm/kg = milliosmoles per kilogram.

Table 3. Diagnostic Differences Between the ADA and UK Guidelines for HHS

Criteria	ADA	UK
Serum glucose	≥ 600 mg/dL	≥ 540 mg/dL
pH	> 7.3	> 7.3
Serum bicarbonate	> 18 mmol/L	> 15 mmol/L
Serum osmolality	≥ 320 mOsm/kg	≥ 320 mOsm/kg
Ketones	Small ketonuria or absent to low ketonemia	Beta hydroxybutyrate < 3 mmol/L
Patient presentation	Stupor or coma	Severe dehydration, feeling unwell

ADA = American Diabetes Association; UK = United Kingdom; HHS = hyperglycemic hyperosmolar state; mg/dL = milligrams per deciliter; mmol/L = millimoles per liter; mOsm/kg = milliosmoles per kilogram.

carbonate > 15 mmol/L, and the presence of a neurologic deficit, which was most commonly altered mental status (1,4,6,7). Differentiating DKA and HHS is not always straightforward. Patients with HHS may have a metabolic acidosis (pH < 7.3, low bicarbonate, increased anion gap), severe hyperglycemia, and hypertonicity, creating difficulty in differentiating HHS from DKA. An anion gap metabolic acidosis may be present due to the precipitating cause, lactic acidosis, or concomitant renal failure resulting in uremia (2,14). Importantly, those taking metformin who develop dehydration and acute renal impairment—which may occur in HHS—are at risk for metformin-associated lactic acidosis. Key components that can be utilized for the diagnosis of HHS include serum glucose over 600 mg/dL per the American Diabetes Association guidelines, or 540 mg/dL per the United Kingdom (U.K.) guidelines, osmolality > 320 mOsm/kg, absence of significant ketoacidosis (i.e., beta-hydroxybutyrate < 3 mmol/L or anion gap < 15 mmol/L), and appearing clinically unwell (e.g., altered mental status, neurologic deficit) (1,4,21).

Initial laboratory evaluation should include a complete blood cell count, electrolytes, renal and liver function testing, lipase, venous blood gas, osmolality, serum and urine ketones, and urinalysis. This laboratory evaluation can assist in differentiating HHS from the other conditions demonstrated in Table 4. Serum glucose is often over 1000 mg/dL, and profound hyperglycemia should trigger consideration of HHS (52,60). The complete blood cell count may demonstrate a leukocytosis due to increased circulating catecholamines. Plasma osmolality (P_{osm}) is typically > 320 mOsm/kg, but an osmolal gap—the difference between the measured and calculated serum osmolality—should not be present. The effective P_{osm} is the total

osmolality due to sodium and glucose, which are unable to penetrate cell membranes, causing water to move across cell membranes to reach osmolar equilibrium. This can be calculated as (61):

$$\text{Effective } P_{osm} = \left[2 \times \text{Sodium(mEq/L)}\right] + \left[\text{glucose(mg/dL)} \div 18\right]$$

or

$$\text{Effective } P_{osm} = [2 \times \text{Sodium(mmol/L)}] + \text{glucose(mmol/L)}$$

Importantly, the sodium utilized in these equations is the actual measured serum sodium, not the corrected sodium. Most patients with hyperglycemia will have a measured hyponatremia due to extensive dilution from the osmotic shift of water from the intracellular to extracellular space. However, patients with HHS may present with a normal or elevated serum sodium concentration due to severe osmotic diuresis and elevated P_{osm} (62). It is important to calculate the corrected sodium in these patients. Sodium concentration will decrease by 1.6–2.4 mEq/L for every 100 mg/100 mL increase in glucose (63). Thus, corrected sodium is approximated by adding 2.4 mEq/L to the measured sodium concentration for every 100-mg/dL increase in glucose concentration above normal (63). Although 1.6 mEq/L is useful for mild glucose elevations, 2.4 mEq/L is more accurate when serum glucose is > 400 mg/dL (63,64). The mean serum potassium approximates 5.7 mEq/L in HHS due to the hypertonicity (7,28,65). Despite initial increases in glomerular filtration during the early stages of hyperglycemia, in patients with HHS and severe hypovolemia, blood urea nitrogen and creatinine are often markedly elevated (1,6,66). Whereas metabolic acidosis is a diagnostic feature of DKA, patients with HHS typically have normal pH, unless another etiology of acidosis is present (e.g., infection, renal disease, ingestion, shock) (1,2,4,6). The urinalysis will reveal glycosuria. The presence of pyuria, leukocyte esterase, and nitrites is suggestive of urinary tract infection. Head computed tomography (CT) should be obtained to evaluate for other etiologies of altered sensorium or another precipitant for HHS. Additionally, chest radiography should be obtained to evaluate for pulmonary infection, as should an electrocardiogram to evaluate for consequences of electrolyte derangements and myocardial ischemia. Blood cultures should be considered if there is concern for sepsis or bacteremia.

Management

There are limited data concerning the optimal management of HHS. The American Diabetes Association guidelines do not separate the management guidelines of DKA and HHS (7). Although there are some similarities, there are differences as well. Table 5 depicts key components in the management of HHS. The primary goals of treatment in HHS include management of the inciting event; fluid repletion; and correction of osmolality, hyperglycemia, electrolyte abnormalities, and mental status (1,7). Physiologic abnormalities should be corrected slowly, as HHS occurs over days, and aggressive, rapid corrections in HHS can lead to dangerous changes in serum electrolytes and osmolality (1,7,61). This differs from DKA, which develops rapidly and requires urgent intervention to correct the ketoacidosis. Frequent monitoring of vital signs, volume and rate of fluid resuscitation, urine output, and electrolytes are recommended for HHS management.

Intravenous fluids

While treating the inciting event, fluid resuscitation is recommended. Patients with HHS typically have a water deficit of 100–200 mL/kg (23). Fluid replacement can improve osmolality, restore perfusion, reduce stress hormones, and enhance insulin responsiveness. However, HHS most commonly occurs in the elderly, and this patient population may have preexisting renal or cardiac disease. There are no clear recommendations on type of fluid repletion and speed of repletion, so these components of management must take into account the physiologic changes that have occurred over days (7,16). Rapid change in osmolality and tonicity may cause significant complications such as cerebral edema and osmotic demyelination syndrome (ODS), so close monitoring of serum osmolality is recommended (1,7,67–69). If the patient is hemodynamically unstable or severely dehydrated, isotonic fluid boluses are recommended to expand the intravascular volume and improve hemodynamics. Fluid repletion alone can result in glucose reduction by 75–100 mg/dL per hour (70). This resuscitation may also decrease the osmolality while increasing the measured serum sodium.

Many guidelines recommend 1.0 to 1.5 L of 0.9% normal saline in the first hour as the initial fluid choice to avoid the rapid correction of hyperosmolality that may occur with hypotonic fluids (4,7). A recent subgroup analysis of a trial comparing normal saline to balanced fluids (Ringer's lactate solution or Plasma-Lyte A solution [Baxter International, Deerfield, IL]) found balanced fluids to be safe and associated with a faster resolution of DKA, though evidence specific to HHS is lacking (1,71). Although there are no strong recommendations with regard to the type of fluid for ongoing volume repletion in HHS, balanced crystalloids (e.g., Ringer's lactate solution or Plasma-Lyte A solution) are a reasonable choice because they reduce the risk of hyperchloremic non-anion gap metabolic acidosis (Table 6) (72). However, the rate must be adjusted to prevent rapid overcorrection of the sodium. With therapy, every decrease

Table 4. Conditions That May Present Similar to HHS

Condition	Consideration
Alcoholic ketoacidosis	– Serum glucose may be low, normal, or mildly elevated (typically $<$ 250 mg/dL) – Elevated serum ketones – Anion gap metabolic acidosis – History of alcohol use – Recent poor oral intake and dehydration
Diabetic ketoacidosis	– Serum glucose elevated but typically $<$ 800 mg/dL – Elevated serum ketones – Anion gap metabolic acidosis – Low serum bicarbonate – Mental status ranges from alert to stupor/coma
Iron overdose	– History of or suspected iron overdose – Presents with gastrointestinal symptoms, hepatic failure – May present with serum glucose $>$ 150 mg/dL, elevated serum white blood cell count – Elevated lactate – Anion gap metabolic acidosis – Serum iron level may be elevated
Liver disease with hepatic encephalopathy	– History of liver disease and uremia – Grades: Altered sleep status, asterixis, disorientation, coma – Serum ammonia may be elevated
Renal failure	– History of renal disease – Elevated serum creatinine, decreased glomerular filtration rate – Alteration in urine output – Anion gap metabolic acidosis may be present
Salicylate overdose	– Altered mental status, tachypnea, gastrointestinal symptoms, hyperthermia, tinnitus – Respiratory alkalosis early with anion gap metabolic acidosis – Low serum bicarbonate – Elevated serum salicylate level

(*continued on next page*)

Table 4. (*continued*)

Condition	Consideration
Sepsis	– Source of infection: lung, urine, cardiac, central nervous system, abdomen, septic arthritis, skin, spine, bacteremia – Elevated lactate with anion gap metabolic acidosis may be present – Elevated white blood cell count may be present
Toxic alcohol ingestion	– History of ethylene glycol or methanol ingestion – Presents with central nervous system, cardiopulmonary, renal, gastrointestinal system abnormalities – Anion gap metabolic acidosis, low serum bicarbonate, hypocalcemia, renal failure, elevated osmolal gap may be present

HHS = hyperglycemic hyperosmolar state.

Table 5. Management of HHS

Treatment	
Fluids	Target euvolemia with 250–500 mL/h of i.v. fluids. If hemodynamically unstable, administer 1–1.5 L of i.v. fluids follow by infusion to correct fluid losses over 24 h
Insulin	0.05–0.1 units/kg/h after initial fluid resuscitation
Laboratory assessment	
Serum osmolality	Correct $\leq$ 3 mOsm/kg/h
Glucose	Correct by 50–75 mg/dL/h, goal $<$ 300 mg/dL
Potassium	Goal 4.0–5.0 mEq/L
Sodium	Correct $<$ 0.5 mEq/L/h or 10 mEq/L per day based on corrected presenting sodium

HHS = hyperglycemic hyperosmolar state; i.v. = intravenous; mL/h = milliliters per hour; L = liter; units/kg/h = units per kilogram per hour; mg/dL/h = milligrams per deciliter per hour; mg/dL = milligrams per deciliter; mOsm/kg/h = milliosmoles per kilogram per hour; mEq/L = milliequivalents per liter.

in serum glucose by 100 mg/dL results in an increase in serum sodium of approximately 2.4 mEq/L (1). This increase in serum sodium does not necessarily indicate the need for free water. However, increases in sodium of $>$ 2.4 mEq/L for every decrease in serum glucose of 100 mg/dL suggest insufficient fluid repletion (1). If the correction suggests evidence of hypernatremia or hyponatremia, the sodium should be slowly corrected at a rate of $<$ 0.5 mEq/L/h or 10 mEq/L per day using the corrected sodium as the baseline (73,74). Slow correction of sodium is most important when patients present with hyponatremia on corrected sodium to avoid ODS (75). For patients with a corrected serum sodium of $<$ 135 mEq/L, 0.9% normal saline should be utilized for fluid repletion. If serum sodium is normal or elevated, a hypotonic solution such as 0.45% normal saline or Ringer's lactate may be utilized while monitoring laboratory studies frequently for overcorrection. A continuous infusion of 250–500 mL/h may be required while monitoring urine output, serum glucose, and serum osmolality (7). The patient should be closely monitored for iatrogenic fluid overload (76).

Table 6. Intravenous Fluid Composition

Solution	Sodium	Chloride	Potassium	Calcium	Lactate	Acetate	Osmolarity	pH
Blood	135–145	96–106	3.5–5	8.5–10.5	0–1	–	275–295	7.35–7.45
Normal saline 0.9%	154	154	–	–	–	–	308	5.5
Ringer's lactate	130	109	4	2.7	28	–	273	6.5
Plasma-Lyte A	140	98	5	–	–	27	294	7.4

Units: Electrolytes: mEq/L; Osmolarity: mOsmol/L.

Serum osmolality and hypertonicity

Managing serum osmolality and hypertonicity are essential components of treatment and linked to correction of sodium. Serial measurements of serum osmolality or calculated serum osmolality is recommended, as rapid correction of osmolality is a proposed precipitant of cerebral edema (1). Younger patients are at greater risk for cerebral edema from rapid correction than older patients (76). Serum osmolality should be monitored every 1–2 h (1,23). A change of 3 mOsm/kg/h or less is recommended, although the UK guidelines have expanded this to 3–8 mOsm/kg/h (1,76). Decreases in osmolality that are faster than the recommended rate may result in neurologic complications (1,61). Slow correction of serum osmolality may indicate the need for more aggressive volume repletion. If osmolality increases or does not improve during the initial resuscitation, a hypotonic fluid such as 0.45% normal saline should be used. However, if the serum osmolality corrects faster than the goal of 3 mOsm/h, insulin and hypotonic fluids should be held or reduced. An infusion of concentrated 25% or 50% intravenous (i.v.) dextrose should be considered in severe cases of overcorrection (i.e., > 8 mOsm/kg/h) (1).

Electrolytes

Electrolyte replacement is typically needed due to the significant abnormalities. Total body potassium is decreased, even in the setting of normal-to-high serum potassium levels. Additionally, insulin administration will shift potassium into cells lowering the serum potassium level. The goal potassium level during therapy is 4.0–5.0 mEq/L (77). For those with a potassium < 3.5 mEq/L, potassium infusion at 20–40 mEq per liter of i.v. fluids is recommended prior to initiation of insulin. If potassium is between 3.5 and 5.5 mEq/L, potassium should be administered at a rate of 20–30 mEq/L per hour, and insulin can be initiated (78). Patients with hypokalemia may also be hypomagnesemic, which will exacerbate renal excretion of potassium. Therefore, magnesium should also be replaced, if low in these patients, with i.v. magnesium sulfate. Patients with severe hypophosphatemia (< 1 mEq/L) should receive phosphate replacement, as these levels can result in cardiac and respiratory dysfunction. Electrolytes should be assessed every 1–2 h to monitor for further derangements (e.g., hypokalemia) (1,23).

Insulin

Severely elevated serum glucose levels typically improve with fluid repletion, and insulin infusion is not mandatory in the initial management of HHS without a ketoacidosis. Insulin can be held until the plateau of serum glucose after initial fluid resuscitation (1). Insulin may improve osmolality and mental status, but many of these patients may be insulin resistant. Insulin dosing in patients with HHS differs from that of DKA, where patients may receive an i.v. insulin bolus of 0.1 units/kg followed by infusion of 0.1 units/kg/h or an i.v. insulin infusion of 0.14 units/kg/h with no bolus. Insulin in DKA is needed for resolution of ketoacidosis, as opposed to HHS, in which insulin treats the hyperosmolality (1,2,4,5,23,78,79). In patients with HHS, an i.v. insulin infusion without bolus is recommended at a starting dose of 0.05–0.1 units/kg/h (1,2,4,5,78,79). Patients on long-acting basal insulin should be administered their home dose. If not on basal insulin, 0.3 units/kg of glargine can be administered. This long-acting insulin can assist with transition from the insulin infusion and reduce rebound hyperglycemia (78). Glucose should be checked hourly while the patient is receiving an insulin infusion. The rate of glucose correction should be 50–75 mg/dL per hour. The infusion should be stopped once serum glucose reaches 300 mg/dL (1). If the glucose level falls below 200 mg/dL, insulin should be stopped and D5W or D10W started with a goal serum glucose of 250–300 mg/dL until the hyperosmolality is resolved (1,7).

Complications

Neurologic complications can be severe and include cerebral edema and ODS (61,80). Thus, repeat assessments of neurologic status are recommended every hour. Gradual correction of sodium, glucose, and water deficits reduces the risk of neurologic complications (25). Cerebral edema occurs from rapid reduction in serum osmolality in excess of the diffusion of intracellular idiogenic osmoles, and ODS occurs due to rapid correction of prolonged hyponatremia (23,25,81,82). Examination findings of ODS include confusion, pseudobulbar palsy, horizontal gaze paralysis, and spastic quadriplegia (81,82). If the neurologic status worsens during reassessment (e.g., worsening mental status, seizures, focal neurologic deficits), a neurologic complication such as cerebral edema or ODS should be suspected. Further neurologic imaging should be pursued, including CT or magnetic resonance imaging (MRI). Head CT for patients with cerebral edema may reveal areas of low density with loss of gray and white matter differentiation, as well as loss of the cisterns and sulcal spaces (83). CT is typically nonspecific in ODS, but may demonstrate low attenuation across the midline in the pons (81,82). MRI is the imaging modality of choice in patients with suspected ODS, which may demonstrate hyperintensities in the pons on T2-weighted imaging (81,82,84). However, neuroimaging (including MRI) may be normal in patients with ODS (84).

Other complications of HHS include circulatory collapse with shock and cardiac arrest, dysrhythmias, pulmonary embolism, rhabdomyolysis, malignant hyperthermia, and multisystem organ failure (1,6,61). Rhabdomyolysis can occur in the setting of HHS and may lead to acute kidney injury (85). This should be suspected in patients with myalgias, weakness, or dark urine with an elevated creatine kinase.

Disposition

Due to the significant fluid depletion, electrolyte abnormalities, neurologic manifestations, and need for frequent monitoring, patients with HHS typically require admission to an intensive care unit. Resolution of HHS is marked by serum osmolality < 310 mOsm/kg, glucose $<$ 250 mg/dL, improved volume status, and resolving neurologic symptoms (5,7). If i.v. insulin is utilized, the infusion can be discontinued once the glucose is controlled and the patient is eating and drinking. Patients can be transitioned to subcutaneous insulin at this time. If the patient was on an oral hypoglycemic agent prior to HHS, transitioning from subcutaneous insulin to the oral hypoglycemic agent can be considered after several weeks.

Conclusions

Hyperglycemic hyperosmolar state is associated with significant morbidity and mortality and is diagnosed by an elevated glucose, elevated osmolality, low ketones, and altered mental status. Treatment involves fluid resuscitation and correction of electrolyte abnormalities. It is important to monitor these patients closely to avoid overcorrection of sodium and other electrolytes. These patients are critically ill and generally require admission to an intensive care unit.

ARTICLE SUMMARY

1. Why is this topic important?

Hyperglycemic hyperosmolar state (HHS) may result in significant patient morbidity and mortality and requires emergent intervention.

2. What does this review attempt to show?

This narrative review focuses on the emergency medicine evaluation and management of adult patients with HHS.

3. What are the key findings?

HHS is diagnosed with elevated glucose and serum osmolality, minimal or absent ketones, and a neurologic abnormality, most commonly altered mental status. Treatment involves fluid resuscitation and correction of electrolyte abnormalities, with admission to the intensive care setting.

4. How is patient care impacted?

Emergency clinicians play an important role in the assessment and management of HHS.

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