HYPERGLYCEMIC HYPEROSMOLAR STATE

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Updated May 18, 2022

CLINICAL RECOGNITION

The hyperglycemic hyperosmolar state (HHS) is a life-threatening metabolic decompensation of diabetes which presents with severe hyperglycemia and profound dehydration, typically accompanied by alteration in consciousness ranging from lethargy to coma. In contrast to diabetic ketoacidosis (DKA) in which acidemia and ketonemia are key features, these are limited in HHS. Mortality in HHS ranges from 5-20% and is higher at the extremes of age and in the presence of coma. HHS is more prevalent in type 2 diabetics and in about 7-17% of cases is the initial presentation classically seen in institutionalized elderly patients with diminished thirst perception or inability to ambulate to get free water as needed. HSS is extremely rare as first presentation in patients with type 1 diabetes. Infections are the leading precipitant of HHS, but it can also be precipitated by poor medication compliance, cerebrovascular accident, myocardial infarction, pancreatitis, trauma, alcohol abuse and drugs such as corticosteroids and atypical antipsychotics.

PATHOPHYSIOLOGY

HHS and DKA represent the two ends of the spectrum of markedly decompensated diabetes, differing mainly in severity of acidosis, ketosis and dehydration. HHS usually occurs with a lesser degree of insulinopenia compared with DKA, but the pathophysiology is otherwise thought to be similar. In both entities, there is a decrease in net effective insulin action with concomitant elevation of counterregulatory hormones. In the setting of relative insulin deficiency, glucagon, catecholamines and cortisol stimulate hepatic glucose production though glycogenolysis and gluconeogenesis. High catecholamines and low insulin reduce peripheral glucose uptake. Unlike DKA, there is adequate insulin available in HHS to restrain lipolysis and ketogenesis, as well as to restrain marked elevation of counterregulatory hormones, such cortisol, glucagon and growth hormone. However, there is significant hyperglycemia with resultant glycosuria leading to loss of water and electrolytes, dehydration, decreased renal perfusion, decreased glucose clearance, and exacerbation of hyperglycemia, ultimately causing impaired level of consciousness. In HHS, the initial increase in proinflammatory cytokines, reactive oxygen species, and plasminogen activator inhibitor-1 can contribute to increased prothrombotic risk.

DIAGNOSIS AND DIFFERENTIAL

HHS usually has a slower onset than DKA, with symptoms developing over several days or weeks. Patients present with polyuria, polydipsia, weakness, and blurred vision. Altered sensorium is classic in HHS, but mental status can range from fully alert to confused, lethargic, or comatose. Seizure can occur in up to 20% of the patients. Exam reveals physical signs of dehydration, including dry mucous membranes, poor skin turgor, cool extremities, hypotension, and tachycardia. Fever may or may not be present, suggesting underlying infection, although normothermia or even hypothermia may be present due to concomitant vasodilatation.

The diagnostic criteria for HHS include severe hyperglycemia and hyperosmolality with preservation of near normal pH and bicarbonate, and minimal or absent serum and/or urine ketones. ADA guidelines note glucose level at presentation should be > 600 mg/dl, with pH > 7.3 and bicarbonate level > 20 mEq/L. These are common diagnostic criteria that differentiate HHS from DKA (Table 1). However, it is clear that a subpopulation of patients with type 2 diabetes can present with overlapping features of HHS and DKA. Patients with ketosis prone type 2 diabetes present with ketosis and milder acidosis than the one expects in DKA and in some cases with near normal pH and bicarbonate. More rarely, HHS can present in the setting of diabetes insipidus where patients are treated with intravenous dextrose for the severe dehydration leading to hyperglycemia and glycosuria.

Table 1. Diagnosis of HHS Versus DKA

	HHS	**DKA**
Diagnostic criteria		
pH	>7.30	≤7.30
Plasma Glucose	>600 mg/dl	>250 mg/dl
Serum bicarbonate	>15 mEq/L	<18 mEq/L
Plasma and urine ketones	None or trace	Positive
Anion gap	<12	>12
Serum Osmolality	>320 mOsm/kg	Variable
Glycosuria	++	++
Typical Deficit		
Water (ml/kg)	100-200 (9L)	100 (6L)
Na^+ (mEq/kg)	5-13	7-10
Cl^- (mEq/kg)	5-15	3-5
K^+(mEq/Kg)	4-6	3-5
$P0^4$ (mmol/kg)	3-7	5-7
Mg^{++}& Ca^{++}(mEq/kg)	1-2	1-2
Adapted from *Kitabchi A, et al. Diabetes Care, 2006, 29: 2739-2747*		

DIAGNOSTIC TESTS NEEDED

Initial laboratory tests should include electrolytes with calculated anion gap, plasma glucose, blood urea nitrogen (BUN), creatinine, serum and urine ketones,

osmolality, and arterial blood gas. Evidence of infection should be sought by checking complete blood count with differential and urinalysis, with consideration of additional evaluation including chest X-ray, and culture of blood, sputum and urine. Electrocardiogram and head CT should be done if clinically indicated. HHS produces significant loss of several electrolytes as well as a prerenal azotemia and increased hematocrit, the latter due to hemoconcentration. An increase of serum sodium in the presence of hyperglycemia indicates severe dehydration. Altered mentation appears to correlate with the degree of hyperosmolality; hence significantly diminished mentation in the setting of an osmolality of <320 mOsm/kg should prompt a search for other causes. It is notable that despite significant potassium losses, serum potassium is usually normal or even elevated on presentation because of extracellular shift in the setting of hyperosmolality and insulin deficiency. HgbA1c may be useful to discriminate chronic uncontrolled hyperglycemia from acute metabolic decompensation.

THERAPY

There is a lack on randomized controlled trials for the treatment of HHS and the American Diabetes Association (ADA) has developed guidelines that combine the treatment of HHS and DKA. The treatment of HHS includes a four-pronged approach:

1- reestablishment of volume status with vigorous intravenous hydration;
2- electrolyte replacement;
3- correction of hyperglycemia with volume expansion and administration of intravenous insulin;
4- diagnosis and management of potential precipitants.

The initial emergent treatment has been summarized in table 2.

Fluid Replacement

Aggressive fluid replacement is critical in order to prevent cardiovascular collapse, with repletion of intravascular and extravascular volume and restoration of renal perfusion. The total fluid deficit should be estimated (usually 100-200 ml/kg), with the goal of replacement over 24 hours. In the absence of heart failure, 1-1.5 liters of isotonic saline should be given over the first hour. Subsequent fluid replacement depends on the hydration and electrolyte status. In patients with hypotension, aggressive isotonic saline infusion should continue until the patient is stabilized. Increased plasma sodium concentration in the setting of hyperglycemia suggests a significant water deficit; clinical practice guidelines recommend adding a correction factor of 1.6 mg/dl to the plasma sodium concentration for each 100 mg/dl of glucose above 100 mg/dl. In the normotensive patient with a corrected serum sodium level that is normal or high, fluid replacement can be continued with half normal saline given at 250-500 cc/hour, whereas if the corrected serum sodium level is low, isotonic saline should be administered at similar rate. When serum glucose reaches 200-300 mg/dl, fluid should be changed to 5% dextrose solution in half normal saline.

Electrolyte Replacement

Electrolyte replacement is the second crucial step in HHS management. Serum potassium can be normal or elevated on presentation despite total body potassium depletion. Osmotic-induced intracellular dehydration results in potassium efflux from the cells. Since insulin causes a shift of potassium into the cell, it is mandatory to correct the potassium level to >3.3 mEq/L before starting insulin therapy. If potassium is between 3.3 and 5.3 mEq/L, 20-30 mEq of potassium should be given in each liter of intravenous fluid to keep serum potassium between 4 to 5 mEq/L. The potassium should be monitored if >5.3 meq/L and potassium replacement initiated when potassium < 5.3 meq/L. Magnesium should be checked and repleted as necessary; this is important to prevent renal wasting of potassium with exacerbation of hypokalemia. Routine administration of phosphate is

not recommended (17); however, careful phosphate replacement can be considered in patients with very low levels (<1 meq/L), cardiac dysfunction, or respiratory distress.

Insulin Therapy

The treatment of choice for correction of hyperglycemia is regular insulin by continuous infusion after adequate fluid and potassium replacement. While randomized controlled studies in patients with DKA have shown that insulin therapy is effective regardless of the route of administration, there is limited data supporting the use of subcutaneous or intramuscular insulin in HHS and continuous intravenous insulin administration remains the treatment of choice in patient with significant dehydration, reduced level of consciousness, and critical illness. Insulin should be given as initial bolus of 0.1 unit per kilogram body weight, followed by a drip of 0.1 unit per kilogram per hour; alternatively, 0.14 units per kilogram per hour can be given as an infusion without a bolus. If the glucose level does not decrease by 50-70 mg/dl in the first hour, the insulin dose may be doubled. When the plasma glucose level reaches 300 mg/dl, insulin infusion may be reduced to 0.05-0.1 unit/kg/hour and dextrose can be added to the fluids to keep the glucose level between 250-300 mg/dl until hyperosmolality has resolved and the patient is alert.

Evaluation of Precipitant Factors

Evaluation for and treatment of potential precipitant factors is important. Patients with HHS have a mortality rate of about 5-20%, 10-fold higher than patients with DKA and several studies have shown that the increased mortality is likely because of the precipitating factors. For this reason, appropriate work up and treatment should be given as indicated.

Table 2. Initial Emergent Treatment for HHS

1--IV Fluids		
a-Cardiogenic shock	b-Severe hypovolemia	c-Mild dehydration
Hemodynamic Monitoring/ Pressors/ 0.9% NaCl	0.9% NaCl (1L/hr.)	Na* low: 0.9% NaCl (250-500 ml/hr.) † Na* normal or high: 0.45% NaCl (250-500 ml/hr.) †
When serum glucose ≤300 mg/dl, 5% dextrose/0.45% NaCl (150-250 ml/hr.)		
2-IV Potassium (with adequate renal function)		
a--K+ <3.3 mEq/L	b--K+ 3.3-5.3 mEq/L	c--K+ >5.3 mEq/L
Hold insulin, K 20-30 mEq/ hr. until K+ >3.3 mEq/L	K 20-30 mEq in each liter of IV fluid to keep K+ 4-5 mEq/L	Do not give K; monitor
3-IV Insulin		
Bolus 0.1 unit/Kg, then 0.1 unit/Kg/hr. infusion (or 0.14 unit/kg/hr. infusion w/o bolus)		
Double infusion if glucose does not decrease by 50-70 mg/dl in the first hour		
When serum glucose 300 mg/dl, ↓ insulin infusion to 0.05-0.1 units/Kg/hr.		

Adapted from *Kitabchi A, et al. Diabetes Care, 2006, 29: 2739-2747*
*Corrected serum sodium; † depending on the hydration status

FOLLOW-UP

Meticulous clinical and laboratory follow up is critical in patients with HHS. Capillary blood glucose levels should be monitored every hour to allow adjustment of the insulin infusion. Electrolytes, BUN, creatinine and plasma glucose should be checked every 2-4 hours until the patient is stable. When plasma osmolality is <315 mOsm/L, and the patient is alert and able to eat, a multidose insulin regime consisting of long-acting insulin and short/rapid acting insulin before meals may be initiated. Intravenous insulin infusion should be continued for 1-2 h after the subcutaneous insulin is given to ensure adequate plasma insulin levels are maintained.

It is also important to monitor for possible treatment-related complications, the most common of which are hypoglycemia and hypokalemia. These are both usually due to overzealous treatment with insulin and can be minimized with frequent monitoring. Cerebral edema is extremely rare in patients with HHS, and usually occurs in younger adults. To reduce the risk of cerebral edema in high-risk patients, sodium, glucose, and water deficit may be more gradually corrected to avoid the rapid decline in plasma osmolality. Recurrence of HHS can be prevented by improved patient as well as caregiver education and enhanced access to medical care. For elderly nursing home residents, nursing home staff should be educated in recognition of signs and symptoms of HHS and on the importance of adequate fluid intake.

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