

Hyperosmolar Coma

J Michael Gonzalez-Campoy, MD, PhD, FACE, Medical Director and CEO, MN Center for Obesity, Metabolism, and Endocrinology

Updated: Jun 1, 2009

Introduction

Background

According to the nomenclature of the American Diabetes Association, the term hyperosmolar nonketotic state (HNS) is preferred to denote an acute metabolic complication of diabetes mellitus (DM) characterized by impaired mental status (MS) and elevated plasma osmolality in a patient with hyperglycemia. Criteria for HNS include serum osmolality of 320 mOsm/kg, plasma glucose level greater than 600 mg/dL (>33.3 mmol/L), profound dehydration, no ketoacidosis, pH of 7.3, HCO_3^- greater than 15 mEq/L, and the absence of severe ketosis.

HNS is the initial presentation of DM for 30-40% of patients. Most cases of HNS occur in patients with type 2 DM, characterized by insulin resistance and defective insulin secretion. HNS has been reported in patients with type 1 DM, in whom diabetic ketoacidosis (DKA) is more common. Both HNS and DKA may occur in the same individual, which suggests these 2 states of uncontrolled DM differ only in the magnitude of dehydration and the severity of acidosis.

Pathophysiology

The key pathophysiological event in HNS is relative or absolute deficiency of insulin activity. Deficient insulin activity may arise from an increase in insulin resistance or an inadequate supply of insulin, either endogenously or exogenously.

Obesity is the most prevalent cause of insulin resistance. Pregnancy is a state of insulin resistance largely due to the action of placental hormones on maternal circulation. High circulating levels of epinephrine, glucagon, growth hormone, and cortisol (the 4 major counterregulatory hormones) cause insulin resistance. Their levels increase during acute illnesses (eg, major infections, myocardial infarction [MI], pancreatitis) or stress (eg, surgery, major psychiatric illness, multiple traumas). Additionally, diseases characterized by excessive production of these hormones (eg, pheochromocytoma, glucagonoma, acromegaly, Cushing syndrome) also induce insulin resistance. Finally, parenteral nutrition and administration of some medications, notably glucocorticoids, Retin-A, antiretrovirals, antipsychotics,^[1,2] and cyclosporine and other immunosuppressive agents, cause insulin resistance.

Insulin deficiency is due to autoimmune destruction of the beta cells in type 1 DM. In type 2 DM, a defect in the first-phase release of insulin occurs, which leads to relative insulinopenia. The defective insulin secretion in persons with type 2 DM is due to the direct toxic effect of glucose on beta cells. Many patients with diabetes treated with insulin become relatively insulinopenic when they fail to adjust the dose of insulin upwards during illnesses or periods of stress.

Insulin-sensitive tissues normally take up glucose during meals, when the glycemic rise of ingested carbohydrates stimulates insulin secretion. Stimulated insulin levels inhibit glucagon release from the pancreatic islets, and the ratio of plasma insulin to

glucagon becomes relatively high. A high insulin-to-glucagon ratio favors storage of glucose as glycogen in liver and muscle and lipogenesis in adipocytes. Insulin-dependent transport of glucose across the cell membranes of insulin-sensitive tissues drives potassium into these cells. A high insulin-to-glucagon ratio during meals also favors amino acid uptake by muscle.

Between meals, insulin secretion is not stimulated, and the insulin-mediated glucagon inhibition in the pancreatic islets stops. The glucagon levels rise in the plasma, leading to a decrease in the ratio of plasma insulin to glucagon. The consequence of this decrease is the breakdown of glycogen in the liver and muscle and gluconeogenesis by the liver, both of which maintain the plasma glucose concentration in the normal range. A fall in the insulin-to-glucagon ratio also favors lipolysis and the formation of ketone bodies by the liver. Several tissues in the body use glucose regardless of the insulin-to-glucagon ratio. These insulin-independent tissues include the brain and the kidneys.

In the absence of adequate insulin activity, hyperglycemia develops. Decreased glucose use occurs in peripheral tissues, including adipocytes and muscles; glucose is unable to be stored as glycogen in muscle and liver; and hepatocytes under the influence of glucagon stimulate gluconeogenesis. The resulting elevation in plasma glucose concentration leads to further impairment of insulin release by pancreatic beta cells. In this setting of inadequate insulin action, the magnitude of the rise in plasma glucose concentration also depends, in part, on the level of hydration and oral carbohydrate (or glucose) loading.

Under normal circumstances, all of the glucose filtered by the kidneys is reabsorbed. When the level of glycemia reaches approximately 180 mg/dL, the proximal tubular transport of glucose from the tubular lumen into the renal interstitium becomes saturated, and further glucose reabsorption is no longer possible. The glucose that remains in the renal tubules continues to travel into the distal nephron and, eventually, the urine, carrying water and electrolytes with it. Osmotic diuresis results. The direct consequence of this osmotic diuresis is a decrease in total body water. Within the vascular space, in which gluconeogenesis and dietary intake continue to add glucose, the loss of water results in further hyperglycemia and loss of circulating volume.

Hyperglycemia and the rise in concentration of plasma proteins that follow intravascular water loss cause a hyperosmolar state. Hyperosmolarity of the plasma triggers antidiuretic hormone release, which ameliorates renal water loss. Hyperosmolarity also stimulates thirst, a defense mechanism that is impaired in people dependent on others for care.

In the presence of a hyperglycemic, hyperosmolar state, if the renal water loss is not compensated by oral water intake, then hypovolemia follows dehydration. Hypovolemia, in turn, leads to hypotension, and hypotension results in impaired tissue perfusion. Coma is the end stage of this hyperglycemic process, when severe electrolyte disturbances occur in association with hypotension. Any process that accelerates water loss, such as diarrhea or severe burns, accelerates the development of hyperosmolarity and hypotension. In this severely dehydrated and hyperosmolar state, hypotension causes a massive stimulation of the renin-angiotensin-aldosterone system and, eventually, renal shutdown. Oliguria precludes further excretion of glucose from the kidneys, which conserves circulating volume but exacerbates hyperglycemia.

Frequency

United States

No population-based studies of HNS have been conducted. According to the US National Hospital Discharge Survey funded by the National Center for Health Statistics, 10,800 annual discharges for HNS occurred from 1989-1991 in the United States. HNS affects approximately 1 of 500 patients with DM.

Mortality/Morbidity

The mortality rate for persons with HNS remains high, ranging from 14-58%. Older age, concurrent illnesses, and severity of the metabolic derangements, especially dehydration, contribute to this high mortality rate. A delay in establishing the diagnosis and a failure to treat HNS aggressively from the outset also may contribute to this high mortality rate.

- **Cerebral edema:** Cerebral edema is rare in HNS and is usually observed in patients much younger than the average age of 60 years. However, cerebral edema may occur from rapid lowering of glucose levels, with an ensuing rapid drop in plasma osmolarity. Brain cells, which trap osmotically active particles, preferentially absorb water and swell during rapid rehydration. Cerebral edema follows, and, given the constraints of the cranium, uncal herniation may be the cause of death in persons with HNS. However, death from cerebral edema due to HNS is rare, presumably because the older population that it affects has underlying cerebral atrophy. Thus, even with the edema of rehydration, the intracranial volume does not reach the critical level that causes uncal herniation. Aggressive correction of hyperglycemia and hyperosmolarity is indicated, especially in older patients.
- **Adult respiratory distress syndrome:** Always monitor pulmonary function carefully during therapy for HNS. A drop in the partial pressure alveolar oxygen during therapy for HNS may signal adult respiratory distress syndrome (ARDS), pulmonary emboli, MI, or a pneumonitis that has worsened with rehydration. ARDS may develop in association with underlying diseases, such as pancreatitis and MI. Although the precise mechanism by which ARDS develops in persons with HNS remains unclear, a likely scenario is that rapid correction of hyperglycemia and hyperosmolarity gives rise to pulmonary edema in a manner analogous to that of cerebral edema. To compensate for hypoxia and for mild acidosis, an increase in the minute ventilation with tachypnea develops. Continuing pulmonary disease may lead to acute respiratory failure requiring full respiratory support, including mechanical ventilation.
- **Vascular complications:** The severe dehydration of HNS leads to hypotension and hyperviscosity of the blood, both of which predispose patients to thromboembolic disease of the coronary, cerebral, pulmonary, and mesenteric beds. Disseminated intravascular coagulation also may complicate HNS. Together, these vascular syndromes account for much of the morbidity and mortality in HNS. Low-dose subcutaneous heparin is advisable for all patients without a contraindication.

Race

Data from 10,800 hospital discharges listing HNS in the United States from 1989-1991 included 6300 white patients and 2900 African American patients; the remainder of discharges were people of other races or of unknown race.

Sex

No sex predilection is noted in most published series of HNS. In the same data base as above, 3700 persons were male and 7100 were female.

Age

The average age of patients with HNS is 60 years. Most published series note an average age at diagnosis of 57-69 years. HNS may also occur in younger people. Nursing home populations are at risk of developing HNS. Underlying comorbidities that prevent adequate hydration, including immobility, advanced age, debility, dementia, agitation, and restraint use, place these patients at risk. Impaired senses, such as deafness and blindness, may lead to social isolation and also increase the risk of HNS.

Clinical

History

For patients who present with a change in MS, obtain a rapid determination of their level of glycemia. Both hypoglycemia and decompensated hyperglycemia may manifest as MS changes.

A fingerstick blood sugar measurement with a reflectance meter is the simplest first step in the evaluation. Blood sugar levels of 65-250 mg/dL exclude significant glycemic derangement and should prompt a search for other causes of MS changes. A blood sugar level outside this range suggests an acute diabetic problem. In this case, obtain a complete history from the patient or a companion, with an emphasis on recent illnesses or other conditions leading to altered insulin requirements, lack of compliance with hypoglycemic medications (including insulin), and dietary indiscretion. Emphasize identifying potential causes of HNS (see Causes). Prior hospitalizations for management of hyperglycemia are important to note and indicate a patient at risk for future episodes.

HNS usually evolves over a period of days to weeks, as opposed to DKA, which develops over the course of a few days. Increasing thirst with polyuria, polydipsia, and weight loss characterize HNS. To quench their thirst, many patients consume beverages containing glucose, including juices and soda. Attempt to quantitate the volume ingested over the preceding 24 hours to try to estimate the degree of osmotic diuresis with which the patient is presenting.

Physical

- Clues to underlying DM
 - The presence of needle pricks or calluses on the fingertips (from home glucose monitoring) indicates glycemic derangement as the etiology of a change in MS. Similarly, ecchymoses on the abdomen, thighs, and arms may be signs of insulin injection.
 - Many patients carry cards in their wallets or purses or wear bracelets or chains with a metallic plate identifying them as having DM.

- Obesity, acanthosis nigricans, diabetic dermopathy, necrobiosis on the pretibial surfaces, lower extremity ulcerations, soft tissue infections (eg, cellulitis or carbuncles), balanitis or vulvovaginitis, thrush, gingivitis, tooth decay, and the moon face of Cushing syndrome are also associated with underlying DM and should indicate consideration of HNS.
- A fundoscopic examination showing findings of retinopathy, premature cataracts, and xanthelasma are also clues to underlying diabetes.
- Assessing the degree of dehydration
 - Body weight is the single most important measurement in assessing the degree of hydration. Every liter lost in body fluids results in 1 kg of loss in body weight. Unfortunately, recently recorded weights are usually not available when assessing patients with HNS, and the weight reported by patients may not be accurate.
 - In the early stages of dehydration, cardiac stroke volume decreases. The body is able to maintain constant cardiac output by increasing the heart rate. Therefore, tachycardia is one of the earliest signs of dehydration. With ongoing volume loss, despite the compensatory tachycardia, cardiac output falls. To compensate for a drop in cardiac output, peripheral resistance increases. With further volume loss, the mean arterial pressure can no longer be maintained by increasing the peripheral resistance. This is most apparent when the patient is sitting or standing; therefore, documentation of orthostatic changes in blood pressure and heart rate are very important in the assessment of volume status. With profound dehydration, hypotension occurs even in the supine position.
 - With moderate-to-severe dehydration, urine output falls because the body engages the renin-angiotensin-aldosterone system and antidiuretic hormone to preserve volume. Dryness of the mucous membranes, anhidrosis, poor skin turgor, and sunken eyes indicate significant dehydration.
 - A careful cardiovascular examination is indicated in all patients with hypotension. Both cardiac pump failure from acute MI and pulmonary emboli can be underlying etiologies of HNS. Distinguishing hypotension due to cardiac pump failure from that of severe dehydration is often difficult, especially when they coexist. Cardiac imaging or central venous pressure measurements may be required.
 - Hypotension also may be due to sepsis. Exclusion of an infectious process, especially intrathoracic, intra-abdominal, or in the soft tissues, must be included in the physical examination of patients with HNS. Document body temperature. Low-grade fever is usually present in patients with HNS, secondary to a reduction in sweating. High-grade fever suggests infection.
- Neurological examination
 - HNS may be associated with several neurological findings, including seizures, hemianopsia, aphasia, paresis, a positive Babinski sign, myoclonic jerks, change in muscle tone, nystagmus, eye deviation, and gastroparesis. For many patients, these neurological symptoms and signs could be the manifestation of an underlying cerebrovascular accident. Cerebral dehydration, neurotransmitter level changes in the CNS, and microvascular ischemia may contribute to these findings.
 - When HNS causes neurological dysfunction, treatment results in resolution of signs and symptoms. When neurological events lead to HNS, signs and symptoms fail to improve with correction of the metabolic derangements.

Causes

Any illness that results in dehydration or that leads to a decrease in insulin activity can precipitate HNS. Acute febrile illnesses, including infections, account for the largest proportion of HNS cases.

Complications of arteriosclerotic diseases, such as stroke, MI, and renal failure, are frequent precipitants of HNS, because of ensuing extracellular fluid changes and because of the humoral stress associated with them. Consider MI in all patients with HNS until proven otherwise.

Elevated levels of the 4 major counterregulatory hormones, whether from endogenous or exogenous sources, may precipitate HNS. Examples include acromegaly, glucocorticoid use, and elevated production of catecholamines in stress states.

Diuretics, because of the propensity toward dehydration, and any drugs capable of inducing or exacerbating insulin resistance are also potential contributors to HNS. Several medications, including beta-blockers, hydrochlorothiazide, phenytoin, encainide, cimetidine, and diazoxide, may precipitate HNS by inhibiting insulin release.

When considering treatment of a patient with HNS, identify and address acute illness and contributions from medications. Many patients with HNS do not have an underlying cause and may be treated as patients with newly diagnosed DM who presented with this syndrome.

- Conditions and illnesses associated with HNS
 - Acromegaly
 - Anesthesia
 - Burns
 - Cerebrovascular accident
 - Cushing syndrome (eg, endogenous, exogenous, ectopic)
 - Hemodialysis and peritoneal dialysis
 - GI hemorrhage
 - Heatstroke
 - Hyperalimentation/total parenteral nutrition
 - Hypothermia
 - Intestinal obstruction
 - Mesenteric thrombosis
 - Myocardial infarction
 - Neuroleptic malignant syndrome
 - Pancreatitis
 - Pneumonia
 - Pulmonary emboli
 - Renal insufficiency (chronic)
 - Rhabdomyolysis
 - Sepsis

- Subdural hematoma
- Surgery (especially cardiac surgery)
- Thyrotoxicosis
- Trauma
- Urinary tract infection
- Medications that may precipitate HNS
 - Antiarrhythmics (eg, encainide, propranolol)
 - Antiepileptics (eg, phenytoin)
 - Antihypertensives (eg, calcium channel blockers, diazoxide)
 - Antipsychotics (eg, chlorpromazine, loxapine)^[1,2]
 - L-asparaginase
 - Corticosteroids
 - Diuretics (eg, chlorthalidone, ethacrynic acid, thiazides)
 - Histamine-receptor blockers (eg, cimetidine)
 - Immunosuppressive agents

Differential Diagnoses

Diabetes Insipidus

Diabetic Ketoacidosis

Myocardial Infarction

Pulmonary Embolism

Other Problems to Be Considered

MS change and/or level of consciousness

Intoxication (eg, with ethanol, narcotics, other drugs)

Postictal state

CNS infections

Arrhythmia

Hypotension

Sepsis

Other causes of dehydration

Acute blood loss (GI, other)

Polyuria

Excessive diuretic use

Workup

Laboratory Studies

- Plasma glucose
 - Hyperglycemia defines HNS. The degree of hyperglycemia in HNS is usually extreme. Many patients present with glucose concentrations greater than 1000 mg/dL.
 - The concentration of glucose in the plasma is directly proportional to the degree of dehydration. Higher concentrations of glucose relate to higher degrees of dehydration, higher plasma osmolality, and a worse prognosis.
 - Monitor the plasma glucose concentration hourly during the first 24-48 hours of treatment.
- Arterial blood gases (pH)
 - Document arterial plasma pH early in the treatment of patients with hyperglycemia presenting with an altered level of consciousness. A pH of 7.3 or higher defines HNS.
 - The arterial blood gas values also indicate underlying diseases associated with HNS. Hypoxemia may be observed in association with cardiac or pulmonary diseases. Hypocarbica may be due to respiratory alkalosis as a compensatory mechanism to a primary metabolic acidosis. Hypocarbica also may be due to tachypnea in response to an elevated alveolar-arterial oxygen gradient from pulmonary disease. A low plasma bicarbonate level is commonly observed in persons with HNS, but very low levels (<15 mEq/L) indicate DKA.
- Plasma ketones
 - A mild degree of ketosis is usually observed in any patient who is dehydrated.
 - In those with HNS, despite the significant degree of dehydration, ketosis is mild and responds readily to treatment. Profound ketosis that does not respond readily to intravenous rehydration is the norm in persons with DKA.
- Serum osmolality and calculated serum osmolality
 - Normal serum osmolality ranges from 280-290 mOsm/kg. A serum osmolality of 320 mOsm/kg or more defines HNS. Rarely, serum osmolality may be greater than 400 mOsm/kg. In HNS, higher serum osmolality relates to worse impairment of the level of consciousness.
 - The serum osmolality may be calculated by adding Na^+ and K^+ , multiplying by 2, adding glucose (mg/dL) divided by 18, and adding BUN divided by 2.8 (ie, $2 [\text{Na}^+ + \text{K}^+] + [\text{mg/dL of glucose}/18] + [\text{BUN}/2.8]$).
 - Urea is freely permeable across cell membranes and therefore does not create an osmotic gradient between the intracellular and extracellular fluids. The last term of the serum osmolality equation may be dropped, giving the effective serum osmolality.
 - The effective serum osmolality may be used to calculate a patient's osmolality quickly at the bedside but should be confirmed by a measured value.
- Urinalysis
 - Urine for analysis may be difficult to obtain in a severely dehydrated patient with HNS. Catheterization of the urinary bladder may be necessary.
 - Exclude urinary tract infection in the evaluation of a patient with HNS.
 - Urinalysis may provide further information about the patient's metabolic state. Ketones are rarely present in persons with HNS, due mostly to dehydration. Gross proteinuria suggests the presence of underlying renal disease. The urinary osmolality and the urine specific gravity should be very high in patients with HNS.

Occasionally, a patient presents with a low urine specific gravity. This is diagnostic of coexisting diabetes insipidus, prompts a more thorough evaluation of pituitary and renal function, and requires aggressive fluid resuscitation and central pressure monitoring.

- Plasma electrolytes
 - Early in the course of HNS, before significant osmotic diuresis has occurred, the elevated plasma glucose level exerts an osmotic drag. This results in the movement of water from the intracellular to the extracellular space, with dilution of all electrolytes in the plasma. Patients with renal insufficiency who may not establish an osmotic diuresis may effectively present with hyponatremia and hypochloremia. As HNS progresses and osmotic diuresis occurs, electrolytes are lost in the urine. All electrolytes are extremely deficient at the time of presentation, at which time the relative deficiencies of water and electrolytes determine their plasma concentrations. Additionally, the presence of hypertriglyceridemia affects the concentration of electrolytes. Triglycerides also exert an osmotic drag and displace electrolytes in the plasma.
 - Potassium does not enter insulin-sensitive tissues in HNS and remains in the extracellular space. The concentration of potassium at presentation depends on water loss, but frequently is high. Realize that despite the high concentration of potassium at presentation, patients experience profound losses. During treatment, insulin drives potassium into cells, and intravenous hydration dilutes potassium in the circulation. Aggressively replace potassium to maintain plasma levels in the normal range during treatment.
 - Monitor plasma electrolyte levels at least every 4 hours during the first 24-48 hours of treatment.
 - Bartoli and colleagues described a mathematical model and formulas that, according to the authors, improve the estimation of the plasma sodium concentrations that patients will have following treatment for hyperosmolar coma.^[3,4] Such estimations are important for avoiding sodium imbalances following coma treatment. The model estimates the amount of glucose added to the plasma, along with associated water loss, but excludes concomitant sodium loss.
- Calculated anion gap
 - The anion gap is calculated by adding Na^+ and K^+ and subtracting the sum of Cl^- and HCO_3^- (ie, $[\text{Na}^+ + \text{K}^+] - [\text{Cl}^- + \text{HCO}_3^-]$).
 - A wide anion gap is observed in most patients with HNS, reflecting mild metabolic acidosis. Bicarbonate levels greater than 15 mEq/L define HNS. The mild acidosis in HNS is often multifactorial and results, in part, from the accumulation of ketoacids in the absence of effective insulin activity. Some patients with profound dehydration may have high anion gaps, reflecting the additional contribution of lactic acid produced by hypoperfusion of tissues. Underlying renal disease with uremia also may contribute to a high anion gap.
- Creatinine and BUN
 - Patients with HNS present with prerenal azotemia. The initial BUN-to-creatinine ratio may exceed 30:1.
 - The renal function of many patients does not normalize after treatment, indicative of irreversible or underlying renal damage.
- CBC count and differential
 - Hemoglobin and hematocrit values are usually elevated because of volume contraction.
 - Leukocytosis is frequently present, with counts often greater than 20,000/mL. Stress, dehydration, and demargination of leukocytes contribute to leukocytosis. Given that infections commonly precipitate HNS,

consider leukocytosis secondary to an infectious process until proven otherwise. Obtain a chest radiograph and urine and blood cultures from all patients with leukocytosis.

- Creatine kinase (rhabdomyolysis)
 - Dehydration causes a rise in the plasma levels of albumin, amylase, bilirubin, calcium, total protein, lactate dehydrogenase, transaminases, and creatine kinase (CK). Up to two thirds of patients with HNS have elevated serum enzyme levels.
 - Avoid the assumption that enzyme level elevation is due to dehydration. Exclude underlying disease associated with each of these abnormal blood levels in patients with HNS. This is especially true in the case of CK elevations.
- Order additional tests as appropriate in the evaluation and management of patients with HNS.

Imaging Studies

- Chest radiograph
 - A chest radiograph (CXR) is almost always advisable in the initial evaluation of patients with HNS to exclude pneumonitis. CXR findings may be falsely negative at first because of the profound dehydration in some patients, and serial studies may document the pneumonitis process as rehydration proceeds.
 - Cardiomegaly in the presence of dehydration implies a severely compromised heart, which is probably affected by cardiomyopathy.
- CT scan of the head
 - Patients with HNS presenting with an altered MS may have an underlying CNS disease. CT scan is indicated to help exclude hemorrhagic strokes, subdural hematoma, subarachnoid bleeding, intracranial abscesses, and intracranial masses.
 - Repeat CT scanning is indicated if cerebral edema is a concern during the treatment of HNS.

Other Tests

- Electrocardiogram
 - ECG is indicated in all patients with HNS because MI and pulmonary emboli frequently precipitate HNS.
 - The height of the T waves in the ECG tracings may point to a potassium derangement. The duration of the QT interval may be abnormal due to calcium abnormalities.

Procedures

- Central venous pressure monitoring
 - Insertion of a central venous catheter is the only procedure that should be considered routinely in patients with HNS.
 - Findings from monitoring of the pulmonary capillary wedge pressure or the central venous pressure may help guide intravenous rehydration therapy.
 - A centrally placed catheter offers an avenue for vigorous rehydration.
- Endotracheal intubation and mechanical ventilation

- Protection of the airway is mandatory in patients with obtundation or unconsciousness. Many patients present with respiratory failure and circulatory collapse and must be ventilated mechanically.
- Because of the underlying metabolic acidosis that is frequently present, take care to hyperventilate patients when mechanical ventilation is instituted. Hyperventilation generates respiratory alkalosis, which compensates for the metabolic acidosis and also decreases the risk of cerebral edema.
- In patients with HNS, consider other procedures, including nasogastric tube placement, thoracentesis, paracentesis, and spinal tap, as appropriate.

Treatment

Medical Care

All patients with HNS require hospitalization, and most should be admitted directly to the intensive care unit (ICU). When available, an endocrinologist should direct the care of these patients. The main goals of treatment are to (1) vigorously rehydrate the patient while maintaining electrolyte homeostasis; (2) correct hyperglycemia; (3) treat underlying diseases; and (4) monitor and assist cardiovascular, pulmonary, renal, and CNS function.

- Intravenous fluid hydration and electrolyte homeostasis
 - If a recent record of the patient's weight is available for comparison, the difference between the admission weight and the preadmission weight may provide a rough estimate of the degree of dehydration.
 - Rapid and aggressive intravascular volume replacement is always indicated as the first line of therapy for patients with HNS.
 - Isotonic sodium chloride solution is the fluid of choice to begin treatment, because sodium and water must be replaced in these severely dehydrated patients.
 - Infuse enough volume to allow for the perfusion of vital organs and the kidneys. Usually, 2 liters of 0.9% isotonic sodium chloride solution may be infused safely over the first hour of treatment. Once renal perfusion is accomplished, as evidenced by adequate urinary output, 0.45% saline may be used for continued hydration.
 - A reasonable goal of treatment is to replace half of the estimated volume deficit in the first 12 hours of therapy. The remainder of the volume deficit may then be replaced over the second 12-hour period.
 - Intravenous fluid treatment allows for renal excretion of sugar and dilutes the extracellular fluid volume, causing a dramatic drop in the plasma glucose concentration.
 - At a serum osmolality of less than 320 mOsm/kg, the intravenous fluids may again be switched to 0.9% isotonic sodium chloride solution. When the blood glucose concentration, checked hourly initially, reaches 300 mg/dL, change the infusion to 5% dextrose in 0.9% isotonic sodium chloride solution again. This helps prevent a precipitous fall of glucose, which may be associated with cerebral edema.
 - In most patients, adequately monitoring volume status entails the use of a urinary catheter. In patients with preexisting or acute cardiac disease or with diseases in which third spacing is a problem, use findings from

pulmonary capillary wedge pressure monitoring to guide rehydration therapy. Patients with hypotension may require pressor support in the ICU while rehydration is accomplished.

- Profound potassium depletion requires careful replacement. With rehydration, the potassium concentration is diluted. With the institution of insulin therapy, potassium is driven into cells. A precipitous drop in the potassium concentration may lead to cardiac arrhythmia. Potassium may be added to the infusion fluid and should be started at a potassium level of 5 mEq/L or less. Hypokalemia at the onset of rehydration requires up to 60 mEq/L to correct the serum potassium concentration. Check the potassium level at least every 4 hours until the blood glucose concentration is stabilized.
- Phosphate, magnesium, and calcium are not replaced routinely, but a patient symptomatic with tetany requires replacement therapy.
- Correction of hyperglycemia
 - All patients with HNS require treatment with intravenous insulin; however, immediate treatment with insulin is contraindicated in the initial management of patients with HNS. The osmotic pressure that glucose exerts within the vascular space contributes to the maintenance of circulating volume in these severely dehydrated patients. Institution of insulin therapy drives glucose, potassium, and water into cells. This results in circulatory collapse if fluid has not been replaced first.
 - After the kidneys show evidence of being perfused, initiating insulin therapy is safe. This is accomplished most effectively in the ICU, where cardiovascular and respiratory support is available if needed. Infuse insulin separately from other fluids, and do not interrupt or suspend the infusion of insulin once therapy is started. The following guideline for insulin infusion may be used.
 - Begin a continuous insulin infusion of 0.1 U/kg/h.
 - Monitor blood glucose by bedside testing every hour. If stable for 3 hours, then decrease the frequency of testing to every 2 hours.
 - Set the target blood glucose level at 250-300 mg/dL. This may be adjusted downwards after the patient is stabilized.
 - For blood glucose concentrations of less than 250 mg/dL, decrease the insulin infusion rate by 0.5 U/h.
 - For a blood glucose concentration of 250-300 mg/dL, do not change the insulin infusion rate.
 - For a blood glucose concentration of 301-350 mg/dL, increase the insulin infusion rate by 0.5 U/h.
 - For a blood glucose concentration of 351 mg/dL or greater, increase the insulin infusion rate by 1 U/h.
 - Do not discontinue the insulin drip.
 - If a decrease of more than 100 mg/dL occurs between consecutive readings, wait to increase the insulin infusion rate.
 - When the glucose level has been 200-300 mg/dL for at least 1 day and the patient's level of consciousness has improved, glycemic control may be tightened. The recommended level of glycemia for most patients with type 2 DM is 80-120 mg/dL. This correlates to the recommended hemoglobin A1c value of 7% recommended by the American Diabetes Association. All patients who have experienced HNS will probably require intensive management of their diabetes initially, and this includes insulin. The severe hyperglycemia with which these patients present implies profound beta cell dysfunction. In most instances, sufficient recovery of endogenous

insulin production is a reasonable expectation, with safe dismissal of the patient from the hospital on oral therapy. After maintaining adequate glycemic control with insulin for several weeks following HNS, consider switching patients to a regimen with an oral agent.

- Treatment of underlying diseases
 - When an underlying disease is responsible for HNS, identify and treat it. The resolution of HNS often lags pending resolution of the underlying process.
 - Some authors advocate prophylactic heparin treatment and broad-spectrum antibiotic coverage, but prophylactic heparin treatment and broad-spectrum antibiotic coverage have not been studied adequately to recommend their use.
- Cardiopulmonary monitoring
 - The mortality rate associated with HNS remains high.
 - The profound electrolyte and metabolic abnormalities present during treatment warrant careful cardiorespiratory monitoring.
 - When patients have compromised gas exchange, endotracheal intubation and mechanical ventilation are indicated.
- Neurological monitoring
 - This is indicated in all patients with HNS who present with altered MS. Hyperosmolarity may trigger many neurological syndromes.
 - If a patient has seizures, phenytoin is not the agent of choice because it inhibits endogenous insulin secretion and because, in general, it is ineffective in persons with HNS.

Consultations

- An emergent consultation with an endocrinologist is indicated for all patients with HNS.
- Consider a consultation with a neurologist for most patients with altered MS. A neurologist should monitor the cases of any patients with underlying neurological disease, such as a cerebrovascular accident or a history of seizures.
- A pulmonologist or critical care specialist should monitor the cases of patients requiring intubation and mechanical ventilation.
- Obtain consultations with other specialists as appropriate.

Diet

- Provide adequate nutritional support for all patients. Most patients with HNS are not able to eat for several days, given the comorbidities with which they present.
- Patients in the ICU who require prolonged mechanical ventilation, patients with impaired airway defenses, and all patients with prolonged MS changes are candidates for enteral or parenteral nutrition. The use of parenteral nutrition often induces insulin resistance and leads to increased insulin requirements.
- Once HNS is resolved, provide dietary counseling for all patients. A registered dietitian with expertise in counseling patients with diabetes helps accomplish this most effectively.

Medication

Insulin and intravenous fluid management are cornerstones in the management of HNS. Aggressive rehydration with intravenous fluids, including isotonic sodium chloride solution, is indicated in every patient with HNS (see Medical Care). Frequently monitoring electrolyte concentrations is indicated when patients are treated with intravenous fluids. Volume overload is the only other potential problem when treating patients with intravenous fluids; therefore, regular assessment of the hydration state is indicated.

Antihyperglycemic agents

Reduce serum glucose concentration.

Regular insulin (Humulin, Novolin)

Stimulates proper use of glucose by cells and reduces blood sugar levels.

Dosing

Adult

Begin 0.1 U/kg/h IV infusion

See Medical Care for management of infusion rate based on treatment goals

Pediatric

Administer as in adults

Interactions

Acetazolamide, AIDS antivirals, asparaginase, phenytoin, nicotine isoniazid, diltiazem, diuretics, corticosteroids, thiazide diuretics, thyroid estrogens, ethacrynic acid, calcitonin, oral contraceptives, diazoxide, dobutamine phenothiazines, cyclophosphamide, dextrothyroxine, lithium carbonate, epinephrine, morphine sulfate, and niacin may decrease hypoglycemic effects

Calcium, ACE inhibitors, alcohol, tetracyclines, beta-blockers, lithium carbonate, anabolic steroids, pyridoxine, salicylates, MAOIs, mebendazole, sulfonamides, phenylbutazone, chloroquine, clofibrate, fenfluramine, guanethidine, octreotide, pentamidine, and sulfinpyrazone may increase hypoglycemic effects

Contraindications

Documented hypersensitivity, hypoglycemia

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Hyperthyroidism may increase renal clearance and may require more insulin to treat hyperkalemia; hypothyroidism may delay turnover, requiring less insulin to treat hyperkalemia; monitor glucose carefully; dose adjustments may be necessary in patients with renal and hepatic dysfunction

Follow-up

Further Outpatient Care

- Following an episode of HNS, enroll all patients in a program of routine diabetes care.
- Adhere to American Diabetes Association guidelines for care of people with diabetes.
- For patients with unknown diabetes prior to HNS, perform a dilated eye examination.
- Advise patients treated with insulin to wear a bracelet or chain identifying them as having diabetes.

Deterrence/Prevention

Having had HNS places patients at risk for further episodes. Patient education is important in preventing a recurrence of HNS. Warn patients to avoid poor glycemic control and dehydration.

Complications

See Mortality/Morbidity.

Patient Education

A certified diabetes educator should instruct all patients on management of sick days and a thorough review of self-care.

References

1. Campanella LM, Lartey R, Shih R. Severe hyperglycemic hyperosmolar nonketotic coma in a nondiabetic patient receiving aripiprazole. *Ann Emerg Med.* Feb 2009;53(2):264-6. [\[Medline\]](#).
2. Ahuja N, Palanichamy N, Mackin P, et al. Olanzapine-induced hyperglycaemic coma and neuroleptic malignant syndrome: case report and review of literature. *J Psychopharmacol.* Nov 21 2008;[\[Medline\]](#).
3. Bartoli E, Sainaghi PP, Bergamasco L, et al. Hyperosmolar coma due to exclusive glucose accumulation: recognition and computations. *Nephrology (Carlton).* Apr 2009;14(3):338-44. [\[Medline\]](#).
4. Bartoli E, Bergamasco L, Castello L, et al. Methods for the quantitative assessment of electrolyte disturbances in hyperglycaemia. *Nutr Metab Cardiovasc Dis.* Jan 2009;19(1):67-74. [\[Medline\]](#).

5. American Diabetes Association. Hospital admission guidelines for diabetes. *Diabetes Care*. Jan 2004;27 Suppl 1:S103. [\[Medline\]](#). [\[Full Text\]](#).
6. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crises in diabetes. *Diabetes Care*. Jan 2004;27 Suppl 1:S94-102. [\[Medline\]](#). [\[Full Text\]](#).
7. Fishbein H, Palumbo PJ. Acute Metabolic Complications in Diabetes. In: *National Diabetes Data Group. Diabetes in America*. 2nd ed. Bethesda, Md: National Institute of Diabetes and Digestive and Kidney Disease; 1995:283-91.
8. Gonzalez-Campoy JM, Robertson RP. Diabetic ketoacidosis and hyperosmolar nonketotic state: gaining control over extreme hyperglycemic complications. *Postgrad Med*. Jun 1996;99(6):143-52. [\[Medline\]](#).
9. Stoner GD. Hyperosmolar hyperglycemic state. *Am Fam Physician*. May 1 2005;71(9):1723-30. [\[Medline\]](#). [\[Full Text\]](#).

Keywords

hyperosmolar coma, diabetic coma, hyperosmolar nonketotic, hyperosmolar nonketotic coma, diabetes, diabetes mellitus, diabetes type 1, diabetes type 2, type 2 diabetes, type 1 diabetes, diabetes 2, diabetes 1, diabetic, insulin, insulin resistance, glucose, blood sugar, hyperglycemia, hyperosmolar nonketotic state

hyperglycemic hyperosmolar nonketotic syndrome, hyperosmolar hyperglycemic syndrome, diabetic hyperosmolar state, hyperosmolar hyperglycemic nonketotic coma, nonketotic hypertonicity, diabetes mellitus type2, diabetes mellitus type 1, type 2 diabetes mellitus, type 1 diabetes mellitus