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Summary

- Occurs most commonly in older patients with type 2 diabetes. Contributes to less than 1% of all diabetes-related admissions. However, mortality is high (5% to 15%).

- Presents with polyuria, polydipsia, weakness, weight loss, tachycardia, dry mucus membranes, poor skin turgor, hypotension, and, in severe cases, shock.

- Altered sensorium (lethargy, disorientation, stupor) is common and correlates best with effective serum osmolality. Coma is rare and, if seen, is usually associated with a serum osmolality >340 mOsm/kg.

- Treatment includes correction of fluid deficit and electrolyte abnormalities, and intravenous insulin.
Hyperosmolar hyperglycemic state

Definition

Hyperosmolar hyperglycemic state (HHS), also known as non-ketotic hyperglycemic hyperosmolar syndrome (NKHS), is characterized by profound hyperglycemia (glucose >600 mg/dL), hyperosmolality (effective serum osmolality ≥320 mOsm/kg), and volume depletion in the absence of significant ketoacidosis (pH >7.3 and HCO3 >15 mEq/L), and is a serious complication of diabetes. HHS may be the first presentation of type 2 diabetes.[1] [2] Although both HHS and diabetic ketoacidosis (DKA) are often discussed as distinct entities, they represent 2 points on the spectrum of metabolic derangements in diabetes.[3] Both HHS and DKA are characterized by relative or absolute insulin deficiency combined with increased counter-regulatory hormones.[1] [4] Approximately one third of patients with hyperglycemic crises present with a mixed picture of DKA and HHS.[5]

Epidemiology

The precise prevalence and incidence of hyperosmolar hyperglycemic state (HHS) is difficult to determine because of the lack of population-based studies and the multiple comorbidities often found in these patients. However, the overall prevalence is estimated at less than 1% of all diabetes-related hospital admissions.[9] [10] The incidence of HHS has been estimated at a rate of 17.5 per 100,000 patient years.[6]

HHS is seen most commonly in older patients and those of African-American ethnicity with diabetes.[10] Mortality rates in HHS have been reported to be 5% to 20%, a rate that is 10-fold higher than that reported for diabetic ketoacidosis.[2] [11] Mortality increases significantly when the patient is above the age of 70 years.[12] A combined state of severe hyperglycemia, hyperosmolality, and metabolic acidosis is seen in approximately 25% of all hyperglycemic emergencies.[5] [13] [14]

Etiology

Infection is the major precipitating factor, occurring in 30% to 60% of patients. Urinary tract infections and pneumonia are the most common infections reported.[2] [8]

In many instances, the trigger is an acute illness, such as stroke, myocardial infarction (MI), or other medical-surgical illnesses, or trauma that provokes the release of counter-regulatory hormones (catecholamines, glucagon, cortisol, and growth hormone) and/or compromises water intake.[1] [2] [15] In elderly patients, being bed-ridden and having an altered thirst response compromise access to water and water intake, leading to severe dehydration and hyperosmolar hyperglycemic state (HHS).[16] HHS can be seen in postoperative patients with a known history of diabetes, especially postcardiac-bypass surgery or neurosurgery.[8]

Patients with pre-diabetes or diabetes who require total parenteral nutrition in their postoperative state and are not started on appropriate insulin therapy may also present with HHS.[8] A patient with a strong family history of diabetes is also at high risk of developing HHS on total parenteral nutrition (TPN) therapy if not treated concomitantly with insulin.[8] [17]

Rarely, endocrine disorders, such as hyperthyroidism[8] and acromegaly,[18] can lead to HHS. In patients with concomitant diabetes, hypercortisolism leads to insulin resistance and promotes HHS development.[19] Ectopic production of adrenocorticotropic hormone has been associated with HHS.[20] Initiation of corticosteroids without adjustment of insulin doses or that of oral antidiabetic agents can trigger HHS.
Nonadherence to insulin or oral antidiabetic medication is found in 12% to 25% of patients admitted for HHS.[5] [6] This association is much higher in urban African-American patients with diabetes, in whom nonadherence is the sole reason for HHS in 42% of cases.[9] Alcohol and cocaine abuse is a major contributing factor to nonadherence of diabetic therapy.

Corticosteroids,[21] thiazide diuretics,[22] [23] beta-blockers,[24] and didanosine,[25] have all been associated with HHS. These drugs are thought to induce HHS by affecting carbohydrate metabolism.[7] Medications that have been associated with hyperglycemia but not with HHS include phenytoin,[26] gatifloxacin,[27] and cimetidine.[28] Drug-induced hyperglycemia has been noted increasingly in HIV clinics; the drugs involved most commonly are megestrol, pentamidine, and corticosteroids.[29] The risk of severe hyperglycemia increases when using a combination of these medications.[30] Atypical antipsychotic medications (in particular, clozapine and olanzapine) have also been implicated in producing diabetes and hyperglycemic crises.[31] [32]

Approximately 7% to 17% of patients have newly diagnosed diabetes.[9]

Pathophysiology

Hyperosmolar hyperglycemic state (HHS) is characterized by extreme elevations in serum glucose concentrations and hyperosmolality without significant ketosis. These metabolic derangements result from relative insulin deficiency and increased concentration of counter-regulatory hormones (catecholamines, glucagon, cortisol, and growth hormone).[1] [16] Although both HHS and diabetic ketoacidosis (DKA) are often discussed as distinct entities, they represent 2 points on the spectrum of metabolic derangements in diabetes. Approximately one third of patients with hyperglycemic crises present with a mixed picture of DKA and HHS.[5]

The pathogenesis of HHS is, however, not fully understood.[33] Measurable insulin secretion in patients with HHS is higher than in patients with DKA.[34] This higher insulin concentration is believed to be sufficient to suppress lipolysis and ketogenesis but inadequate to regulate hepatic glucose production and promote glucose utilization. This concept is supported by clinical studies both in animals and in humans, which have shown that the half-maximal concentration of insulin for antilipolysis is lower than for glucose use by peripheral tissues.[16] [35] Another potential mechanism for the lack of ketosis in HHS involves the effect of hyperosmolality on inhibiting lipolysis, insulin secretion, and glucose uptake.[34]

A reduction in the net effective concentration of insulin owing to any etiology leads to impaired carbohydrate, lipid, and ketone metabolism in hyperglycemic crises. Decreased insulin results in increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues.[1] [9] [15]

Disturbances in hydration and electrolyte balance are of great importance in the pathogenesis of HHS. Because HHS evolves over several days, continued osmotic diuresis leads to hypernatremia, particularly in older patients with compromised renal function and/or inability to drink water to keep up with urinary losses. The resulting hypernatremia and hyperglycemia, coupled with inadequate water intake and excess water loss, result in profound volume contraction. Hypovolemia leads to a progressive decline in the glomerular filtration rate, which aggravates the hyperglycemic state.[1] [15]

Counter-regulatory hormones, particularly epinephrine, are increased as a systemic response to infection. They induce insulin resistance, decrease insulin production and secretion, and increase lipolysis,
Hyperosmolar hyperglycemic state

**Basics**

ketogenesis, and volume depletion, thereby contributing to the hyperglycemic crises in patients with diabetes.[1]
Primary prevention

In the majority of patients, hyperosmolar hyperglycemic state evolves over several days and so frequent blood glucose monitoring may help to recognize patients at risk, especially in older patients and in those in long-term care facilities.

Many episodes could be prevented through education and effective outpatient treatment programs. Patients and family members should be educated about the following:[2]

- Which symptoms or blood sugar readings should prompt the patient to contact the diabetes care team
- The importance of insulin use during an illness, and never discontinuing insulin without contacting their healthcare provider
- Frequent monitoring of blood sugars (i.e., at least every 3-4 hours including overnight; this is especially important in children)[4]
- Blood glucose goals and the use of supplemental short- or rapid-acting insulins to correct elevated blood sugars
- Initiation of an easily-digestible, liquid carbohydrate diet when nauseated.

All patients with diabetes, as well as patients with HIV or schizophrenia, and their caregivers should receive education about medications that may cause or worsen hyperglycemia.[1] [12] [15] [29]

Screening

If a patient is brought to the emergency department with signs and symptoms of hyperglycemia (polyuria, polydipsia, and abdominal pain), volume depletion, acidic breath, and changes in mental status (even without a history of diabetes), then plasma glucose and urine ketones should be checked. In the presence of high plasma glucose and/or positive urine ketones, full diagnostic laboratory evaluations for diabetic ketoacidosis and hyperosmolar hyperglycemic state should be performed.[1] [15]
Case history

Case history #1

A 72-year-old man is brought to the emergency department from a nursing home for progressive lethargy. The patient has a history of hypertension complicated by a stroke 3 years previously. This has impaired his speech and rendered him wheelchair bound. He also has a schizothymic disorder for which he was started recently on clozapine. On presentation, he is disoriented to time and place and febrile with a temperature of 101°F (38.3°C). Vital signs include a BP of 106/67 mmHg, heart rate of 106 beats per minute, and a respiratory rate of 32 breaths per minute. Initial laboratory workup reveals a serum glucose of 950 mg/dL, a serum sodium of 127 mEq/L, BUN of 59 mg/dL, and a serum creatinine of 2.3 mg/dL. Serum osmolality is calculated as 338 mOsm/kg. Urinalysis reveals numerous white blood cells and bacteria. Urine is positive for nitrates but negative for ketones. Serum is negative for beta-hydroxybutyrate.

Case history #2

A 45-year-old African-American man with a history of type 2 diabetes is admitted directly from clinic for a serum glucose of 970 mg/dL. He was started recently on basal bolus insulin therapy after several years of treatment with oral antiglycemic agents. However, he reports not having filled his insulin prescription owing to its high cost. For the past 2 weeks he has had polyuria, polydipsia, and has lost 5 kg in weight. He has also noted a progressively worsening cough for approximately 3 weeks that is productive of greenish brown sputum. On examination, he is febrile with a temperature of 101.3°F (38.5°C), tachypneic (respiratory rate of 24 breaths per minute), and normotensive. Urinalysis reveals trace ketones but serum beta-hydroxybutyrate is not elevated. Serum bicarbonate is 17 mEq/L and venous pH is 7.32.

Other presentations

Up to 20% of patients admitted with hyperosmolar hyperglycemic state (HHS) have previously undiagnosed diabetes.[1] [5] [6] [7] Approximately one third of patients with hyperglycemic crises present with a mixed picture of diabetic ketoacidosis and HHS.[5] Coma is a very rare presentation of HHS. Typically, coma is associated with serum osmolality levels >330 to 340 mOsm/kg and is most often due to hypernatremia rather than hyperglycemia. Occasionally, patients with HHS may present with seizures or hemiparesis.[8] A mild acidemia and ketoacidosis may often be present.

Step-by-step diagnostic approach

Hyperosmolar hyperglycemic state (HHS) usually evolves insidiously over days to weeks.[2] The aim of initial laboratory investigations is to establish the diagnosis and assess the severity. Subsequent investigations are used to identify underlying triggers, such as infection or myocardial infarction (MI).

History and physical examination

Patients usually present with polyuria, polydipsia, polyphagia, weakness, and weight loss.[7] Altered mental status is frequently present on admission,[2] and correlates with the severity of hyperglycemia and serum osmolality. Coma is a very rare presentation of HHS. Typically, coma is associated with serum
osmolality levels >330 to 340 mOsm/kg and is most often hypernatremic rather than hyperglycemic in nature.

Important factors to consider in the patient's past or current medical history include changes or omissions of insulin therapy, recent infection, and recent or previous MI or stroke because these may be precipitants or risk factors for HHS.[1] [15]

It is essential to take a full medication history, in particular looking for recent use of corticosteroids, pentamidine, didanosine, sympathomimetic agents or thiazides, or second-generation (atypical) antipsychotic agents, because these affect carbohydrate metabolism and may participate in the development of hyperglycemic crises.[1] [7] [15]

Physical signs of volume depletion include dry mucus membranes, poor skin turgor, tachycardia, hypotension, and, in severe cases shock. Volume depletion may be difficult to assess in the form of poor skin turgor in older patients. Assessment of the buccal mucosa for dryness is more informative in these patients.[2] [8] Mild hypothermia may be observed in some patients, as a result of peripheral vasodilation.[1] [2] [8] Severe hypothermia is a poor prognostic sign.[1] [2] [8] [15]

Abdominal pain is uncommon in HHS but frequent (>50%) in diabetic ketoacidosis (DKA).[2] [7] Therefore, in patients with hyperglycemic emergencies, the presence of unexplained abdominal pain should guide the clinician toward a diagnosis of DKA rather than HHS.[7] Occasionally, patients with HHS may present with focal neurologic signs (hemianopia and hemiparesis) and seizures (either focal or generalized).[2] [7] [8] This presentation can often be mistaken for acute stroke. However, correction of hyperglycemia with fluid and insulin therapy leads to rapid resolution of these signs in HHS.[7] [8] Epilepsia partialis continua is an unusual form of seizure that is present in 6% of HHS patients in the early phase of HHS.[40] Seizures related to hyperglycemia in HHS are usually resistant to anticonvulsive therapy and phenytoin may further exacerbate HHS.[8]

Initial investigations

The aim of initial laboratory investigations is to establish the diagnosis and assess the severity.

Plasma glucose

- Usually shows severe hyperglycemia (>600 mg/dL).

Blood urea nitrogen (BUN) and creatinine

- Elevated due to volume depletion.

Serum electrolytes[8] [15]

- Serum sodium is usually low owing to the osmotic flux of water from the intracellular to extracellular space in the presence of hyperglycemia. The total sodium deficit is 5 to 13 mEq/kg. Hypernatremia in the presence of hyperglycemia in HHS patients indicates profound volume depletion. To assess the severity of sodium and water deficit, the patient’s corrected sodium can be calculated by adding 1.6 mEq/L of sodium to the measured value for every 100 mg/dL of glucose above 100 mg/dL.[2] Coma, if present, is most often due to hypernatremia rather than hyperglycemia.
- Total potassium deficit is 4 to 6 mEq/kg, owing to increased loss of potassium by diuresis. In spite of the total body potassium deficit, serum potassium is usually elevated. This is because insulin
Hyperosmolar hyperglycemic state

Diagnosis

Insufficiency, hypertonicity, and acidemia cause a large extracellular shift of potassium. A low potassium level on admission indicates severe total-body potassium deficit. Serum chloride levels are usually low. There is usually a total chloride deficit of 5 to 15 mEq/kg; this is secondary to the sodium deficit.

- Serum chloride levels are usually low. There is usually a total chloride deficit of 5 to 15 mEq/kg; this is secondary to the sodium deficit.
- Serum magnesium levels are usually low. There is usually a total magnesium deficit of 1 to 2 mEq/kg, as a result of increased magnesium loss from diuresis.
- Serum calcium levels are usually low. There is usually a total calcium deficit of 1 to 2 mEq/kg, as a result of increased calcium loss from diuresis.
- Serum phosphate levels are usually low. The total body phosphate deficit is 3 to 7 mmol/kg, as a result of increased phosphate loss from diuresis.

Serum osmolality

- Effective serum osmolality is calculated as \(2 \times (\text{measured Na (mEq/L)} + \frac{\text{(glucose (mg/dL))}}{18}) = \text{mOsm/kg.}\) BUN concentration is not taken into account, because it is freely permeable and its accumulation does not change the osmotic gradient.
- Elevated in all patients (≥320 mOsm/kg).

Serum or urinary ketones

- Beta-hydroxybutarate is the main product of ketogenesis, with acetoacetic acids constituting the remainder of the ketones. Beta-hydroxybutarate is converted to acetoacetate over time, which is excreted in the urine. When measuring serum ketones, the nitroprusside reaction will not detect beta-hydroxybutarate. Thus, serum or urine ketones measured by the nitroprusside reaction may be initially negative at the time of presentation, or remain positive when DKA has resolved (giving the appearance that there are no ketones in the serum, or that DKA is not resolving). Therefore, guidelines recommend that, in addition to using the nitroprusside reaction to detect ketones, direct measurement of beta-hydroxybutarate should be undertaken whenever possible.

Anion gap

- Anion gap is calculated as \((\text{Na})-(\text{Cl + HCO}_3)\) (mEq/L). Levels ≥10 to 12 mEq/L signify an anion gap acidosis (i.e., lactic or ketoacidosis).

Serum lactate

- Lactic acid levels can be elevated if concomitant lactic acidosis is present.

Urinalysis

- Urine ketones are usually negative or only mildly positive. Urine glucose is positive. If infection is present, urine will be positive for leukocytes and nitrites; urinary tract infection is a common precipitant of HHS.

Blood gases

- Arterial pH is usually >7.30 and arterial bicarbonate is >15 mEq/L. A venous pH sample is usually 0.03 units lower than arterial pH. Several studies have suggested that the difference between venous and arterial pH samples is not sufficiently significant to change clinical management. Furthermore, venous pH sampling is easier, more convenient, and less painful.

Complete blood count (CBC)
• Leukocytosis is present in hyperglycemic crises. However, leukocytosis of >25,000 per microliter may indicate infection and requires further evaluation.[15]

Liver function tests (LFTs)

• Typically normal. Abnormalities may exist if underlying diseases, such as fatty liver or congestive heart failure, are present.

Additional investigations

Subsequent investigations are used to identify underlying triggers, such as infection or MI, or an alternative diagnosis.

Chest x-ray (CXR)

• Used to exclude pneumonia, a common precipitant of HHS.

ECG

• Should be performed if cardiovascular diseases, such as MI, are suspected as the trigger or if severe electrolyte abnormalities are present.[1] [15] Evidence of hypo- (U waves) or hyperkalemia (tall T waves) may also be present.

Myocardial enzymes

• Should be tested if an MI is suspected as the trigger.

Blood, urine, or sputum cultures

• Used to identify precipitating infections. Further workup for sepsis should be performed if clinically indicated.

Risk factors

Strong infection

• Infection is the major precipitating factor, occurring in 30% to 60% of patients. Urinary tract infections and pneumonia are most commonly reported.[5] [36]

• Counter-regulatory hormones, particularly epinephrine, are increased as a systemic response to infection. They induce insulin resistance, decrease insulin production and secretion, and increase lipolysis, ketogenesis, and volume depletion, thereby contributing to the hyperglycemic crises in patients with diabetes.[1] [15]

Inadequate insulin or oral antidiabetic therapy

• Nonadherence to insulin or oral antidiabetic medication is found in 12% to 25% of patients admitted with hyperosmolar hyperglycemic state (HHS).[5] [6] This association is much higher in urban African-American patients with diabetes, in whom nonadherence is the sole reason for HHS in 42% of cases.[9]
• Alcohol and cocaine abuse is a major contributing factor to nonadherence of diabetic therapy. In one study of urban, underprivileged, African-American patients with HHS, alcohol abuse was seen in 49% of patients and cocaine use was seen in 9%. [9]
• Reduction in the net effective concentration of insulin produces a relative insulin deficiency. The deficiency may trigger HHS if sufficiently large. [1] [9] [15]

**Diagnosis**

**Acute illness in a known patient with diabetes**

• Underlying cardiovascular events, particularly myocardial infarction (MI), provoke the release of counter-regulatory hormones that may result in HHS. [6] [8]
• Stroke, with increased levels of counter-regulatory hormones and compromised access to water and insulin, may contribute to the development of hyperglycemic crises. [6] [8]

**Nursing home residents**

• Restricted water intake in nursing home residents with diabetes places these patients at high risk of developing HHS.
• Diabetes in these patients may go undiagnosed and their bedridden or restrained state with or without altered thirst mechanism predisposes them to severe volume depletion. Multiple comorbid diseases further increase their risk of developing HHS.
• In patients with diabetes, failure to detect hyperglycemia or inappropriate treatment of diabetes, leads to the same sequence of events. [5] [12]

**Weak postoperative state**

• Procedure-related increase in intravenous osmotic load with dextrose-containing fluids can trigger HHS, especially in patients who receive large volumes of dextrose fluid resuscitation (e.g., cardiac or orthopedic procedures). [6] [37] Failure to initiate insulin therapy postoperatively exacerbates the risk.
• Neurosurgical procedures are also associated with HHS, although it remains unclear whether this is a result of direct central nervous system injury, solute load, glucocorticoids, or phenytoin. [8]

**Precipitating medications**

• Medications that have been associated with hyperglycemia, but not directly with HHS, include phenytoin, [26] gatifloxacin, [27] and cimetidine. [28] Drug-induced hyperglycemia has been noted increasingly in HIV clinics; the drugs commonly involved are megestrol, pentamidine, and corticosteroids. [29] The risk of severe hyperglycemia increases with concomitant use of these medications. [30]
• Atypical antipsychotic medications (in particular, clozapine and olanzapine) have also been implicated in producing diabetes and hyperglycemic crises. [31] [32] Possible mechanisms include: induction of peripheral insulin resistance; a direct influence on pancreatic beta-cell function by 5-HT1A/2A/2C receptor antagonism; inhibitory effects through alpha2-adrenergic receptors, or by toxic effects. [7] [32]

**Total parenteral nutrition (TPN)**

• Any patient with a strong family history of diabetes is at high risk of developing HHS on TPN therapy if not treated concomitantly with insulin. [8] [17]
Hyperosmolar hyperglycemic state

Cushing syndrome

• In patients with concomitant diabetes, hypercortisolism leads to insulin resistance and promotes HHS development.[19]
• Ectopic production of adrenocorticotropic hormone has been associated with HHS.[20]

hyperthyroidism

• Hyperthyroidism induces glucose intolerance by lowering insulin levels and peripheral insulin sensitivity.[38] A case series of HHS in hyperthyroidism has been reported.[39]

acromegaly

• A few cases of HHS associated with acromegaly have been reported.[18]

History & examination factors

Key diagnostic factors

altered mental status (common)

• Altered mental status is frequently present on admission,[2] and correlates with the severity of hyperglycemia and serum osmolality.
• Coma is a very rare presentation of hyperosmolar hyperglycemic state (HHS). Typically, coma is associated with serum osmolality levels >330 to 340 mOsm/kg and is most often more hypernatremic than hyperglycemic in nature.

Other diagnostic factors

polyuria (common)

• Symptom of hyperglycemia.

polydipsia (common)

• Symptom of hyperglycemia.

weight loss (common)

• Symptom of hyperglycemia.

weakness (common)

• Symptom of hyperglycemia.

dry mucus membranes (common)

• Sign of volume depletion.

poor skin turgor (common)

• Sign of volume depletion. Volume depletion may be difficult to assess in the form of poor skin turgor in older patients.
• Assessment of the buccal mucosa for dryness is more informative in these patients.[2] [8]

tachycardia (common)

• Sign of volume depletion.
Hyperosmolar hyperglycemic state

**Diagnosis**

**hypotension (common)**
- Sign of volume depletion.

**seizures (common)**
- Seizures are seen in up to 25% of patients and can be either focal or generalized.
- Epilepsia partialis continua is an unusual form of seizure that is present in 6% of HHS patients in the early phase of HHS.[40]
- Seizures related to hyperglycemia in HHS are usually resistant to anticonvulsive therapy and phenytoin may further exacerbate HHS.[8]

**hypothermia (uncommon)**
- Although concomitant infection is common in HHS, patients are usually normothermic or hypothermic owing to peripheral vasodilation.
- Severe hypothermia is a poor prognostic sign.[1] [2] [8] [15]

**shock (uncommon)**
- Sign of volume depletion.

**abdominal pain (uncommon)**
- Abdominal pain is uncommon in HHS but frequent (>50%) in diabetic ketoacidosis (DKA).[2] [7]
  Therefore, in patients with hyperglycemic emergencies, the presence of unexplained abdominal pain should guide the clinician towards a diagnosis of DKA over HHS.[7]

**focal neurologic signs (uncommon)**
- Focal neurologic signs in HHS can be in the form of hemianopia or hemiparesis at presentation.[1] [2] [15]
- This presentation can often be mistaken for acute stroke. However, correction of hyperglycemia with fluid and insulin therapy leads to rapid resolution of these signs in HHS.[7] [8]
## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>plasma glucose level</strong></td>
<td>elevated</td>
</tr>
<tr>
<td>• Plasma glucose is &gt;600 mg/dL</td>
<td></td>
</tr>
<tr>
<td><strong>serum or urinary ketone level</strong></td>
<td>negative or low</td>
</tr>
<tr>
<td>• Beta-hydroxybuturate is the main product of ketogenesis, with acetoacetic acids constituting the remainder of the ketones.</td>
<td></td>
</tr>
<tr>
<td>• When measuring serum ketones, the nitroprusside reaction will not detect beta-hydroxybuturate. Thus, serum or urine ketones measured by the nitroprusside reaction may be initially negative at the time of presentation, or remain positive when diabetic ketoacidosis (DKA) has resolved (giving the appearance that there are no ketones in the serum, or that DKA is not resolving).</td>
<td></td>
</tr>
<tr>
<td>• Guidelines recommend that, in addition to using the nitroprusside reaction to detect ketones, direct measurement of beta-hydroxybutrate should be undertaken whenever possible.</td>
<td>[2] [41]</td>
</tr>
<tr>
<td><strong>serum BUN level</strong></td>
<td>elevated</td>
</tr>
<tr>
<td>• Increased owing to volume depletion.</td>
<td>[15]</td>
</tr>
<tr>
<td><strong>serum creatinine level</strong></td>
<td>elevated</td>
</tr>
<tr>
<td>• Increased owing to volume depletion (pre-renal azotemia).</td>
<td>[15]</td>
</tr>
<tr>
<td><strong>serum sodium level</strong></td>
<td>variable; usually low but hypernatremia may be present</td>
</tr>
<tr>
<td>• Usually low due to osmotic flux of water from the intra- to extracellular space in the presence of hyperglycemia.</td>
<td></td>
</tr>
<tr>
<td>• The total sodium deficit is 5 to 13 mEq/kg. Hypernatremia in the presence of hyperglycemia indicates profound volume depletion.</td>
<td></td>
</tr>
<tr>
<td><strong>serum potassium level</strong></td>
<td>usually elevated; decreased in severe cases</td>
</tr>
<tr>
<td>• The total potassium deficit is 4 to 6 mEq/kg owing to increased diuresis.</td>
<td></td>
</tr>
<tr>
<td>• However, serum potassium is usually elevated owing to extracellular shift of potassium caused by insulin insufficiency, hypertonicity, and acidemia.</td>
<td></td>
</tr>
<tr>
<td>• Low potassium level on admission indicates severe total-body potassium deficit.</td>
<td>[15]</td>
</tr>
<tr>
<td><strong>serum chloride level</strong></td>
<td>usually low</td>
</tr>
<tr>
<td>• The total chloride deficit is 5 to 15 mEq/kg.</td>
<td></td>
</tr>
<tr>
<td><strong>serum magnesium level</strong></td>
<td>usually low</td>
</tr>
<tr>
<td>• The total body deficit of magnesium is usually 1 to 2 mEq/kg owing to increased magnesium loss from diuresis.</td>
<td></td>
</tr>
<tr>
<td><strong>serum calcium level</strong></td>
<td>usually low</td>
</tr>
<tr>
<td>• The total body calcium deficit is usually approximately 1 to 2 mEq/kg owing to increased calcium loss from diuresis.</td>
<td></td>
</tr>
<tr>
<td><strong>serum phosphate level</strong></td>
<td>usually low</td>
</tr>
<tr>
<td>• The total body phosphate deficit is 3 to 7 mmol/kg owing to increased phosphate loss from diuresis.</td>
<td></td>
</tr>
</tbody>
</table>
## Hyperosmolar hyperglycemic state

### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>serum osmolality</strong></td>
<td>≥320 mOsm/kg</td>
</tr>
<tr>
<td>• Effective serum osmolality is calculated as: 2 (measured Na (mEq/L)) + (glucose (mg/dL))/18 = mOsm/kg.[15]</td>
<td></td>
</tr>
<tr>
<td>• BUN concentration is not taken into account, because it is freely permeable and its accumulation does not change the osmotic gradient.[2] [42]</td>
<td></td>
</tr>
<tr>
<td>• Coma, if present, is most often due to hypernatremia rather than hyperglycemia.</td>
<td></td>
</tr>
<tr>
<td><strong>anion gap calculation</strong></td>
<td>variable; usually 7 to 9 mEq/L</td>
</tr>
<tr>
<td>• Anion gap is calculated as (Na)-(Cl + HCO3) as mEq/L.[15]</td>
<td></td>
</tr>
<tr>
<td>• Levels ≥10 to 12 mEq/L signify an anion gap acidosis (i.e., lactic or ketoacidosis).[2]</td>
<td></td>
</tr>
<tr>
<td><strong>serum lactate level</strong></td>
<td>usually normal</td>
</tr>
<tr>
<td>• Serum lactate is &gt;5 mmol/L in lactic acidosis.[15]</td>
<td></td>
</tr>
<tr>
<td>• Lactic acid levels can be elevated if concomitant lactic acidosis is present.[2]</td>
<td></td>
</tr>
<tr>
<td><strong>blood gas</strong></td>
<td>arterial pH usually &gt;7.30; arterial bicarbonate is &gt;15 mEq/L</td>
</tr>
<tr>
<td>• Venous pH sample is usually 0.03 units lower than arterial pH and this difference should be considered.</td>
<td></td>
</tr>
<tr>
<td><strong>urinalysis</strong></td>
<td>variable; positive for glucose; positive for leukocytes and nitrites in the presence of infection; negative or only mildly positive for ketones</td>
</tr>
<tr>
<td>• Infection is the major precipitating factor occurring in 30% to 60% of patients. Urinary tract infections (UTIs) and pneumonia are reported most commonly.[5] [36] Mild ketonuria is sometimes seen.</td>
<td></td>
</tr>
<tr>
<td><strong>liver function tests</strong></td>
<td>usually normal</td>
</tr>
<tr>
<td>• Abnormalities may exist if underlying diseases, such as fatty liver or congestive heart failure, are present.</td>
<td></td>
</tr>
<tr>
<td><strong>CBC</strong></td>
<td>leukocytosis</td>
</tr>
<tr>
<td>• Leukocytosis is present in hyperglycemic crises. However, leukocytosis &gt;25,000 per microliter may indicate infection and requires further evaluations.[15]</td>
<td></td>
</tr>
</tbody>
</table>
### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CXR</strong></td>
<td>The most common infections that precipitate hyperosmolar hyperglycemic state are pneumonia and UTIs.[15]</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>Used to identify precipitating cardiovascular diseases, such as MI, or if severe electrolyte abnormalities are present.[1] [15]</td>
</tr>
<tr>
<td></td>
<td>Evidence of hypo- (U waves) or hyperkalemia (tall T waves) may be present.</td>
</tr>
<tr>
<td>cardiac biomarkers</td>
<td>Should be tested if an MI is suspected as the trigger.</td>
</tr>
<tr>
<td>blood, urine, or sputum cultures</td>
<td>If indicated clinically, further sepsis workup should be performed.[1] [8] [15]</td>
</tr>
</tbody>
</table>
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic ketoacidosis (DKA)</td>
<td>• Patients are often younger and leaner; usually with type 1 diabetes.</td>
<td>• Venous pH &lt;7.3.</td>
</tr>
<tr>
<td></td>
<td>• Abdominal pain is uncommon in hyperosmolar hyperglycemic state (HHS) but frequently seen (&gt;50%) in patients in DKA.[7]</td>
<td>• HCO3 &lt;15 mEq/L; anion gap &gt;12 mEq/L.</td>
</tr>
<tr>
<td></td>
<td>• Patients with ketosis-prone type 2 diabetes are almost exclusively African-American or Hispanic in origin.[43]</td>
<td>• Presence of serum ketones or beta-hydroxybutyrate.</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>• May be clinically indistinguishable from HHS and DKA although most patients do not have a history of diabetes.</td>
<td>• Venous pH &lt;7.3.</td>
</tr>
<tr>
<td></td>
<td>• Sometimes occurs in association with HHS and DKA.</td>
<td>• HCO3 &lt;15 mEq/L; anion gap &gt;12 mEq/L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lactic acid &gt;5 mmol/L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serum glucose and ketones are normal.</td>
</tr>
<tr>
<td>Alcohol ketoacidosis</td>
<td>• A history of chronic alcohol abuse is present.</td>
<td>• Venous pH is variable and can be normal.</td>
</tr>
<tr>
<td></td>
<td>• Produced by starvation due to poor food intake.</td>
<td>• HCO3 &lt;15 mEq/L; anion gap &gt;12 mEq/L.</td>
</tr>
<tr>
<td></td>
<td>• Peripheral signs of chronic liver disease, such as spider nevi, leukonychia, palmar erythema, bruising, jaundice, scratch marks, and hepatomegaly, are present.</td>
<td>• Serum glucose is low or normal but serum ketones or beta-hydroxybutyrate is elevated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lactate levels are usually elevated but elevation is insufficient to account for acidosis.</td>
</tr>
<tr>
<td>Ingestion of toxic substances</td>
<td>• History of ingestion of ethanol, methanol, ethylene glycol (constituent of automobile antifreeze), and/or propylene glycol (diluent in many intravenous medications, such as lorazepam) is present.</td>
<td>• Serum methanol levels will be elevated.[2]</td>
</tr>
<tr>
<td></td>
<td>• Paraldehyde ingestion is suggested by its characteristic strong odor in the breath.[2]</td>
<td>• Calcium oxalate and hippurate crystals in the urine suggest ethylene glycol ingestion.[2]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• These organic toxins can produce an osmolar gap in addition to an anion gap due to their low molecular weight.[2]</td>
</tr>
<tr>
<td>Acetaminophen overdose</td>
<td>• A history of chronic acetaminophen ingestion or acetaminophen overdose is present.</td>
<td>• Urine and serum acetaminophen levels will be positive but not necessarily in the toxic range.</td>
</tr>
</tbody>
</table>
### Condition

#### Differentiating signs / symptoms

- Clinical signs include confusion, tinnitus, hyperventilation, and pulmonary edema.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylate overdose</td>
<td>• A history of chronic salicylate ingestion or salicylate overdose is present.</td>
<td>• Serum salicylate levels will be elevated.</td>
</tr>
<tr>
<td>Seizures</td>
<td>• Patient may have a history of prior seizure events.</td>
<td>• Blood chemistry may be normal.</td>
</tr>
<tr>
<td></td>
<td>• May present with widespread motor manifestations.</td>
<td>• Electroencephalogram (EEG) will show epileptiform activity.</td>
</tr>
<tr>
<td>Stroke</td>
<td>• In most cases, the symptoms of stroke appear rapidly, over seconds or minutes.</td>
<td>• Blood chemistries are normal.</td>
</tr>
<tr>
<td></td>
<td>• Patients may present with limb and/or facial weakness (typically affects face, leg, and arm equally); may show visual disturbance.</td>
<td>• Cranial CT or MRI demonstrates hemorrhage or attenuation.</td>
</tr>
</tbody>
</table>

### Diagnostic criteria

#### Diagnostic features of hyperosmolar hyperglycemic state (HHS)

- Plasma glucose: ≥600 mg/dL
- Osmolality: ≥320 mOsm/kg
- Arterial or venous pH: ≥7.30
- Serum bicarbonate: usually ≥15 mEq/L
- Urine ketone: negative or small
- Serum ketone: negative or small
- Beta-hydroxybutyrate: ≤3 mmol/L
- Effective serum osmolality: ≥320 mOsm/kg
- Variable anion gap: usually <12 mEq/L
- Mental status: lethargy/stupor/coma.

#### Criteria for resolution of HHS

- Plasma glucose <250 to 300 mg/dL
- Plasma effective osmolality <315 mOsm/kg
- Improvement in hemodynamic and mental status.
Step-by-step treatment approach

The main goals of treatment in hyperosmolar hyperglycemic state (HHS) are:

- Restoration of volume deficit. Fluid therapy should be started immediately after initial laboratory evaluations. Infusion of 0.9% sodium chloride should begin at a rate of 1 to 2 L/hour for the first hour.
- Resolution of hyperglycemia.
- Correction of electrolyte abnormalities (the potassium level should be >3.3 mEq/L before initiation of insulin therapy). Use of insulin in a patient with hypokalemia may further decrease serum potassium owing to potassium shifting to the intracellular space, which may result in respiratory paralysis, cardiac arrhythmias, and death.
- Treatment of the precipitating events and prevention of complications.

Although it is possible to manage mild HHS without admission to the intensive care unit (ICU), many cases will require ICU care. Successful treatment requires frequent monitoring of clinical and laboratory parameters to achieve resolution criteria. A treatment protocol and a flow sheet for recording the treatment stages and laboratory data should be maintained.[1] [2] [8] [15]

Diagnosis of precipitating factors, such as urinary-tract infection (UTI), pneumonia, or causative medications, and appropriate treatment with antibiotics, and removal of the offending medication should be sought.[14]

Patients with hemodynamic, cardiovascular, or respiratory instability or altered mental status

The diagnosis of hemodynamic instability is made by observing hypotension and clinical signs of poor tissue perfusion, including oliguria, cyanosis, cool extremities, and altered mental state. These patients require urgent admission to the ICU.

After admission to the ICU, frequent blood pressure and hemodynamic monitoring is needed. A central venous catheter and/or a Swan-Ganz catheterization and continuous percutaneous oximetry are also required. Oxygenation and airway protection are crucial. Intubation and mechanical ventilation are commonly required, with constant monitoring of respiratory parameters.

[VIDEO: Tracheal intubation: animated demonstration ]
[VIDEO: Bag-valve-mask ventilation: animated demonstration ]

Supportive care

Diagnosis of precipitating factors, such as infections or causative medications, and appropriate treatment (e.g., antibiotics for infection or removal of an offending medication) should be performed in all patients, as appropriate.[14] Monitoring of hemodynamic status, respiratory parameters, and urine output are essential, particularly in hemodynamically unstable patients. Frequent glucose monitoring at the bedside should be performed every 1 to 2 hours until hyperglycemia is corrected.

Subsequent to initial laboratory evaluation, serum electrolytes should be checked every 2 to 4 hours, and calcium, magnesium phosphate, BUN, and creatinine checked every 2 to 6 hours, depending on the patient’s clinical condition and response to therapy. Repeated measurement of serum/urine ketone levels is not indicated. A flow sheet classifying these findings as well as mental status, vital signs, insulin dose, fluid, electrolyte therapies, and urine output enables easy analysis of response to therapy and resolution of crises.[1] [8] [15]
Fluid therapy
Patients with severe volume depletion (100 mL/kg or approximately 7 to 9 L, orthostatic or supine hypotension, dry mucus membranes, poor skin turgor) should receive fluid resuscitation in addition to maintenance fluid therapy. Hydration status should be continuously evaluated clinically.

In the setting of severe volume deficit and shock, and in the absence of cardiac compromise, patients should receive 0.9% sodium chloride at a rate of 15 to 20 mL/kg/hour or 1 to 2 L during the first hour.[2] [45] Once hypotension is corrected, fluid resuscitation should be continued with 0.9% sodium chloride at 500 mL/hour for 4 hours, then 250 mL/hour for another 4 hours.[45]

Maintenance fluid therapy is based on the corrected serum sodium level. Corrected sodium (mEq/L) = measured sodium (mEq/L) + 0.016 (glucose (mg/dL)-100).

- In hyponatremic patients: subsequent fluid therapy may be continued with 0.9% sodium chloride at 250 to 500 mL/hour; when plasma glucose reaches 250 to 300 mg/dL, fluid therapy should be changed to 5% dextrose with 0.9% sodium chloride at 150 to 250 mL/hour.[1] [2] [3] [8] [15] [45]
- In hypernatremic or eunatremic patients, subsequent fluid therapy should be changed to 0.45% sodium chloride at 250 to 500 mL/hour; when plasma glucose reaches 250 to 300 mg/dL, it should be changed to 5% dextrose with 0.45% sodium chloride at 150 to 250 mL/hour.[1] [2] [3] [8] [15] [45]

Hyperosmolality therapy
Plasma osmolality is usually greater than 320 mOsm/kg in HHS. A rapid reduction of plasma osmolality can lead to cerebral edema, and it is therefore recommended that plasma osmolality not be lowered by more than 3 mOsm/kg/hour. This can be achieved by monitoring plasma osmolality, adding dextrose to intravenous fluids once plasma glucose falls below 250 to 300 mg/dL, and selecting the correct concentration of intravenous saline depending on serum sodium concentration.[13] [45]

Vasopressors
If hypotension persists after forced hydration, a vasopressor agent should be started. Norepinephrine or dopamine are considered first-line drugs. Dopamine increases stroke volume and heart rate and norepinephrine increases mean arterial pressure.

Insulin therapy
The goal is the steady, gradual reduction of serum glucose and plasma osmolality (to reduce the risk of treatment complications, e.g., hypoglycemia and hypokalemia) by low-dose insulin therapy.

A continuous intravenous infusion of regular insulin is usually recommended if the serum potassium is >3.3 mEq/L. The insulin can be started with a bolus of 0.1 units/kg followed by 0.1 units/kg/hour continuous infusion. Alternatively, a continuous insulin infusion of 0.14 units/kg/hour can be commenced without the initial insulin bolus.[2]

If the serum glucose does not fall by at least 10% in the first hour, then a bolus of 0.14 units/kg of intravenous insulin should be administered, while continuing the previous insulin infusion rate (i.e., either 0.1 units/kg/hour or 0.14 units/kg/hour). Once the blood glucose reaches 300 mg/dL or less, the insulin infusion should be reduced to 0.02 to 0.05 units/kg/hour, while maintaining the blood glucose between 200 and 300 mg/dL, until the patient is mentally alert.[2]
Rapid reductions in blood glucose concentrations must be avoided to prevent sudden osmolar changes and cerebral edema. One series reported that the mean duration of treatment until correction of hyperglycemia is 9 ± 1 hours.[9] Fluid replacement and low-dose insulin therapy decrease plasma glucose concentration at a rate of 50 to 75 mg/dL/hour.

Insulin injection by a sliding scale is no longer recommended in the treatment of HHS.[15]

### Potassium therapy

Insulin therapy and correction of hyperosmolality drive potassium into cells, which may cause serious hypokalemia. The goal is to maintain potassium levels within the normal range in order to prevent complications of hypokalemia, including respiratory paralysis and cardiac dysrhythmia. An adequate urine output of >50 mL/hour should be ensured while the patient is on potassium therapy and the hydration status should be continuously evaluated clinically.

- If baseline serum potassium is <3.3 mEq/L, insulin therapy should be delayed until 40 mEq/L of potassium chloride has been given.
- Potassium replacement should be started at 20 to 40 mEq/L if the baseline serum potassium level is between 3.3 to 5.3 mEq/L.
- If the baseline serum potassium level is >5.3 mEq/L, potassium replacement is not needed but levels should be checked every 2 hours.[1] [15] [45]

### Phosphate therapy

Whole-body phosphate is low in HHS, but routine phosphate replacement has not resulted in clinical benefits to patients.[49] In the presence of severe hypophosphatemia (<1 mg/dL) in patients with cardiac dysfunction (e.g., with signs of left ventricular dysfunction), symptomatic anemia, or respiratory depression (e.g., decreased oxygen saturation), careful phosphate therapy may be indicated to avoid cardiac, respiratory, and skeletal muscle dysfunction.[15]

### Ongoing therapy

Management and monitoring should continue until resolution of HHS. Criteria for resolution of HHS are:[15]

- Plasma glucose <250 to 300 mg/dL
- Plasma effective osmolality <315 mOsm/kg
- Improvement in hemodynamic and mental status.

Once HHS is resolved and the patient is able to tolerate oral intake, transition to subcutaneous insulin needs to be initiated. Patients should be given subcutaneous insulin 1 to 2 hours before the termination of insulin infusion to enable sufficient time for subcutaneous insulin to start work. Intermediate or long-acting insulin is recommended for basal requirements and short-acting insulin for prandial glycemic control.

[VIDEO: Central venous catheter insertion: animated demonstration ]

[VIDEO: Peripheral venous cannulation: animated demonstration ]
### Acute

**all patients**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline serum potassium &lt; 3.3 mEq/L</td>
<td>1st intravenous fluid therapy, plus supportive care ± ICU admission, adjunct vasopressor, plus potassium therapy with frequent serum measurements, plus insulin therapy once serum potassium measurement ≥ 3.3 mEq/L, adjunct phosphate therapy</td>
<td>(summary)</td>
</tr>
<tr>
<td>Baseline serum potassium 3.3 to 5.3 mEq/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline serum potassium &gt; 5.3 mEq/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Ongoing

**HHS resolved and patient able to tolerate oral intake**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st subcutaneous insulin therapy</td>
<td></td>
</tr>
</tbody>
</table>
Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
Acute

all patients

1st intravenous fluid therapy

» In the setting of severe volume deficit and shock, and in the absence of cardiac compromise, patients should receive 0.9% sodium chloride at a rate of 15 to 20 mL/kg/hour or 1 to 2 L during the first hour.[2] [45] Once hypotension is corrected, fluid resuscitation should be continued with 0.9% sodium chloride at 500 mL/hour for 4 hours, then 250 mL/hour for another 4 hours.[45]

» In hyponatremic patients: subsequent fluid therapy may be continued with 0.9% sodium chloride at 250 to 500 mL/hour; when plasma glucose reaches 250 to 300 mg/dL, fluid therapy should be changed to 5% dextrose with 0.9% sodium chloride at 150 to 250 mL/hour.[1] [2] [8] [15] [45]

» In hypernatremic or eunatremic patients, subsequent fluid therapy should be changed to 0.45% sodium chloride at 250 to 500 mL/hour; when plasma glucose reaches 250 to 300 mg/dL, it should be changed to 5% dextrose with 0.45% sodium chloride at 150 to 250 mL/hour.[1] [2] [8] [15] [45]

plus supportive care ± ICU admission

Treatment recommended for ALL patients in selected patient group

» Glucose should be checked every 2 hours and electrolytes, BUN, venous pH, creatinine checked every 2 to 6 hours, until resolution of hyperosmolar hyperglycemic state (HHS). Urinary output should be monitored.

» Diagnosis of precipitating factors (e.g., infection or causative medications) and appropriate treatment with antibiotics and removal of the offending medication should be initiated.[14]

» Patients with hemodynamic, cardiovascular, or respiratory instability or altered mental status may require intensive care unit (ICU) admission with frequent blood pressure and hemodynamic monitoring, a central venous catheter and/or Swan-Ganz catheterization and continuous percutaneous oximetry.

» Oxygenation and airway protection are crucial. Intubation and mechanical ventilation are commonly required, with constant monitoring of respiratory parameters.
### Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>with baseline serum potassium &lt;3.3 mEq/L</td>
<td>plus</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>adjunt vasopressor</td>
</tr>
<tr>
<td></td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td>Primary options</td>
<td></td>
</tr>
<tr>
<td>» norepinephrine: 0.5 to 3 micrograms/minute intravenous infusion initially, adjust according to response, maximum 30 micrograms/minute</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» dopamine: 5-20 micrograms/kg/minute intravenous infusion, adjust according to response</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If hypotension persists after forced hydration, a vasopressor agent should be started.</td>
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</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment recommended for ALL patients in selected patient group</td>
</tr>
<tr>
<td></td>
<td>Insulin therapy and correction of hyperosmolality may cause serious hypokalemia. Insulin therapy should therefore be delayed until 40 mEq/L of potassium has been given with intravenous fluids over 2 hours until serum potassium is ≥3.3 mEq/L.</td>
</tr>
<tr>
<td></td>
<td>Serial potassium measurements should be monitored every 2 hours and the infusion adjusted to give 20 to 40 mEq/L once a serum potassium ≥3.3 mEq/L is achieved.</td>
</tr>
<tr>
<td></td>
<td>Adequate urine output of &gt;50 mL/hour should be ensured and clinical hydration status continuously evaluated.</td>
</tr>
<tr>
<td></td>
<td>Treatment recommended for ALL patients in selected patient group</td>
</tr>
<tr>
<td></td>
<td>plus</td>
</tr>
</tbody>
</table>
**Acute**

<table>
<thead>
<tr>
<th><strong>Primary options</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>» insulin regular: consult local protocol for dose guidelines</td>
</tr>
<tr>
<td>» A continuous intravenous infusion of regular insulin is usually recommended if the serum potassium is &gt;3.3 mEq/L.</td>
</tr>
<tr>
<td>» The insulin can be started with a bolus of 0.1 units/kg followed by 0.1 units/kg/hour continuous infusion. Alternatively, a continuous insulin infusion of 0.14 units/kg/hour can be commenced without the initial insulin bolus.[2]</td>
</tr>
<tr>
<td>» If the serum glucose does not fall by at least 10% in the first hour, then a bolus of 0.14 units/kg of intravenous insulin should be administered, while continuing the previous insulin infusion rate (i.e., either 0.1 units/kg/hour or 0.14 units/kg/hour). Once the blood glucose reaches 300 mg/dL or less, the insulin infusion should be reduced to 0.02 to 0.05 units/kg/hour, while maintaining the blood glucose between 200 and 300 mg/dL, until the patient is mentally alert.[2]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>adjunct phosphate therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td>» Routine phosphate replacement has not resulted in clinical benefits to patients.[49] In the presence of severe hypophosphatemia (&lt;1 mg/dL) in patients with cardiac dysfunction (e.g., with signs of left ventricular dysfunction), symptomatic anemia, or respiratory depression (e.g., decreased oxygen saturation), careful phosphate therapy may be indicated to avoid cardiac, respiratory, and skeletal muscle dysfunction.[15]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>with baseline serum potassium 3.3 to 5.3 mEq/L</strong> plus insulin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
</tr>
</tbody>
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</table>

### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>insulin infusion of 0.14 units/kg/hour can be commenced without the initial insulin bolus.</td>
<td>[2]</td>
</tr>
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» If the serum glucose does not fall by at least 10% in the first hour, then a bolus of 0.14 units/kg of intravenous insulin should be administered, while continuing the previous insulin infusion rate (i.e., either 0.1 units/kg/hour or 0.14 units/kg/hour). Once the blood glucose reaches 300 mg/dL or less, the insulin infusion should be reduced to 0.02 to 0.05 units/kg/hour, while maintaining the blood glucose between 200 and 300 mg/dL, until the patient is mentally alert. | [2] |

<table>
<thead>
<tr>
<th>plus</th>
<th>potassium therapy with frequent serum measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
<td></td>
</tr>
</tbody>
</table>

» Insulin therapy and correction of hyperosmolality may cause serious hypokalemia.

» Potassium chloride therapy at 20 to 40 mEq/L should be administered until serum potassium is 5.3 mEq/L. | [1] [15] |

» An adequate urine output of >50 mL/hour should be ensured while the patient is on potassium therapy and the hydration status should be continuously evaluated clinically.

» Potassium replacement is not needed once the level is >5.3 mEq/L but potassium levels should be checked every 2 hours. | [1] [15] [45] |

<table>
<thead>
<tr>
<th>adjunct</th>
<th>phosphate therapy</th>
</tr>
</thead>
<tbody>
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<td></td>
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</tr>
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<tbody>
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</tr>
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</table>

**Primary options**

» insulin regular: consult local protocol for dose guidelines
Hyperosmolar hyperglycemic state

Treatment

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</tr>
<tr>
<td>» If the serum glucose does not fall by at least 10% in the first hour, then a bolus of 0.14 units/kg of intravenous insulin should be administered, while continuing the previous insulin infusion rate (i.e., either 0.1 units/kg/hour or 0.14 units/kg/hour). Once the blood glucose reaches 300 mg/dL or less, the insulin infusion should be reduced to 0.02 to 0.05 units/kg/hour, while maintaining the blood glucose between 200 and 300 mg/dL, until the patient is mentally alert.[2]</td>
</tr>
</tbody>
</table>

adjunct  phosphate therapy

Treatment recommended for SOME patients in selected patient group

» Routine phosphate replacement has not resulted in clinical benefits to patients.[49] In the presence of severe hypophosphatemia (<1 mg/dL) in patients with cardiac dysfunction (e.g., with signs of left ventricular dysfunction), symptomatic anemia, or respiratory depression (e.g., decreased oxygen saturation), careful phosphate therapy may be indicated to avoid cardiac, respiratory, and skeletal muscle dysfunction.[15]
Ongoing

HHS resolved and patient able to tolerate oral intake

1st subcutaneous insulin therapy

Primary options

» insulin glargine
  -or-
  » insulin detemir
  -or-
  » insulin NPH

--AND--

» insulin lispro
  -or-
  » insulin aspart
  -or-
  » insulin glulisine

» Management and monitoring should continue until resolution of HHS. Criteria for resolution of HHS are plasma glucose <250 mg/dL, plasma effective osmolality <315 mOsm/kg, and an improvement in hemodynamic and mental status.[15]

» Once HHS is resolved transition to subcutaneous insulin is initiated. Subcutaneous insulin should be given 2 hours before the termination of insulin infusion.

» Intermediate or long-acting insulin is recommended for basal requirements and short-acting insulin for prandial glycemic control.

» Patients already on insulin treatment prior to admission may be continued on the same dose.
Recommendations

Monitoring

Successful treatment requires frequent monitoring of clinical and laboratory parameters to achieve resolution criteria. Glucose measurement should be repeated every 1 to 2 hours, and serum potassium every 2 to 4 hours. Serum calcium, magnesium, phosphate, BUN, and creatinine should be repeated every 4 to 6 hours, depending on the patient's clinical condition and response to therapy.

A flow sheet classifying these findings as well as mental status, vital signs, insulin dose, fluid and electrolyte therapies, and urine output enables easy analysis of response to therapy and resolution of crises.[1][14]

Criteria for resolution of hyperosmolar hyperglycemic state include plasma glucose <250 to 300 mg/dL, plasma effective osmolality <315 mOsm/kg, and an improvement in hemodynamic and mental status.[15]

Patient instructions

Sick-day management should be reviewed periodically with all patients. This should include:

- When to contact the healthcare provider
- Blood glucose goals and the use of supplemental short- or rapid-acting insulin during illness
- Means to suppress fever and treat infection.

Patients should be advised to never discontinue insulin during illness and to seek professional advice early.

The patient/family member must be able to accurately measure and record blood glucose, insulin administration, temperature, respiratory rate, and pulses. The frequency of blood-glucose monitoring varies between patients depending upon individual clinical condition.

Further information is available from the American Diabetes Association. [American Diabetes Association: Living with diabetes]
## Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>insulin-related hypoglycemia</td>
<td>short term</td>
<td>high</td>
</tr>
</tbody>
</table>

This iatrogenic complication can occur with excessive high-dose insulin therapy. It can be prevented by following treatment protocols with frequent monitoring of plasma glucose and use of glucose-containing intravenous fluids.[1] [15] [61]

| treatment-related hypokalemia             | short term  | high       |

This iatrogenic complication can occur with excessive high-dose insulin therapy, inadequate potassium replacement, and bicarbonate therapy. It can be prevented by following treatment protocols with frequent monitoring of potassium levels and appropriate replacement.[15] [62]

| stroke                                    | short term  | low        |

Reported as a complication of hyperosmolar hyperglycemic state (HHS). Predisposing factors include volume depletion with increased viscosity, hyperfibrinogenemia, and elevated levels of plasma plasminogen activator inhibitor (PAI-1).[14] [63]

Aggressive early hydration is helpful in reducing the incidence of these complications to approximately 2%. [14] There is no evidence for full anticoagulation. Prophylactic treatment is based on clinical evaluation of risk factors for thromboembolic events.[8]

| myocardial infarction                     | short term  | low        |

Reported as a complication of HHS. Predisposing factors include volume depletion with increased viscosity, hyperfibrinogenemia, and elevated levels of plasma PAI-1.[14] [63]

Aggressive early hydration is helpful in reducing the incidence of these complications to approximately 2%. [14] There is no evidence for full anticoagulation. Prophylactic treatment is based on clinical evaluation of risk factors for thromboembolic events.[8]

| pulmonary embolism                        | short term  | low        |

Reported as a complication of HHS. Predisposing factors include volume depletion with increased viscosity, hyperfibrinogenemia, and elevated levels of plasma PAI-1.[14] [63]

Aggressive early hydration is helpful in reducing the incidence of these complications to approximately 2%. [14] There is no evidence for full anticoagulation. Prophylactic treatment is based on clinical evaluation of risk factors for thromboembolic events.[8]

| disseminated intravascular coagulation     | short term  | low        |

Reported as a rare complication of HHS. Predisposing factors include volume depletion with increased viscosity, hyperfibrinogenemia, and elevated levels of plasma PAI-1.[14] [63]

Aggressive early hydration is helpful in reducing the incidence of these complications to approximately 2%. [14] There is no evidence for full anticoagulation. Prophylactic treatment is based on clinical evaluation of risk factors for thromboembolic events.[8]
### Complications

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<tr>
<th>Complication</th>
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</thead>
<tbody>
<tr>
<td>mesenteric vessel thrombosis</td>
<td>short term</td>
<td>low</td>
</tr>
</tbody>
</table>

Reported as a rare complication of HHS. Predisposing factors include volume depletion with increased viscosity, hyperfibrinogenemia, and elevated levels of plasma PAI-1.[14] [63]

Aggressive early hydration is helpful in reducing the incidence of these complications to approximately 2%. [14] There is no evidence for full anticoagulation. Prophylactic treatment is based on clinical evaluation of risk factors for thromboembolic events.[8]

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<tr>
<th>Complication</th>
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</thead>
<tbody>
<tr>
<td>cerebral edema</td>
<td>short term</td>
<td>low</td>
</tr>
</tbody>
</table>

This is rare in adults with HHS. It presents with headache, lethargy, papillary changes, and seizure. Mortality is high.

Mannitol infusion and mechanical ventilation should be used. Cerebral edema can be prevented by avoiding a reduction in plasma osmolality of more than 3 mOsm/kg/hour. This can be achieved by monitoring plasma osmolality, adding dextrose to intravenous fluids once plasma glucose falls below 250 to 300 mg/dL, and selecting the correct concentration of intravenous saline.[13] [45] [64] [65]

<table>
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<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>coma</td>
<td>short term</td>
<td>low</td>
</tr>
</tbody>
</table>

Usually associated with serum osmolality levels >330 to 340 mOsm/kg and is most often more hypernatremic than hyperglycemic in nature.[7] [8]

Intensive care unit admission, close monitoring, and aggressive fluid and insulin therapy are necessary. Many patients may require airway protection and mechanical ventilation.

### Prognosis

Mortality attributed to hyperosmolar hyperglycemic state (HHS) ranges from 5% to 15%. This is mostly owing to the older patient population affected by HHS and their comorbid conditions. Mortality in HHS is rarely caused by the metabolic complications of hyperglycemia but rather relates to the underlying illness. The prognosis of HHS is worsened substantially at the extremes of age and in the presence of coma and hypotension.[8] [15]
Diagnostic guidelines

International

Standards of medical care in diabetes - 2018 [44]
Published by: American Diabetes Association  Last published: 2018

Hyperglycemic emergencies in adults [45]
Published by: Canadian Diabetes Association  Last published: 2018

Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association [2]
Published by: American Diabetes Association  Last published: 2009

Treatment guidelines

International

Standards of medical care in diabetes - 2018 [44]
Published by: American Diabetes Association  Last published: 2018

Hyperglycemic emergencies in adults [45]
Published by: Canadian Diabetes Association  Last published: 2018

Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association [2]
Published by: American Diabetes Association  Last published: 2009

Management of hyperosmolar hyperglycemic state in adults with diabetes [60]
Published by: Joint British Diabetes Societies (JBDS) for Inpatient Care  Last published: 2015
Online resources

1. American Diabetes Association: Living with diabetes (external link)
Key articles


References


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