Hyperosmolar Hyperglycemic State

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Hyperosmolar hyperglycemic state is a life-threatening emergency manifested by marked elevation of blood glucose, hyperosmolarity, and little or no ketosis. With the dramatic increase in the prevalence of type 2 diabetes and the aging population, this condition may be encountered more frequently by family physicians in the future. Although the precipitating causes are numerous, underlying infections are the most common. Other causes include certain medications, noncompliance, undiagnosed diabetes, substance abuse, and coexisting disease. Physical findings of hyperosmolar hyperglycemic state include those associated with profound dehydration and various neurologic symptoms such as coma. The first step of treatment involves careful monitoring of the patient and laboratory values. Vigorous correction of dehydration with the use of normal saline is critical, requiring an average of 9 L in 48 hours. After urine output has been established, potassium replacement should begin. Once fluid replacement has been initiated, insulin should be given as an initial bolus of 0.15 U per kg intravenously, followed by a drip of 0.1 U per kg per hour until the blood glucose level falls to between 250 and 300 mg per dL. Identification and treatment of the underlying and precipitating causes are necessary. It is important to monitor the patient for complications such as vascular occlusions (e.g., mesenteric artery occlusion, myocardial infarction, low-flow syndrome, and disseminated intravascular coagulopathy) and rhabdomyolysis. Finally, physicians should focus on preventing future episodes using patient education and instruction in self-monitoring. (Am Fam Physician 2005;71:1723-30. Copyright© 2005 American Academy of Family Physicians.)

Hyperosmolar hyperglycemic state is a relatively common, life-threatening endocrine emergency that is reported in all age groups,[1] but it most frequently affects older patients with type 2 diabetes.[2] The hallmark of hyperosmolar hyperglycemic state is profound dehydration, marked hyperglycemia, and often some degree of neurologic impairment with mild or no ketosis. Traditionally, hyperosmolar hyperglycemic state and diabetic ketoacidosis (the other result of severe diabetic decompensation; see the Trachtenbarg article[3] on p. 1705 of this issue) have been described as distinct entities; however, one third of patients exhibit findings of both conditions.[2]

Hyperosmolar hyperglycemic state and diabetic ketoacidosis may represent opposite ends of the spectrum of decompensated diabetes that differ in the time of onset, the degree of dehydration, and the severity of ketosis.[4] *Table 1* compares the conditions associated with mild to severe diabetic ketoacidosis with those of hyperosmolar hyperglycemic state.[5]

Over the past few decades, hyperosmolar hyperglycemic state has had many names and acronyms, including nonketotic hypertonicity, hyperosmolar nonketosis, and, most often, hyperosmolar hyperglycemic nonketotic coma. The latter designation is a misnomer, because a mild degree of ketosis often is present, and a true coma is uncommon.

The mortality rate of hyperosmolar hyperglycemic state ranges from 10 to 50 percent,[2,6-10] a considerably higher rate than that of diabetic ketoacidosis (1.2 to 9 percent).[2,7,8] However, true mortality data are difficult to interpret secondary to the high incidence of coexisting diseases. Age, degree of dehydration,[2] hemodynamic instability,[9] underlying precipitating causes, and degree of consciousness[6] all are powerful predictors of a fatal outcome.

Pathophysiology

The initiating event in hyperosmolar hyperglycemic state is glucosuric diuresis. Glucosuria impairs the concentrating capacity of the kidney, further exacerbating water loss. Under normal conditions, the kidneys act as a safety valve to eliminate glucose above a certain

threshold and prevent further accumulation. However, decreased intravascular volume or underlying renal disease decreases the glomerular filtration rate, causing the glucose level to increase. The loss of more water than sodium leads to hyperosmolarity.[10] Insulin is present, but it is not adequate to reduce blood glucose levels, particularly in the presence of significant insulin resistance.[11]

Precipitating Factors

Precipitating factors may be divided into six categories: infections, medications, non-compliance, undiagnosed diabetes, substance abuse, and coexisting diseases *(Table 2)*.[11-17] Infections are the leading cause of hyperosmolar hyperglycemic state (57.1 percent)[6]; the most common infection is pneumonia, often gram negative, followed by urinary tract infection and sepsis.[13] Poor compliance with diabetic medications also is thought to be a frequent cause (21 percent).[6]

Undiagnosed diabetes often is associated with hyperosmolar hyperglycemic state because of failure to recognize early symptoms of the disease. Myocardial infarc-

TABLE 1
Comparison of Diabetic Ketoacidosis to Hyperosmolar Hyperglycemic State

| Variables | Diabetic ketoacidosis | | | Hyperosmolar hyperglycemic state |
	Mild	Moderate	Severe	
Plasma glucose level (mg per dL [mmol per L])	> 250 (13.9)	> 250	> 250	> 600 (33.3)
Arterial pH level	7.25 to 7.30	7.00 to 7.24	< 7.00	> 7.30
Serum bicarbonate level (mEq per L)	15 to 18	10 to < 15	< 10	> 15
Urine or serum ketones	Positive	Positive	Positive	Small or negative
Effective serum osmolality (mOsm per kg)	Variable	Variable	Variable	> 320
Anion gap	> 10	> 12	> 12	Variable
Alternative sensoria in mental obtundation	Alert	Alert, drowsy	Stupor, coma	Stupor, coma

Adapted with permission from Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, et al. Hyperglycemic crises in diabetes. Diabetes Care 2004;27(suppl 1):S95.

tion,[13,16] cerebrovascular accident, pulmonary embolus, and mesenteric thrombosis have been identified as causes of hyperosmolar hyperglycemic state. In one study[18] of an urban population presenting with hyperosmolar hyperglycemic state, the three leading causes were poor compliance with medication, ethanol ingestion, and cocaine use. Long-term steroid use[19] and gastroenteritis[20] are common causes of hyperosmolar hyperglycemic state in children.

Clinical Evaluation

Typically, patients presenting with hyperosmolar hyperglycemic state are older and have undiagnosed diabetes or type 2 diabetes managed by diet and/or oral diabetic medication. They often take medications that aggravate the problem, such as a diuretic that causes mild dehydration. These patients often live alone or may be in a nursing home environment in which they are unable to communicate their needs secondary to restraints, sedation, or coma.[21]

In addition to one or more of the precipitating factors listed in *Table 2*,[11-17] patients with hyperosmolar hyperglycemic state typically present with weakness, visual disturbance, or leg cramps.[10,21] Nausea and vomiting may occur, but are much less frequent than in patients with diabetic ketoacidosis. Eventually, patients develop neurologic symptoms of lethargy, confusion, hemiparesis (often misdiagnosed as cerebrovascular accident), seizures, or coma[10,13,22] that eventually lead to medical care.

Physical findings reveal profound dehydration that is manifested by poor tissue turgor[10] (which may be difficult to evaluate in older patients)[23]; dry buccal mucosa membranes; soft, sunken eyeballs; cool extremities; and a rapid, thready pulse.[10] A low-grade fever often is present. Abdominal distention may occur because of gastroparesis induced by hypertonicity,[23] but resolves quickly following adequate rehydration. Abdominal distention that persists after rehydration may be related to other underlying causes.

Various changes in mental status may manifest, ranging from complete lucidity to disorientation to lethargy to coma. The degree of neurologic impairment is related directly to the effective serum osmolarity,[15] with coma often occurring once the serum osmolarity is greater than 350 mOsm per kg (350 mmol per kg). Seizures are present in up to 25 percent of patients and may be generalized, focal, myoclonic jerking, or movement induced.[23] Hemiparesis may occur,[13,23] but it is reversible with correction of the fluid deficit.

Diagnostic Testing

Initial laboratory findings in patients with hyperosmolar hyperglycemic state include marked elevations in blood glucose (greater than 600 mg per dL [33.3 mmol per L]) and serum osmolarity (greater than 320 mOsm per kg of water [normal = 290 ± 5]), with a pH level greater than 7.30 and mild or absent ketonemia. One half of patients will demon-

> **Typical laboratory findings in hyperosmolar hyperglycemic state include blood glucose levels greater than 600 mg per dL (33.3 mmol per L), serum osmolarity greater than 320 mOsm per kg, pH levels greater than 7.30, and mild or absent ketonemia.**

TABLE 2

Precipitating Factors in Hyperosmolar Hyperglycemic State

Coexisting diseases	Medications
Acute myocardial infarction	Calcium channel blockers
Adrenocorticotropic hormone-producing tumors	Chemotherapeutic agents
Cerebrovascular accident	Chlorpromazine (Thorazine)
Cushing's syndrome	Cimetidine (Tagamet)
Hyperthermia	Diazoxide (Hyperstat)
Hypothermia	Glucocorticoids
Mesenteric thrombosis	Loop diuretics
Pancreatitis	Olanzapine (Zyprexa)
Pulmonary embolus	Phenytoin (Dilantin)
Renal failure	Propranolol (Inderal)
Severe burns	Thiazide diuretics
Thyrotoxicosis	Total parenteral nutrition
Infection	Noncompliance
Cellulitis	Substance abuse
Dental infections	Alcohol
Pneumonia	Cocaine
Sepsis	Undiagnosed diabetes
Urinary tract infection	

Information from references 11 through 17.

TABLE 3
Electrolyte Losses in Hyperosmolar Hyperglycemic State

Electrolytes	Losses
Sodium	7 to 13 mEq per kg
Chloride	3 to 7 mEq per kg
Potassium	5 to 15 mEq per kg
Phosphate	70 to 140 mmol per kg
Calcium	50 to 100 mEq per kg
Magnesium	50 to 100 mEq per kg
Water	100 to 200 mL per kg

Information from reference 10.

strate a mild anion-gap metabolic acidosis (i.e., 10 to 12). If the anion gap is severe (i.e., greater than 12), the differential diagnosis should include lactic acidosis or other entities not related to hyperosmolar hyperglycemic state. Vomiting and use of thiazide diuretics may cause a metabolic alkalosis that could mask the severity of acidosis.[13] Serum potassium levels may be elevated or normal.[13] Creatinine, blood urea nitrogen (BUN), and hematocrit levels are almost always elevated.[24] Hyperosmolar hyperglycemic state produces significant total body losses of many electrolytes *(Table 3)*.[10]

The reported sodium level should be corrected when the patient's glucose level is markedly elevated. The types of fluids administered depend on the corrected serum sodium level,[25] which is calculated using the following formula[13,26]:

Corrected serum sodium =

$$\text{sodium (mEq per L)} + \frac{1.65 \times (\text{glucose [mg per dL]} - 100)}{100}$$

For example, if the reported serum sodium level was 145 mEq per L (145 mmol per L) and the glucose level was 1,100 mg per dL (61.1 mmol per L):

Corrected serum sodium =

$$145 + \frac{1.65 \times (1,100 - 100)}{100} = 145 + 16.5 = 161.5 \text{ mEq per kg}$$

Although some formulas for calculating osmolarity include the BUN level, because it is in equal distribution in the intracellular and extracellular spaces, BUN does not contribute to the "effective" serum osmolarity, which is calculated using the following formula:

Effective serum osmolarity =

$$(2 \times \text{sodium [mEq per L]}) + \frac{\text{glucose (mg per dL)}}{18}$$

Although potassium is included in some formulas, it is not included in the formula recommended by the American Diabetes Association (ADA).

For example, if the sodium level was 150 mEq per L (150 mmol per L), and the glucose level was 1,100 mg per dL:
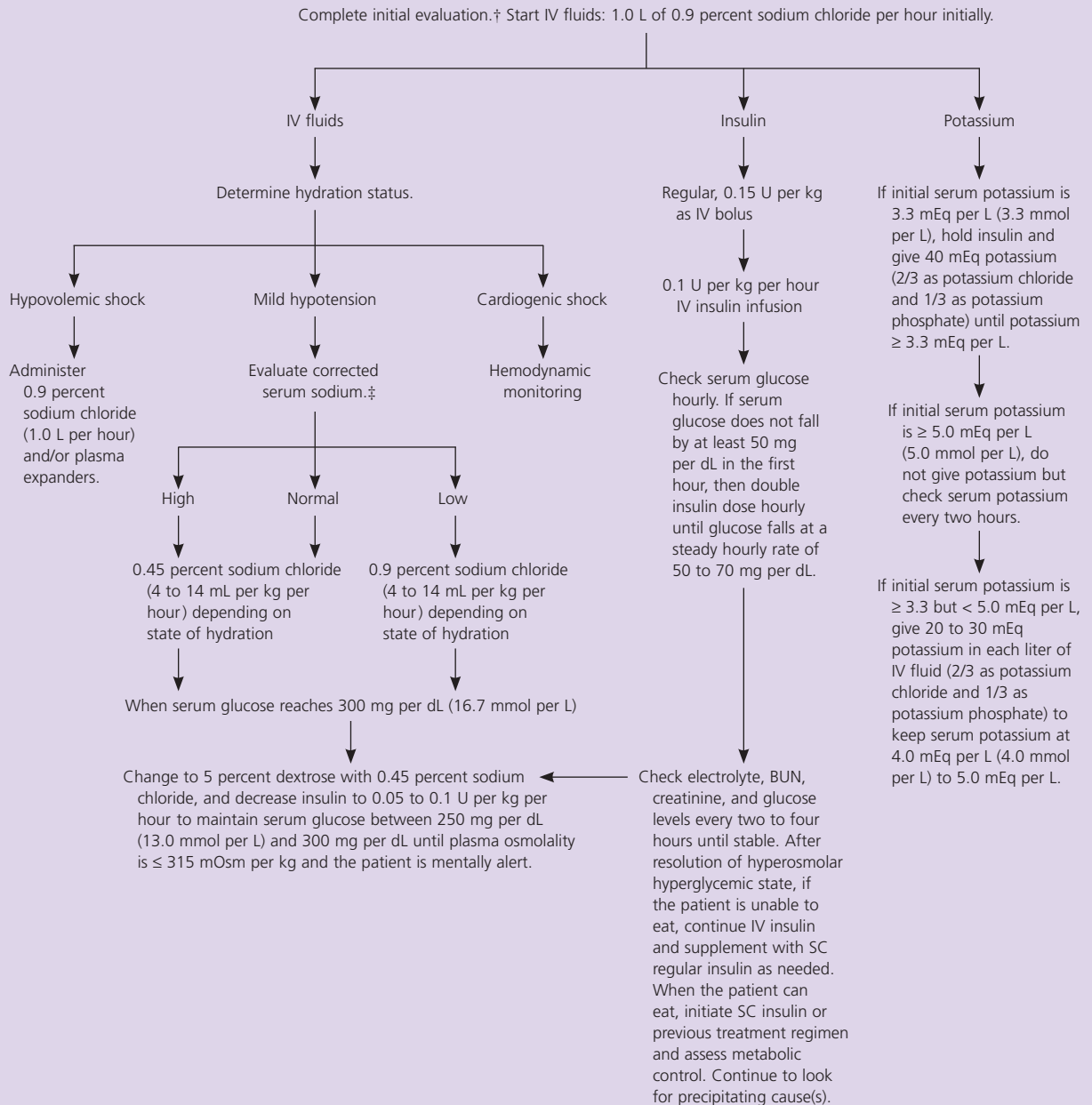
Effective serum osmolarity =

$$(2 \times 150) + \frac{1,100}{18} = 300 + 51 = 351 \text{ mOsm per kg}$$

Treatment

The treatment of hyperosmolar hyperglycemic state involves a five-pronged approach: (1) vigorous intravenous rehydration, (2) electrolyte replacement, (3) administration of intravenous insulin, (4) diagnosis and management of precipitating and coexisting problems, and (5) prevention.[24] An evidence-based algorithm from the ADA that summarizes the management of adults with hyperosmolar hyperglycemic state is shown in *Figure 1*.[5] Patients should be managed in the intensive care environment if they have any cardiovascular instability, are unable to maintain an airway, have obtundation or acute abdominal symptoms, or if they cannot be monitored adequately on the general medical ward.[27]

Management of children with hyperosmolar hyperglycemic state generally follows that of adults. While a detailed discussion of the management of hyperosmolar hyperglycemic state in children and adolescents is beyond the scope of this article, an algorithm from the ADA guideline is included in the Trachtenbarg[3] article on page 1705 of this issue. A chart for the management of patients with hyperosmolar hyperglycemic state is provided in the ADA guideline, and it is available online at http://care.diabetes journals.org/content/vol25/issue90001/images/large/dc1110012004.jpeg.

Management of Adult Patients with Hyperosmolar Hyperglycemic State*

Complete initial evaluation.† Start IV fluids: 1.0 L of 0.9 percent sodium chloride per hour initially.

IV fluids

Determine hydration status.

Hypovolemic shock

Administer 0.9 percent sodium chloride (1.0 L per hour) and/or plasma expanders.

Mild hypotension

Evaluate corrected serum sodium.‡

High

0.45 percent sodium chloride (4 to 14 mL per kg per hour) depending on state of hydration

Normal

Low

0.9 percent sodium chloride (4 to 14 mL per kg per hour) depending on state of hydration

When serum glucose reaches 300 mg per dL (16.7 mmol per L)

Change to 5 percent dextrose with 0.45 percent sodium chloride, and decrease insulin to 0.05 to 0.1 U per kg per hour to maintain serum glucose between 250 mg per dL (13.0 mmol per L) and 300 mg per dL until plasma osmolality is ≤ 315 mOsm per kg and the patient is mentally alert.

Cardiogenic shock

Hemodynamic monitoring

Insulin

Regular, 0.15 U per kg as IV bolus

0.1 U per kg per hour IV insulin infusion

Check serum glucose hourly. If serum glucose does not fall by at least 50 mg per dL in the first hour, then double insulin dose hourly until glucose falls at a steady hourly rate of 50 to 70 mg per dL.

Check electrolyte, BUN, creatinine, and glucose levels every two to four hours until stable. After resolution of hyperosmolar hyperglycemic state, if the patient is unable to eat, continue IV insulin and supplement with SC regular insulin as needed. When the patient can eat, initiate SC insulin or previous treatment regimen and assess metabolic control. Continue to look for precipitating cause(s).

Potassium

If initial serum potassium is 3.3 mEq per L (3.3 mmol per L), hold insulin and give 40 mEq potassium (2/3 as potassium chloride and 1/3 as potassium phosphate) until potassium ≥ 3.3 mEq per L.

If initial serum potassium is ≥ 5.0 mEq per L (5.0 mmol per L), do not give potassium but check serum potassium every two hours.

If initial serum potassium is ≥ 3.3 but < 5.0 mEq per L, give 20 to 30 mEq potassium in each liter of IV fluid (2/3 as potassium chloride and 1/3 as potassium phosphate) to keep serum potassium at 4.0 mEq per L (4.0 mmol per L) to 5.0 mEq per L.

*—Diagnostic criteria: blood glucose level > 600 mg per dL (33.3 mmol per L), arterial pH level > 7.3, bicarbonate level > 15 mEq per L, mild keto-nuria or ketonemia, and effective serum osmolality > 320 mOsm per kg of water. This protocol is for patients admitted with mental status change or severe dehydration who require admission to an intensive care unit. For less severe cases, see text for management guidelines. Normal ranges vary by laboratory; check local laboratory normal ranges for all electrolytes.

Effective serum osmolality calculation: (2 × sodium [mEq per L]) + (glucose [mg per dL] ÷ 18).

†—After history and physical examination, immediately obtain arterial blood gases, complete blood count with differential, urinalysis, plasma glucose, BUN, electrolytes, chemistry profile, creatinine levels, and an electrocardiogram. Obtain chest radiograph and cultures as needed.

‡—Serum sodium should be corrected for hyperglycemia (for each 100 mg per dL of glucose > 100 mg per dL, add 1.6 mEq to sodium value for corrected serum value).

Figure 1. Protocol for the management of adult patients with hyperosmolar hyperglycemic state. (BUN = blood urea nitrogen; IV = intravenous; SC = subcutaneous)

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FLUID REPLACEMENT

The first and most important step in the treatment of hyperosmolar hyperglycemic state is aggressive fluid replacement, which should begin with an estimate of the fluid deficit (usually 100 to 200 mL per kg, or an average total of 9 L).[5,13] The use of isotonic fluids may cause fluid overload and hypotonic fluids may correct deficits too rapidly with a potential for diffuse myelinolysis and death.[13] Therefore, 1 L of normal saline should be given per hour to start. If the patient is in hypervolemic shock, plasma expanders also may be needed. If the patient is in cardiogenic shock, hemodynamic monitoring is required. Details about the addition of potassium to the intravenous fluids are provided in the next section.

Once there is only mild hypotension, the corrected serum sodium level should be calculated. If the corrected serum sodium level is high (greater than 145 mEq per L) or normal (135 mEq per L [135 mmol per L] to 145 mEq per L), then 0.45 percent sodium chloride may be administered at a rate of 4 to 14 mL per kg per hour depending on the state of dehydration. If the corrected serum sodium level is low (less than 135 mEq per L), 0.9 percent sodium chloride is infused at the same rate. When the serum glucose level is less than 300 mg per dL (16.7 mmol per L), the fluid may be changed to 5 percent dextrose solution with 0.45 percent sodium chloride.[13,25] One half of the calculated deficit should be given in the first 18 to 24 hours and the remainder over the next 24 hours.

In adults, the risk of cerebral edema is low and the consequences of undertreatment include vascular occlusion and increased rate of mortality. Good clinical judgment should be employed, especially when the patient has comorbid conditions such as acute myocardial infarction, a history of congestive heart failure, or renal failure. In such cases, close hemodynamic monitoring is indicated.

Early in the course of treatment, the plasma glucose level will decrease, even before insulin is started, and this may serve as an index for the adequacy of fluid replacement.[10] If the plasma glucose level fails to decline by 75 to 100 mg per dL (4.2 to 5.6 mmol per L) per hour, this usually implies inadequate fluid volume or renal impairment.[10]

Children are at greater risk of developing potentially fatal cerebral edema during treatment. For this reason, the rate at which serum tonicity is returned to normal should be somewhat slower than in adults.[28]

ELECTROLYTE MANAGEMENT

Electrolyte replacement is critical. Total body potassium depletion often is unrecognized[10] because the level of potassium in the blood may be normal or high.[13] The serum potassium level may plummet when insulin is replaced because this forces potassium into the cell. Once urine output is established, potassium replacement should be initiated. Electrolytes should be followed closely (every one to two hours initially) and the patient's cardiac rhythm should be monitored continuously.

If the patient's serum potassium level is less than 3.3 mEq per L (3.3 mmol per L) initially, insulin should be held and potassium given as two thirds potassium chloride and one third potassium phosphate until the potassium level reaches at least 3.3 mEq per L. If the potassium level is greater than 5.0 mEq per L (5.0 mmol per L), potassium should be held until the level is less than 5.0 mEq per L, but the potassium level should be monitored every two hours. If the initial serum potassium level is between 3.3 and 5.0 mEq per L, 20 to 30 mEq of potassium should be given in each liter of intravenous fluid (two thirds as potassium chloride, one third as potassium phosphate) to maintain the serum potassium level between 4.0 mEq per L (4.0 mmol per L) and 5.0 mEq per L.[25]

Despite a lack of evidence that treatment

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with phosphate, calcium, or magnesium alters outcomes,[23] these electrolytes must be considered. Most studies[1,5,10] that have examined the need for phosphate replacement involved patients with diabetic ketoacidosis that developed over hours to days. However, because hyperosmolar hyperglycemic state occurs slowly (over days to weeks), the patient is much more likely to be phosphate depleted.

Although phosphate replacement makes physiologic sense, no controlled data have demonstrated improved outcomes.[10] Phosphate replacement may be considered when the patient's serum phosphate level is below 1.0 mEq per L (1.0 mmol per L) and muscle weakness is a concern, as in patients with respiratory impairment. Because phosphate replacement can cause severe hypocalcemia in this setting, serum calcium levels should be monitored closely.[25]

Hypomagnesemia may manifest as arrhythmias, muscle weakness, convulsions, stupor, and agitation. Hypomagnesemia may be present in up to 90 percent of patients with uncontrolled diabetes.[10] Unless the patient is in renal failure, administration of magnesium is safe and physiologic.

INSULIN THERAPY

The critical point regarding insulin management is to remember that adequate fluids must be given first. If insulin is administered before fluids, the water will move intracellularly, causing potential worsening of hypotension, vascular collapse, or death. Insulin should be given as an initial bolus of 0.15 U per kg intravenously, followed by a drip of 0.1 U per kg per hour until the blood glucose level falls to between 250 mg per dL (13.9 mmol per L) and 300 mg per dL. If the glucose level does not decrease by 50 to 70 mg per dL per hour, this rate of administration may be doubled. Once the serum glucose concentration is below 300 mg per dL, dextrose should be added to the intravenous fluid and insulin should be titrated by a low-dose sliding scale until the mental obtundation and hyperosmolarity are resolved. When the patient is able to eat, subcutaneous insulin or the previous treatment regimen may be initiated.[1]

IDENTIFY AND TREAT THE CAUSE

Although routine administration of antibiotics for all patients with suspected infection is not recommended, antibiotic therapy is warranted while awaiting culture results in older patients or in those with hypotension. According to a recent study,[29] elevated C-reactive protein and interleukin-6 levels are early indicators of sepsis in patients with hyperosmolar hyperglycemic state.

It also is important to review any medications that may have precipitated or aggravated the event, and discontinue or reduce the dosage of any suspected agent. Investigation of other causes may be performed as indicated after reviewing the list of precipitating factors listed in *Table 2*.[11-17]

Complications of Treatment

Complications from inadequate treatment include vascular occlusions (e.g., mesenteric artery occlusion, myocardial infarction, low-flow syndrome, and disseminated intravascular coagulopathy)[10,27] and rhabdomyolysis.[11,24,30] Overhydration may lead to adult respiratory distress syndrome and induced cerebral edema, which is rare but often fatal in children and young adults. Cerebral edema should be treated with intravenous mannitol (Osmitrol) in a dose of 1 to 2 g per kg over 30 minutes and intravenous dexamethasone (Decadron). Slowing the correction of hyperosmolarity in children may prevent cerebral edema.[28]

Prevention

The patient and another responsible party should be engaged in a significant educational effort that encourages adherence to blood glucose monitoring and compliance with prescribed medications. It is especially important that the patient have access to an adequate water supply. If the patient lives alone, a family member or friend should check in on the patient daily to watch for any changes in mental status and to notify the physician if this occurs. In the nursing home setting, the above recommendations should be followed and the nursing home staff should be educated regarding the signs and symptoms of hyperosmolar hyperglycemic state and the importance of adequate fluid intake and monitoring.[10,23,24]

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