Current Diagnosis and Treatment of Hyperglycemic Emergencies

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KEYWORDS

• Diabetic ketoacidosis (DKA) • Hyperosmolar hyperglycemic state (HHS)
• Hyperglycemic crisis • Insulin therapy • Electrolyte management

KEY POINTS

- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are 2 hyperglycemic crises frequently encountered in emergency departments.
- DKA, characterized by hyperglycemia, ketonemia, and anion gap metabolic acidosis, results from absolute or relative insulin deficiency and counterregulatory hormone excess.
- HHS, characterized by hyperglycemia, hyperosmolarity, and profound dehydration without significant ketoacidosis, results from prolonged poor glycemic control and inadequate hydration.
- The management of both DKA and HHS hinges on treatment of precipitating illnesses, fluid resuscitation, and correction of hyperglycemia, acidosis, and electrolyte abnormalities.

INTRODUCTION

Hyperglycemia is a common occurrence in emergency department patients. As the number of new cases of diabetes mellitus increases worldwide, emergency providers are frequently faced with hyperglycemic patients and challenges surrounding their care. DKA and HHS are the most feared and life-threatening hyperglycemic emergencies in diabetes. Both of these diseases are associated with uncontrolled diabetes mellitus and may lead to significant neurologic morbidity and death. Early diagnosis and management in an emergency department is paramount to improve patient outcomes. The mainstays of treatment in both DKA and HHS are aggressive rehydration, insulin therapy, electrolyte management, and discovery and treatment of any underlying precipitating events.

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EPIDEMIOLOGY

The prevalence and financial burden of diabetes are tremendous and rising. Approximately 10% of the US population lives with diabetes, and approximately 2 million Americans are diagnosed with diabetes yearly.[1] It is projected that by the year 2050, up to 1 in 3 American adults will be diabetic.[2] An estimated 10% of health care dollars are spent treating diabetes and its complications, and 20% of health care dollars are spent caring for diabetics overall; in 2012, the direct medical costs of treating diabetes totaled $176 billion.[3]

The incidence of DKA has been estimated in older studies to range from 4 to 8 episodes per 1000 patient admissions for diabetes.[4] In 2009, DKA accounted for approximately 140,000 hospitalizations.[5] In the United States, DKA accounts for more than $1 billion in hospital costs per year.[6] The incidence of DKA is much higher among young children and persons of lower socioeconomic status. There is often low family income, poor parental support and patient education levels, and less health insurance coverage with decreased access to care, all contributing to poor compliance and high rates of recurrent DKA.[7]

The incidence of HHS is more difficult to quantify because there have been no population-based studies, but it has been estimated to account for approximately 1% of diabetic admissions.[8] This number is likely an underestimation. The mortality in HHS is much higher, however, ranging from 10% to 20%, compared with 1% to 5% in DKA.[8,9]

PATHOPHYSIOLOGY

DKA and HHS are both characterized by hyperglycemia, which stems from insulin resistance or deficiency of insulin secretion from the pancreas. In DKA, the driving force is insulin insufficiency and a subsequent increase in insulin counterregulatory hormones (ICRHs), which prevents the body from metabolizing carbohydrates.[10,11] Insulin normally stimulates the transference of glucose from the bloodstream into tissues of the body, where it is needed for energy, glycogen storage, and lipogenesis. Insulin also inhibits hepatic gluconeogenesis, preventing further glucose production by the body.[12] When insulin is absent, hepatic gluconeogenesis continues, yet glucose cannot move into the cells and instead builds up in the bloodstream. This elevated glucose leads to osmotic diuresis and dehydration.

In DKA, metabolism shifts from normal carbohydrate metabolism to a state of fasting fat metabolism. There is an increase in the aforementioned ICRHs: glucagon, catecholamines, cortisol, and growth hormones.[13] These stress hormones stimulate lipolysis, which leads to free fatty acid oxidation into the ketone bodies, acetone, acetoacetate, and β-3-hydroxybutyrate, the last being the primary contributor to the resultant metabolic acidosis.[8] The body can initially buffer mild ketonemia, and this results in a mild anion gap with a normal blood pH. Once ketonemia reaches excess of the body's limits, however, it begins to spill into urine and causes an anion gap acidosis with a drop in pH and bicarbonate levels.[8] Respiratory compensation ensues with rapid deep breathing, called Kussmaul respirations. Ketonemia further leads to nausea and vomiting, often worsening dehydration.[8] The course of DKA is usually a quick progression, often occurring in hours to days.

DKA occurs more frequently in type 1 diabetes mellitus; however, it can also occur in non–insulin-dependent (type 2) diabetes mellitus. It is growing increasingly common in type 2 diabetes mellitus, which is thought due to an acute halt of insulin secretion by temporary pancreatic beta islet cell dysfunction and temporary insulin resistance. The condition often resolves after treatment of the acute DKA episode, and patients may

later resume their home oral hypoglycemic agent, not requiring long-term insulin therapy.[14]

Type 2 diabetics are more likely to develop HHS when in a hyperglycemic state. In HHS, there is enough pancreatic production of insulin to prevent the initiation of lipolysis required to generate ketosis and acidemia.[13] There is significantly higher hyperglycemia, however, with associated osmotic diuresis and worsened dehydration compared with DKA. HHS often has a longer and more protracted course, over days to weeks prior to presentation.

In either condition, fluid deficits are significant. Fluid losses in DKA average between 10% and 15% body weight, or approximately 100 mL/kg, for a net loss of between 5 and 7 L.[8,15,16] In HHS, fluid losses average between 20% and 25% body weight, or approximately 100 and 200 mL/kg, for a net loss of between 8 and 12 L.[8,16,17] There are total body losses of important electrolytes through the urine, such as sodium, chloride, and potassium. Initial laboratory measurements may appear falsely elevated secondary to volume contraction.[13]

Causes

Lack of exogenous insulin (noncompliance or undertreatment) and infection are the most common precipitants of DKA and HHS.[8,13] There are many possible triggers, however, for hyperglycemic crisis (**Box 1** lists of the most common precipitating causes for hyperglycemic crisis). Mortality, especially in HHS, is frequently due to an underlying cause rather than the complications of the condition itself; therefore, a thorough investigation for the cause should always be performed.

Differential Diagnosis

There are many disease states that may mimic the presentation of hyperglycemic crisis. DKA can be mimicked by any of the causes of anion gap metabolic acidosis. Similarly, the differential diagnosis for HHS is extensive because it can mimic many other causes of altered mental status. Other causes for confusion, acidosis, and ketosis should be sought out during initial work-up. **Box 2** outlines a list of differential diagnoses. Unfortunately, one of these alternative diagnoses can also be a precipitating event leading to the development of either hyperglycemic crisis. Therefore, it is important to keep a broad differential in acutely ill patients and realize that there may be many other concomitant conditions.

Clinical Presentation

Patients with DKA often present with nonspecific complaints, such as fatigue or classic symptoms of hyperglycemia: polyuria, polydipsia, and weight loss.[10] They commonly present with generalized abdominal pain, nausea, and vomiting, which are due to ketosis or possible decreased mesenteric perfusion secondary to dehydration.[10] Patients with DKA may present with decreased mental status, which may be due to respiratory fatigue, acidosis, or an inciting cause, such as sepsis or cerebrovascular accident (CVA). It is also important to garner a history of any possible inciting events, such as chest pain for an acute myocardial infarction (MI) or neurologic deficits for an acute cerebrovascular event. Any information in review of symptoms to suggest an infectious source, missed medication doses, new medications, or illicit drug use is a vital aspect of history taking.

Similarly, patients with HHS also complain of symptoms of hyperglycemia. The most common presenting symptom for patients with HHS is neurologic deficit. The mainstay of the diagnosis of HHS is the presence of neurologic deficits due to the profound

Box 1
Precipitating factors for hyperglycemic crisis

- Medication noncompliance
- Infection
  - Urinary tract infection
  - Pneumonia
  - Dental abscess
  - Skin infections
  - Sepsis/septic shock
- Cardiovascular incidents
  - MI
  - CVA
- Abdominal inflammation
  - Appendicitis
  - Pancreatitis
- Trauma
- Pregnancy
- Ingestions
  - Cocaine
  - Alcohol abuse
- Medications
  - Sympathomimetics
  - Atypical antipsychotics
  - Corticosteroids
  - Thiazide diuretics

dehydration and hyperosmolarity. It can be as simple as limb weakness or sensory deficits or as complicated as seizures or coma.

On physical examination, patients often present with vital sign abnormalities, such as tachycardia or hypotension, due to volume loss or infection. Patients in DKA may exhibit Kussmaul respirations. The breath may have a classic fruity odor in DKA patients due to acetone exhalation in ketosis,[10] which is absent in HHS. Both DKA and HHS likely show fatigue or lethargy and signs of dehydration with dry mucous membranes and poor skin turgor.

The rest of the physical examination should focus on searching for possible inciting causes. Abdominal examination is a key portion of the assessment to evaluate for additional pathology; however, palpation may reveal diffuse tenderness in DKA patients.[10] Efforts should be made to discern any localized tenderness necessitating further evaluation. Additional history should elicit a search for other physical examination findings to suggest an inciting event, such as pulmonary examination for possible pneumonia and dental, ear, and full skin examination to evaluate for hidden causes of infection, such as oral abscess, otitis media, cellulitis, abscess, or decubitus ulcers.

Box 2
Differential diagnosis in hyperglycemic crisis

- Alcoholic ketoacidosis
- Wernicke encephalopathy
- Seizure/postictal state
- Opiate overdose
- Salicylate toxicity
- Methanol
- Toxic alcohol ingestion
- Paraldehyde ingestion
- Isoniazid
- Lactic acidosis
- Appendicitis
- Pancreatitis
- Pneumonia
- MI
- CVA
- Renal failure

Diagnostic Evaluation

The diagnostic criteria for DKA and HHS are outlined in Table 1. The blood glucose for DKA rarely reaches the elevations seen in HHS, which are frequently greater than 600 mg/dL. Also, the presence of a neurologic deficit is necessary for the diagnosis of HHS. Calculating the serum osmolarity reveals all hyperglycemic patients to also be hyperosmolar. The hyperosmolarity leading to neurologic sequelae requires, however, much more aggressive treatment than simple hyperglycemia.

Initial evaluation should include bedside finger-stick glucose or a chemistry panel, including serum glucose, electrolytes, and serum urea nitrogen (SUN) and creatinine. Preliminary electrolyte evaluation may reveal false hypernatremia or hyperkalemia due

Table 1
Diagnostic criteria for DKA and HHS

	Mild DKA	Moderate DKA	Severe DKA	HHS
Plasma glucose (mg/dL)	>250	>250	>250	>600
pH	7.25–7.3	7.0–7.24	<7.0	>7.3
Serum bicarbonate (mEq/L)	15–18	10–15	<10	>18
Ketones (urine or serum)	Positive	Positive	Positive	Minimal or negative
Anion gap	>10	>12	>12	Variable
Osmolality (mOsm/kg)	Variable	Variable	Variable	>320
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Data from Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32(7):1335–43.

to volume depletion, when in reality hyperglycemic osmotic diuresis causes hyponatremia and hypokalemia.[13] Hyperkalemia occurs when potassium shifts out of cells in exchange for hydrogen ions in an attempt to compensate for acidosis. This may cause the measured potassium to appear artificially normal or elevated when total body potassium levels are depleted due to urinary and gastrointestinal losses.[18]

Despite the official definition of DKA involving serum glucose of greater than 250 mg/dL, there are reported cases of euglycemic DKA with normal to low serum glucose levels of less than 200 mg/dL, also called pseudonormoglycemic DKA. Cases are rare, occurring in 0.8% to 1.1% of DKA episodes.[19] This condition has been seen in pregnancy; in states of fasting or low caloric intake, starvation, persistent vomiting, depression, or extreme hyperlipidemia; and in those with glycogen storage disorders.[18–20] Physiology of true euglycemic DKA (not secondary to insulin administration) is thought to be due to relative insulin deficiency with increased urinary loss of glucose from increased ICRHs or decreased rate of hepatic gluconeogenesis during fasting.[21]

DKA causes an elevated anion gap metabolic acidosis due to ketogenesis, notably from the ketone body β-hydroxybutyrate, followed by acetoacetate.[8] The anion gap is calculated using the measured sodium and not the corrected sodium. **Box 3** contains a list of commonly used calculation. A venous blood gas level should be obtained for serial evaluations of pH. Studies show good correlation between arterial blood gas and venous blood gas measurement and no benefit to arterial versus venous testing in the diagnosis and treatment of DKA in an emergency department.[22] Other sources of anion gap metabolic acidosis may be assessed based on clinical suspicion, such as lactate level for differentiating lactic acidosis, salicylate level, acetaminophen level, SUN, and toxic alcohols.

Serum ketones or β-hydroxybutyrate should be obtained. Urine testing detects only acetoacetate levels meaning that a patient's urine may initially show no or low ketones. Therefore, serum β-hydroxybutyrate is more sensitive compared with urine ketones.[23] Point-of-care bedside β-hydroxybutyrate testing is available as well. These tests have been found as accurate as laboratory methods, which can shorten time to diagnosis of DKA.[7,24,25] Bedside testing may replace serial blood gas measurements in the future.[26] Another quick bedside test is end-tidal capnography. In one study, capnography values greater than 24.5 mm Hg were suggestive of the absence of DKA in hyperglycemic emergency department patients.[27]

HHS has an absence of the major laboratory findings in DKA. There are no anion gap acidosis and no ketones present, unless an alternative cause of these laboratory abnormalities is present concurrently with HHS. The serum osmolarity, however, is elevated. Therefore, serum osmolarity should also be obtained.

Glucose-induced hyponatremia is another side effect of hyperglycemic crisis. Corrected serum sodium in hyperglycemia is routinely calculated with the correction factor of 1.6.[28] Hillier and colleageus,[29] in 1999, however, found more accurate

Box 3
Calculations in DKA and HHS

- Anion gap: [Na (mEq/L) − [Cl (mEq/L) + HCO_3 (mEq/L)]
- Serum osmolality: [2 × measured Na (mEq/L)] + [glucose (mg/dL)/18] + [SUN (mg/dL)/2.8]
- Corrected serum sodium
  - Measured Na (mEq/L) + 0.016 × [glucose(mg/dL) − 100] for glucose <400 mg/dL
  - Measured Na (mEq/L) + 0.024 × [glucose (mg/dL) − 100] for glucose >400 mg/dL

mean correction factor of 2.4, particularly in glucose levels greater than 400. The standard correction factor of 1.6 may still remain accurate for blood glucose up to 400 mg/dL.

TREATMENT

Successful treatment of DKA and HHS involves the correction of hypovolemia, hyperglycemia, ketoacid production, and electrolyte abnormalities and treating any precipitating illnesses. The fluid, electrolyte, and insulin regimens for initial emergency department resuscitation of DKA and HHS share many commonalities.

Fluid Resuscitation

Fluid replacement therapy should be initiated immediately after diagnosis, because further delay while awaiting initial electrolyte results could lead to further deterioration of hemodynamic status. As discussed previously, the osmotic diuresis from hyperglycemia results in significant volume depletion.

Fluid resuscitation serves several functions. Initial resuscitation helps restore depleted intravascular volume, achieve normal tonicity, and decrease the level of ICRHs. Additionally, fluid resuscitation increases tissue/organ perfusion decreasing lactate formation, improves renal perfusion promoting renal excretion of glucose and ketone bodies, and decreases plasma osmolarity by decreasing serum glucose concentration.[6] Mean plasma glucose concentrations have been noted to drop by approximately 25 to 70 mg/dL/h on average, solely in response to saline in the absence of insulin.[12,14] This rate of decrease may be even more pronounced in HHS. The main function in HHS treatment is to restore intravascular volume and decrease plasma osmolarity.

The fluid of choice for initial resuscitation is 0.9% normal saline (NS). Other concentrations of saline are not useful initially. Fluids should be infused as quickly as possible in patients who are in shock. In adult patients without signs of overt shock or heart failure, 1 L of NS may be administered in the first 30 to 60 minutes with a goal of 15 to 20 mL/kg/h over the first 2 hours. Another 2 L of fluid may be given over the following 2 to 6 hours, and an additional 2 L may be given over the following 6 to 12 hours. A good rule of thumb for the subsequent rate of fluid administration is between 250 and 500 mL/h because faster rates have not been shown to be beneficial.[8,30–32] This resuscitation strategy repletes approximately 50% of the fluid losses in the first 12 hours. Similarly, in HHS, due to the larger fluid deficits, the goal is to correct one-half of the fluid deficit in the first 8 to 12 hours. The remaining fluid requirement is addressed in the following 12 to 36 hours during admission.

After initial fluid resuscitation, the subsequent type of fluid replacement should be individualized based on the corrected serum sodium. If hyponatremia is present, continued fluid hydration with 0.9% NS is recommended. If the corrected serum sodium is normal or elevated, consider transitioning using 0.45% NS (half NS). Additionally, the need for concurrent potassium administration may prompt the use of half NS. Addition of potassium to NS results in an overall hypertonic solution, thereby worsening serum osmolarity. In HHS, continued fluid administration with 0.9% NS is also recommended. Maintenance of proper circulating intravascular volume takes precedence over correcting serum osmolarity. The initial resuscitative fluid should be NS even when patients may be initially hypernatremic, because this still corrects the hyperosmolarity due to NS being hypo-osmotic to patients. NS is hyperosmolar relative to the serum when the serum osmolarity is greater than 308 mOsm/L.

Correction of hypernatremia can proceed once initial volume depletion has been corrected with half NS.

In both DKA and HHS, when the plasma glucose level falls to between 250 and 300 mg/dL, dextrose-containing fluids should be initiated. Further reduction in serum glucose below this range is unnecessary. The plasma glucose level tends to fall more rapidly than the plasma ketone level and resultant closure of the anion gap. There is no difference in capillary blood pH or level of bicarbonate when using 5% or 10% glucose solutions, although use of 10% glucose results in a greater level of hyperglycemia[33]; 5% dextrose in half NS at an initial rate of 150 to 250 mL/h is a reasonable first choice. If the serum glucose continues to fall, increasing the concentration to 10% dextrose is recommended.

Insulin

Volume therapy should always precede insulin therapy. Insulin does not need to be started at the time of diagnosis and should never be started until electrolyte results are available to prevent potentially lethal complications.

DKA cannot be reversed without insulin. Insulin therapy also addresses the core physiologic derangements of DKA. Insulin lowers the serum glucose primarily by inhibiting gluconeogenesis rather than enhancing peripheral utilization.[34] Insulin inhibits lipolysis, ketogenesis, and glucagon secretion, thereby decreasing the production of ketoacids. Insulin allows glucose to be used as the substrate for cellular energy production. This causes a steady fall in serum glucose, a decreasing anion gap, and an improvement in serum pH. In HHS, insulin serves primarily to lower the serum glucose and, subsequently, the serum osmolarity.

Continuous intravenous (IV) infusion of regular insulin is the treatment of choice. Traditional insulin regimens list 0.1 U/kg IV bolus and then 0.1 U/kg/h IV continuous infusion. This bolus dosing, or priming, bolus dose, however, prior to continuous infusion has not proved significantly different from just starting a continuous infusion.[8,35] Insulin infused at a rate of 0.14 U/kg/h achieved similar treatment endpoints as the bolus regimen.[36] Therefore, initial insulin infusion can be started with either an IV bolus (0.1 U/kg) followed by a continuous hourly infusion (0.1 U/kg/h) or with a continuous infusion alone (0.14 U/kg/h). This treatment approach mirrors normal physiology and, in combination with fluid therapy, produces a linear, predictable clearance of elevated serum glucose and ketones.

In the first 2 hours of therapy, IV administration results in a more significant decline in serum ketones and glucose compared with other routes.[37] Furthermore, this approach helps to avoid traditional complications (hypoglycemia/hypokalemia) that are more likely with large volume bolus dosing. Advantages of IV insulin administration include ease of titration, short half-life, and physician comfort.

There may be a role for subcutaneous or IV rapid-acting insulin analogs, however, such as glulisine, aspart, and lispro. Initial subcutaneous and intramuscular insulin administration has unpredictable or inadequate absorption in ill DKA/HHS patients who are likely vasoconstricted and volume depleted.[12] Subcutaneous regular insulin has a prolonged half-life and a delayed onset of action. This regimen also raises the possibility of creating an insulin deposit in tissues, which, once adequate perfusion is achieved, is released as a bolus causing a sudden fall in serum glucose. In mild, uncomplicated DKA patients, however, several small studies have demonstrated safety, efficacy, and cost effectiveness (30%–39% reduction) with this approach as well as similar amounts of insulin used, time to resolution of ketoacidosis, rates of hypoglycemia, and total hospital length of stay compared with traditional continuous insulin infusions.[38–43] Cost savings were derived from avoiding the added costs of

care stemming from ICU admission. The method calls for intermittent boluses of 0.1 U/kg of subcutaneous or intramuscular insulin every 1 to 2 hours with frequent monitoring of glucose, electrolytes, and acid-base status. Care should be taken to safely implement this approach because it anticipates that hospital nursing protocols allow for frequent glucose monitoring that is inherently necessary for safe implementation and may not be applicable to most standard hospital floor care. This does represent an important area of investigation as a way to improve emergency department flow during times of hospital crowding and scarce ICU beds.

Secondary insulin resistance is suggested when the serum glucose does not decrease in an expected manner (glucose drop of 50–75 mg/dL in the first hour).[37] In these cases, the insulin infusion can be doubled every hour until a steady decline in serum glucose occurs (beginning with 0.2 U/kg/h). When the fluids are changed to dextrose-containing fluids, the insulin infusion can be reduced to half (0.02–0.05 U/kg/h), with a goal of keeping the serum glucose between 150 and 200 mg/dL until the anion gap has resolved.[44] Alternatively, at this point, the insulin drip may be discontinued and subcutaneous administration of rapid acting insulin may be started (0.1 U/kg) and repeated every 2 hours.[8,45] Subcutaneous insulin can also be started in an emergency department once ketosis has cleared and the patient's overall condition is improved. There may be a role for long-acting insulin analogs during this transition.[46]

Discontinuation of the insulin infusion can be tricky. Because of the short half-life of insulin, abrupt cessation of the insulin supply restarts ketogenesis, rebounding patients into hyperglycemia and metabolic acidosis, and DKA recurs. Appropriate patients for discontinuation of the infusion must have serum glucose below 200 to 250 mg/dL in DKA and between 250 and 300 mg/dL in HHS. Also, DKA patients must have a normal anion gap, venous pH greater than 7.30, and a serum bicarbonate greater than or equal to 18 mEq/L. A long-acting insulin agent, such as glargine, should be administered subcutaneously approximately 30 minutes before a meal and 60 to 120 minutes before discontinuing the continuous insulin infusion. This overlap allows for maintenance of steady serum insulin concentrations and for the insulin to be given at a physiologically appropriate time, preventing both a worsening hyperglycemia and a rebound into DKA. Patients who are unable to eat should continue to receive both IV insulin and fluid replacement. DKA and HHS patients with previously known diabetes can be restarted on their previous insulin regimens. Insulin-naive patients can be started on a subcutaneous multidose insulin regimen (0.5–0.8 U/kg/d).

Potassium

Potassium is the major electrolyte of importance in discussing management of DKA and HHS. Potassium replacement is always necessary, although the timing of repletion differs. Repletion is guided by initial electrolyte measurements and presence of adequate urine output. The average potassium deficit is 3 to 5 mEq/Kg in DKA and 4 to 6 mEq/Kg in HHS, although it may be as high as 10 mEq/kg.[8] The initial potassium level is commonly normal or high despite large total-body deficits.[47,48] This apparent contradiction is due to hyperosmolarity, insulin deficiency, and, to a lesser extent, the intracellular exchange of potassium for hydrogen ions in the setting of severe acidosis. Therefore, initial hypokalemia reflects a very large total-body potassium deficit and clinicians should anticipate very large repletion requirements during the hospital course.

Table 2 contains a potassium repletion guide. Insulin therapy should be held if the initial serum potassium is low (less than 3.3–3.5 mEq/L). Once adequate renal function and urine output are confirmed, hypokalemia is treated by adding 20 to 30 mEq/h of

Table 2
Potassium repletion in DKA and HHS

Serum Potassium (mEq/L)	Repletion
>5.3	No repletion, repeat in 1 h.
4.0–5.3	Add 10 mEq/L KCl/h to IV fluids.
3.5–<4.0	Add 20 mEq/L KCl/h to IV fluids.
<3.5	Hold insulin. Add 20–60 mEq/L/h to IV fluids, place on continuous cardiac monitor.

Data from McNaughton CD, Self WH, Slovis C. Diabetes in the emergency department: acute care of diabetes patients. Clin Diabetes 2011;29(2):51–9.

KCL to 0.45% NS in the IV fluids until the serum potassium is between 3.3 and 3.5 mEq/L.[8,44] In cases of initial hyperkalemia, potassium repletion is normally not necessary during the first several hours of therapy. If the initial potassium level is normal (3.3–5.0 mEq/L), 20 to 30 mEq KCL can be added to each subsequent liter of fluid with a goal of keeping serum potassium in a physiologic normal range (4–5 mEq/L). Total body potassium depletion is usually greater in HHS than in DKA, with an average requirement of 20–30 mEq/h. Furthermore, because there is no underlying acidosis in HHS, the intracellular shift of potassium is accelerated in response to treatment.

Frequent re-evaluation of serum electrolytes is recommended due to the rapid electrolyte shifts that occur during therapy and guides subsequent replacement. In the setting of renal impairment and/or oliguria, potassium replacement must be decreased and should only occur when either the serum potassium is less than 4 mEq/L or an ECG shows signs of hypokalemia. In the setting of profound hypokalemia (<3 mEq/L), due to limitations in the rate of potassium repletion through a peripheral line, peripheral infusion through 2 peripheral lines should be considered. Simultaneous oral potassium replacement has good absorption and is a recommended additional option in the absence of ileus or vomiting.

Bicarbonate

The use of bicarbonate has been long debated, although currently it is not recommended in the treatment of most cases of DKA and has no role in the treatment of HHS.[8,49] Bicarbonate therapy does not alter patient outcomes nor does it increase the rate at which the pH is corrected. Potential risks of bicarbonate use include hypokalemia, rebound metabolic alkalosis, and potential delay in improvement of both hyperosmolarity and ketosis. Furthermore, in patients with DKA with an initial pH less than 7.0, IV bicarbonate therapy did not decrease time to resolution of acidosis or time to hospital discharge.[50] Bicarbonate administration has also been implicated as an increased risk factor for cerebral edema in children.[7,51] Because of the potential adverse cardiovascular effects, the American Diabetes Association guidelines suggest using bicarbonate when the serum pH is less than 6.9 and may likely only apply when patients also have concomitant cardiogenic shock, respiratory failure, or renal failure.[8] Even this recommendation is controversial, however, and there is little supportive evidence.

Phosphate

Hypophosphatemia is common in DKA and HHS. As with potassium, initial phosphate concentration may be normal or elevated due to movement of phosphate out of the cells and dehydration. Furthermore, serum levels fall with institution of insulin therapy. Levels of hypophosphatemia in DKA and HHS are self-limited, however, and are not

associated with marked whole-body phosphate depletion. Furthermore, studies on phosphate repletion in DKA have not demonstrated any benefit on morbidity/mortality or on typical clinical outcome measures for DKA, such as duration of ketoacidosis.[52,53] Therefore, there is no indication for the routine repletion of phosphate for most patients in DKA or HHS.

COMPLICATIONS

Many complications of treatment are evident only later during an ICU stay yet may result from early inappropriate management. Most complications in DKA and HHS are due to either the predisposing or associated condition or the treatment of the hyperglycemia itself. The most common complications are hypoglycemia and hypokalemia. Less common, yet significant, complications include cerebral edema, volume overload, and acute respiratory distress syndrome (ARDS). Emergency providers must be knowledgeable regarding the full course of treatment to avoid such complications.

Cerebral Edema

Cerebral edema is a rare but well-known complication during the resuscitation of patients with DKA although more commonly reported in pediatric patients. Cerebral edema has an approximate incidence of only 1%; however, this is the most common cause of mortality in children with diabetes.[51,54] The mortality rate is between 20% and 40%[8]; 95%, of cases of cerebral edema occurred in patients less than 20 years of age, and one-third of those were in children under 5 years old.[10,55]

The pathophysiology is poorly understood.[8] Risk factors may include pH less than 7.1, P_{CO_2} less than 20 mm Hg, greater than 50 mL/kg of fluid administered within the first 4 hours of treatment, high SUN at presentation, initiation of insulin before initial rehydration bolus, treatment with bicarbonate, and failure of serum sodium to rise as glucose decreases.[51,56] Symptoms can include headache and vomiting and progress to decreased arousal and altered mental status.[51] They may also include Cushing triad, hypertension, bradycardia, and irregular respirations—signs of increased intracranial pressure.[57] Severe cases may progress to decorticate or decerebrate posturing and, finally, herniation and death.[51] Cerebral edema can develop within 4 to 12 hours of initiating treatment.[10]

Treatment involves decreasing intracranial pressure by shifting fluid back out of the central nervous sytem. Therapy should not be delayed to obtain imaging. Initial treatment includes reducing IV fluids and elevating the head of the bed. Mannitol is recommended as soon as possible with dosing of 0.5 to 1 g/kg over 20 minutes.[10,54] This may be repeated if there is no clinical improvement in 30 to 120 minutes[58]; 3% hypertonic saline may also be given at 5 to 10 mL/kg over 30 minutes.[57,59] Be sure to monitor for rising serum sodium, because a falling level is associated with cerebral edema.[56] The best therapy is always prevention.

Pulmonary Edema

Fluid resuscitation in DKA and HHS requires large volumes of IV fluids that may be detrimental, especially to those with underlying cardiac disease or renal insufficiency.[10] Cardiogenic pulmonary edema can occur when the amount of fluid administered overwhelms the capabilities of the heart to pump or the kidneys to excrete it. Careful monitoring of fluid input and urine output should be performed in addition to slow fluid infusion, frequent pulmonary auscultation, and continued pulse oximetry monitoring in those with known disease. Treatment may require diuretics and oxygen

administration with severe cases necessitating either noninvasive positive pressure ventilation or intubation.

Even those without known cardiac disease may develop noncardiogenic pulmonary edema from fluid shifts secondary to excessive or rapid volume repletion.[10,18] ARDS is a rare but potentially fatal complication in DKA that may also present with rales and pulmonary edema.[10,18] It is defined as acute-onset respiratory failure, bilateral infiltrates on chest x-ray, hypoxemia ($Pa_{O_2}/F_{I_{O_2}}$ ratio <200 mm Hg), and no evidence of cardiogenic edema.[60,61] ARDS is thought to develop from the chemical stress of DKA, which can lead to epithelial and endothelial cell damage with neutrophil infiltration and increased vascular permeability with resultant alveolar edema.[60] Patients with ARDS also require slow and lower volume fluid resuscitation and often necessitate mechanical ventilation.[10,60]

DISPOSITION

Most patients with a diagnosis of DKA or HHS require admission to a hospital for treatment, observation, and resolution of the underlying cause or modification to an appropriate medication regimen.

All patients benefit from frequent clinical and laboratory reassessment while in an emergency department for adequate urine output, electrolyte correction, and the absence of fluid overload. Emergency practitioners should anticipate that the fluid, metabolic, and electrolyte deficits be gradually corrected over a period of 18 to 24 hours. Finger-stick glucose should be monitored every hour to prevent hypoglycemia. Basic metabolic panel testing should be obtained every 1 to 2 hours to assess the potassium levels and the anion gap, because they provides a good estimate of the serum ketoacid (anion) levels. Normalization (closure) of the anion gap reflects disappearance of serum ketoacids and correction of the ketoacidosis. Criteria for resolution of DKA include a serum glucose less than 200 mg/dL and at least 2 of the following criteria: normalization of the anion gap, a venous pH greater than 7.3, and a serum bicarbonate level greater than or equal to 15 mEq/L.[30] Ketonemia and ketonuria may persist for 24 to 36 hours due to slower elimination time. In HHS, treatment endpoints indicating resolution include a normalization of serum osmolarity and a corresponding restoration of baseline mental status.

Many of those patients in DKA or HHS should be placed in an ICU or step-down unit to accommodate the requirements of hourly finger-stick glucose and frequent laboratory assessments. Patients who present with sepsis, hypoxia, altered mental status, hypotension, or persistent tachycardia despite fluid resuscitation and those with significant laboratory derangements, such as acidosis or severe electrolyte abnormalities, warrant a higher level of care.[13] Acute comorbidities, such MI or CVA, may also dictate disposition to a cardiac care unit or neurologic unit. Pediatric patients should be admitted to an ICU setting for frequent monitoring and neurologic checks due to increased risk associated with cerebral edema.

Hyperglycemic crisis itself can often be resolved in an emergency department. This is something not often performed in emergency departments. Because of the scarcity of ICU beds, emergency department overcrowding, and longer emergency department stays, however, it is becoming more of a reality to correct patients in emergency departments and lower their level of care. Average time to the resolution of anion gap acidosis is 3 hours.[10] Many patients are stable enough for general floor admission pending improved volume status after resuscitation, closed anion gap, discontinuation of the insulin infusion, and ability to tolerate fluids by mouth. They may be admitted to continue subcutaneous insulin,

monitor minor electrolyte abnormalities, and determine proper medication dosing for later discharge.

Some select patients may be discharged home from an emergency department after an episode of mild DKA with a known cause, such as missed insulin doses, with resolution of hyperglycemia, acidosis, electrolyte abnormalities, normalization of vital signs, and ability to tolerate oral hydration.[13] These patients must have a predetermined insulin regimen with available supplies and medication, a reliable way of checking their blood sugar, and close outpatient follow-up for re-evaluation.

SUMMARY

Diabetes is an increasingly prevalent chronic illness and, along with DKA and HHS, is associated with significant morbidity, mortality, and cost. Both DKA and HHS are complicated hyperglycemic states characterized by dehydration and electrolyte disturbances. The treatment of both conditions must be tailored to individual patients and relies on aggressive fluid resuscitation, strictly monitored insulin replacement, and electrolyte management, while correcting the underlying causes and monitoring for complications.

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