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# Diabetic Emergencies

## Background

Diabetes is a global health problem. More than 400 million people worldwide have type 2 diabetes.[1] The 2014 National Diabetes Statistic Report (available at: https://www.cdc.gov/diabetes/data/statistics/2014StatisticsReport.html) notes that in the United States, 29.1 million people have diabetes, which is about 9% of the population. It is estimated that 27.8% of those people are living with undiagnosed diabetes. Every year, there are 1.7 million new cases of patients with diabetes diagnosed in the United States.[2] Hispanics, non-Hispanic blacks, and Native Americans/Alaskan natives have the highest disease rates. In pediatric patients (those younger than age 20 years), about 207,000 have diabetes, representing 0.25% of the population. Furthermore, it is estimated that in the United States, 81 million patients (37% of the U.S. population) older than the age of 20 years have prediabetes, based on HbA1c and fasting serum glucose concentration.

Many diabetics also have concomitant diseases such as hypertension (71%) and hypercholesterolemia (65%), which require medications. Diabetics have higher rates for cardiovascular disease deaths (1.7), acute myocardial infarction hospitalization (1.8), and cerebrovascular events hospitalizations (1.5). These patients have an increased burden of significant eye disease (retinopathy and macular edema) that has the potential to cause blindness. In the United States, there are more than 250,000 patients with kidney failure due to diabetes living on hemodialysis or with a kidney transplant. Finally, most of the lower limb nontraumatic amputations in the United States are due to diabetes complications. Other conditions associated with diabetes include nerve problems (neuropathies), complications of pregnancy, hearing loss, erectile dysfunction, periodontal disease, and non-alcoholic fatty liver disease.[2]

In 2011, more than 250,000 emergency department (ED) visits for adults listed hypoglycemia as the first diagnosis. In that same year, about 175,000 reported either diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state (HHS) as the first diagnosis. More than 2,300 deaths were reported associated with diabetic emergencies that year. This article focuses on the major diabetic emergencies: diabetic ketoacidosis, hyperosmolar non-ketotic state, and hypoglycemia.

## Diabetic Ketoacidosis

DKA is the pathologic combination of hyperglycemia, ketoacidosis, and dehydration. The condition typically has a rapid onset. The diagnosis and severity of DKA is assessed by analysis of serum values of glucose, pH, bicarbonate, and ketones. (*See Table 1.*) It is more common in the younger age groups, but can occur at any age. In about one-third of cases, it is the presenting condition

## EXECUTIVE SUMMARY

- Suspect diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state (HHS) in an ill patient with hyperglycemia.
- In DKA, the acidosis is prominent.
- In HHS, volume contraction and hyperosmolality are prominent.
- DKA treatment sequence is fluids, potassium (if low), and insulin.
- Identify and treat precipitating causes.
- Point-of-care glucose testing devices may give false values, especially using capillary blood.
- In the treatment of an unresponsive hypoglycemic patient, consider serial 10 mL boluses of D10W every minute until recovery of consciousness instead of one amp (25 mL) of D50.

in new diabetes.[3] The most common presenting symptoms include polyphagia and polyuria, fatigue, dyspnea, weight loss, abdominal pain, and nausea and vomiting.[3] Although DKA has an estimated mortality rate between 1-5%, pediatric patients are at a higher risk of death, often due to cerebral edema.[3]

### Pathophysiology

DKA is caused by the combination of insulin deficit and insulin resistance compounded by a pathologic increase in counter-regulatory stress hormones, namely glucagon, epinephrine, norepinephrine, cortisol, and growth hormone.

Glucose is absorbed into the splanchnic circulation where it is transported to the liver. A portion of the ingested glucose is stored in the liver as glycogen or metabolized, with about two-thirds reaching the systemic circulation. The beta cells of the pancreatic islets detect increased glucose in the arterial blood supply to that organ. Through a second messenger system, it triggers the beta cells of the pancreas to release insulin. Insulin works to lower serum glucose concentration in two ways. First, it drives glucose into cells, allowing the sugar to be used to create ATP. Second, it acts on the liver to stop both the breakdown of glycogen stores into glucose (glycogenolysis) and to inhibit the production of new glucose from non-carbohydrate substrates (gluconeogenesis). Inhibition of glycogenolysis and gluconeogenesis is accomplished by an insulin-mediated decrease in glucagon release from the pancreatic alpha cells. Hyperglycemia results from either absence of insulin, insulin resistance, or, more often, a combination of the two.

In the setting of insulin deficiency or resistance, adipocytes release fatty acids to the circulation. These fatty acids are taken up by hepatocytes, which convert them via beta-oxidation to acetyl-CoA. Some of the acetyl-CoA enters the Krebs cycle to make ATP, and some enters the ketogenic pathway where it is converted into acetoacetic acid. In low insulin and high glucagon states, like the diabetic patient who has not taken his or her medication, the liver's ability to oxidize acetyl-CoA in the Krebs cycle is overwhelmed. The ketone acetoacetic acid accumulates in high levels, some of which is converted to another organic acid (beta-hydroxybutyrate) and some is converted to acetone. Acetone itself is not an acid. These ketone bodies are an important energy source for cellular metabolism, but they also cause an anion gap metabolic acidosis. Ketoacids are excreted in the urine as anions. Urinary excretion decreases the anion gap; however, the ketoacids are excreted as sodium and potassium salts and, thus, their elimination does not benefit systemic acidemia.

Hyperglycemia causes significant dehydration by osmotic diuresis. When serum glucose concentrations exceed the capacity of glomerular filtration, glucose spills into the urine. This elevated osmolarity in the urine results in an osmotic diuresis, in which high volumes of urine are produced. In addition to water, the body endures a net loss of sodium, potassium, calcium, magnesium, chloride, and phosphate. As acidosis develops and worsens, hydrogen ions are buffered inside the cells, and potassium ions move from the intracellular space to the extracellular space to maintain electroneutrality. Thus, patients in DKA may have a total body potassium deficit even when the serum potassium concentration is normal. The above processes combine to produce the classic triad of DKA: hyperglycemia, acidosis, and volume depletion.

### Presentation

The clinical presentation of DKA is variable. Patients may come to the ED seemingly asymptomatic and simply concerned about an elevated glucose reading at home. On the other end of the spectrum are the patients brought in for altered mental status and even coma in severe cases. Typical symptoms are those of hyperglycemia, including polyuria and polydipsia, seen in about 75% of patients with DKA. Dehydration and electrolyte depletion results in fatigue, dry mucus membranes, poor skin turgor, and tachycardia, identified in about 40% of patients. Variable degrees of confusion are seen in about 30% of patients. Acidosis is compensated with rapid and deep breathing (Kussmaul respirations). Ketone bodies cause gastric irritation, which results in abdominal pain in about 25%, and anorexia, nausea, and vomiting in about 75%. Some clinicians may notice a fruity odor of the patient's breath from acetone.[4]

There are four main categories of DKA precipitants. DKA is a classic presentation for new-onset diabetes (both type 1 and type 2), and these constitute about one-third of the DKA cases. The rest of the cases usually are caused by insulin non-compliance or acute illness. Non-compliance can result from complications such as pump failure in patients with insulin delivery pumps. It also can be due to financial problems and psychological factors. Any acute illness can precipitate DKA; however, infection is the most common.[5] DKA also can be triggered by pancreatitis, stroke, and myocardial infarction. The

## Table 1. Definitions of DKA and HHS

| | Mild DKA | Moderate DKA | Severe DKA | HHS |
|---|---|---|---|---|
| Plasma glucose (mg/dL) | > 250 | > 250 | > 250 | > 600 |
| Arterial pH | 7.25 to 7.30 | 7.00 to 7.24 | < 7.00 | > 7.3 |
| Serum bicarbonate (mEq/L) | 15 to 18 | 10 to < 15 | < 10 | > 15 |
| Urine ketones | Positive | Positive | Positive | Minimal |
| Effective serum osmolality (mOsm/kg) | Variable | Variable | Variable | > 320 |
| Anion gap | > 10 | > 12 | > 12 | < 12 |
| Alteration in sensoria or mental status | Alert | Alert/drowsy | Stupor/coma | Drowsy/stupor/coma |

Adapted from *Diabetes Care* 2006;29. Information updated from Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335.

fourth and least prevalent cause of DKA is medications. Implicated drugs include antipsychotics, such as clozapine, risperidone, and olanzapine,[6] in addition to corticosteroids, glucagon, pentamidine, cocaine,[7] lithium, ethanol, and terbutaline.[8] The sodium glucose transporter 2 (SGLT2) inhibitors also have been associated with the development of DKA.[9] The SGLT2 inhibitors are a novel group of medications that inhibit renal resorption of glucose from the kidney, resulting in glycosuria.[1]

**Differential Diagnosis of DKA.** The differential diagnosis of DKA includes alcoholic ketoacidosis (AKA), starvation ketosis, and metformin-associated metabolic acidosis (MALA).

Some conditions may mask the expected biochemical findings in DKA, making the diagnosis sometimes difficult. If there is excessive vomiting, the resulting metabolic alkalosis can raise the serum bicarbonate. Excessive osmotic diuresis may include ketones reducing the anion gap into the normal range. The nitroprusside assay for ketones is 10 times more sensitive to acetoacetate than acetone, but does not detect beta-hydroxybutyrate. In severe DKA, the ratio between beta-hydroxybutyrate to acetoacetate may increase to 6:1, owing to the presence of large concentration of NADH, which favors beta-hydroxybutyrate production. Thus, the nitroprusside reaction may not detect the ketone bodies in severe cases. One of the hallmarks of DKA is hyperglycemia, so a normal or minimally elevated serum glucose is considered a finding which discounts that diagnosis. However, euglycemia, with normal to minimally elevated glucose, is seen sometimes in DKA associated with pregnancy, SGLT2 inhibitors, clozapine, starvation, and gastroparesis.

### Workup

The workup for DKA consists of three parts: establishing the diagnosis, gathering data to direct a treatment plan, and searching for a precipitant. The bare minimum to reach a diagnosis is the presence of an elevated glucose (defined as > 250 mg/dL), finding urinary ketones, and evidence of a high anion gap metabolic acidosis (defined as a pH < 7.3, or an anion gap > 16, or a serum bicarbonate < 18 mEq/L). There is debate about the specific test and level necessary to establish acidosis. The 2009 American Diabetes Association (ADA) position paper on hyperglycemic crises states that arterial blood gas (ABG) is necessary to classify DKA into mild, moderate, or severe.[4] However, a 2005 review in the *Annals of Emergency Medicine* found no difference between ABG and venous blood gas (VBG) in the detection and determination of severity in DKA.[10] Numerous studies have found VBG to be as reliable and accurate as ABG in estimating blood pH.[11] Others, like Josh Farkas, MD, assistant professor of Pulmonary and Critical Care Medicine at the University of Vermont and author of the PulmCrit blog, argue that any ABG measurement is unnecessary.[12] The ADA classification of DKA severity uses either the bicarbonate or the pH to quantify acidemia.[4] The serum bicarbonate and anion gap are adequate for initial assessment, response monintoring, and therapy titration.

The ADA states that serum beta-hydroxybutyrate is the gold standard for establishing ketonemia. Beta-hydroxybutyrate is the main ketone body found in DKA cases. This test is more sensitive than the nitroprusside test performed on serum or urine, which only detects acetone and acetoacetate.[4] However, a positive urine dip often is enough to establish the diagnosis. Some physicians will trend beta-hydroxybutyrate and use this marker to guide insulin titration and potentially discharge from the ED.

Determining serum potassium level is a time-sensitive priority. Patients in DKA are total-body potassium depleted. Insulin will drive extracellular potassium into the cells, thereby lowering serum potassium. Before starting insulin therapy, the serum potassium must be measured and corrected as necessary. There are a few ways to obtain this: in a basic metabolic panel, as a point-of-care (POC) test, and from a venous blood gas. Insulin therapy should be held until the serum potassium level is > 3.3 mEq/L, which is the generally accepted value to define profound hypokalemia.[4]

Initial serum sodium measurements are usually quite low, which results from hyperglycemia and the shift of water from cells into the extracellular space. As this sodium value most often represents a dilutional pseudohyponatremia, the sodium value must be corrected. There is mild disagreement on the

correction factor to be used; values from 1.5 to 2.8 mEq/L for each increase in glucose of 100 mg/dL above 100 mg/dL have been proposed. Most clinicians use the generally accepted value of 1.6 mEq/L for every 100 mg/dL increase in glucose over 100 mg/dL. Normal or elevated uncorrected serum sodium may indicate more profound dehydration.[4]

Evaluation for the DKA precipitant will be different for each patient and should be guided by the findings of the history and physical examination. Keep in mind that a leukocytosis in the 10,000-15,000 cells/$mm^3$ range is expected. White blood cell counts greater than 20,000 and/or the presence of bandemia (100% sensitivity and 80% specificity) should prompt additional evaluation for occult infection.[13] The serum amylase and/or lipase can be elevated in DKA, but such elevations do not necessarily indicate acute pancreatitis.[14]

Elevated transaminases can be seen in DKA. These elevations usually are transient and have not been associated with increased mortality.[15,16] Elevated creatinine kinase and troponins can be seen, and they are not associated with an acute coronary syndrome.[17,18]

## Management

**Overview.** The critical tasks in DKA resuscitation are rehydration and correction of ketoacidosis. Hyperglycemia is corrected in about half the time (average six hours) it takes to correct the ketoacidosis (average 12 hours).[19] Therefore, when the serum glucose falls below 200 mg/dL, dextrose should be added to the infusion to allow continued correction of ketoacidosis while avoiding hypoglycemia.[4] The ADA has published guidelines for the management of DKA for both adults and for patients younger than the age of 20 years.[4]

**Fluids.** The appropriate volume of fluid resuscitation will vary for each patient. In general, calculating a fluid deficit has not been shown to be a useful step in directing resuscitation.[20] First, consider comorbidities. Patients with heart failure or pulmonary hypertension may not tolerate a rapid infusion of large volumes of isotonic fluids. Next, use the physical examination and laboratory studies to determine the patient's volume status. Finally, look at the urine output. Patients should be making at least 0.5 mL/kg per hour of urine.

The ADA recommends initial fluid resuscitation with normal saline for those not in acute heart failure. It advocates starting with a 1 L bolus of 0.9% NaCl in the severely hypovolemic patient. In the mildly dehydrated patient, the guidelines recommend calculating the corrected serum sodium first. For those with normal-high corrected sodium, the recommendation is to use half-normal saline (0.45% saline) at 250-500 mL/hr. For those with a low corrected serum sodium, administer normal saline (NS) at the same rate.[4] (*See Table 2.*)

There is considerable debate, however, about the selection of fluid type for initial resuscitation. Many clinicians have observed worsening of acidemia, as evidenced by decreased serum bicarbonate concentration, after aggressive resuscitation with normal saline. It is thought that this results from the higher chloride ion concentration in NS.[21]

Some evidence suggests possible superiority of Ringer's lactate (lactated Ringer's or LR) and balanced electrolyte solution (BES, e.g., Plasma-lyte) in correcting serum bicarbonate during the first 1-4 hours of treatment. A 2012 randomized, controlled trial (RCT) of 57 patients in DKA compared LR to NS and found a trend toward better correction of acidemia with LR.[22] The difference was not statistically significant, and the authors concluded it was a negative study. However, in the NS group, the average serum bicarbonate dropped during the first hour of treatment (from 8.86 to 8.21 mEq/L). In contrast, the LR group had an increase in average serum bicarbonate during the first hour of treatment (from 7.71 mEq/L to 8.83 mEq/L). A 2011 RCT of 45 patients in DKA showed superiority of BES (Plasma-lyte) in correcting acidosis when compared to NS.[21] After four hours of resuscitation, the mean bicarbonate was 17 mmol/L (95% confidence interval [CI], 15-18) in the NS group and 20 mmol/L (95% CI, 18-21) in the BES group ($P = 0.020$). Despite these biochemical differences, there is no evidence that clinical outcome is better with one of these isotonic fluids compared to the others.

**Insulin.** Insulin is the cornerstone of therapy in DKA and the only way of correcting ketoacidosis. Before insulin became available, DKA was universally fatal. Both intravenous and subcutaneous insulin are effective. Intravenous regular insulin infusion is preferred because its short half-life makes it titratable.[4] Bolusing insulin before starting an infusion has no mortality benefit over infusion alone. For example, a 2008 RCT found that a bolus dose of insulin is not necessary, provided patients receive an insulin infusion of 0.14 units/kg per hour.[23] In 2009, Mazer et al looked at rapid-acting subcutaneous insulin in patients with uncomplicated DKA and found similar outcomes when compared to IV insulin infusions.[24,25]

As a practical consideration, an insulin infusion takes up to an hour to be mixed and delivered to your patient. On the other hand, a 10-unit bolus of regular insulin can be administered immediately after the serum potassium results. For the critically ill DKA patient, the ADA guidelines recommend giving the bolus (0.1 unit/kg) while the pharmacist is mixing the infusion (to be given at 0.1 units/kg per hour). The infusion is continued until the serum glucose concentration falls below 250 mg/dL. At that time, the insulin infusion rate should be decreased, usually by 50%. Continued serum glucose monitoring is necessary, and for those who develop hypoglycemia, an even more reduced infusion rate may be required. The insulin infusion is continued until the acidosis resolves and the serum bicarbonate is normal.[26] (*See Table 2.*) The pediatric guidelines call for an infusion of insulin at 0.05-0.1 units/kg per hour.[27]

**Potassium.** Potassium repletion is less controversial and should follow the current ADA guidelines (*see Table 2*). In a patient with adequate renal function (making > 50 mL/hr), hold insulin and replace potassium until the concentration is > 3.3 mEq/L. For potassium concentrations between 3.3 and 5.2 mEq/L, start the insulin infusion and add 20-30 mEq potassium chloride to each liter of IV fluid. If the potassium is greater than 5.2 mEq/L, start insulin and do not give potassium.[4] The goal of therapy is to maintain a serum

## Table 2. Management of Adult Patients with DKA or HHS

| IV Fluids | Bicarbonate | Regular insulin (DKA) | Regular insulin (HHS) | Potassium | Magnesium | Phosphate |
|---|---|---|---|---|---|---|
| Initial:<br>1 L bolus 0.9 NS (15-20 mL/kg/hr) | pH ≥ 6.9:<br>No need for bicarbonate | Bolus and infusion: 0.1 units/kg IV bolus and 0.1 units/kg/hr IV infusion | Bolus and infusion:<br>0.1 units/kg IV bolus and 0.1 units/kg/hr IV infusion | Establish adequate renal function<br>Keep serum K between 4-5 mEq/L | Mg < 1.8 mEq/L:<br>Give $MgSO_4$ 1 g IV over 1 hour | $PO_4$ < 1 mg/dL:<br>add potassium phosphates 20-30 mEq to one liter of IV fluids |
| Determine hydration status:<br>1. Hypovolemia:<br>1.0 L/hr 0.9 NS IV<br>2. Hypervolemia:<br>Consider hemodynamic monitoring and/or pressors | pH < 6.9:<br>Add 100 mmol $NaHCO_3$ to 400 mL water and 20 mEq KCl and infuse over 2 hours<br>Monitor serum pH and serum K every 2 hours<br>Continue bicarbonate infusion until serum pH ≥ 7 | Infusion only:<br>0.14 units/kg/hr IV infusion | Infusion only:<br>0.14 units/kg/hr IV infusion | K < 3.3 mEq/L:<br>Hold insulin<br>Give KCl 20-30 mEq/h IV until K > 3.3 mEq/L | | |
| Evaluate corrected sodium:<br>1. Elevated or normal:<br>0.45 NS at 250-500 mL/hr<br>2. Low: 0.9 NS at 250-500 mL/hr | | When glucose reaches 200 mg/dL:<br>Reduce regular insulin infusion to 0.02–0.05 units/kg/hr IV<br>OR<br>Give rapid-acting insulin at 0.1 units/kg SC every 2 hours | When glucose reaches 300 mg/dL:<br>Reduce regular insulin infusion to 0.02–0.05 units/kg/hr IV | K between 3.3 and 5.2 mEq/L:<br>Give 20-30 mEq KCl per liter of IV fluids | | |
| 5% Dextrose with 0.45% NaCl at 150-250 mL/hr when glucose reaches 200 mg/dL (DKA) or 300 mg/dL (HHS) | | Maintain serum glucose between 150-200 mg/dL until resolution of ketoacidosis | Maintain serum glucose between 200-300 mg/dL until resolution of hyperosmolarity | K > 5.2 mEq/L:<br>Do not give K<br>Check serum K every 2 hours | | |

Adapted from: Kitabchi AE, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335-1343.

potassium concentration between 4 mEq/L and 5 mEq/L.

**Bicarbonate.** The effect of bicarbonate administration in DKA has been studied over many decades. For patients with pH greater than 6.9, numerous RCTs have shown no benefit.[28] Other studies have raised concerns about the undesirable side effects of bicarbonate therapy in DKA, including hypokalemia, cerebral edema, paradoxical central nervous system acidosis, and decreased oxygen uptake. No RCTs have been done studying the effect of bicarbonate therapy in patients with pH less than 6.9. However, the ADA does advocate its use for these patients.[4] The 2009 position paper states, "Because severe acidosis may lead to numerous adverse vascular effects, it is recommended that adult patients with a pH < 6.9 should receive 100 mmol sodium bicarbonate (two ampules) in 400 mL sterile water (an isotonic solution) with 20 mEq KCl administered at a rate of 200 mL/h for 2 h until the venous pH is > 7.0. If the pH is still < 7.0 after this is infused, we recommend repeating infusion every 2 h until pH reaches ≥ 7.0."[4] (*See Table 2.*)

**Phosphate.** Phosphate should be repleted only in select patients. In DKA, serum phosphate typically is normal or elevated, while total body stores are low. Randomized controlled studies have not shown a benefit from repleting phosphate.[29] Hypocalcemia can result from aggressive phosphate repletion. However, in patients with serum phosphate levels less than 1.0 mg/dL, or those at high risk of cardiac dysrhythmia or respiratory depression, potassium phosphates 20-30 mEq may be added to one liter of IV fluids.[4]

**Magnesium.** Patients with DKA often will have magnesium deficits.

Levels below 1.8 mEq/L should be repleted, starting with 1 g of magnesium sulfate IV over 1 hour. Patients usually are symptomatic with levels below 1.2 mg/dL.[30,31]

### Complications

The most feared complication of DKA is cerebral edema. Fortunately, it is rare (0.5-1% of DKA cases develop this complication), but it carries high mortality (cited by some as > 70%).[26,32] Symptoms of cerebral edema include headache, altered mental status, seizures, lethargy, and hypertension/bradycardia.[33] Risk factors for cerebral edema include young age, lower serum bicarbonate, higher glucose levels, and rapid rehydration.[3] Although not evidence-based, most recommend not reducing the plasma osmolality faster than 3 mOsm/kg per hour.[34,35] The management of cerebral edema includes mannitol and possibly mechanical ventilation, in collaboration with critical care physicians.

Although clinically insignificant, hyperchloremia and non-gap acidosis from excessive use of NS during the initial resuscitation may develop during the convalescent phase of the disease.[26] Hypoxemia and non-cardiogenic pulmonary edema, thought to occur from rapid osmotic shifts, are also possible.[36] Increased risk of venous thromboembolism is thought to occur secondary to disruption of the vascular endothelium from the dehydration and hypertonicity of the serum. In population studies, the risk of venous thromboembolism is just slightly lower than in patients who have undergone orthopedic procedures.[37]

### Prevention

Emergency physicians and providers play a role not only in the treatment of DKA but also in its prevention. As the most common precipitant is absence of exogenous insulin, anything the provider can do to promote diabetes management and compliance will decrease the number of patients presenting to EDs with hyperglycemia, ketoacidosis, and dehydration. Key steps include patient education, arranging rapid follow-up, prescribing affordable and simple insulin regimens, and communicating with primary care physicians.[14]

## Hyperglycemic Hyperosmolar State

### Definition

Hyperglycemic hyperosmolar state (HHS), formerly called hyperosmolar hyperglycemia nonketotic coma (HHNC), is the most serious hyperglycemic complication of type 2 diabetes. The first cases were described in the 1880s by von Frerichs and Dreschfeld.[38] It is generally defined (for example, by the ADA) as a serum glucose concentration > 600 mg/dL, a plasma osmolality > 320 mOsm/kg, and dehydration in the absence of significant ketoacidosis.[4,27,39] (*See Table 1.*) The incidence of HHS is < 1% of patients admitted for diabetes. The mortality is reported at 10-20%, which is about 10 times higher than the mortality for DKA.[38] Although HHS can be seen in any age group, it is seen most commonly in elderly patients.

The older term HHNC was replaced with the HHS terminology. This is due in part to the fact that less than one-third of patients present with coma or significantly altered mentation. In addition, up to 20% of patients can present with mixed features with DKA and have some ketosis.[8]

### Pathophysiology

HHS results from a relative insulin deficit, coupled with high levels of counterregulatory hormones (glucagon, growth hormone, cortisol, epinephrine). This leads to increased gluconeogenesis and glycogenolysis. As the serum glucose increases, the glomerular filtration rate (GFR) also increases, which leads to an osmotic diuresis and glycosuria. Eventually, this excessive diuresis leads to dehydration, which further exacerbates the hyperglycemia.[38] In HHS, endogenous insulin levels are higher than in DKA. This is thought to prevent significant ketogenesis by inhibiting lipolysis.

### Presentation and Precipitating Factors

Although it can occur at every age, HHS occurs more frequently in older type 2 diabetics. In contrast to DKA, it tends to have a slower onset, typically over the course of days. In about 40-60% of reported cases, the precipitating event is infection, with pneumonia and urinary tract infections being the most common. Other acute medical illnesses and trauma, particularly those that result in limited access to water, also can trigger HHS. Acute stroke and myocardial infarctions are two medical problems that are associated with HHS. Several medications are known triggers of HHS, and they overlap with the causes of DKA. HHS also tends to cause more profound mental status changes than DKA.

### Management

Treatment is aimed at correcting the hyperglycemia and hyperosmolality along with the electrolyte derangements. Addressing the precipitating event also is critical.[38] Of note, no RCTs have been conducted on HHS, so all the current protocols are based on data available from DKA.

**Fluids.** Current recommendations use isotonic saline at 15-20 mL/kg for the first 1-2 hours and then half normal saline (0.45 saline solution) at 250-500 mL/hr until symptoms resolve.[26,38] The Pediatric Endocrine Society Guidelines from 2011 recommend 20 mL/kg boluses with normal saline until tissue perfusion is restored.[27] Rehydration alone has been shown to reduce counter-regulatory hormones and restore renal perfusion, both resulting in lowered serum glucose concentrations.[40]

**Insulin.** The current ADA guidelines recommend 0.1 mg/kg bolus of regular insulin, followed by 0.1 units/kg per hour as an infusion until the serum glucose is at 250 mg/dL. At that point, the rate of the insulin infusion should be halved.[26] The pediatric guidelines do not recommend an insulin bolus and simply start an infusion at 0.025 to 0.05 units/kg per hour if the fluids do not cause a drop in serum glucose concentrations.[27]

**Potassium and Other Electrolytes.** Since HHS patients are total body potassium depleted, it is recommended that IV potassium be initiated when the serum potassium falls below 5.5 mEq/L. The target is to maintain a serum potassium between 4-5 mEq/L.[38]

### Outcomes

Rapid and aggressive glucose correction can lead to the development of brain edema.[41] The identification and management of cerebral edema is described in the DKA section. As noted before, the mortality for HHS is higher than that for DKA, and ranges between 10-20%.

## Pearls and Pitfalls

• The diagnosis of DKA hinges on finding the triad of hyperglycemia, volume depletion, and a metabolic acidosis (acidemia). However, there are reported cases of normoglycemic DKA.

• Hypokalemia is an uncommon but worrisome finding. In the setting of a serum potassium < 3.3 mEq/L, potassium replacement must occur before insulin is administered.

• Cerebral edema is a deadly complication of DKA, particularly in pediatric patients. It is estimated to occur in 1% of pediatric DKA cases.[42]

• Venous blood gases are sufficient for most DKA and HHS patients.

• The most common ketone body in DKA is beta-hydroxybutyrate, which is not measured in the urinary nitroprusside-based assays. Those assays measure acetoacetate.

• Insulin boluses are not needed in most DKA or HHS cases. An infusion of 0.14 units/kg per hour is sufficient in most DKA cases.

• Several medications place patients at risk of DKA and HHS: clozapine, risperidone, olanzapine, corticosteroids, glucagon, pentamidine, cocaine, lithium, ethanol, terbutaline, and the sodium glucose transporter 2 (SGLT2) inhibitors have all been implicated.

• Know how to calculate the corrected Na level. The most common correction factor is: Corrected Na = measured Na + 1.6 for every 100 mg/dL increase in glucose over 100 mg/dL.[43]

• HHS usually has an underlying precipitant cause.

## Hypoglycemia

### Symptoms and Presentation

The typical biochemical definition of hypoglycemia includes the basis that most people will show symptoms of hypoglycemia when serum glucose concentration falls below 40-50 mg/dL. These symptoms are typically grouped as neuroglycopenic (weakness, tiredness, dizziness, inappropriate behavior, difficulty with concentration, confusion, blurred vision, and, in extreme cases, coma) and sympathoadrenal (sweating, tremor, tachycardia, anxiety, and a sensation of hunger). However, patients can experience symptoms at higher glucose levels.[44] For people who have diabetes, hypoglycemia is defined as a blood glucose level ≤ 70 mg/dL.[3]

The clinical presentation of hypoglycemia is extremely varied, depending on the patient's age, other medical comorbidities, medication use that can mask symptoms of hypoglycemia, the prior diagnosis of diabetes, and the frequency of poor glucose control. The clinician's ability to measure hypoglycemia at the bedside is affected by the accuracy of capillary glucose measurements.

For non-diabetics, Whipple's triad is used to determine if the patient has hypoglycemia and needs further evaluation. This triad consists of: 1) the signs and symptoms of hypoglycemia; 2) low plasma glucose levels; and 3) clinical improvement of symptoms after plasma glucose levels are normalized.[45]

**Pitfalls of Measuring Capillary Glucose.** For glucose levels > 75 mg/dL, the International Organization for Standardization (ISO) recommends a goal for glucometer error of within 20% when compared with a reference (venous) glucose sample, but for glucose levels < 75 mg/dL, the goal is for 95% of readings to be within 15 mg/dL of the reference. The U.S. Food and Drug Administration (FDA) goal for glucometers is within 20% of the reference value when glucose is greater than 100 mg/dL, and within 20 mg/dL when glucose is less than 100 mg/dL.[46,47] No standard exists, but the ISO guidelines are widely used. To put these numbers into a real life situation, a true glucose level of 55 mg/dL could in fact yield a reading of as low as 40 mg/dL or as high as 70 mg/dL. This is alarming in that a reading around 70 mg/dL could reassure a clinician or patient that glucose is not the issue, when in fact the level could be as low as 55 mg/dL.

Issues also exist when taking into account measurements in the setting of peripheral circulatory failure and severe dehydration, which can be direct results of the diabetic complications of DKA or HHS. This can lead to artificially low capillary blood glucose (CBG) measurements due to poor peripheral circulation, causing the body compensatory mechanism to extract more glucose into the tissues and increasing glucose transit time. Similarly, CBG measurements may not be reliable in patients who have defects in microcirculation, such as those with Raynaud's phenomenon and severe peripheral vascular disease.[48] Critically ill patients with peripheral edema, hypotension, or who require vasopressors also have inaccurate CBG results.[49-51] In critically ill patients who present to the ED, point-of-care glucose measurements are ill-suited to provide accurate measurements and should be followed by venous or arterial glucose measurements.

User error also can influence readings. Unfortunately, the technique of the user is responsible for more inaccuracy than the glucometer itself. Factors that influence accuracy include an insufficient blood sample, old strips, or strips out of date and/or exposed to excess moisture or humidity.[52]

### Hypoglycemia from Insulin: The Somogyi Phenomenon

The Somogyi phenomenon is known as a period of unrecognized hypoglycemia late at night that produces a rebound hyperglycemia when the patient awakens.[1] It occurs around 3 a.m. when the patient is sleeping and can give a false sense of hyperglycemia in the morning.[53] This hyperglycemia can result in an increased morning insulin dose by the patient or their provider. It is important to ask if the patient's primary care physician has recently changed his/her insulin, or if he/she consistently runs high in the morning despite not eating. Treatment includes increasing their food intake or lowering insulin dose in the evening.[53]

### Hypoglycemia from Sulfonylureas

The sulfonylureas (glipizide, glyburide, glimepiride) are medications that are classified as secretagogues because they cause increased secretion of endogenous insulin. As a family, the

sulfonylureas have long half-lives. This drug class is dangerous because of the prolonged and delayed hypoglycemia occurring more than 8-18 hours post ingestion. As an example, glipizide has a time to peak of 6-12 hours, a half-life of 7 hours, and duration of action of 24 hours.[54] It is for this reason that patients with an overdose of sulfonylurea agents require a minimum observation period of 24 hours if hypoglycemia is recurrent in the ED after management of the initial episode.[55-58] Patient populations taking sulfonylureas at highest risk for hypoglycemia include patients with impaired renal function, pediatric patients, and patients naive to hypoglycemic agents.

After correction of hypoglycemia with dextrose solutions, the treatment for sulfonylurea overdose is octreotide, which inhibits insulin release from the pancreas. An RCT concluded that patients receiving octreotide had decreased glucose supplementation requirement.[59] There is no consensus guideline for octreotide dosing in sulfonylurea overdose. However, typical adult recommended doses have ranged from 50-100 µg intravenously or subcutaneously every 12 hours, and pediatric dosages have ranged from 1-1.5 µg/kg intravenously or subcutaneously.[59,60]

## Hypoglycemia in Nondiabetics

Hypoglycemia in the nondiabetic patient may be divided into postprandial or fasting. Postprandial hypoglycemia is caused by alimentary hyperinsulinism, and is seen in patients who have undergone gastrectomies, gastrojejunostomies, pyloroplasties, or vagotomies. In contrast, fasting hypoglycemia involves an intact gastrointestinal tract and is the result of an imbalance in glucose metabolism, specifically implying improper production and consumption. Inadequate glucose production includes abnormal hormone conditions, enzyme defects, liver disease, and drugs. Some examples include insulinomas, exogenous insulin, sulfonylureas, sepsis, extrapancreatic tumors, and enzyme deficiencies.

Pregnancy can be seen as a diabetogenic state. During pregnancy, postprandial glucose levels are elevated and insulin sensitivity is decreased. Fluctuations in insulin levels are due to hormonal changes, most notably cortisol, progesterone, estrogen, prolactin, and human placental lactogen.[61] Glucose level variation complicates insulin replacement during pregnancy, increasing the likelihood of hypoglycemic episodes.[61]

## Management

Patients who are alert, have mild signs and symptoms, and are able to tolerate food can be given oral glucose-containing foods. This can be in the form of graham crackers, orange juice, etc., which can vary by institution. Just two graham crackers or one cup of orange juice contains about 30 g of glucose. The sugar obtained from these snacks often is adequate for resolution of symptoms and improvements of blood sugar levels.

Patients who are exhibiting symptoms and behavior that make oral intake unfeasible or dangerous should be treated with an intravenous bolus of glucose; the most commonly used agent is 50% dextrose (D50W) administered as one 50 mL ampule. Since D50W is hypertonic, it is recommended to push slowly and also only through an IV with good access. It is important to utilize a well-flowing intravenous line, as extravasation of D50W can result in tissue necrosis. It also is important to note that hypoglycemia and hyperglycemia are a delicate balance. D50W has been known to overshoot glycemic targets (on average, the administration of 50 mL of D50W [25 g of dextrose] increases blood glucose to approximately 160 mg/dL,[62] which can be detrimental in the critically ill population).[63] These sudden surges in serum glucose concentrations suppress gluconeogenesis and glycogenolysis, resulting in rebound hypoglycemia.[63]

Concentrated glucose solutions, such as D50W, are not necessary in the treatment of hypoglycemia; a 10% solution (D10W) is adequate, provided an appropriate dose is used. In a 2005 prehospital study, 51 unresponsive hypoglycemic (< 70 mg/dL) patients were randomized to receive IV boluses of either 50 mL of D10W (5 g) or 10 mL of D50W (5 g), with repeat doses every minute until the patient had recovered full consciousness or a total dextrose dose of 25 g had been administered.[64] The study found no difference in time to return to a Glasgow Coma Score of 15 (8 minutes in each arm was the average). The doses of dextrose used were the same in both arms of the study. The mean post-treatment glucose was 111 mg/dL in the D10W group and 169 mg/dL in the D50W group, showing that there is some overshooting of serum glucose concentration with the use of more concentrated dextrose solutions. The rates of rebound hypoglycemia were equal, at 18%.[64,65] In cases of tenuous peripheral IV access and in cases in which overshooting glycemic targets is a concern, a protocol using D10W is a reasonable alternative to the standard D50W bolus.

Special considerations in hypoglycemic patients include alcohol abuse, the pediatric population, and conditions involving no IV access. Thiamine is recommended if alcohol abuse is suspected. Thiamine also should be administered when malnutrition is suspected, such as in patients with eating disorders, cases of hyperemesis gravidarum, and in those who have had bariatric surgery. In these cases, the immediate administration of dextrose is not to be delayed, but the thiamine should be administered around the time of dextrose administration. Dosing of at least 100-200 mg three times daily IV for 3-5 days, followed by oral thiamine 100 mg three times daily for 1-2 weeks is recommended.[66,67] D50W should not be used in the pediatric population because of the risk of venous sclerosis. Patients younger than the age of 8 years should receive 25% (D25W) or even 10% (D10W) dextrose. If IV access cannot be obtained rapidly, intramuscular glucagon 1-2 mg can be given. Glucagon's onset of action is 10-20 minutes, and the peak response occurs in 30-60 minutes. It is important to remember that glucagon is dependent on hepatic glycogen stores and will prove ineffective if glycogen stores are absent, such as in alcohol-induced hypoglycemia.

Of note, in one recent study, up to one-third of ED patients with serum glucose measurements < 50 mg/dL had recurrent or refractory hypoglycemia. Therefore, serial glucose measurements should occur after treatment.

Depending on the clinical situation and the cause of the hypoglycemia, patients either should be offered oral glucose or should be placed on dextrose-containing fluids.[68]

### Disposition

In cases that involve severe hypoglycemic reactions, aspiration and seizure precautions should be implemented. Intravenous correction of hypoglycemia can vary in patient population and with the duration of the hypoglycemic period, with elderly patients having an extended clearance time before full recovery is reached. Type 1 diabetic patients who present with uncomplicated hypoglycemia and make a full recovery in the ED may be discharged, provided the cause was a therapeutic dose of insulin and forgetting to eat. Although rare, patients with an insulin overdose need extended monitoring and treatment. All patients with refractory or recurrent hypoglycemia need admission. As mentioned earlier, any patient presenting with hypoglycemia linked to sulfonylurea use requires at least 24 hours of monitoring because of the drug's extended half-life and duration of action.[56] Patients who are critically ill will be hospitalized because of their condition but could be hypoglycemic due to sepsis, decreased cortisol levels, or malnutrition. In patients satisfying Whipple's triad, causes should be evaluated, and discharge or admission will be determined on a case-by-case basis. Any overdose, suspected or confirmed, should have a mental health evaluation prior to discharge.

It is good practice to give patients a meal before discharge to evaluate their ability to tolerate oral intake and to replenish glycogen stores. If the clinician thinks that the patient has an explanation for the hypoglycemia and responded appropriately, discharge is appropriate. However, any patient discharged from the ED for hypoglycemia should have a very strict follow-up plan to ensure compliance.

## Pearls and Pitfalls

• The diagnosis of hypoglycemia is not always easy. Do not rely on capillary blood glucose levels alone.

• Look for symptoms of neuroglycopenia, which might occur at higher serum glucose concentrations in frail diabetics.

• When in doubt, treat, especially for low-normal serum glucose concentrations. Oral and IV dextrose are low-cost medical interventions that can benefit patients.

• For nondiabetics, use Whipple's triad to determine if the patient has hypoglycemia and needs a workup.

• A point-of-care glucose test using capillary blood in a critically ill patient in the ED with edema, hypotension, or who requires vasopressors has been shown to be inaccurate, especially in the lower areas of the range.

• Sulfonylureas have an extended half-life and cause a delayed hypoglycemia requiring an extended observation period.

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## CME/CE Questions

1. In which of the following patients is starting an insulin infusion the correct next step?
   a. 52-year-old male with a heart rate of 110 and point-of-care glucose in triage of > 500 mg/dL
   b. 52-year-old male with altered mental status, tachypnea, and hyperglycemia; blood gas, urinalysis, and electrolytes have not yet resulted
   c. 52-year-old male with Kussmaul breathing, hyperglycemia; serum sodium is 124 mmol/L, potassium 4.8 mmol/L, and bicarbonate of 10 mmol/L
   d. 52-year-old male in whom you have diagnosed diabetic ketoacidosis; serum sodium is 128 mmol/L, potassium 2.8 mmol/L, and bicarbonate of 10 mmol/L
2. Which of the following patients is most likely in severe DKA?
   a. 20-year-old male with glucose 285 mg/dL, serum sodium 135 mmol/L, potassium 4.8 mmol/L, and bicarbonate of 8 mmol/L
   b. 20-year-old male with glucose 700 mg/dL, serum sodium 124 mmol/L, potassium 3.2 mmol/L, and bicarbonate of 18 mmol/L
   c. 20-year-old male with glucose 480 mg/dL, serum sodium 129 mmol/L, potassium 4.8 mmol/L, and bicarbonate of 13 mmol/L
   d. 20-year-old male with glucose 285 mg/dL, serum sodium 135 mmol/L, potassium 4.8 mmol/L, and bicarbonate of 18 mmol/L
3. Which of the following statements is correct?
   a. A negative urine dip for ketones rules out DKA.
   b. Despite low serum potassium levels, total body potassium is increased in DKA.
   c. Leukocytosis is a common finding in DKA.
   d. With appropriate resuscitation, ketoacidosis corrects before hyperglycemia.
4. Which of the following statements about fluid resuscitation in DKA is correct?
   a. All patients should receive an initial 30 cc/kg bolus of crystalloid regardless of underlying medical problems.
   b. Lactated Ringer's has been conclusively shown to provide superior outcomes in DKA.
   c. Patients in DKA should never receive glucose-containing fluids.
   d. The correct first step for all patients in DKA is assessing their volume status.
5. Which of the following is correct regarding pH measurements in DKA?
   a. An arterial pH must be measured to stratify DKA severity.
   b. Venous blood gas gives a sufficiently accurate measurement of serum pH.
   c. Patients in whom severe DKA is suspected must have an arterial blood gas performed to guide therapy.
   d. The venous blood gas gives inaccurate measurements of both pH and serum bicarbonate.
6. What is the antidote treatment for a sulfonylurea overdose?
   a. Glucagon
   b. Insulin
   c. Octreotide
   d. Vasopressin
   e. None of the above
7. What condition can greatly alter the accuracy of capillary blood glucose levels?
   a. Severe peripheral vascular disease
   b. Vasculitis
   c. Hypotension
   d. Edema
   e. All of the above
8. Which of the following statements regarding HHS is *false*?
   a. HHS has a higher mortality than DKA.
   b. HHS is seen in all age groups but is more common in the elderly.
   c. HHS is most commonly precipitated by medication non-compliance.
   d. HHS has a slower onset than DKA.
9. If D50W is pushed quickly and through a small IV, what can occur?
   a. Hypertension
   b. Tissue necrosis
   c. Hypotension
   d. Faster absorption

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EMERGENCY MEDICINE REPORTS

# Diabetic Emergencies

## Definitions of DKA and HHS

| | Mild DKA | Moderate DKA | Severe DKA | HHS |
|---|---|---|---|---|
| Plasma glucose (mg/dL) | > 250 | > 250 | > 250 | > 600 |
| Arterial pH | 7.25 to 7.30 | 7.00 to 7.24 | < 7.00 | > 7.3 |
| Serum bicarbonate (mEq/L) | 15 to 18 | 10 to < 15 | < 10 | > 15 |
| Urine ketones | Positive | Positive | Positive | Minimal |
| Effective serum osmolality (mOsm/kg) | Variable | Variable | Variable | > 320 |
| Anion gap | > 10 | > 12 | > 12 | < 12 |
| Alteration in sensoria or mental status | Alert | Alert/drowsy | Stupor/coma | Drowsy/stupor/coma |

Adapted from *Diabetes Care* 2006;29. Information updated from Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335.

## Management of Adult Patients with DKA or HHS

| IV Fluids | Bicarbonate | Regular insulin (DKA) | Regular insulin (HHS) | Potassium | Magnesium | Phosphate |
|---|---|---|---|---|---|---|
| Initial:<br>1 L bolus 0.9 NS (15-20 mL/kg/hr) | pH ≥ 6.9:<br>No need for bicarbonate | Bolus and infusion: 0.1 units/kg IV bolus and 0.1 units/kg/hr IV infusion | Bolus and infusion:<br>0.1 units/kg IV bolus and 0.1 units/kg/hr IV infusion | Establish adequate renal function<br>Keep serum K between 4-5 mEq/L | Mg < 1.8 mEq/L:<br>Give $MgSO_4$ 1 g IV over 1 hour | $PO_4$ < 1 mg/dL:<br>add potassium phosphates 20-30 mEq to one liter of IV fluids |
| Determine hydration status:<br>1. Hypovolemia:<br>1.0 L/hr 0.9 NS IV<br>2. Hypervolemia:<br>Consider hemodynamic monitoring and/or pressors | pH < 6.9:<br>Add 100 mmol $NaHCO_3$ to 400 mL water and 20 mEq KCl and infuse over 2 hours<br>Monitor serum pH and serum K every 2 hours<br>Continue bicarbonate infusion until serum pH ≥ 7 | Infusion only:<br>0.14 units/kg/hr IV infusion | Infusion only:<br>0.14 units/kg/hr IV infusion | K < 3.3 mEq/L:<br>Hold insulin<br>Give KCl 20-30 mEq/h IV until K > 3.3 mEq/L | | |
| Evaluate corrected sodium:<br>1. Elevated or normal:<br>0.45 NS at 250-500 mL/hr<br>2. Low: 0.9 NS at 250-500 mL/hr | | When glucose reaches 200 mg/dL:<br>Reduce regular insulin infusion to 0.02–0.05 units/kg/hr IV<br>OR<br>Give rapid-acting insulin at 0.1 units/kg SC every 2 hours | When glucose reaches 300 mg/dL:<br>Reduce regular insulin infusion to 0.02–0.05 units/kg/hr IV | K between 3.3 and 5.2 mEq/L:<br>Give 20-30 mEq KCl per liter of IV fluids | | |
| 5% Dextrose with 0.45% NaCl at 150-250 mL/hr when glucose reaches 200 mg/dL (DKA) or 300 mg/dL (HHS) | | Maintain serum glucose between 150-200 mg/dL until resolution of ketoacidosis | Maintain serum glucose between 200-300 mg/dL until resolution of hyperosmolarity | K > 5.2 mEq/L:<br>Do not give K<br>Check serum K every 2 hours | | |

Adapted from: Kitabchi AE, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335-1343.

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