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Diabetic Emergencies: New Strategies For An Old Disease

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Abstract

Diabetic emergencies are common presentations to the emergency department. It is estimated that diabetes affects 25.8 million people in the United States, at an annual total cost of over $174 billion. There are 2 general categories of diabetic emergencies: hyperglycemic and hypoglycemic. The hyperglycemic emergencies include diabetic ketoacidosis and hyperosmolar hyperglycemic state. Management of these conditions requires a careful hydration strategy to restore volume and improve perfusion, intravenous insulin therapy, and electrolyte monitoring. Management of hypoglycemia includes identification of the underlying etiology, oral food and/or glucose, intravenous dextrose, and consideration of glucagon. This review evaluates the current strategies for management of diabetic emergencies and offers new information regarding effective diagnostic strategies, selection of fluids for rehydration, correction of potassium, the use of subcutaneous insulin for mild hyperglycemia, and management of metformin-induced lactic acidosis.

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CME Objectives

Upon completion of this article, you should be able to:

1. Recognize the epidemiology of hypoglycemic and hyperglycemic emergencies.
2. Describe the pathophysiology and the potential sequelae from the various diabetic emergencies.
3. Identify the important historical and physical examination findings in diabetic emergencies.
4. Formulate management strategies for diabetic emergencies.

Prior to beginning this activity, see "Physician CME Information" on the back page.

Case Presentations

You walk into a busy Monday evening shift, and one of the nurses asks you to see a patient who has been waiting for several hours. The nurse states that the 26-year-old woman is sleepy, with a heart rate of 126 beats/min. He advises you that the patient has diabetes, for which she has been medically compliant by taking her insulin. The patient stated that she had not been feeling well for a few days, after which she developed fever, nausea, and vomiting. As you enter the room, you observe the patient retching. You note her respiratory rate is 32 breaths/min, her heart rate is 124 beats/min, and that her blood pressure is 88/50 mm Hg. You start considering your differential and wonder if this presentation is due to her diabetes or if there is something else you might be missing.

After giving your orders on the first patient, a nurse requests that you see a 56-year-old man who is unresponsive. You enter the room and note that the patient's blood pressure is 110/60 mm Hg, respiratory rate is 16 breaths/min, and heart rate is 110 beats/min. He also appears mildly diaphoretic. As you glance though the patient's chart, you note that he has a history of diabetes. There are no family or friends in the patient's room, and EMS has already departed to another call. Since the airway is always your first priority in unresponsive patients, you begin to prepare for intubation when a medical student asks what the patient's finger-stick glucose was.

Your next patient is an 87-year-old man with diabetes who has been compliant with his medicines and is being treated for pneumonia that developed about a week ago. His primary care physician started him on an oral antibiotic and sent him home with strict instructions to return if his symptoms worsened. He has been taking his antibiotics as prescribed; however, he continues to have fevers, and today he felt progressive, generalized weakness with malaise. His family notes that he has also been getting more confused over the last few days. You request a STAT finger-stick glucose and realize that this Monday shift is going to be a long one!

Introduction

Diabetes is estimated to affect 6% of the world's population, with more than 97% having type 2 diabetes.[1] The prevalence of diabetes has increased almost 700% in the United States since 1958. In 2010, diabetes affected the lives of 25.8 million people in the United States, which is about 8.3% of the United States population. Of those affected, about 18.8 million carry the diagnosis of diabetes, with 7 million people later being diagnosed as diabetic.[1]

According to the Centers for Disease Control and Prevention (CDC), diabetes carried an annual cost of about $174 billion in 2007, with approximately $116 billion for direct medical costs and $58 billion for indirect costs (such as loss of wages, disability, and mortality). The cost to society is substantial, since patients with diabetes have twice the medical expenses compared to patients of a similar age without diabetes. In terms of mortality, the CDC recognizes diabetes as the seventh leading cause of death, and patients with diabetes have death rates 2 to 4 times higher than those without diabetes.[1] The morbidity associated with diabetes is also substantial. The risk for stroke is 2 to 4 times higher than for those without diabetes. Diabetes is the primary etiology of vision loss and blindness among adults in the United States.[1] Similarly, diabetes is the primary etiology of kidney failure. In 2008, 44% of all new cases of renal failure were attributable to diabetes.[1] Recent data estimate that 60% to 70% of people with diabetes also have nervous system injury from their disease.[1] Examples of nervous system injury include neuropathy of the hands and/or feet, erectile dysfunction, and gastroparesis. Neuropathy, combined with poor wound healing, contribute to lower-extremity amputation. About 60% of nontraumatic lower-extremity amputations are sequelae of diabetes.[1]

With these financial and health impacts, diabetes carries substantial costs to both society and the individual. In the emergency department (ED), successful management of these patients reduces mortality and morbidity. This issue of *Emergency Medicine Practice* examines the best evidence available on the evaluation and management diabetic emergencies and provides best-practice management recommendations.

Critical Appraisal Of The Literature

A literature review was conducted utilizing MEDLINE® and PubMed. The following keywords were used for the MEDLINE® search; the number of articles that were identified are presented in parentheses: *diabetic emergencies* (73), *diabetic ketoacidosis and treatment and hyperosmolar hyperglycemia* (3), *sulfonylurea and hypoglycemia* (932), *potassium and diabetic ketoacidosis* (75), *fluids and diabetic ketoacidosis* (51), *fluids and hyperosmolar hyperglycemia* (0), *diabetic ketoacidosis treatment* (11), *hyperosmolar hyperglycemia treatment* (0), *hypoglycemia treatment* (30), *sodium bicarbonate and diabetic ketoacidosis* (95), and *factitious hypoglycemia* (67). The following keywords were used for the PubMed search: *diabetic emergencies* (421), *diabetic ketoacidosis and treatment and hyperosmolar hyperglycemia* (112), *sulfonylurea and hypoglycemia* (2099), *potassium and diabetic ketoacidosis* (78), *fluids and diabetic ketoacidosis* (65), *fluids and hyperosmolar hyperglycemia* (34), *diabetic ketoacidosis treatment* (3876), *hyperosmolar hyperglycemia treatment* (302), *hypoglycemia treatment* (18), *sodium bicarbonate and diabetic ketoacidosis* (131), and *factitious hypoglycemia* (129). Each of these articles was evaluated further only if written in English and based upon human studies. Once these criteria were applied, the articles were examined for relevance. The pertinent studies were then used as

part of the review for this article.

In addition to these databases, the American College of Emergency Physicians clinical policies were reviewed, but no articles were found. Additionally, the Cochrane Library was searched for the following terms: *DKA* (36), *diabetic ketoacidosis* (3), *hyperglycemia* (15), *and hyperosmolar hyperglycemia* (0). Finally, the National Guideline Clearinghouse (www.guideline.gov) was searched for the following terms: *DKA* (18), *diabetic ketoacidosis* (19), *hyperglycemia* (88), and *hyperosmolar hyperglycemia* (12). Only articles written in English and based upon human studies were reviewed. Once these criteria were applied, the articles were examined for relevance.

There are many articles related to diabetic emergencies; however, most of these articles are reviews, and there are few well-designed studies to provide a high level of evidence on which to base clinical practice. Overall, the literature is based more upon consensus than on objective studies, with many of the evaluation and management strategies based more upon previous practice than on science. Recently, there have been several new research articles discussing evaluation and management strategies.[2-7]

Etiology And Pathophysiology

The sequelae for diabetes include hypoglycemia and hyperglycemia, either of which can cause life-threatening acute or chronic problems. Hypoglycemia presents a unique challenge for the human brain. Under normal circumstances, about 90% of the brain's needed energy is in the form of glucose immediately available in the serum.[8] When serum glucose levels drop, brain dysfunction starts to occur.

Glucose homeostasis is a complex endocrine function. It is controlled primarily by 2 hormones, glucagon and insulin, which are released by the islets of Langerhans in the pancreas. Insulin increases the storage of glucose, amino acids, and fatty acids. It is released in the pancreas from the beta cells in the islets of Langerhans.[8]

After a meal, serum glucose rises and glucose enters the pancreatic beta cells. The beta cells then release insulin. There is an initial rapid release of insulin followed by a slower release.[8] Insulin affects almost every tissue in the body; however, its most profound effect is on muscle, adipose tissue, and the liver. Insulin increases glycogen synthesis in these tissues (mostly muscle and liver) while, at the same time, inhibiting glycogenolysis and gluconeogenesis. Additionally, insulin increases the movement of glucose into muscle and adipose cells. It also augments fatty acid synthesis in the adipose tissues and liver. Finally, it increases muscle amino acid uptake and decreases muscle protein catabolism.

Glucagon is responsible for decreasing the body's stores of glucose, fatty acids, and amino acids, and is lipolytic, glycogenolytic, ketogenic, and gluconeogenic. It is released from the alpha cells, which comprise only about 20% of the cells of the islets of Langerhans. In response to hypoglycemia, alpha cells increase the secretion of glucagon. Glucagon secretion is also elicited by beta-adrenergic stimulators and inhibited by alpha-adrenergic stimulators. Glucagon secretion is inhibited by insulin; as serum insulin increases in response to a rise in serum glucose, glucagon secretion is inhibited.

Diabetes Mellitus Type 1

In diabetes mellitus type 1 (which accounts for about 5% of all cases of diabetes), there is a reduction in the amount of insulin secreted secondary to a loss of islet cell mass. In other words, there is an absolute insulin deficiency. This is believed to be caused by an autoimmune injury of the beta cells, which is believed to be affected by both genetic and environmental factors.[9] Since the largest number of cells in the islets of Langerhans are beta cells, there is a commensurate decrease in the production of insulin. As more of the islet cells are affected, the amount of insulin released is insufficient to bring serum glucose levels back to baseline and cells become increasingly unable to move glucose intracellularly to use as a source of energy. The body responds by catabolizing protein and fat stores to produce a different intracellular energy source. In the muscle tissue, the body uses amino acids for gluconeogenesis. In the adipose tissue, it increases beta oxidation of fatty acids, leading to increased serum ketones. In a fasting state or when there is insufficient insulin, the body produces catabolic hormones (primarily glucagon, but also catecholamines, growth hormone, and cortisol), which results in an increase in serum ketones and glucose. Glucagon is released from the alpha cells of the pancreas during a fasting state or when there is insufficient insulin. This hormone increases breakdown of liver glycogen stores (glycogenolysis), increases liver production of glucose (gluconeogenesis), and increases liver ketone production. It is the free fatty acids that are converted by the liver to ketone bodies. The hyperglycemia seen in diabetic ketoacidosis (DKA) is due to the increased gluconeogenesis, especially with the more readily available precursors (such as amino acids and glycerol). The 2 primary ketone bodies that cause the metabolic acidosis in DKA are acetoacetic acid and beta-hydroxybutyrate. Epinephrine also elevates serum glucose through increased liver glycogenolysis and gluconeogenesis. To survive, patients will need exogenous insulin to compensate for their inability to produce insulin. If left untreated, spontaneous ketoacidosis develops.

Diabetes Mellitus Type 2

In diabetes mellitus type 2, there is a relative deficiency in the release of insulin from the beta cells

relating to the development of insulin resistance in the liver, muscle, and adipose tissues.[9] Unlike in diabetes type 1, there is rarely a serum ketosis, since there is sufficient insulin production to suppress ketosis, but there is insufficient insulin to prevent hyperglycemia. Over time, as the insulin resistance and relative reduction in insulin production progresses, the patient develops hyperglycemia.

Diabetic Ketoacidosis

DKA can present as the first manifestation of diabetes. It can also present in patients who are medically noncompliant, affected by a medication, or experiencing a physiologic stressor (eg, an infection). DKA is more commonly seen in type 1 diabetes, and DKA is rarely seen in type 2 diabetes.[10,11] In a retrospective chart review of pediatric patients hospitalized for new-onset diabetes, the authors reported that about 29% of the patients had type 1 diabetes and about 10% had type 2 diabetes, which was expected since type 1 diabetes is more common in the pediatric population.[12] Typically, the onset of DKA is short, usually within a few hours of a precipitating event.[16] DKA carries a lower mortality rate (< 2%) compared to hyperosmolar hyperglycemic (HHS) state (5% to 20%).[13]

Hyperosmolar Hyperglycemic State

HHS typically affects patients with type 2 diabetes that is undiagnosed or not well controlled, and when patients experience a physiologic stressor or have limited ability to gain access to water.[14] The etiology of HHS is usually an inflammatory state with: (1) subsequent elevation of inflammatory cytokines (eg, tumor necrosis factor [TNF], C-reactive protein [CRP], or interleukins); (2) elevation of counterregulatory hormones (eg, glucagon, cortisol, growth hormone, and catecholamines) with subsequent increase in gluconeogenesis and glycogenolysis; and (3) osmotic diuresis due to hyperglycemia. Typically, the onset of HHS is gradual, occurring over days to weeks, and it is more commonly seen in elderly type 2 diabetes patients.[16] HHS has a mortality rate of 5% to 20%, compared to DKA, which has a mortality rate of < 2%.[13] Stupor is more common in HHS than in DKA, and the etiology is thought to be due to increased hyperosmolality and dehydration.[15-20] In case reports, Arieff suggested that cerebral edema may be caused by hyperosmolality, leading to mentation changes.[16]

Hypoglycemia

Recent guidelines recommend that diabetes patients keep their hemoglobin A_{1C} levels < 7%;[20] however, there is the potential for hypoglycemic events with diabetes patients who are trying to be compliant with this goal.[21] Hypoglycemia occurs most frequently with insulin or sulfonylurea medications. According to Ha et al, the most common sulfonylurea associated with hypoglycemia is glimepiride (Amaryl®).[21] In their retrospective review of 320 ED patients, nutrition, medication change, alcohol use, and exercise were associated with hypoglycemia.[21] This study also found that hypoglycemia occurred more often in patients aged > 60 years.[21] In a retrospective study of 1020 patients, an episode of severe hypoglycemia was associated with a 3.4 times increased risk of death.[22]

Differential Diagnosis

The presentation of diabetic emergencies varies with the patient's baseline health status and reserve. Presentations include abdominal pain, nausea/vomiting, chest pain, shortness of breath, breathing difficulty, seizure, and altered mental status. The possible diagnoses for each of these presentations is large, emphasizing the need to keep disorders of glucose regulation in the differential diagnosis of patients with nonspecific complaints. For common etiologies of hypoglycemia and hyperglycemia, see **Tables 1 and 2.** These etiologies are not intended to be complete, but they present the most common considerations. To best identify whether a patient is experiencing a diabetic emergency or some other ailment, a thorough history and physical examination are fundamental.

Prehospital Care

In the prehospital environment, diabetic emergencies have variable presentations, and the underlying etiol-

Table 1. Etiologies Of Hyperglycemia

- Hyperglycemia in a patient with diabetes due to medication noncompliance
- Diabetic ketoacidosis
- Hyperosmolar hyperglycemia syndrome
- Alcoholic ketoacidosis
- Sepsis
- Myocardial infarction
- Pulmonary embolism
- Salicylate toxicity or other drug-induced state
- Acute pancreatitis
- Acute surgical abdomen (eg, appendicitis)

Table 2. Etiologies Of Hypoglycemia

- Medication-induced hypoglycemia (eg, insulin, oral hypoglycemics)
- Stroke
- Cardiogenic shock
- Seizure
- Addison disease
- Adrenal crisis
- Sepsis
- Insulinoma
- Drug toxicity (eg, beta blockers, trimethoprim/sulfamethoxazole)

ogy will often be unclear. The most common presentations in the prehospital environment are altered mental status, shortness of breath, nausea/vomiting, or tachypnea.

Hypoglycemia

When a patient presents with altered mental status, the prehospital provider's preliminary investigation and intervention are based on the available history and physical examination. An electrocardiogram (ECG) and, if available, a finger-stick glucose test may also help the provider narrow the differential diagnosis. When a hypoglycemic state is suspected, the preferred method for increasing the blood sugar is to provide glucose tablets or some form of liquid or carbohydrate-containing solid (if the patient can tolerate oral food and fluids).[23] A dose suggested in an Endocrine Society clinical practice guideline for adults is about 20 grams of glucose.[23] After oral intake, the blood glucose should rise gradually in 15 to 20 minutes, with subsequent clinical improvement.[23] After clinical improvement, a meal or sizeable snack should be consumed to help reduce the risk of recurrence of hypoglycemia.[23]

If a patient is unable to tolerate oral foods, sublingual delivery of sucrose is an alternative route. In a randomized nonblinded pediatric study, the mean increase in blood glucose within 10 minutes after the administration of sublingual sucrose solution was 44 mg/dL.[2] Another randomized nonblinded pediatric study found that sublingual sugar had similar efficacy to intravenous administration of dextrose.[3] While both of these studies were small and the technique for sugar administration is not widespread, it does provide an additional option. This technique may have utility with patients who are maintaining their airway, as the sucrose solution is placed under the tongue and not swallowed. No studies were found that examined the risk of aspiration during sublingual administration of sucrose. Further research is needed on this alternative administration route before it can be accepted as a mainstream option for increasing serum glucose.

If the patient is unable to tolerate oral foods/medications or is too drowsy to take oral foods/medications, then management with intravenous dextrose is recommended. The usual dose is 25 grams (ie, 50 mL of a 50% dextrose solution [D50]). If the patient responds well to this treatment, a meal or sizeable snack should follow to help reduce the risk of recurrence of hypoglycemia.[23] If intravenous or intraosseous access is not possible, intramuscular injection of glucagon is an alternative; the usual dose is 1 mg.[23] Glucagon does have the potential side effects of nausea and/or transient hyperglycemia.[26]

Cases of hypoglycemia-induced cardiac arrest have been discussed in the literature.[24-26] In a retrospective cohort study examining patients with acute myocardial infarction, a substantially higher inhospital mortality rate was noted in patients who were hypoglycemic compared to patients who were euglycemic.[27] The prehospital provider should consider hypoglycemia as a potential etiology of cardiac arrest and administer intravenous or intraosseous dextrose in appropriate circumstances.

Hyperglycemia

Although the prehospital provider may suspect that the presenting complaint of a patient with diabetes may be secondary to hyperglycemia, it will be difficult to determine whether the hyperglycemia is due to DKA, HHS, or simply hyperglycemia. If available, a point-of-care blood glucose test will usually show an elevated blood glucose with all of these conditions. If the blood glucose is extremely elevated, the measuring device may simply show that the blood glucose is too high to measure. After determining that the patient has elevated serum glucose, the prehospital provider may consider administration of intravenous normal saline, if permitted by protocol. Since one of the underlying issues in a hyperglycemic state is dehydration, rehydration is an important intervention to address the underlying pathophysiology. The prehospital provider can mitigate this through the administration of fluids. Normal saline helps to increase intravascular volume.[20] Additionally, it increases interstitial and intracellular volume.[20] Normal saline helps to return normal renal perfusion and starts decreasing the serum glucose, and it increases the body's response to low-dose insulin.[20] In general, 1 to 1.5 liters should be administered during the first hour in adult patients, although in most areas, the prehospital transport will be completed before this time.

With DKA, disequilibrium of the electrolytes may occur. The electrolyte that is of the greatest concern is potassium. Hyperkalemia can induce cardiac arrest, and there are many case reports of this phenomenon.[28,29] In the prehospital environment, hyperkalemia may be suspected in patients with diabetes when the potassium is unknown; however, if DKA is high on the differential and a bradycardia, tachycardia, or cardiac dysrhythmia is noted on the monitor, evaluation for hyperkalemia should be considered. Performing an ECG will help better risk stratify the patient for hyperkalemia. Peaked T waves, QT shortening, QRS-complex widening, small P waves, and prolongation of the PR interval are all potential indicators for hyperkalemia.[30] As the serum potassium exceeds about 8 mEq/L, the P waves become difficult to discern; the QRS-T complex may start to resemble a sine wave **(see Figure 1, page 6);** a left or right bundle branch may develop; and asystole, ventricular tachycardia, or ventricular fibrillation may occur.[30] The treatment for hyperkalemia should follow the institution's protocols,

which may include intravenous calcium gluconate **(see Figure 2)**, nebulized albuterol, and intravenous sodium bicarbonate.[31] This is particularly relevant in patients who are in cardiac arrest.

Emergency Department Evaluation

History

In the ED, the initial evaluation of a patient suspected of hypoglycemia or hyperglycemia focuses on predisposing conditions and includes a history and physical examination. As part of the history, inquire about infection or recent illness, fever, nausea/vomiting, abdominal pain, urinary frequency, weight loss, skin breakdown, weakness, thirst, cough, and confusion or change in mental status. If the patient is known to be diabetic, inquire about dietary and medication compliance. A past medical history of diabetes, pancreatitis, heart disease, and kidney disease should be explored. Family history of diabetes or hypoglycemia may be helpful.

The onset of symptoms should also be determined. HHS tends to occur over several days to weeks, while the metabolic derangements common in DKA usually evolve in a short time, typically in < 24 hours.[20] Medication compliance and drug-drug interactions should be determined. Inquire about whether the patient is taking the appropriate dose at the appropriate time through the appropriate route.

Figure 1. Electrocardiogram In A Patient With Hyperkalemia, Showing A Sine Wave Pattern

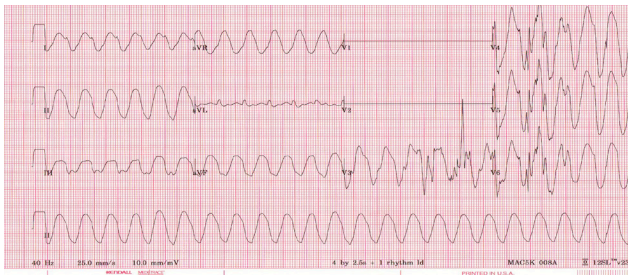
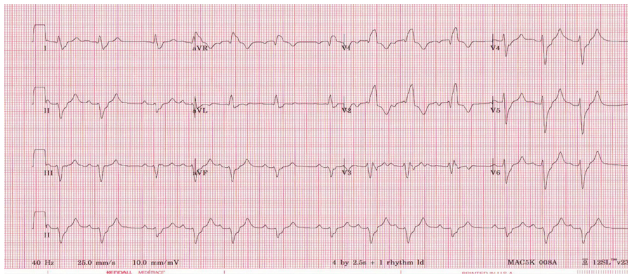


Figure 2. Electrocardiogram In The Same Patient After Administration Of Calcium Gluconate



If the patient has been vomiting repeatedly, medication delivery may be a contributor to the presentation, as the patient may be vomiting medicines taken. **Table 3** presents common drugs and their effect on serum glucose.

A good social history may provide insight into the etiology of a diabetic emergency. Although it is not common, certain illicit drugs are known to cause hyperglycemia, and in some cases, DKA. Very rarely, cocaine may precipitate DKA, and it is a potential risk factor for DKA in diabetes patients.[39,40] Patients at greatest risk for DKA are those who have poorly controlled diabetes.

It is important to determine not just that a patient has hyperglycemia or hypoglycemia but also the trigger for the condition (such as infection).

Physical Examination

The physical examination focuses on vital signs, airway, breathing, circulation, skin, abdomen, and neurological evaluation. Low blood pressure, tachycardia, tachypnea, and/or hypoxia are indicators of a potentially critically ill patient, demonstrating compensatory responses or hemodynamic decompensation.

Evaluation of the airway, including the patient's ability to handle secretions, and examination of the oral mucosa for insight into the patient's hydration status is critical. Respiratory rate should be observed, as tachypnea may result from compensating for metabolic acidosis and DKA. Kussmaul breathing (tachypnea as well as increased depth of breathing) may be present in DKA as well.[31] A fruity odor may be detected on the patient's breath, suggesting ketonemia.[41] Tachycardia may indicate dehydration or an underlying physiologic stressor, such as infection or sepsis. Poor skin turgor may indicate dehydration, while diaphoresis may indicate an adrenergic response to hypoglycemia. Poor skin color may also indicate hypovolemia.

Table 3. Common Drugs And Their Effects On Serum Glucose[21,32-38]

Drug	Potential Effect on Serum Glucose	Comment
Beta blockers	May decrease	In toxicity, may cause hypoglycemia and mask the signs of hypoglycemic emergency
Calcium-channel blockers	May increase	In toxicity, may cause hyperglycemia
Sulfonylureas	Decreases	Most often seen with glyburide[37] or glimepiride[24]
Steroids	May increase	Can cause diabetic ketoacidosis or hyperosmolar hyperglycemic state

Abdominal tenderness to palpation may indicate that hyperglycemia may be secondary to DKA. In a prospective cohort study of 200 hyperglycemic patients, Umpierrez and Freire reported that the amount of abdominal pain the patient experienced correlated with the degree of metabolic acidosis.[42] The amount of abdominal pain was not found to be related to the level of hyperglycemia or dehydration. This study found that abdominal pain was present in 86% of those with a serum bicarbonate (HCO_3) of < 5 mmol/L and in 66% of patients with a serum HCO_3 < 10 mmol/L. Interestingly, none of the patients with HHS had abdominal pain.

The neurological examination focuses on identifying etiologies for the patient's symptoms. Examination of sensation, strength, reflexes, pupillary response and size, visual acuity, and cranial nerves may help to narrow down the differential. A systematic review by Yong et al identified patients with stroke-like symptoms who, in fact, had hypoglycemia, which was the source of their focal neurological deficit.[43] Similarly, several case reports discuss patients with seizure-like activity due to hyperglycemia.[43-45]

Diagnostic Studies

The diagnostic evaluation of a diabetic emergency is directed by the information obtained from the history and physical examination. A summary of diagnostic studies that may be considered for patients with a diabetic emergency is in **Table 4**.

Table 4. Diagnostic Testing Considerations In Hypoglycemia And Hyperglycemia

Test	Comments
Complete blood count	Evaluates for infectious etiology or bleeding
Urinalysis, urine culture, blood culture	Evaluate for infectious etiology
Complete metabolic profile (including calcium)	Tests for electrolyte imbalance
Electrocardiogram	Should be performed if there is suspected dysrhythmia, electrolyte imbalance, or acute coronary syndromes
Plasma insulin, C-peptide	Tests for insulinoma or factitious etiology in hypoglycemia
Chest x-ray	Should be ordered if infectious pulmonary or cardiac etiology is being considered as possible etiology
Beta-hydroxybutyrate	Should be ordered if diabetic ketoacidosis is suspected
Proinsulin, insulin antibodies	Should be ordered if insulinoma is being considered in hypoglycemia

Hypoglycemia

Once hypoglycemia is identified, initiate management and seek out the underlying etiology. Determine whether the hypoglycemia is due to not eating, accidental overdose on home diabetes medications, or an infection. In nondiabetic patients suspected of ingesting a sulfonylurea, consider measuring serum sulfonylurea, although this is not typically available at most laboratories.[46] Evaluation of serum insulin levels can be performed, but this, too, is not typically available at most laboratories.[47-50] Similarly, measurement of C-peptide may help to clarify whether an exogenous source of insulin has decreased serum glucose, but this test is also not always available.[51,52] With factitious hypoglycemia via insulin, the C-peptide level will be low compared to insulin levels.[51] Insulin antibodies may provide information on differentiating whether the hypoglycemia is secondary to autoimmune effects or insulinoma.[23,53] If the patient had fasting or postprandial hypoglycemia with elevated insulin levels without insulin antibodies, then evaluation for an insulinoma may be appropriate.[23]

Hyperglycemia

In contrast to hypoglycemia, diagnostic laboratory tests are helpful in distinguishing a patient who has a primary or secondary hyperglycemic emergency. Testing can help differentiate DKA from HHS, and it provides baseline measures from which the admitting team can observe trends as they continue the management of the patient.

Sodium And Serum Osmolality

A patient's vital signs (such as blood pressure and pulse) and urinary output provide the most rapid assessment of the patient's hydration status. Measured serum osmolality is the most accurate assessment of hydration, and it can help guard against the risk of iatrogenic fluid overload during fluid replacement.[54]

Hyperglycemia affects serum sodium concentration, and it reflects the balance between osmotic dilution of sodium due to cellular water movement from the intracellular fluid to the extracellular fluid as well as renal-induced diuresis secondary to hyperglycemia. Most often, a serum hyponatremia is noted, as more intracellular water shifts extracellularly than is renally diuresed. To better reflect the total body sodium, a sodium correction factor accounting for the serum glucose is used:

$$\text{Corrected sodium} = \text{measured sodium} + 0.016\,(\text{serum glucose} - 100)$$

For example, a patient in HHS with a measured glucose of 1010 mg/dL and a measured serum sodium of 122 mEq/L would have a corrected total body sodium of 137 mEq/L. Some authors argue

that the correction factor of 0.016 is too small, especially when serum glucose is > 400 mg/dL. A recent study by Hillier demonstrates a more accurate measure using a correction factor of 0.024, which is what this author uses to more accurately reflect the total body sodium.[55]

$$\text{Corrected sodium} = \text{measured sodium} + 0.024\ (\text{serum glucose} - 100)$$

Using this formula, the previous example would show a corrected sodium of 144 mEq/L. A corrected serum sodium will guide the type of fluid that should be used for hydration.[55]

Measurement of serum osmolality may help to differentiate HHS from the other hyperglycemic ailments.[20,56] Serum osmolality can be calculated as:

$$2 \times (Na + K) + (BUN/2.8) + (glucose/18) + (ethanol/4.6)$$

Serum osmolality is usually elevated in HHS and may be > 380 mOsm/kg.[20,56] This author does not typically order the serum osmolality test unless the patient has altered mental status. Euglycemia with a substantial elevation in effective serum osmolality (> 320 mOsm/kg) necessitates consideration of other causes of the altered mental status, such as alcohol toxicity.

Serum Potassium

Total body potassium may be low in hyperglycemia, even though, due to acidosis, the measured serum potassium may be normal or elevated. Because of the risk of dysrhythmias associated with hypokalemia and hyperkalemia, potassium should be measured to guide management.[57-60]

Serum Phosphate

Though traditionally considered part of the evaluation, in most cases of DKA, measurement of serum phosphate has no utility. In a randomized controlled study of 20 patients, Fisher found that phosphate repletion had no influence on tissue oxygenation or clinical response to insulin during DKA.[61] In a randomized controlled study of 44 patients, Wilson found that phosphate repletion did not affect the duration of DKA, abnormal muscle enzyme levels, the dose of insulin to correct acidosis, or morbidity and mortality.[62] Based on these studies, regular monitoring of phosphate in the ED is not recommended. Similarly, several textbooks recommend monitoring of magnesium, but no human studies supporting this recommendation were found in our literature review.

Serum pH And Anion Gap

Blood gas testing provides further insight into whether the patient's hyperglycemia is due to DKA or HHS, since DKA usually presents with an anion gap metabolic acidosis.[56,63] Consequently, DKA would present with a decreased pH while HHS would typically present with a normal pH. In general, the venous blood gas is preferred to the arterial blood gas because it provides similar information about pH and HCO_3 with less risk for iatrogenic injury.[64,65] The anion gap is calculated based on sodium, chloride, and bicarbonate:

$$\text{Anion gap} = Na - (Cl + HCO_3)$$

A normal anion gap is < 12. Patients in DKA have an increase in ketoacids which causes a metabolic acidosis and subsequent decrease in bicarbonate.

Serum Glucose

If hyperglycemia, HHS, or DKA is suspected, then a point-of-care test for blood glucose should be obtained as soon as possible after patient presentation. In DKA, the blood glucose is often < 800 mg/dL, but it may be higher, especially if the patient is stuporous or comatose.[20,56] In HHS, the serum glucose can exceed 1000 mg/dL with minimal or no ketone bodies.[20,56]

Serum Ketones

Measurement of serum ketones can help to risk stratify the severity of DKA.[63] In DKA, the body produces 3 types of ketone bodies: acetoacetic acid, which is the ketoacid;[56,63] beta-hydroxybutyrate, which is a breakdown product of acetoacetic acid;[56] and acetone (which is what gives patients the fruity breath).[56,63] In DKA, the ratio of the beta-hydroxybutyrate to acetoacetate changes in response to the increased ketones,[63] from a ratio of 1:1 to as much as 5:1. Many laboratories have the ability to test for acetoacetate, but a more helpful measure is the beta-hydroxybutyrate, since it better reflects the amount of ketones present from the DKA.[63] Some emergency clinicians measure serum ketones; however, beta-hydroxybutyrate is the preferred diagnostic laboratory test for evaluating for DKA, as it is a more cost-effective and sensitive test compared to the serum ketone test (acetone). Even more interesting is a presentation of euglycemic DKA. Typically, the patient has vomiting but continues to use his or her insulin. In this instance, the patient may have near-normal or only mildly elevated serum glucose but still develops DKA.[63] The serum beta-hydroxybutyrate levels will be crucial to the successful diagnosis of DKA in the setting of normal or near-normal blood glucose.

Urine Ketones

The original measurement method of urine ketones had inherent inaccuracy because the older urine test measured acetoacetate while the greatest increase in ketones is in beta-hydroxybutyrate.[66] The current urine dipstick method is more accurate. The sensitiv-

ity of today's urine dipstick for DKA is 98.1% (95% confidence interval [CI], 90.1-100) with a specificity of 35.1% (95% CI, 30.8%-39.6%).[4] The positive predictive value of the urine dipstick is 15% (95% CI, 11.5%-19.2%) while the negative predictive value is 99.4% (95% CI, 96.6%-100%). While the urine ketone test is very sensitive, it is not specific, and it has the potential to lead to unnecessary testing. Dehydration and lack of eating for reasons other than DKA can also elevate urine ketones.

Treatment

Diabetic Ketoacidosis

Rehydration

In DKA, the initial management strategy includes rehydration, correction of hyperglycemia and electrolyte imbalances, and serum ketone clearance.[20] Intravenous isotonic saline (0.9% saline) is the initial fluid used to increase intravascular, intracellular, and interstitial volumes.[20] Appropriate hydration increases the body's response to low-dose insulin.[20] Initial fluid volume should be 1 to 1.5 liters in the first hour.[20] It is estimated that the average fluid loss in a patient with DKA is between 3 and 6 liters.[67] After the second liter has been given, subsequent fluid choice is dependent on the patient's electrolyte balance and hydration status. Both blood pressure and urinary output should be used as the initial determinants of hydration status. Corrected serum sodium should be used to guide the preferred intravenous fluid. If the patient's corrected serum sodium is high or normal, with only mild dehydration, administration of half-normal saline at 250 to 500 mL/h should be initiated.[13,20] If the patient's corrected sodium is low, with only mild dehydration after the initial 1 to 2 liters of normal saline, then administration of normal saline at 250 to 500 mL/h has been suggested in some protocols.[13,20] If the patient is still severely dehydrated after the first liter of normal saline, then normal saline at 1 L/h should be continued.[13,20] Although no high-quality evidence exists for the exact amount of fluid to administer in severe dehydration, this author follows this strategy because the intravenous fluids will aid in decreasing the serum glucose (through glycosuria) while also rehydrating the patient.

Rapid reduction in plasma osmolality should be avoided, given the rare complication of cerebral edema.[67-71] A retrospective cohort study of 69 patients noted an association between a drop in the plasma osmolality and development of cerebral edema.[68] This phenomenon occurs primarily in children, but there have been case reports of this occurring in adults.[69-71] The exact pathophysiology of cerebral edema has not been fully elucidated, but a drop in effective serum osmolality of ≥ 9 mOsm/kg has been noted to have an association with cerebral edema in children.[68]

In summary, for patients in DKA, hydration is important for restoring homeostasis, but a hydration strategy that is too aggressive may increase the risk for cerebral edema. For these patients, once the serum glucose reaches about 200 mg/dL, the fluids should be changed to include dextrose.[20] Serum glucose can be maintained between 150 and 200 mg/dL while the serum ketones are cleared by adjusting the concentration of the dextrose solution or the rate of insulin infusion.[20]

Insulin

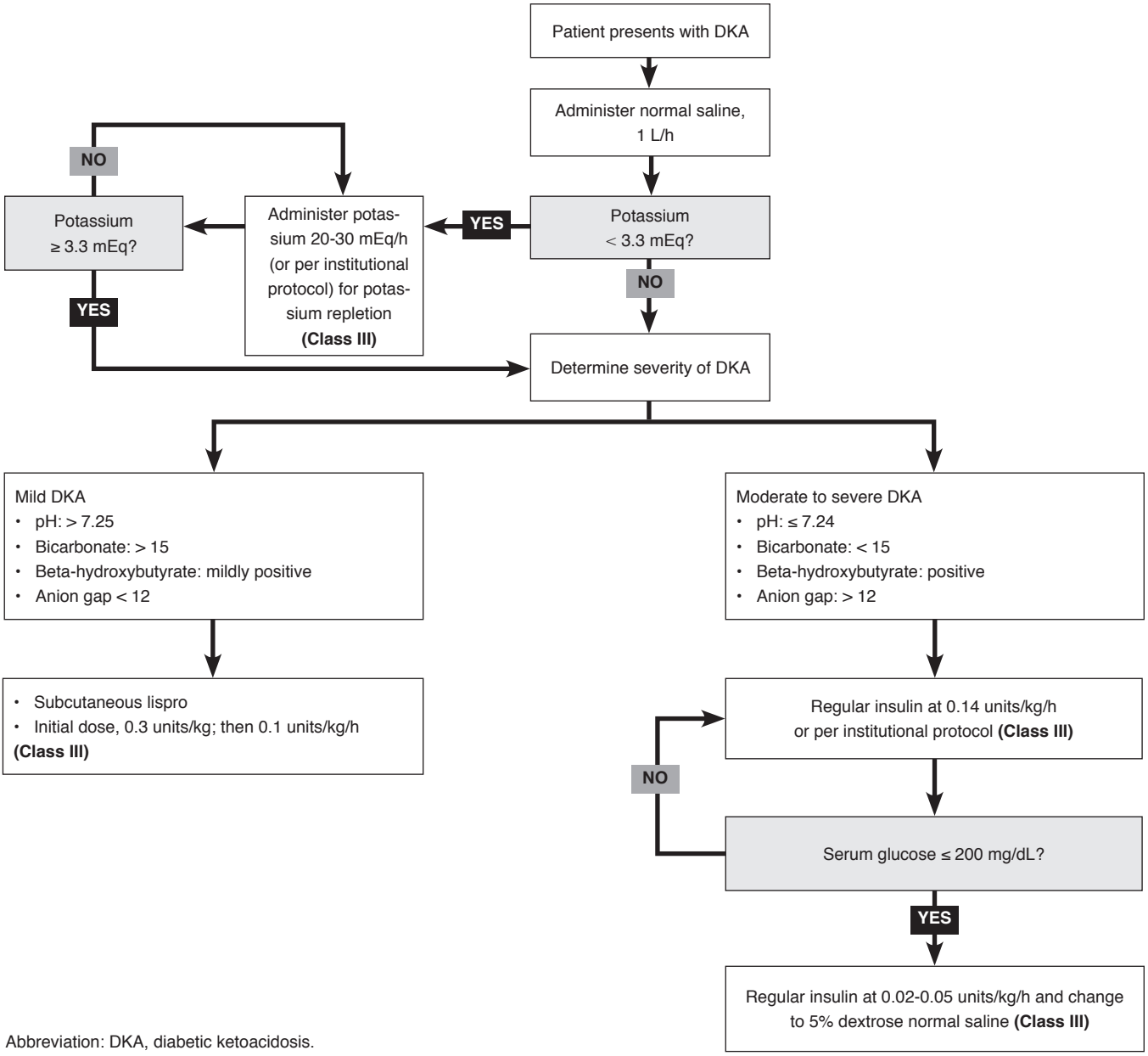
Intravenous insulin is also a key component in the management of DKA. It reduces serum glucose and helps to clear the serum ketones.[67] Some resources recommend an initial bolus of insulin (0.1 units/kg) followed by a continuous infusion of insulin (0.1 units/kg/h).[13,20,31] However, a recent prospective observational cohort study found that a continuous infusion of insulin provides similar outcomes as compared to an initial insulin bolus.[5] A small prospective randomized study also found similar results while using a slightly higher infusion rate of 0.14 units/kg/h.[6]

Based on this evidence, this author initiates insulin treatment at the rate of 0.14 units/kg/h and forgoes the insulin bolus to reduce the potential risk of iatrogenic complication (eg, hypoglycemia). This may not be possible at all institutions, in which case the insulin should be titrated per the institution's DKA protocol. Although there is a paucity of high-quality evidence, this author recommends withholding insulin if the serum potassium is < 3.3 mEq/L (or 3.3 mmol/L) and initiating the insulin infusion once the potassium has been increased to ≥ 3.5 mEq/L to avoid potential iatrogenic complications.[31,72,73] When the serum glucose is 200 mg/dL, insulin infusion should be decreased to 0.02 to 0.05 units/kg/h, while dextrose is included in the infusing fluids.[13,20]

Subcutaneous Insulin

In mild cases of DKA, subcutaneous rapid-acting insulin (such as insulin lispro [HumaLOG®] or insulin aspart [NovoLog®]) can be administered instead of intravenous regular insulin. While intravenous infusion with regular insulin has the advantage of easy titration and a short half-life, it does require an intravenous line. In a randomized controlled study by Umpierrez et al, it was found that in mild or uncomplicated cases of DKA in a non-intensive care unit setting, patients given subcutaneous insulin did as well as those given regular insulin through an intravenous infusion.[7] There were no deaths in either group, no differences in length of hospital stay, and no differences in the rate of hypoglycemia. The authors described a dosing scheme with insulin lispro of 0.3 units/kg as an initial dose and then 0.1 units/kg/h for subsequent doses.[7]

Clinical Pathway For Management Of Diabetic Ketoacidosis In The Emergency Department



Abbreviation: DKA, diabetic ketoacidosis.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Correction Of Potassium

Correction of potassium is another key task in managing DKA. In DKA, the patient's total-body potassium is often decreased even when hyperkalemia is observed.[20] Insulin, fluid infusion, and subsequent correction of acidosis will correct the elevated serum potassium in all but extreme cases.[13,20] In extreme cases, more aggressive management of hyperkalemia may need to be considered, such as treatment with calcium, albuterol, sodium bicarbonate, and insulin (or with insulin and dextrose, if there is risk of hypoglycemia with insulin treatment). To prevent hypokalemia, potassium repletion is usually initiated once the potassium level is at the high end of the normal range, or < 5.3 mEq/L.[13,20] This is done by providing 20 to 30 mEq of potassium in each liter of fluid, with the goal of maintaining the potassium level in the normal range.[13,20] If a patient is already hypokalemic (potassium < 3.3 mEq/L), then administration of insulin should be deferred until the potassium level is ≥ 3.3 to 3.5 mEq/L, in order to avoid potentially life-threatening dysrhythmias and/or respiratory muscle paresis.[13,20,21] This can be achieved by repletion of potassium at 20 to 30 mEq/h (or as institutional protocol permits). Usually, 40 to 60 mEq of potassium is mixed in half-normal saline, with these fluids being run at the aforementioned rate.[67]

Sodium Bicarbonate

Sodium bicarbonate has little or no role in the management of DKA. Authors of a systematic review that included 44 articles found no improvement in clinical outcomes or biochemical parameters in patients with DKA who were treated with sodium bicarbonate.[74] In fact, the authors of this review found evidence for increased risk for cerebral edema and lengthier hospital stays as well as weak evidence of worsening ketosis and increased need for potassium repletion with the use of sodium bicarbonate.[74] Despite the lack of evidence, some authors still advocate for the use of sodium bicarbonate when the pH is < 6.9.[13,31] Sodium bicarbonate may have the theoretical benefit of improving cardiac contractility, thereby improving perfusion. Although no large prospective studies exist on the use of sodium bicarbonate in DKA, this author recommends considering the use of sodium bicarbonate in the appropriate clinical setting when the pH is < 6.9, since it may have an effect on the contractility of the myocardium, which has been observed in several animal studies.[74-78]

Hyperosmolar Hyperglycemic State

In HHS, fluid repletion is extremely important. These patients are usually dehydrated, with an estimated average fluid loss of 8 to 10 liters.[67] Similar to DKA, one of the key elements in managing this disease state is rehydration. The management strategy is virtually the same as in DKA, except that transition to 5% dextrose in half-normal saline occurs earlier, when the serum glucose is around 300 mg/dL.[13,20] Appropriate hydration also increases the body's response to low-dose insulin.[20] An overview of this strategy is demonstrated in **Figure 5**. Maintaining a goal serum glucose between 250 and 300 mg/dL while fluid and electrolyte homeostasis is reestablished by the body reduces the potential risk for iatrogenic complications (such as hypoglycemia and cerebral edema).[20]

Insulin is also a key element of management of HHS. A bolus followed by a continuous infusion of insulin or only an insulin infusion at a slightly higher rate provides similar results. This author recommends the insulin infusion at a higher rate (ie, 0.14 units/kg/h) to minimize the risk of iatrogenic effects (such as hypoglycemia and cerebral edema).[13,20] The timing of the deceleration of the insulin infusion distinguishes the management of HHS and DKA. In hyperosmolar hyperglycemia, the insulin infusion should be decreased when the serum glucose is 250 to 300 mg/dL.[13,20] At that point, the insulin infusion is slowed to 0.02-0.05 units/kg/h, and the fluids should incorporate dextrose.[13,20]

Hypoglycemia

When hypoglycemia is identified (usually < 70 mg/dL), the initial management strategy is to increase serum glucose. In a patient without diabetes mellitus who has hypoglycemia and is awake and alert, providing food may reverse the hypoglycemia. Fifteen to 20 grams of simple sugar (from a hard candy or oral glucose tablet or gel) is usually sufficient to increase the blood glucose.[23,79] This should be followed by a snack or meal.[23,79] If the patient does not respond to this treatment or is too sleepy or agitated to tolerate food, then intravenous administration of dextrose (25 gm of 50% dextrose) is indicated.[23] If unable to obtain intravenous access, administration of 1 mg of glucagon intramuscularly can be considered. Glucagon can induce nausea and vomiting, so its use is generally limited to circumstances when intravenous access cannot be obtained. If hypoglycemia recurs, an infusion of dextrose should be started. Admission may be appropriate if there is concern that the patient's serum glucose may decrease again.[8]

Although hypoglycemia occurs more frequently in patients with diabetes type 1, it does occur in diabetes type 2 as well.[23] When a diabetic patient presents with hypoglycemia (usually < 70 mg/dL), the initial management strategy is similar to that of a nondiabetic patient.

Sulfonylurea-Induced Hypoglycemia

In some cases, hypoglycemia may be secondary to sulfonylurea use. In the management of patients with early type 2 diabetes, metformin is recommended as a first-line oral agent, with sulfonylurea added if the diabetes remains uncontrolled. The authors of a systematic review found that severe hypoglycemia did not occur more frequently with a particular

therapy or therapies in type 2 diabetes mellitus, but they did find that sulfonylureas increased the risk due to recurrence of hypoglycemia.[80] In 2007, poison control centers across the United States received some 4384 calls about sulfonylureas, and they accounted for about one-third of the overdoses from antihyperglycemic drugs and oral hypoglycemics.[81]

The initial management of hypoglycemia due to sulfonylurea usage is administration of an oral simple sugar (such as a hard candy or oral glucose tablet or gel).[81] A further increase in serum glucose can be achieved through intravenous administration of dextrose, since glucagon has the potential to increase hyperinsulinemia.[81] The typical dosing of bolus infusions of dextrose is 0.5 to 1 gm/kg intravenously.[81] A dose of 50 mL of 50% dextrose (D50W) provides 25 grams of carbohydrate.[81]

In cases of pediatric hypoglycemia due to a sulfonylurea, children are typically given 2 mL/kg of a 25% dextrose solution, while infants are typically provided 5 mL/kg of a 10% dextrose solution.[81] If unable to obtain intravenous access, intramuscular glucagon (1 mg) can be administered. This is a temporizing measure, as it raises serum glucose through glycogenolysis and gluconeogenesis.[81] After the bolus with intravenous dextrose, an infusion of a dextrose solution will prevent recurrence of the hypoglycemia.[81]

Refractory Hypoglycemia

In cases of refractory hypoglycemia, octreotide can be used to increase serum glucose. There are multiple case reports using octreotide to treat refractory serum hypoglycemia.[82-84] In a prospective double-blind placebo-controlled trial of 40 patients with 18 in the placebo arm (standard therapy) and 22 in the octreotide arm (standard therapy plus octreotide), the mean serum glucose levels were consistently higher in the octreotide arm.[85] The mean glucose difference between the 2 arms approached clinical significance in 1 to 3 hours in the octreotide arm when compared to the standard therapy arm (56 mg/dL; 95% CI, -3 to 115 mg/dL; $P = 0.08$) and maintained statistical significance for up to 4 to 8 hours (127 mg/dL; 95% CI, 68-187 mg/dL; $P < 0.001$).[85] A 2012 review of case reports suggested that octreotide should be considered as a primary therapy in hypoglycemic pediatric and adult sulfonylurea poisonings.[84] The usual dosing for an octreotide infusion is up to 100 to 125 mcg/h intravenously, but the preferred route is subcutaneously, from 50 to 100 mcg every 6 to 12 hours, as needed.[81] There are several case reports that caution providers about the use of octreotide, since hyperkalemia occurred with its administration in these cases.[86-88]

Special Circumstances

Cardiac Arrest

In cardiac arrest, the American Heart Association Advanced Cardiovascular Life Support (ACLS) guidelines recommend consideration of reversible causes of the cardiac arrest. These reversible causes include: hypovolemia, hypoxia, hydrogen ion (acidosis), hypokalemia, hyperkalemia, tension pneumothorax, tamponade (cardiac), toxins, and thrombosis (pulmonary and coronary).[89] In a patient with diabetes, several of these reversible causes should be evaluated and managed empirically. Hypovolemia in both DKA and HHS could be considered in cardiac arrest, with the initial management strategy being intravenous normal saline. Metabolic acidosis due to DKA may also be a reversible cause of cardiac arrest. In this case, initial management may include not only insulin but also initiation of sodium bicarbonate if hyperkalemia is suspected. If laboratory results have not returned and the patient may be in DKA, then interventions for hyperkalemia may be considered. If an arrest ensues after starting management of DKA, hypokalemia may be a possible cause.

Metformin-Induced Lactic Acidosis

Metformin has been associated with lactic acidosis. Retrospective studies have revealed that most patients who developed lactic acidosis had an underlying risk factor or medical comorbidity predisposing them to this complication. Metformin has a much lower likelihood ratio (LR) of inducing hypoglycemia (LR, 1.42; 95% CI, 1.22-1.64) compared to sulfonylurea (LR, 3.73; 95% CI, 3.16-4.42). Descriptions of successful management of lactic acidosis induced by metformin have been limited to case reports. Alivanis presented a case report of continuous renal replacement therapy to successfully manage a patient. Continuous venovenous hemodiafiltration in this case lasted about 16 hours, but it corrected acidosis and removed lactate as well as metformin without the risk of hypernatremia or fluid overload that can be seen in conventional intermittent hemodialysis.[90] Similarly, Bruijstens discussed management of suspected lactic acidosis secondary to metformin use. In this study, the author described 3 cases successfully managed with continuous venovenous hemodiafiltration (1 patient later died of other complications).[91] Although there is no strong objective evidence, this author recommends utilization of continuous venovenous hemodiafiltration in cases of metformin-induced lactic acidosis with associated hypoglycemia until better evidence is available. In the extremely rare case where there is no lactic acidosis and the patient is hemodynamically stable and well-appearing, this author recommends oral glucose replacement with a small meal and observation for 6 to 8 hours after the ingestion of metformin prior to discharging the patient.

Management Of New-Onset Diabetes

There is a dearth of literature on the management of new-onset diabetes. In the past, patients with new-onset diabetes would be admitted to allow for further evaluation and education of the patient. The education on weight reduction, exercise, and lifestyle modification would help maximize the likelihood of patient comprehension of the disease and compliance with the treatment. In the new medical landscape, the option of admission may be met with increased resistance from both the hospital administration (which may not be reimbursed for this type of admission) as well as the patients (who may have to pay the entire bill).

New-onset diabetes is diagnosed by a hemoglobin A_{1C} of ≥ 6.5%, a fasting plasma glucose ≥ 126 mg/dL, a 2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test, or a random glucose level of ≥ 200 mg/dL in a patient with classic symptoms of hyperglycemia.[92] The hemoglobin A_{1C} has limited utility in the ED, as not every institution can obtain these results in a timely fashion.

Education on weight reduction is an important facet of overall diabetes management, and diet is a key component to weight loss. In a prospective trial of 93 patients with type 2 diabetes, Wing et al found the amount of caloric restriction and the amount of weight loss have independent effects on improving glycemic control and insulin sensitivity.[93]

Education of the patient on the importance of exercise is another key element to successful weight loss. Exercise also has the benefit of increasing insulin sensitivity.[94,95] A study by Pi-Sunyer et al demonstrated that intensive lifestyle intervention (including weight loss through decreased calories and increased physical activity) had a significant effect on the hemoglobin A_{1C} by reducing it from a mean of 7.3% to 6.6% compared to 7.3 to 7.2% in patients with only support and education.[96] The intensive lifestyle intervention included caloric restriction, moderate physical activity, and regularly occurring group or individual sessions with dieticians, psychologists, and exercise trainers. Each of these elements requires good follow-up and reliability for success of outpatient management.

In cases of well-appearing patients who have stable vital signs, are reliable, do not have DKA or HHS, have good outpatient follow-up, are not showing signs of dehydration, are not experiencing severe thirst, and are reliable, then discharge may be a good alternative to admission. There is no strong evidence on how to manage these types of patients; however, coordinating with a primary care provider is key, and consideration may be given to starting the patient on metformin.

Controversies And Cutting Edge

Cerebral Edema

Cerebral edema is seen primarily in children, with case control studies finding an incidence between 0.51% [97] and 0.9%.[98] There are also case reports in of cerebral edema in adults. It may manifest with altered mental status, decorticate or decerebrate posturing, cranial nerve palsies, and unusual breathing or respiratory patterns. This devastating disorder can be prevented by limiting the rate at which serum osmolality is decreased and avoiding an overly aggressive rehydration strategy.

Several sources recommend the use of mannitol once neurological symptoms occur.[31,99] The recommended dose is 1 to 2 gm/kg over 20 minutes, with repeated dosing every 1 to 2 hours as needed. Fluid infusion rates should be decreased, and the head of the bed should be elevated. An alternative to mannitol is hypertonic saline, which can be given at a dose of 5 to 10 mL/kg of 3% saline over 30 minutes.[100,101]

New Oral Hypoglycemic Agent

On March 29, 2013, the United States Food and Drug Administration (FDA) approved canagliflozin (Invokana®) for the treatment of type 2 diabetes. This drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The dosing is 100 mg or 300 mg once a day before the first meal of the day. The phase 3 trials demonstrated that the most common adverse effects were hypoglycemia, superficial fungal genital infection, urinary tract infections, and osmotic diuresis/volume-related effects.[102] This medication is a sodium glucose cotransporter inhibitor, and it inhibits the proteins in the heart, small intestine, trachea, and the proximal tubules of the kidney from absorbing glucose. This effect in the kidneys prevents reabsorption of glucose and increases the renal excretion of glucose.[102,103] Although this medication will not be commonly prescribed in the ED, its adverse effects should be understood by emergency clinicians to better help patients using this drug.

Disposition

Diabetic Ketoacidosis

There is very limited research discussing the best disposition for DKA patients. Most of the literature is limited to consensus documents. Patients with severe DKA who are on an insulin drip should be managed in an intensive care unit or step-down unit. If a patient has an anion gap of ≤ 18 mEq/L with a blood glucose of ≤ 300 mg/dL and stable vital signs, then it may be reasonable to admit the patient to a regular medical unit. Determining which patients can go to the regular medical unit, step-down unit, or the intensive care unit is institution-specific.

Hyperosmolar Hyperglycemic State

In patients with HHS, admission to the intensive care unit is typical, because they require close monitoring and are on an insulin drip. Often, this population has significant underlying medical conditions that also require close monitoring. If a patient has limited or no underlying medical conditions and responds well to management in the ED (as observed through laboratory tests and vital signs), then it may be reasonable to admit the patient to a step-down unit.[14]

Hypoglycemia

In patients with type 1 diabetes who have a transient episode of hypoglycemia but can tolerate food, whose hypoglycemia is readily corrected by oral foods and/or IV dextrose, and in whom the etiology of the hypoglycemia can be ascertained and mitigated, then discharge is reasonable. In patients who are hypoglycemic and unable to tolerate oral food or fluids, admission is advisable.

In diabetics who are using oral medicines (specifically, sulfonylureas), admission is generally advisable due to the high risk of recurrence of hypoglycemia. This is especially true with the longer-acting sulfonylureas.

In nondiabetics who develop hypoglycemia, the admission decision should incorporate the potential cause as well as the factors related to the episode, such as the severity of the hypoglycemia, the risk of recurrence of the episode, and the persistence of the hypoglycemia. If the patient is at a low risk for recurrence, the hypoglycemia is brief, and the drop in serum glucose was minor, then discharge with outpatient follow-up would be a reasonable option. Otherwise, if the hypoglycemia was severe, the risk of recurrence is high, or the hypoglycemia was prolonged, then admission would be advisable.

Summary

Diabetic emergencies can be classified into 2 categories: hyperglycemic and hypoglycemic.

Hyperglycemic emergencies can be further stratified into DKA and HHS. The management for hyperglycemia is similar in both DKA and HHS. Normal saline is the initial resuscitation fluid, and adjustment of the crystalloid solution is dependent on the patient's hydration status. Intravenous insulin is also given in both DKA and HHS. Monitoring of the electrolytes, especially potassium, is critical to reducing morbidity and mortality.

In hypoglycemia, the underlying etiology of the hypoglycemia should be investigated and underlying comorbidities should be considered. In most cases, a patient with type 1 diabetes with a known cause of the hypoglycemia who is tolerating food and fluids, discharge is a reasonable candidate for discharge. If the cause of the hypoglycemia is unknown or the risk of recurrence of the hypoglycemia is high, admission should be considered. In cases where a patient using oral medications for diabetes develops hypoglycemia and the risk of recurrence is high, the hypoglycemia was severe, or the hypoglycemia was prolonged, then admission is generally advisable. In cases of oral medications for diabetes where the risk of recurrence is low, the hypoglycemia was mild, or the hypoglycemia was brief and transient, then discharge with close outpatient follow-up would be reasonable. In nondiabetics who develop hypoglycemia, the decision for admission should factor in the potential etiology as well as factors related to the episode.

Case Conclusions

You ordered the appropriate tests for the first patient, the 26-year-old woman who was vomiting and sleepy, and discovered that her serum beta-hydroxybutyrate was 4 times normal. You asked the nurse to start the normal saline IV, and the patient received several liters prior to the lab tests returning. The tests showed that she had a serum potassium of 5.8 mEq/L, so you initiated the insulin drip at 0.14 units/kg/h and decided to forgo the insulin bolus, based on your recent reading about insulin in DKA. Since the patient's bicarb was 9 mEq/L, you decided to admit her to the ICU. Unfortunately, there were no ICU beds, so for the next 8 hours you managed the patient in the ED. When her serum glucose approached 200 mg/dL, you changed to D5 half-normal saline for the fluid infusion, and decreased the insulin infusion to 0.04 units/kg/h. By the time she went up to the ICU, her gap had decreased from 29 to 19 mEq/L and her bicarbonate had increased to 18 mEq/L. She had an unremarkable course in the ICU, was eventually transferred to the floor, and by her fourth day in the hospital, was able to be safely discharged.

Because of your 56-year-old unresponsive patient's altered mental status, you considered hypoglycemia, hypoxia, and opioid overdose in your differential. His oxygen saturation was 98%. His pupils did not appear pinpoint, so you requested that the nurse obtain a capillary serum glucose and empirically administered 25 gm dextrose through his IV. Within several minutes, the patient became more awake and started answering questions. At that time, the nurse advised you that the patient's serum glucose was 58 mg/dL. The patient said that he normally takes a glyburide at home and that he had been having trouble with his blood sugar being too low. Given that the frequency and severity of his hypoglycemic events had been increasing, you started him on a D5 normal saline infusion, consulted his private physician, and discussed admission to the ICU with the intensivist. You ordered octreotide be at the bedside for subcutaneous administration in case the dextrose infusion was unsuccessful. The patient was admitted to the ICU, and he had several additional episodes of hypoglycemia. In the last episode, he did not respond to the dextrose infusion or boluses, so subcutaneous octreotide was administered. His serum glucose improved on this regimen, and after a 1-day stay in the ICU

Risk Management Pitfalls For Diabetic Emergencies

1. **"I ordered a serum ketone, and it was mildly elevated. I was told later that the patient was in severe DKA."**
   The preferred laboratory value to examine for DKA is beta-hydroxybutyrate. In DKA, the ratio of the beta-hydroxybutyrate to acetoacetate or acetone changes in response to the increased ketones. Instead of 1:1, it increases to as much as 5:1 of beta-hydroxybutyrate to acetoacetate. Beta-hydroxybutyrate will more accurately reflect whether the patient is in DKA.

2. **"The elderly patient had HHS, but I thought the floor could handle him."**
   In patients with HHS, admission to the intensive care unit is prudent, given that they will be on insulin drips and because of their underlying medical conditions. If a patient has few or no underlying medical conditions and responds well to management in the ED as observed through laboratory tests and vital signs, then it may be reasonable to admit the patient to a step-down unit.

3. **"The patient had family members with nausea, vomiting, and diarrhea. I didn't think that his diabetes was the cause of his nausea and vomiting."**
   Have a low threshold for checking blood sugar and a basic metabolic profile. The etiology of the diabetic emergency can be from a viral illness or some other physiologic stressor.

4. **"The patient had HHS, but also a history of congestive heart failure, so I started him on an insulin infusion but held back the fluids. I thought treating the hyperglycemia alone would help resolve the patient's tachycardia."**
   Patients with HHS have an average deficit of 8 to 10 liters of fluid. Rehydration is a key initial management strategy in treating this ailment. Both hydration and insulin would have helped manage this patient's pathology.

5. **"The patient who had DKA received 9 liters of fluid and then started to develop mental status changes."**
   Although rare, cerebral edema does develop in adults. Using the correct rehydration may reduce the risk of this devastating illness.[68] Mannitol may be considered once neurological symptoms occur.[31,99] Additionally, fluid infusion rates should be decreased and the head of the bed should be elevated. An alternative to mannitol is hypertonic saline, which can be given at a dose of 5 to 10 mL/kg of 3% saline over 30 minutes.[100,101]

6. **"The patient's potassium was elevated and he was in DKA, so I gave him kayexalate."**
   In DKA, the serum potassium may be elevated, but unless there are ECG changes, the management for the elevated potassium is to manage the DKA. The insulin infusion will allow the potassium to transition intracellularly, thereby decreasing the serum potassium. If the potassium is decreased prior to the insulin infusion, the patient may become hypokalemic and develop life-threatening dysrhythmias.

7. **"The patient was diabetic, and I checked his serum glucose and it was not elevated; therefore, he could not be in DKA."**
   A patient may have DKA with a normal blood sugar. This pathology is referred to as euglycemic DKA. Typically, the patient has vomiting, but continues to use his/her insulin. In this situation, the beta-hydroxybutyrate levels will be crucial to the successful diagnosis of DKA.

8. **"I knew the patient was in DKA, so I started the insulin infusion. I did not know that his potassium of 2.8 mEq/L was going to be problematic."**
   Patients in DKA tend to have a normal to low body potassium level. If the serum potassium is < 3.3 mEq/dL, then the initial management strategy is to administer fluids with potassium intravenously; once the serum potassium is ≥ 3.3 mEq/dL, then the insulin infusion can be initiated. If this is not done, the patient may develop life-threatening dysrhythmias from the hypokalemia. Repletion of potassium can be achieved by infusing potassium at 20 to 30 mEq/h, usually mixing 40 to 60 mEq of potassium in a liter of half-normal saline.[67,68]

9. **"The patient's blood sugar improved and she was tolerating food, so I discharged her. She was on a sulfonylurea, but her vitals looked fine."**
   In diabetics who are using sulfonylureas, admission is generally advisable due to the high risk of recurrence of hypoglycemia. This is especially true with the longer-acting sulfonylureas.

10. **"There were no intensive care unit beds and the ED was very busy. I kept the patient with DKA on the normal saline infusion and insulin, but I didn't expect him to become so hypoglycemic."**
    When the serum glucose is 200 mg/dL, consider decreasing the insulin infusion rate from 0.1 or 0.14 units/kg/h to 0.02 to 0.05 units/kg/h and adding dextrose to the infusing fluids. If this is not done, the patient's glucose can drop too rapidly and hypoglycemia may ensue.

and a 1-day stay on the floor, he was discharged home with primary care follow-up in 1 to 2 days.

The family of your elderly third patient who was being treated for pneumonia related that over the last few days he had been getting more confused and tired. You ordered the appropriate lab work. He had very dry oral mucosa, and you started IV fluids. The lab called you and advised that his blood glucose was 1044 mg/dL. His labs did not show an anion gap, and his pH was normal. You diagnosed HHS and started resuscitation with several liters of normal saline. You also started him on an insulin infusion at a rate of 0.14 units/kg/h and called the ICU to admit him. He had an unremarkable 2-day stay in the ICU and was then transferred to the floor. He stayed there for 2 days and was discharged home with follow-up with his primary doctor in 1-2 days. By discharge, his confusion had resolved, and he stated he felt that he was back to baseline. The ICU and hospitalist attributed his hyperglycemia to the pneumonia as well as a stress response. They noted that they changed his antibiotic from the outpatient amoxicillin to IV vancomycin and levofloxacin. Once on the floor, his antibiotic was narrowed down to only levofloxacin, without any return of his symptoms.

Time- And Cost-Effective Strategies

- When a patient presents with altered mental status or there is a concern for hypoglycemia or hyperglycemia, a capillary blood glucose (ie, finger-stick glucose) is an inexpensive screening tool that may help narrow down the differential and guide further diagnostic studies.
- When evaluating a patient for DKA, consider measuring the level of beta-hydroxybutyrate instead of acetoacetate or acetone, as it better reflects the amount of serum ketones. In DKA, the ratio of the beta-hydroxybutyrate changes in response to the increased ketones.[63] Instead of 1:1, it increases to as much as 5:1 of beta-hydroxybutyrate to acetoacetate or acetone.[63]
- When managing a patient with DKA or hyperosmolar hyperglycemia, the initial management is to provide intravenous fluids. Isotonic saline (0.9%) is the initial fluid used to increase intravascular, intracellular, and interstitial volumes.[20] Normal saline helps to return normal renal perfusion and start to decrease the serum glucose through glycosuria. It also increases the body's response to low-dose insulin.[20]
- In stable patients with mild DKA, subcutaneous insulin is an alternative to intravenous treatment.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

1. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: Centers for Disease Control and Prevention; 2011.
2. Graz B, Dicko M, Willcox ML, et al. Sublingual sugar for hypoglycaemia in children with severe malaria: a pilot clinical study. *Malar J.* 2008;7:242. **(Randomized nonblinded trial; 151 patients)**
3. Barennes H, Valea I, Nagot N, et al. Sublingual sugar administration as an alternative to intravenous dextrose administration to correct hypoglycemia among children in the tropics. *Pediatrics.* 2005;116(5):e648-e653. **(Randomized nonblinded trial; 69 patients)**
4. Arora S, Henderson SO, Long T, et al. Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: beta-hydroxybutyrate versus the urine dipstick. *Diabetes Care.* 2011;34(4):852-854. **(Prospective observational study; 516 patients)**
5. Goyal N, Miller JB, Sankey SS, et al. Utility of initial bolus insulin in the treatment of diabetic ketoacidosis. *J Emerg Med.* 2010;38(4):422-427. **(Prospective observational cohort chart review; 157 patients)**
6.* Kitabchi AE, Murphy MB, Spencer J, et al. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? *Diabetes Care.* 2008;31(11):2081-2085. **(Randomized prospective study; 47 patients)**
7. Umpierrez GE, Latif K, Stoever J, et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. *Am J Med.* 2004;117(5):291-296. **(Randomized controlled trial; 40 patients)**
8. Ganong WF. *Review of Medical Physiology.* 22nd ed. New York: The McGraw-Hill Companies; 2005.
9. Ganong WF. *Ganong's Review of Medical Physiology.* 24th ed. New York: The McGraw Hill Companies; 2012.
10. Lin MV, Bishop G, Benito-Herrero M. Diabetic ketoacidosis in type 2 diabetics: a novel presentation of pancreatic adenocarcinoma. *J Gen Intern Med.* 2010;25(4):369-373. **(Case report)**
11. Welch BJ, Zib I. Case study: diabetic ketoacidosis in type 2 diabetes: "look under the sheets." *Clinical Diabetes.* 2004;22(4):198-200. **(Case reports)**
12. Rewers A, Klingensmith G, Davis C, et al. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the search for diabetes in youth study. *Pediatrics.* 2008;121(5):e1258-e1266. **(Retrospective chart review; 2824 patients)**
13. Chaithongdi N, Subauste JS, Koch CA, et al. Diagnosis and management of hyperglycemic emergencies. *Hormones* (Athens). 2011;10(4):250-260. **(Review)**

14. Graffeo CS. Hyperosmolar hyperglycemic state. In: *Tintinalli's Emergency Medicine*. Tintinalli JE, Stapczynski JS, Cline DM, et al, eds. 7th ed. New York: McGraw-Hill Companies, Inc. 2011. **(Textbook)**
15. Lorber D. Nonketotic hypertonicity in diabetes mellitus. *Med Clin North Am.* 1995;79(1):39-52. **(Review)**
16. Arieff AI. Cerebral edema complicating nonketotic hyperosmolar coma. *Miner Electrolyte Metab.* 1986;12(5-6):383-389. **(Case reports; 5 patients)**
17. Maccario M, Messis CP, Vastola EF. Focal seizures as a manifestation of hyperglycemia without ketoacidosis. A report of seven cases with review of the literature. *Neurology*. 1965;15:195-206. **(Case report)**
18. Maccario M. Neurological dysfunction associated with nonketotic hyperglycemia. *Arch Neurol.* 1968;19(5):525-534. **(Case report)**
19. Guisado R, Arieff AI. Neurologic manifestations of diabetic comas: correlation with biochemical alterations in the brain. *Metabolism.* 1975;24(5):665-679. **(Review)**
20.* Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care.* 2009;32(7):1335-1343. **(Guidelines)**
21. Ha WC, Oh SJ, Kim JH, et al. Severe hypoglycemia is a serious complication and becoming an economic burden in diabetes. *Diabetes Metab J.* 2012;36(4):280-284. **(Retrospective analysis; 320 patients)**
22. McCoy RG, Van Houten HK, Ziegenfuss JY, et al. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care.* 2012;35(9):1897-1901. **(Retrospective study; 1020 patients)**
23. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2009;94(3):709-728. **(Review)**
24. Graveling AJ, Frier BM. Review: does hypoglycaemia cause cardiovascular events? *The British Journal of Diabetes & Vascular Disease.* 2010;10(1):5-13. **(Review)**
25. Svensson AM, McGuire DK, Abrahamsson P, et al. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J.* 2005;26(13):1255-1261. **(Retrospective analysis of prospectively collected data; 713 consecutive patients)**
26. Tanenberg RJ, Newton CA, Drake AJ. Confirmation of hypoglycemia in the "dead-in-bed" syndrome, as captured by a retrospective continuous glucose monitoring system. *Endocr Pract.* 2010;16(2):244-248. **(Case report)**
27. Kosiborod M, Inzucchi SE, Krumholz HM, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation.* 2008;117(8):1018-1027. **(Retrospective cohort; 16,871 patients)**
28. Prakash S, Galluccio S. Three strikes and you're out: unanticipated hyperkalaemic cardiac arrest following rapid sequence intubation. *Anaesth Intensive Care.* 2012;40(1):187-188. **(Case report)**
29. Jackson MA, Lodwick R, Hutchinson SG. Hyperkalaemic cardiac arrest successfully treated with peritoneal dialysis. *BMJ.* 1996;312(7041):1289-1290. **(Case report)**
30. Ritchie JV, Juliano ML, Thurman, RJ. ECG Abnormalities. In: *The Atlas of Emergency Medicine.* 3rd edition. New York: The McGraw Hill Companies; 2009. **(Textbook)**
31. Chansky MEL, C. L. Diabetic Ketoacidosis. In: *Tintinalli's Emergency Medicine: A Comprehensive Study Guide.* New York: The McGraw Hill Companies; 2011. **(Textbook)**
32. Newton CR, Delgado JH, Gomez HF. Calcium and beta receptor antagonist overdose: a review and update of pharmacological principles and management. *Semin Respir Crit Care Med.* 2002;23(1):19-25. **(Review)**
33. Levine M, Boyer EW, Pozner CN, et al. Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil. *Crit Care Med.* 2007;35(9):2071-2075. **(Retrospetive chart review; 40 patients)**
34. Gangji AS, Cukierman T, Gerstein HC, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care.* 2007;30(2):389-394. **(Meta-analysis)**
35. Agarwal DK, Jeloka T, Sharma A, et al. Steroid-induced diabetes mellitus presenting as diabetic ketoacidosis. *Indian Journal of Nephrology.* 2002;12(4):122. **(Case report)**
36. Alavi IA, Sharma BK, Pillay VK. Steroid-induced diabetic ketoacidosis. *Am J Med Sci.* 1971;262(1):15-23. **(Case reports; 13 patients)**
37. Alavi IA, Pillay VKG. Steroid-induced diabetic ketoacidosis. *Ann Intern Med.* 1970;72(5):787-787. **(Case reports; 4 patients)**
38. Kang SH, Lee JY, Park HS, et al. Hyperglycemic hyperosmolar syndrome caused by steroid therapy in a patient with lupus nephritis. *J Korean Med Sci.* 2011;26(3):447-449. **(Case report)**
39. Warner EA, Greene GS, Buchsbaum MS, et al. Diabetic ketoacidosis associated with cocaine use. *Arch Intern Med.* 1998;158(16):1799-1802. **(Retrospective case-control study; 720 patients)**
40. Nyenwe EA, Loganathan RS, Blum S, et al. Active use of cocaine: an independent risk factor for recurrent diabetic ketoacidosis in a city hospital. *Endocr Pract.* 2007;13(1):22-29. **(Retrospective cohort analysis; 168 patients)**
41. Kearney T, Dang C. Diabetic and endocrine emergencies. *Postgrad Med J.* 2007;83(976):79-86. **(Review)**
42. Umpierrez G, Freire AX. Abdominal pain in patients with hyperglycemic crises. *J Crit Care.* 2002;17(1):63-67. **(Prospective evaluation; 200 consecutive patients)**
43. Yong AW, Morris Z, Shuler K, et al. Acute symptomatic hypoglycaemia mimicking ischaemic stroke on imaging: a systematic review. *BMC Neurol.* 2012;12:139. **(Systematic review; 42 papers)**
44. Chang Y, Zhang MC, Wan HH, et al. Magnetic resonance imaging features in seizures associated with nonketotic hyperglycemia. *Neurol India.* 2013;61(5):528-530.
45. Aquino A, Gabor AJ. Movement-induced seizures in nonketotic hyperglycemia. *Neurology.* 1980;30(6):600-604. **(Case reports; 2 patients)**
46. Hoizey G, Lamiable D, Trenque T, et al. Identification and quantification of 8 sulfonylureas with clinical toxicology interest by liquid chromatography-ion-trap tandem mass spectrometry and library searching. *Clin Chem.* 2005;51(9):1666-1672. **(Laboratory analysis; 134 cases)**
47. Walfish PG, Feig DS, Bauman WA. Factitious hyperinsulinemic hypoglycemia: confirmation of the diagnosis by a species-specific insulin radioimmunoassay. *J Endocrinol Invest.* 1987;10(6):601-604. **(Case report)**
48. Andersen L, Jorgensen PN, Jensen LB, et al. A new insulin immunoassay specific for the rapid-acting insulin analog, insulin aspart, suitable for bioavailability, bioequivalence, and pharmacokinetic studies. *Clin Biochem.* 2000;33(8):627-633. **(Laboratory analysis)**
49. Moriyama M, Hayashi N, Ohyabu C, et al. Performance evaluation and cross-reactivity from insulin analogs with the ARCHITECT insulin assay. *Clin Chem.* 2006;52(7):1423-1426. **(Laboratory analysis of ARCHITECT assay)**
50. Neal JM, Han W. Insulin immunoassays in the detection of insulin analogues in factitious hypoglycemia. *Endocr Pract.* 2008;14(8):1006-1010. **(Case report)**
51. Grunberger G, Weiner JL, Silverman R, et al. Factitious hypoglycemia due to surreptitious administration of insulin. Diagnosis, treatment, and long-term follow-up. *Ann Intern Med.* 1988;108(2):252-257. **(Follow-up study; 10 patients)**
52. Murray BJ. Hypoglycemia secondary to factitious hyperinsulinism. *Postgrad Med.* 1981;69(2):237, 240-231. **(Case report)**

53. Lupsa BC, Chong AY, Cochran EK, et al. Autoimmune forms of hypoglycemia. *Medicine* (Baltimore). 2009;88(3):141-153. **(Case report)**
54. Cheuvront SN, Ely BR, Kenefick RW, et al. Biological variation and diagnostic accuracy of dehydration assessment markers. *Am J Clin Nutr.* 2010;92(3):565-573.
55. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. *Am J Med.* 1999;106(4):399-403.
56. Kitabchi AE. Clinical features and diagnosis of diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults. 2013. Available at: http://www.uptodate.com/contents/clinical-features-and-diagnosis-of-diabetic-ketoacidosis-and-hyperosmolar-hyperglycemic-state-in-adults?source=preview&anchor=H12&selectedTitle=1~150#H12. Accessed March 2, 2013.
57. Lin CJ, Chen YC, Chen HH, et al. Life-threatening ventricular arrhythmia induced by hypokalemia during sodium bicarbonate infusion. *South Med J.* 2008;101(2):215-216. **(Case report)**
58. Cortesi C, Bettinelli A, Emma F, et al. Severe syncope and sudden death in children with inborn salt-losing hypokalaemic tubulopathies. *Nephrol Dial Transplant.* 2005;20(9):1981-1983. **(Chart analysis; 249 patients)**
59. Facchini M, Sala L, Malfatto G, et al. Low-K+ dependent QT prolongation and risk for ventricular arrhythmia in anorexia nervosa. *Int J Cardiol.* 2006;106(2):170-176. **(Evaluation of 29 patients with anorexia nervosa compared to 29 controls)**
60. Maeder M, Rickli H, Sticherling C, et al. Hypokalaemia and sudden cardiac death--lessons from implantable cardioverter defibrillators. *Emerg Med J.* 2007;24(3):206-208. **(Case reports; 4 patients)**
61. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab.* 1983;57(1):177-180. **(Randomized control study; 30 patients)**
62. Wilson HK, Keuer SP, Lea AS, et al. Phosphate therapy in diabetic ketoacidosis. *Arch Intern Med.* 1982;142(3):517-520. **(Randomized control study; 44 patients)**
63. Wallace TM, Matthews DR. Recent advances in the moni3oring and management of diabetic ketoacidosis. *QJM.* 2004;97(12):773-780. **(Review)**
64. Gennis PR, Skovron ML, Aronson ST, et al. The usefulness of peripheral venous blood in estimating acid-base status in acutely ill patients. *Ann Emerg Med.* 1985;14(9):845-849. **(Prospective pilot study; 183 patients)**
65.* Kelly AM, Kyle E, McAlpine R. Venous pCO(2) and pH can be used to screen for significant hypercarbia in emergency patients with acute respiratory disease. *J Emerg Med.* 2002;22(1):15-19. **(Prospective study; 196 patients)**
66.* MacGillivray MH, Li PK, Lee JT, et al. Elevated plasma beta-hydroxybutyrate concentrations without ketonuria in healthy insulin-dependent diabetic patients. *J Clin Endocrinol Metab.* 1982;54(3):665-668. **(Case control study; 30 subjects)**
67. Kitabchi AE. Treatment of diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults. 201. Available at: http://www.uptodate.com/contents/treatment-of-diabetic-ketoacidosis-and-hyperosmolar-hyperglycemic-state-in-adults?source=search_result&search=diabetic+ketoacidosis+. Accessed March 3, 2013.
68. Hoorn EJ, Carlotti AP, Costa LA, et al. Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. *J Pediatr.* 2007;150(5):467-473. **(Retrospective study; 79 patients)**
69. Haringhuizen A, Tjan DH, Grool A, et al. Fatal cerebral oedema in adult diabetic ketoacidosis. *Neth J Med.* 2010;68(1):35-37. **(Case report)**
70. Troy PJ, Clark RP, Kakarala SG, et al. Cerebral edema during treatment of diabetic ketoacidosis in an adult with new onset diabetes. *Neurocrit Care.* 2005;2(1):55-58. **(Case report)**
71. Hiller KM, Wolf SJ. Cerebral edema in an adult patient with diabetic ketoacidosis. *Am J Emerg Med.* 2005;23(3):399-400. **(Case report)**
72. Abramson E, Arky R. Diabetic acidosis with initial hypokalemia. Therapeutic implications. *JAMA.* 1966;196(5):401-403. **(Case report)**
73. Tillman CR. Hypokalemic hypoventilation complicating severe diabetic ketoacidosis. *South Med J.* 1980;73(2):231-233. **(Case report)**
74.* Chua HR, Schneider A, Bellomo R. Bicarbonate in diabetic ketoacidosis - a systematic review. *Ann Intensive Care.* 2011;1(1):23. **(Systematic review)**
75. Darby TD, Aldinger EE, Gadsden RH, et al. Effects of metabolic acidosis on ventricular isometric systolic tension and the response to epinephrine and levarterenol. *Circ Res.* 1960;8:1242-1253. **(Prospective animal study; 78 dogs)**
76. Monroe RG, French G, Whittenberger JL. Effects of hypocapnia and hypercapnia on myocardial contractility. *Am J Physiol.* 1960;199:1121-1124. **(Prospective animal study; 15 dogs)**
77. Ng ML, Levy MN, Zieske HA. Effects of changes of pH and of carbon dioxide tension on left ventricular performance. *Am J Physiol.* 1967;213(1):115-120. **(Prospective animal study; 74 dogs)**
78. Wildenthal K, Mierzwiak DS, Myers RW, et al. Effects of acute lactic acidosis on left ventricular performance. *Am J Physiol.* 1968;214(6):1352-1359. **(Prospective animal study; 15 dogs)**
79. Cryer PE. Management of hypoglycemia during treatment of diabetes mellitus. 2014. Available at: http://www.uptodate.com/contents/management-of-hypoglycemia-during-treatment-of-diabetes-mellitus?source=search_result&search=management+of+hypoglycemia&selectedTitle=1~150. Accessed March 3, 2013.
80. Bloomfield HE, Greer N, Newman D, et al. Predictors and consequences of severe hypoglycemia in adults with diabetes - a systematic review of the evidence. VA-ESP Project #09-009. Minneapolis, MN; 2012. **(Government report)**
81. Dougherty PP, Klein-Schwartz W. Octreotide's role in the management of sulfonylurea-induced hypoglycemia. *J Med Toxicol.* 2010;6(2):199-206. **(Review)**
82. Hanchard B, Boulouffe C, Vanpee D. Sulfonylurea-induced hypoglycaemia: use of octreotide. *Acta Clin Belg.* 2009;64(1):56-58. **(Case report)**
83. Carr R, Zed PJ. Octreotide for sulfonylurea-induced hypoglycemia following overdose. *Ann Pharmacother.* 2002;36(11):1727-1732. **(Case report)**
84. Glatstein M, Scolnik D, Bentur Y. Octreotide for the treatment of sulfonylurea poisoning. *Clin Toxicol* (Phila). 2012;50(9):795-804. **(Case series review; 53 patients)**
85. Fasano CJ, O'Malley G, Dominici P, et al. Comparison of octreotide and standard therapy versus standard therapy alone for the treatment of sulfonylurea-induced hypoglycemia. *Ann Emerg Med.* 2008;51(4):400-406. **(Prospective double-blind placebo controlled trial; 40 patients)**
86. Sargent AI, Overton CC, Kuwik RJ, et al. Octreotide-induced hyperkalemia. *Pharmacotherapy.* 1994;14(4):497-501. **(Case report)**
87. Brown RO, Hamrick KD, Dickerson RN, et al. Hyperkalemia secondary to concurrent pharmacotherapy in a patient receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1996;20(6):429-432. **(Case report)**
88. Sharma AM, Thiede HM, Keller F. Somatostatin-induced hyperkalemia in a patient on maintenance hemodialysis. *Nephron.* 1991;59(3):445-448. **(Case report)**
89. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2010;122(18 Suppl

3):S729-S767. **(Review)**
90. Alivanis P, Giannikouris I, Paliuras C, et al. Metformin-associated lactic acidosis treated with continuous renal replacement therapy. *Clin Ther.* 2006;28(3):396-400. **(Case report)**
91. Bruijstens LA, van Luin M, Buscher-Jungerhans PM, et al. Reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment. *Neth J Med.* 2008;66(5):185-190. **(Case reports; 3 patients)**
92. No authors listed. Standards of medical care in diabetes--2011. *Diabetes Care.* 2011;34 Suppl 1:S11-S61. **(Consensus document)**
93. Wing RR, Blair EH, Bononi P, et al. Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. *Diabetes Care.* 1994;17(1):30-36. **(Prospective; 93 patients)**
94. Kirwan JP, Solomon TP, Wojta DM, et al. Effects of 7 days of exercise training on insulin sensitivity and responsiveness in type 2 diabetes mellitus. *Am J Physiol Endocrinol Metab.* 2009;297(1):E151-E156. **(Prospective; 14 patients)**
95. Winnick JJ, Sherman WM, Habash DL, et al. Short-term aerobic exercise training in obese humans with type 2 diabetes mellitus improves whole-body insulin sensitivity through gains in peripheral, not hepatic insulin sensitivity. *J Clin Endocrinol Metab.* 2008;93(3):771-778. **(Prospective; 18 patients)**
96. Pi-Sunyer X, Blackburn G, Brancati FL, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care.* 2007;30(6):1374-1383. **(Prospective randomized controlled trial; 5145 patients)**
97. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med.* 2001;344(4):264-269. **(Case control; 416 patients)**
98. Lawrence SE, Cummings EA, Gaboury I, et al. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. *J Pediatr.* 2005;146(5):688-692. **(Case control; 39 patients)**
99. Rosenbloom AL. The management of diabetic ketoacidosis in children. *Diabetes Ther.* 2010;1(2):103-120. **(Review)**
100. Kamat P, Vats A, Gross M, et al. Use of hypertonic saline for the treatment of altered mental status associated with diabetic ketoacidosis. *Pediatr Crit Care Med.* 2003;4(2):239-242. **(Case series; 4 patients)**
101. Curtis JR, Bohn D, Daneman D. Use of hypertonic saline in the treatment of cerebral edema in diabetic ketoacidosis (DKA). *Pediatr Diabetes.* 2001;2(4):191-194. **(Case report)**
102. Davis SN. Canagliflozin versus glimepiride treatment in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU trial). *Expert Rev Clin Pharmacol.* 2014;7(1):21-23. **(Randomized double-blind phase 3 noninferiority trial)**
103. Song JC, Kaubisch S, Doan T, et al. Canagliflozin--an emerging treatment option for type 2 diabetes mellitus. 2013. Available at: http://formularyjournal.modernmedicine.com/formulary-journal/news/user-defined-tags/canagliflozin/canagliflozin-emerging-treatment-option-type-. Accessed March 3, 2013. **(Review)**

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1. Insulin provides which of the following functions?
   a. Increases the storage of glucose, amino acids, and fatty acids
   b. Decreases the body's stores of glucose, fatty acids, and amino acids
   c. Mediates adrenergic response to stress stimuli
   d. Increases red blood cell production

2. Diabetes arises from:
   a. Solely genetic factors
   b. Solely environmental factors
   c. From early allergen exposure
   d. From genetic and environmental factors

3. The mortality rate for DKA is:
   a. < 2% b. 5% to 20%
   c. 40% to 50% d. > 70%

4. The mortality rate for HHS is:
   a. < 2%
   b. 5% to 20%
   c. 40% to 50%
   d. > 70%

5. HHS is more commonly seen in:
   a. Men
   b. Elderly people
   c. Women
   d. Young people

6. The onset for HHS is:
   a. Minutes
   b. Hours to days
   c. Days to weeks
   d. Weeks to months

7. **The average fluid deficit in DKA is:**
   a. 1 to 3 liters
   b. 3 to 6 liters
   c. 6 to 8 liters
   d. 8 to 10 liters

8. **Intravenous fluids and insulin infusion rate in DKA should be changed when the serum glucose is approximately:**
   a. 200 mg/dL
   b. 300 mg/dL
   c. 400 mg/dL
   d. 600 mg/dL

9. **Potassium should be administered in DKA prior to administration of insulin when the potassium level is:**
   a. > 6.5 mEq/L
   b. 5.5 to 6.5 mEq/L
   c. 4.5 to 5.5 mEq/L
   d. < 3.3 mEq/L

10. **In cases of sulfonylurea-induced hypoglycemia refractory to intravenous dextrose, the following agent may be useful:**
   a. Glucagon
   b. Epinephrine
   c. Octreotide
   d. Insulin

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Physician CME Information

Date of Original Release: June 1, 2014. Date of most recent review: May 10, 2014. Termination date: June 1, 2017.

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Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

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