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2018 Clinical Practice Guidelines

Hyperglycemic Emergencies in Adults

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetic ketoacidosis and hyperosmolar hyperglycemic state should be suspected in people who have diabetes and are ill. If either diabetic ketoacidosis or hyperosmolar hyperglycemic state is diagnosed, precipitating factors must be sought and treated.
- Diabetic ketoacidosis and hyperosmolar hyperglycemic state are medical emergencies that require treatment and monitoring for multiple metabolic abnormalities and vigilance for complications.
- A normal or mildly elevated blood glucose level does not rule out diabetic ketoacidosis in certain conditions, such as pregnancy or with SGLT2 inhibitor use.
- Diabetic ketoacidosis requires intravenous insulin administration (0.1 units/kg/h) for resolution. Bicarbonate therapy may be considered only for extreme acidosis (pH ≤7.0).

KEY MESSAGES FOR PEOPLE WITH DIABETES

When you are sick, your blood glucose levels may fluctuate and be unpredictable:

- During these times, it is a good idea to check your blood glucose levels more often than usual (for example, every 2 to 4 hours).
- Drink plenty of sugar-free fluids or water.
- If you have type 1 diabetes with blood glucose levels remaining over 14 mmol/L before meals, or if you have symptoms of diabetic ketoacidosis (see Table 1), check for ketones by performing a urine ketone test or blood ketone test. Blood ketone testing is preferred over urine testing.
- Develop a sick-day plan with your diabetes health-care team. This should include information on:
  - Which diabetes medications you should continue and which ones you should temporarily stop
  - Guidelines for insulin adjustment if you are on insulin
  - Advice on when to contact your health-care provider or go to the emergency room.

Note: Although the diagnosis and treatment of diabetic ketoacidosis (DKA) in adults and in children share general principles, there are significant differences in their application, largely related to the increased risk of life-threatening cerebral edema with DKA in children and adolescents. The specific issues related to treatment of DKA in children and adolescents are addressed in the Type 1 Diabetes in Children and Adolescents chapter, p. S234.

Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are diabetes emergencies with overlapping features. With insulin deficiency, hyperglycemia causes urinary losses of water and electrolytes (sodium, potassium, chloride) and the resultant extracellular fluid volume (ECFV) depletion. Potassium is shifted out of cells, and ketoacidosis occurs as a result of elevated glucagon levels and insulin deficiency (in the case of type 1 diabetes). There may also be high catecholamine levels suppressing insulin release (in the case of type 2 diabetes). In DKA, ketoacidosis is prominent while, in HHS, the main features are ECFV depletion and hyperosmolarity. HHS is the preferred term to describe this condition as opposed to hyperosmolar nonketotic coma (HONKC) since less than one-third of people with HHS actually present with a coma (1).

Risk factors for DKA include new diagnosis of diabetes mellitus, insulin omission, infection, myocardial infarction (MI), abdominal crisis, trauma and, possibly, continuous subcutaneous insulin infusion (CSII) therapy, thyrotoxicosis, cocaine, atypical antipsychotics and, possibly, interferon. HHS is much less common than DKA (2,3). In addition to the precipitating factors noted above for DKA, HHS also has been reported following cardiac surgery and with the use of certain drugs, including diuretics, glucocorticoids, lithium and atypical antipsychotics. Infections are present in 40% to 60% of people with HHS (4). In up to 20% of cases of HHS, individuals had no prior history of diabetes (4).

The clinical presentation of DKA includes symptoms and signs of hyperglycemia, acidosis and the precipitating illness (Table 1). In HHS, there is often more profound ECFV contraction and decreased level of consciousness (proportional to the elevation in plasma osmolality). In addition, in HHS, there can be a variety of neurological presentations, including seizures and a stroke-like state that can resolve once osmolality returns to normal (3,5,6). In HHS, there also may be evidence of a precipitating condition similar to DKA.

In individuals with type 2 diabetes, the incidence of DKA is estimated to be in the range of 0.32 to 2.0 per 1,000 patient-years (7) while, in people with type 1 diabetes, the incidence is higher at 4.6

Table 1
Clinical presentation of DKA

	Symptoms	Signs
Hyperglycemia	Polyuria, polydipsia, weakness	ECFV contraction
Acidosis	Air hunger, nausea, vomiting and abdominal pain Altered sensorium	Kussmaul respiration, acetone-odoured breath Altered sensorium
Precipitating condition	See list of conditions in Table 2	

Conflict of interest statements can be found on page S113.

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to 8.0 per 1000 patient-years (8). There is a group of individuals with diabetes that present with DKA but do not have the typical features of type 1 diabetes. There are various terms given to characterize this condition, such as flatbush diabetes, type 1.5 diabetes, atypical diabetes or type 1B diabetes, but it may be most useful to label this state as ketosis-prone diabetes (KPD). There are several classification systems used to describe KPD that take into account pathophysiology and prognosis. Individuals with KPD have very little beta cell function, may or may not have beta cell antibodies, and some may require temporary or lifelong insulin therapy (9).

Prevention

Sick-day management that includes capillary beta-hydroxybutyrate monitoring reduces emergency room visits and hospitalizations in young people (10).

SGLT2 Inhibitors and DKA

SGLT2 inhibitors may lower the threshold for developing DKA through a variety of different mechanisms (11–13). The presentation of the DKA is similar to those who develop DKA without SGLT2 inhibitor exposure, except that the blood glucose (BG) levels on presentation may not be as elevated as expected. In randomized controlled trials, the incidence of DKA associated with SGLT2 inhibitors is low (≤0.1% of treated people) (14,15). In most cases, there is usually a known precipitant as a contributing factor, such as insulin dose reduction or omission, bariatric surgery or other surgery, alcohol, exercise, or low carbohydrate or reduced food intake (16–20).

Diagnosis

DKA or HHS should be suspected whenever people have significant hyperglycemia, especially if they are ill or highly symptomatic (see above). As outlined in Figure 1, to make the diagnosis and determine the severity of DKA or HHS, the following should be assessed: plasma levels of electrolytes (and anion gap), plasma glucose (PG), creatinine, osmolality and beta-hydroxybutyric acid (beta-OHB) (if available), blood gases, serum and urine ketones, fluid balance, level of consciousness, precipitating factors and complications (1). Arterial blood gases may be required for more ill individuals, when knowing the adequacy of respiratory compensation and the A-a gradient is necessary. Otherwise, venous blood gases are usually adequate—the pH is typically 0.015 to 0.03 lower than arterial pH (21-23). Point-of-care capillary blood beta-OHB measurement in emergency is sensitive and specific for DKA and, as a screening tool, may allow more rapid identification of hyperglycemic persons at risk for DKA (24–29). This test is less accurate with hemoconcentration and/or when the beta-OHB level is >3 mmol/L (30).

There are no definitive criteria for the diagnosis of DKA. Typically, the arterial pH is ≤7.3, serum bicarbonate is ≤15 mmol/L and the anion gap is >12 mmol/L with positive serum and/or urine ketones (1,31–33). PG is usually ≥14.0 mmol/L but can be lower, especially with the use of SGLT2 inhibitors (34). DKA is more challenging to diagnose in the presence of the following conditions: 1) mixed acid-base disorders (e.g. associated vomiting, which will raise the bicarbonate level); 2) if there has been a shift in the redox potential, favouring the presence of beta-OHB (rendering serum ketone testing negative); or 3) if the loss of keto anions with sodium or potassium in osmotic diuresis has occurred, leading to a return of the plasma anion gap toward normal. It is, therefore, important to measure ketones in both the serum and urine. If there is an elevated anion gap and serum ketones are negative, beta-OHB levels should be measured. Negative urine ketones should not be used to rule out DKA (35).

Measurement of serum lactate should be considered in hypoxic states. In HHS, a more prolonged duration of relative insulin insufficiency and inadequate fluid intake (or high glucose intake) results in higher PG levels (typically ≥34.0 mmol/L), plasma osmolality >320 mOsm/kg and greater ECFV contraction, but minimal acid-base disturbance (1,31).

Pregnant women in DKA typically present with lower PG levels than nonpregnant women (36), and there are case reports of euglycemic DKA in pregnancy (37,38).

Management

Objectives of management include restoration of normal ECFV and tissue perfusion; resolution of ketoacidosis; correction of electrolyte imbalances and hyperglycemia; and the diagnosis and treatment of coexistent illness. The issues that must be addressed in the individual presenting with DKA or HHS are outlined in Table 2. A summary of fluid therapy is outlined in Table 3, and a management algorithm and formulas for calculating key measurements are provided in Figure 1.

People with DKA and HHS are best managed in an intensive care unit or step-down setting (1,31,32) with specialist care (39,40). Protocols and insulin management software systems (41) may be beneficial (42,43), but there can be challenges with achieving adherence (44,45). Volume status (including fluid intake and output), vital signs, neurological status, plasma concentrations of electrolytes, anion gap, osmolality and glucose need to be monitored closely, initially as often as every 2 hours (1,31,32). Capillary blood glucose (CBG) measurements are unreliable in the setting of severe acidosis (46). Precipitating factors must be diagnosed and treated (1,31,32).

Table 2
Priorities* to be addressed in the management of adults presenting with hyperglycemic emergencies

Metabolic	Precipitating cause of DKA/HHS	Other complications of DKA/HHS
• ECFV contraction • Potassium deficit and abnormal concentration • Metabolic acidosis • Hyperosmolality (water deficit leading to increased corrected sodium concentration plus hyperglycemia)	• New diagnosis of diabetes • Insulin omission • Infection • Myocardial infarction • Stroke • ECG changes may reflect hyperkalemia (78,79) • A small increase in troponin may occur without overt ischemia (80) • Thyrotoxicosis (81) • Trauma • Drugs	• Hyper/hypokalemia • ECFV overexpansion • Cerebral edema • Hypoglycemia • Pulmonary emboli • Aspiration • Hypocalcemia (if phosphate used) • Stroke • Acute renal failure • Deep vein thrombosis

DKA, diabetic ketoacidosis; *ECFV*, extracellular fluid volume; *HHS*, hyperosmolar hyperglycemic state.
* Severity of issue will dictate priority of action.