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Clinical Practice Guidelines

Hyperglycemic Emergencies in Adults

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) should be suspected in ill patients with diabetes. If either DKA or HHS is diagnosed, precipitating factors must be sought and treated.
- DKA and HHS are medical emergencies that require treatment and monitoring for multiple metabolic abnormalities and vigilance for complications.
- A normal blood glucose does not rule out DKA in pregnancy.
- Ketoacidosis requires insulin administration (0.1 U/kg/h) for resolution; bicarbonate therapy should be considered only for extreme acidosis (pH \leq 7.0).

Note to readers: 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. S153.

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 absolute insulin deficiency (in the case of type 1 diabetes) or 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.

Risk factors for DKA include new diagnosis of diabetes mellitus, insulin omission, infection, myocardial infarction, abdominal crisis, trauma and, possibly, treatment with insulin infusion pumps, thyrotoxicosis, cocaine, atypical antipsychotics and, possibly, interferon. HHS is much less common than DKA (1,2). 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.

The clinical presentation of DKA includes symptoms of hyperglycemia, Kussmaul respiration, acetone-odoured breath, ECFV contraction, nausea, vomiting and abdominal pain. There also may be a decreased level of consciousness. 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 (2–4). In both conditions, there also may be evidence of a precipitating condition.

Prevention

Sick day management that includes capillary beta-hydroxybutyrate monitoring reduces emergency room visits and hospitalizations in young people (5).

Diagnosis

DKA or HHS should be suspected whenever patients 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), glucose, 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 (6). Arterial blood gases may be required for sicker patients, when knowing the adequacy of respiratory compensation and the A-gradient is necessary. Otherwise, venous blood gases are usually adequate—the pH is typically 0.015 to 0.03 lower than arterial pH (7–9).

Point-of-care capillary blood beta-hydroxybutyrate measurement in emergency is sensitive and specific for DKA and, as a screening tool, may allow more rapid identification of hyperglycemic patients at risk for DKA (10–15).

There are no definitive criteria for the diagnosis of DKA. Typically, the arterial pH is \leq 7.3, serum bicarbonate is \leq 15 mmol/L, and the anion gap is $>$ 12 mmol/L with positive serum and/or urine ketones (6,16,17). Plasma glucose is usually \geq 14.0 mmol/L but can be lower (18). 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.

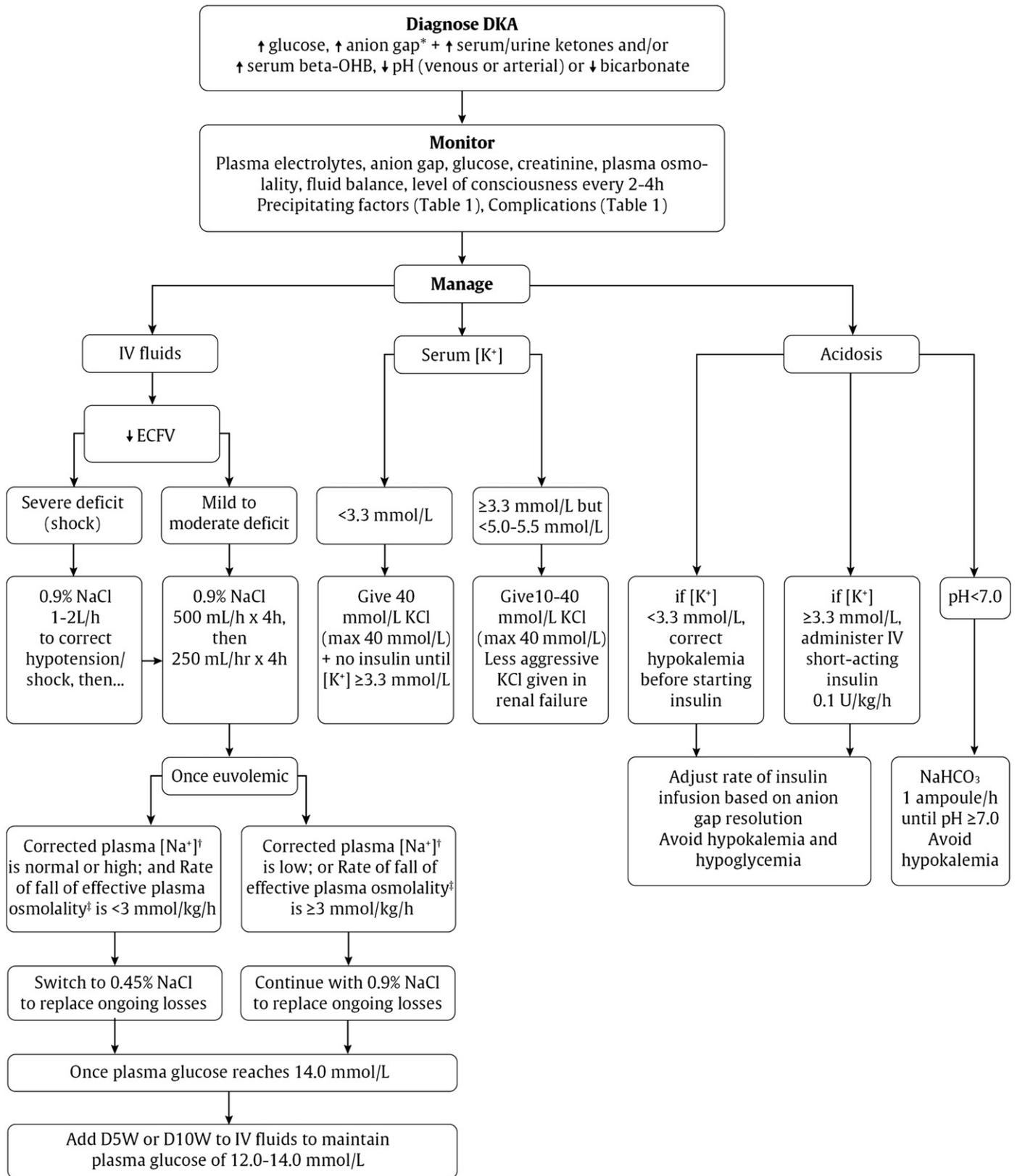


Figure 1. Management of diabetic ketoacidosis (DKA) in adults.

*Anion gap = Plasma [Na⁺] – Plasma [Cl⁻] – Plasma [HCO₃⁻]. †Corrected plasma [Na⁺] = Measured [Na⁺] + [3/10 × ([Glucose (mmol/L)] – 5)]. ‡Effective plasma osmolality = ([Na⁺] × 2) + [Glucose (mmol/L)] + [Urea (mmol/L)] reported as mmol/kg. Beta-OHB, beta-hydroxybutyric acid; ECFV, extracellular fluid volume; IV, intravenous.

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 glucose levels (typically ≥ 34.0 mmol/L) and greater ECFV contraction, but minimal acid-base disturbance (6,16).

Pregnant women in DKA typically present with lower glucose levels than nonpregnant women (19), and there are case reports of euglycemic DKA in pregnancy (20,21).

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 patient presenting with DKA or HHS are outlined in Table 1. A summary of fluid therapy is outlined in Table 2, and a management algorithm and formulas for calculating key measurements are provided in Figure 1.

Patients with DKA and HHS are best managed in an intensive care unit or step-down setting (6,16,17) with specialist care (22,23). Protocols, when followed, may be beneficial (24,25), but there can be challenges with achieving adherence (26,27). 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 (6,16,17). Precipitating factors must be diagnosed and treated (6,16,17).

ECFV contraction

The sodium deficit is typically 7–10 mmol/kg in DKA (28) and 5 to 13 mmol/kg in HHS (29), which, along with water losses (100 mL/kg and 100 to 200 mL/kg, respectively), results in decreased ECFV, usually with decreased intracellular fluid volume (28,29). Restoring ECFV improves tissue perfusion and reduces plasma glucose levels both by dilution and by increasing urinary glucose losses. ECFV re-expansion, using a rapid rate of initial fluid administration, was associated with an increased risk of cerebral edema (CE) in 1 study (30) but not in another (31). In adults, one should initially administer

Table 1

Priorities* to be addressed in the management of patients presenting with hyperglycemic emergencies

Metabolic	Precipitating cause of DKA/HHS	Other complications of DKA/HHS
<ul style="list-style-type: none"> • ECFV contraction • Potassium deficit and abnormal concentration • Metabolic acidosis • Hyperosmolality (water deficit leading to increased corrected sodium concentration plus hyperglycemia) 	<ul style="list-style-type: none"> • New diagnosis of diabetes • Insulin omission • Infection • Myocardial infarction • ECG changes may reflect hyperkalemia (57,58) • A small increase in troponin may occur without overt ischemia (59) • Thyrotoxicosis (60) • Drugs 	<ul style="list-style-type: none"> • Hyper/hypokalemia • ECFV overexpansion • Cerebral edema • Hypoglycemia • Pulmonary emboli • Aspiration • Hypocalcemia (if phosphate used) • Stroke • Acute renal failure • Deep vein thrombosis

ECFV, extracellular fluid volume; ECG, electrocardiographic; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state.

* Severity of issue will dictate priority of action.

Table 2

Summary of fluid therapy for DKA and HHS in adults

1. Administer IV normal saline initially. If the patient is in shock, give 1–2 L/h initially to correct shock; otherwise, give 500 mL/h for 4 hours, then 250 mL/h for 4 hours.
2. Add potassium immediately if patient is normo- or hypokalemic. Otherwise, if initially hyperkalemic, only add potassium once serum potassium falls to <5 to 5.5 mmol/L and patient is diuresing.
3. Once plasma glucose reaches 14.0 mmol/L, add glucose to maintain plasma glucose at 12.0–14.0 mmol/L.
4. After hypotension has been corrected, switch normal saline to half-normal saline (with potassium chloride). However, if plasma osmolality is falling more rapidly than 3 mmol/kg/h and/or the corrected plasma sodium is reduced, maintain IV fluids at higher osmolality (i.e. may need to maintain on normal saline).

DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; IV, intravenous.

intravenous (IV) normal saline 1 to 2 L/h to correct shock, otherwise 500 mL/h for 4 hours, then 250 mL/h of IV fluids (32,33).

Potassium deficit

The typical potassium deficit range is 2 to 5 mmol/kg in DKA and 4 to 6 mmol/kg in HHS (29,30). There have been no randomized trials that have studied strategies for potassium replacement. Typical recommendations suggest that potassium supplementation should be started for plasma potassium <5.0 to 5.5 mmol/L once diuresis has been established, usually with the second litre of saline. If the patient at presentation is normo- or hypokalemic, potassium should be given immediately, at concentrations in the IV fluid between 10 and 40 mmol/L, at a maximum rate of 40 mmol/h. In the case of frank hypokalemia (potassium <3.3 mmol/L), insulin should be withheld until potassium replacement at 40 mmol/h has restored plasma potassium to ≥ 3.3 mmol/L (6,16). It is reasonable to treat the potassium deficit of HHS in the same way.

Metabolic acidosis

Metabolic acidosis is a prominent component of DKA. Patients with HHS have minimal or no acidosis. Insulin is used to stop ketoacid production; IV fluid alone has no impact on parameters of ketoacidosis (34). Short-acting insulin (0.1 U/kg/h) is recommended (35–37). Although the use of an initial bolus of IV insulin is recommended in some reviews (6), there has been only 1 randomized controlled trial (RCT) in adults examining the effectiveness of this step (38). In this study, there were 3 arms: a bolus arm (0.07 units/kg, then 0.07 units/kg/h), a low-dose infusion group (no bolus, 0.07 units/kg/h), and a double-dose infusion group (no bolus, 0.14 units/kg/h). Outcomes were identical in the 3 groups, except 5 of 12 patients needed extra insulin in the no-bolus/low-dose infusion group, and the double dose group had the lowest potassium (nadir of 3.7 mmol/L on average). Unfortunately, this study did not examine the standard dose of insulin in DKA (0.1 units/kg/h). In children, using an initial bolus of IV insulin does not result in faster resolution of ketoacidosis (39,40) and increases the risk of CE. The use of subcutaneous boluses of rapid-acting insulin analogues at 1- to 2-hour intervals results in similar duration of ketoacidosis with no more frequent occurrence of hypoglycemia compared to short-acting IV insulin 0.1 U/kg/h (41–43). The dose of insulin should subsequently be adjusted based on ongoing acidosis (44), using the plasma anion gap or beta-OHB measurements. Plasma glucose levels will fall due to multiple mechanisms, including ECFV re-expansion (45), glucose losses via osmotic diuresis (34), insulin-mediated reduced glucose production and increased cellular uptake of glucose. Once plasma glucose reaches 14.0 mmol/L, IV glucose should be started to prevent hypoglycemia, targeting a plasma glucose of 12.0 to 14.0 mmol/L.

Similar doses of IV insulin can be used to treat HHS, although subjects are not acidemic, and the fall in plasma glucose concentration is predominantly due to re-expansion of ECFV and osmotic diuresis (45). Insulin has been withheld successfully in HHS (46), but generally its use is recommended to reduce plasma glucose levels (6,16).

Use of IV sodium bicarbonate to treat acidosis did not affect outcome in RCTs (47–49). Sodium bicarbonate therapy can be considered in adult patients in shock or with arterial pH ≤ 7.0 . For example, one can administer 1 ampoule (50 mmol) sodium bicarbonate added to 200 mL D5W (or sterile water, if available) over 1 hour, repeated every 1 to 2 hours until pH is ≥ 7.0 (6,16). Potential risks associated with the use of sodium bicarbonate include hypokalemia (50) and delayed occurrence of metabolic alkalosis.

Hyperosmolality

Hyperosmolality is due to hyperglycemia and a water deficit. However, serum sodium concentration may be reduced due to shift of water out of cells. The concentration of sodium needs to be corrected for the level of glycemia to determine if there is also a water deficit (Figure 1). In patients with DKA, plasma osmolality is usually ≤ 320 mmol/kg. In HHS, plasma osmolality is typically >320 mmol/kg. Because of the risk of CE with rapid reductions in osmolality (51), it has been recommended that the plasma osmolality be lowered no faster than 3 mmol/kg/h (6,16). This can be achieved by monitoring plasma osmolality, by adding glucose to the infusions when plasma glucose reaches 14.0 mmol/L to maintain it at that level and by selecting the correct concentration of IV saline. Typically, after volume re-expansion, IV fluid is switched to

half-normal saline because urinary losses of electrolytes in the setting of osmotic diuresis are usually hypotonic. The potassium in the infusion will also add to the osmolality. If osmolality falls too rapidly despite the administration of glucose, consideration should be given to increasing the sodium concentration of the infusing solution (6,16). Water imbalances can also be monitored using the corrected plasma sodium. Central pontine myelinolysis has been reported in association with overly rapid correction of hyponatremia in HHS (52).

Phosphate deficiency

There is currently no evidence to support the use of phosphate therapy for DKA (53–55), and there is no evidence that hypophosphatemia causes rhabdomyolysis in DKA (56). However, because hypophosphatemia has been associated with rhabdomyolysis in other states, administration of potassium phosphate in cases of severe hypophosphatemia may be considered for the purpose of trying to prevent rhabdomyolysis.

Complications

In Ontario, in-hospital mortality in patients hospitalized for acute hyperglycemia ranged from $<1\%$ at ages 20 to 49 years to 16% in those over 75 years (61). Reported mortality in DKA ranges from 0.65% to 3.3% (2,22,62–64). In HHS, recent studies found mortality rates to be 12% to 17%, but included patients with mixed DKA and hyperosmolality (1,3,65). About 50% of deaths occur in the first 48 to 72 hours. Mortality is usually due to the precipitating cause, electrolyte imbalances (especially hypo- and hyperkalemia) and CE.

Other Relevant Guidelines

Type 1 Diabetes in Children and Adolescents, p. S153

RECOMMENDATIONS

1. In adult patients with DKA, a protocol should be followed that incorporates the following principles of treatment: 1) fluid resuscitation, 2) avoidance of hypokalemia, 3) insulin administration, 4) avoidance of rapidly falling serum osmolality, and 5) search for precipitating cause (as illustrated in Figure 1) [Grade D, Consensus].
2. In adult patients with HHS, a protocol should be followed that incorporates the following principles of treatment: 1) fluid resuscitation, 2) avoidance of hypokalemia, 3) avoidance of rapidly falling serum osmolality, 4) search for precipitating cause, and 5) possibly insulin to further reduce hyperglycemia (as illustrated in Figure 1) [Grade D, Consensus].
3. Point-of-care capillary beta-hydroxybutyrate may be measured in the hospital in patients with type 1 diabetes with capillary glucose >14.0 mmol/L to screen for DKA, and a beta-hydroxybutyrate >1.5 mmol/L warrants further testing for DKA [Grade B, Level 2 (10–15)].
4. In individuals with DKA, IV 0.9% sodium chloride should be administered initially at 500 mL/h for 4 hours, then 250 mL/h for 4 hours [Grade B, Level 2 (32)] with consideration of a higher initial rate (1–2 L/h) in the presence of shock [Grade D, Consensus]. For persons with a HHS, IV fluid administration should be individualized based on the patient's needs [Grade D, Consensus].
5. In individuals with DKA, an infusion of short-acting IV insulin of 0.10 U/kg/h should be used ([Grade B, Level 2 (36,37)]. The insulin infusion rate should be maintained until the resolution of ketosis [Grade B, Level 2 (42)] as measured by the normalization of the plasma anion gap [Grade D, Consensus]. Once the plasma glucose concentration reaches 14.0 mmol/L, IV dextrose should be started to avoid hypoglycemia [Grade D, Consensus].

Abbreviations:

DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; IV, intravenous.

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