Diabetic Ketoacidosis

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KEYWORDS

• Diabetic ketoacidosis • Hyperglycemic crisis • Ketonemia • Insulin deficiency

HOSPITAL MEDICINE CLINICS CHECKLIST

1. The defining features of diabetic ketoacidosis (DKA) are metabolic acidosis, ketonemia, and hyperglycemia.
2. The most common precipitating factors of DKA are acute medical illness (infection), nonadherence to insulin therapy, new onset diabetes, and medications that interfere with carbohydrate metabolism.
3. DKA can also occur in a subset of patients with ketosis-prone type 2 diabetes.
4. DKA occurs when the combination of insulin deficiency and increase of counteregulatory hormones causes release of free fatty acids from adipose tissue as the body is unable to use glucose. These free fatty acids are subsequently oxidized in the liver to ketone bodies, which results in metabolic acidosis.
5. The diagnostic criteria for DKA include acidosis, low serum bicarbonate, increased anion gap, ketonemia, and ketonuria.
6. Treatment of DKA includes intravenous fluid resuscitation, correction of hyperglycemia and ketoacidosis with insulin, management of electrolyte abnormalities, and the treatment of any precipitating causes of DKA.
7. Implementation of standardized protocols to treat DKA can improve outcomes and potentially reduce hospital length of stay.

DEFINITION

What are the defining clinical features of diabetic ketoacidosis?

The most important clinical features of diabetic ketoacidosis (DKA) are:

- Metabolic acidosis
- Hyperglycemia
- Ketonemia

DKA can range from mild to severe depending on the degree of metabolic acidosis and the presence of altered mental status.[1,2]

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How does DKA differ from hyperglycemic hyperosmolar state?

Both DKA and hyperglycemic hyperosmolar state (HHS) are severe complications of uncontrolled diabetes and are life-threatening. There can be some overlap between these two syndromes in about one-third of patients.[3] HHS typically involves a greater severity of hyperglycemia and dehydration than DKA. HHS is defined by the presence of hyperosmolality, altered mental status, and the absence of significant ketosis.[1]

EPIDEMIOLOGY

How common is DKA?

The incidence of DKA varies widely worldwide.[4] In the United States, the number of hospital discharges with DKA listed as the first diagnosis has been trending up. The incidence was reported by the National Diabetes Surveillance Program of the Centers for Disease Control and Prevention as 140,000 in 2009.[5]

PATHOPHYSIOLOGY

What is the mechanism for the development of DKA?

DKA occurs in the setting of reduced or absent insulin concentrations in addition to increased levels of counter-regulatory hormones such as catecholamines, cortisol, glucagon, and growth hormone.[3]

This imbalance leads to lipolysis, or the release of free fatty acids from adipose tissue. In the setting of impaired carbohydrate use caused by insulin deficiency, the fatty acids are oxidized in the liver into ketone bodies (primarily acetoacetate and beta-hydroxybutyrate), which results in ketonemia and metabolic acidosis.[3]

Hyperglycemia is caused by increased gluconeogenesis and glycogenolysis and decreased use by peripheral tissues.[1]

How does this differ from the development of HHS?

In HHS there is enough insulin present to prevent unrestrained free fatty acid oxidation and thus prevent ketonemia and metabolic acidosis.[1]

As glucose levels continue to increase in HHS, there is a marked osmotic diuresis resulting in severe dehydration with typical total body water deficits of 7 to 12 L. Elderly patients with impaired thirst mechanism or reduced access to water are particularly at risk.[3]

What are the precipitating factors that can lead to DKA?

- Underlying medical illness[1]
  - Infection: often pneumonia or urinary tract infection
  - Ischemic events such as myocardial infarction or cerebrovascular accident
  - Acute pancreatitis
- Discontinuation of usual insulin therapy[3]
  - Noncompliance with medication
  - Poor patient education regarding diabetes management
  - Intentional discontinuation of insulin in patients with eating disorders because insulin causes weight gain[1]

- New-onset type 1 diabetes mellitus (about 15% of DKA cases[3])
- Medications that affect carbohydrate metabolism[1,3]
  - Corticosteroids
  - Thiazides
  - Pentamadine
  - Atypical antipsychotics
- Substance abuse[3]
  - Alcohol
  - Cocaine

Which patients are at risk for DKA?

In general, DKA occurs in patients with type 1 diabetes, whereas HHS occurs in patients with type 2 diabetes. However, there is overlap between the two syndromes.[2]

What is ketosis-prone type 2 diabetes?

There is a subset of patients with type 2 diabetes who are prone to developing DKA, usually without a precipitant. Many names have been used to describe this variant in the literature, including idiopathic type 1 diabetes, atypical diabetes, type 1.5 diabetes, and Flatbush diabetes. Ketosis-prone type 2 diabetes is particularly common in patients of African and Hispanic descent. More than half of newly diagnosed adult African American and Hispanic patients with unprovoked DKA have type 2 diabetes. However, this phenomenon has also been reported in white, Asian, and Native American populations.[1,6]

These patients tend to be obese, middle aged, with a strong family history of type 2 diabetes, and low prevalence of autoimmune markers including glutamic acid decarboxylase and IA-2. At presentation they have impairment of both insulin secretion and insulin action. Therefore, initial management of DKA is the same regardless of the underlying diagnosis.

Aggressive diabetes management in these patients results in significant improvement in B-cell function and insulin sensitivity.[7] Recognizing this subset of patients is important because they can be titrated off insulin and managed successfully with oral diabetes medication within 3 to 6 months of initial presentation.[6,8] Ketosis-prone type 2 diabetes can only be diagnosed weeks after the initial presentation with DKA. At that point, measurement of fasting or stimulated C-peptide levels can be used to confirm pancreatic beta-cell recovery.

PATIENT EVALUATION AND DIAGNOSIS

How do patients present with DKA?

General symptoms of hyperglycemia, such as polydipsia and polyuria, may precede the onset of DKA by several days. Symptoms of DKA usually develop over less than 24 hours. Common symptoms include nausea, vomiting, abdominal pain, dehydration, weakness, and altered mental status. In contrast, HHS typically has a slow onset, typically occurring over days to weeks.[1]

Physical examination findings can include signs of dehydration such as tachycardia and hypotension and Kussmaul respirations secondary to the metabolic acidosis. A patient's mental status may vary from fully alert to comatose. Profound mental status changes are more suggestive of HHS.[1] History and physical examination should also

focus on eliciting possible precipitating factors, including infection, ischemia (such as myocardial infarction or stroke), and medication changes.

What tests and studies should be performed?

Initial laboratory evaluation suggested by the American Diabetes Association (ADA) consensus statement includes serum glucose, serum electrolytes and blood urea nitrogen/creatinine (with calculation of the anion gap), arterial blood gas, serum osmolality, serum and urinary ketones, urinalysis, and complete blood count. Initial studies include an electrocardiogram, chest radiograph, and cultures.

Additional studies that should be considered in the appropriate clinical setting are liver enzymes, cardiac enzymes, coagulation profile, amylase, and lipase.[3]

Further work-up should be driven by the clinical presentation and may include lumbar puncture or imaging of the head or abdomen.[3]

What are the diagnostic criteria for DKA?

Diagnostic criteria for DKA and HHS are shown in **Table 1**.

What if my patient does not clearly fit into one of these categories?

DKA and HHS exist along a spectrum of hyperglycemic crisis. They can be distinguished based on history and laboratory findings, but some patients may have features of both syndromes.[5]

What if serum and/or urine ketones are negative?

Most routine serum and urine tests for ketones use the nitroprusside reaction. This test can underestimate the severity of ketosis because it does not test for the presence of beta-hydroxybutyrate. Some institutions offer a separate test for beta-hydroxybutyrate.[1]

What other laboratory abnormalities are commonly seen in DKA?

- Hyperkalemia is common on initial presentation, although patients with DKA usually have a total body potassium deficit. Potassium is driven extracellularly as a

Table 1
Diagnostic criteria for DKA and HHS

	Mild DKA	Moderate DKA	Severe DKA	HHS
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10–15	<10	>18
Urine ketone	Positive	Positive	Positive	Small
Serum ketone	Positive	Positive	Positive	Small
Serum osmolality	Variable	Variable	Variable	>320 mOsm/kg
Anion gap	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

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

result of insulin deficiency and acidosis causing hyperkalemia. However, significant amounts of potassium can be lost through osmotic diuresis and gastrointestinal losses resulting in an overall deficiency.[3] The initiation of insulin therapy and correction of the acidosis drives extracellular potassium back into cells and can cause hypokalemia. Patient who present with normal or low potassium levels have severe total body potassium deficits and require careful monitoring and repletion.

- Hyperphosphatemia also reflects an extracellular phosphate shift rather than true increased levels. This is caused by insulin deficiency, dehydration, and acidosis.[3] Treatment of DKA can also lead to hypophosphatemia, which needs to be monitored and repleted.[1]
- Leukocytosis is commonly seen in DKA, even in the absence of infection, caused by increased levels of stress hormones such as catecholamines and cortisol.[3] On admission, leukocytosis in the range of 10,000 to 15,000 mm 3 may not be indicate an infectious process. However, leukocytosis with cell counts greater than 25,000 mm are more concerning for infection and require further evaluation and treatment if found.[1]
- Increased amylase and lipase can both be present in DKA in the absence of true pancreatitis. One study found that nonspecific increases of amylase and lipase occur in 16% to 25% of cases of DKA.[9] Increase in amylase correlated with pH and serum osmolality. Lipase increase correlated with serum osmolality. The diagnosis of acute pancreatitis cannot be made on serum amylase and lipase levels alone in patients with DKA.[9] However, pancreatitis can be a precipitant for DKA. Clinical judgment should be used to determine the need for further investigation for true pancreatitis and to manage the patient accordingly.

Can a patient have DKA without hyperglycemia?

There have been cases of DKA occurring with normal glucose levels (<250 mg/dL). In these cases, patients often have a clinical history of starvation, vomiting, pregnancy, or depression.[10,11]

DIFFERENTIAL DIAGNOSIS

Are there other causes of ketoacidosis?

Both starvation and alcoholic ketoacidosis can occur. These patients usually have normal to low glucose levels and their condition can be differentiated from DKA by history and by other associated laboratory findings.[1]

What other causes of increased anion gap metabolic acidosis are there?

Other causes include lactic acidosis, uremia secondary to acute or chronic renal failure, and ingestions such as methanol, salicylates, ethylene glycol, and paraldehyde.[1]

PATIENT MANAGEMENT

What are the primary management goals in treatment of DKA?[1,3]

1. Treatment of dehydration with intravenous fluids
2. Correction of hyperglycemia and ketoacidosis with insulin therapy

3. Correction of electrolyte abnormalities
4. Treatment of precipitating events:
   - Management of infection, ischemia, and so forth
   - Patient education regarding proper insulin and diet management

What tests are monitored during treatment?

Serum glucose should be monitored every hour until it stabilizes. Serum electrolytes, renal function, osmolality, and venous pH should be monitored every 2 to 4 hours. Frequency of laboratory draws can be adjusted based on the severity of DKA and how quickly the patient is responding to treatment.[1]

What is the optimal fluid management strategy for DKA?

The goal of initial fluid therapy in DKA is intravascular volume expansion and maintaining adequate renal perfusion. The initial fluid recommendation from the ADA is isotonic saline (0.9% NaCl) at a rate of 15 to 20 mL/kg/h or 1 to 1.5 L during the first hour.[1]

Fluids should subsequently be chosen based on hemodynamic stability, hydration status, serum electrolytes, and urinary output of the patient. Patients are typically converted to half normal saline (0.45% NaCl) at a rate of 250 to 500 mL/h if serum sodium level is normal or increased. If serum sodium level is low when corrected for serum glucose, 0.9% NaCl can be continued at a rate of 250 to 500 mL/h. The provider should frequently reassess the choice of fluids based on the patient's hydration status, fluid input and output, and laboratory results (**Fig. 1**).[1]

The goal is to correct fluid deficits within the first 24 hours. Patients with significant cardiac or renal dysfunction need to be monitored closely to avoid volume overload.[1]

What is the optimal insulin management for patients with DKA?

Although the goal is to correct both hyperglycemia and ketoacidosis, hyperglycemia resolves faster than the ketoacidosis. On average, glucose decreases less than 250 mg/dL 6 hours after initiation of treatment, whereas resolution of ketoacidosis takes an average of 12 hours. Ongoing insulin therapy is required until the ketoacidosis is resolved. For this reason, when glucose levels decrease less than or equal to 200 mg/dL, 5% dextrose should be added to the fluid regimen in order to prevent hypoglycemia. The amount of dextrose in the fluids may need to be adjusted to keep glucose between 150 and 200 mg/dL.[1]

Many studies have been performed to determine the optimal dose and route of administration of insulin. One study showed that insulin given intravenously, intramuscularly, or subcutaneously is effective for treatment of DKA.[10] In general, treatment algorithms recommend a continuous intravenous infusion of regular insulin because it has a short half-life and can easily be titrated.[1] Previous treatment protocols have recommended giving an initial intravenous bolus dose of regular insulin at 0.1 units/kg and then starting the continuous infusion at 0.1 units/kg/h.[12] A recent study found that the bolus dose (or priming dose) is not necessary if the continuous infusion is started at a rate of 0.14 units/kg/h.[12] The current ADA treatment protocol recommends either of these treatment plans.

If glucose levels do not decrease by 10% in the first hour, a bolus of 0.14 units/kg should be given. The infusion is then resumed at the same rate.[1]

When glucose levels reach 200 mg/dL, the infusion rate should be reduced to 0.02 to 0.05 units/kg/h. As earlier, dextrose should be added to the intravenous fluids at this time. Insulin and fluid infusion rates should be adjusted to maintain serum glucose between 150 and 200 mg/dL (See **Fig. 1**).[1]

Can patients with DKA be managed with subcutaneous insulin?

Studies have shown success in management with subcutaneous rapid-acting insulin for uncomplicated mild to moderate DKA. One study used an initial dose of lispro 0.3 units/kg subcutaneously, followed by 0.1 units/kg subcutaneously each hour. When glucose levels decreased to less than 250 mg/dL, the dose was reduced to 0.05 units/kg/h until DKA was resolved. This study showed no difference in hospital length of stay or time to resolution of DKA. The investigators were able to show a 39% reduction in hospital costs with this protocol because patients could be managed on general medical wards or step-down units rather than in the intensive care unit.[13,14] Another study compared subcutaneous aspart insulin with intravenous aspart insulin or intravenous regular insulin guided by simultaneous bedside measurement of blood glucose and beta-hydroxybutyrate for the management of DKA. There was no significant difference in median time to reach resolution of DKA as defined by a beta-hydroxybutyrate less than 0.6 mmol/L, serum bicarbonate greater than 18 mEq/L, venous pH greater than 7.3, and anion gap less than 16.[15]

A review of the literature concluded that the use of subcutaneous rapid-acting insulin every 1 or 2 hours to treat DKA would be safe and effective.[16] However, these studies excluded patients with severe DKA, hypotension, anasarca, and other critical illnesses. Patients with any of these conditions should continue to be managed with intravenous insulin infusion.[1]

What is the appropriate management of electrolyte abnormalities in DKA?

Potassium is often high at the time of presentation with DKA, but begins to decrease with the initiation of treatment. In patients with adequate renal function, potassium repletion should be started when levels decrease to less than the upper limit of normal (5.0–5.2 mEq/L). A goal potassium level of 4 to 5 mEq/L can generally be maintained by adding 20 to 30 mEq of potassium in each liter of intravenous fluids given.[1]

When patients present with hypokalemia less than 3.3 mEq/L repletion must begin with initiation of fluid infusion. In this case, the initiation of insulin therapy should be delayed until potassium is repleted to greater than 3.3 mEq/L.[1]

Phosphate is often normal or high at presentation but also decreases with the initiation of treatment with insulin. There is no evidence that phosphate repletion changes clinical outcomes in the management of DKA. However, severe hypophosphatemia should be avoided because this can cause cardiac and skeletal muscle weakness with subsequent respiratory depression.[10]

Bicarbonate use in the treatment of DKA is controversial. Studies have failed to show any improvement in patient outcomes with the administration of bicarbonate to patients with pH between 6.9 and 7.1.[17,18]

The current ADA consensus recommendation is to treat with bicarbonate in patients with severe acidosis (pH<6.9). The recommended dose is 100 mmol of sodium bicarbonate in 400 mL sterile water with 20 mEq of potassium chloride administered at 200 mL/h over 2 hours until the venous pH increases to more than 7.0. Bicarbonate

administration can cause hypokalemia, therefore the addition of potassium to the infusion is recommended (See **Fig. 1**).[1]

What criteria can be used to determine when DKA has resolved?

DKA is resolved when serum glucose is less than 200 mg/dL and the patient meets 2 of the following 3 criteria: serum bicarbonate level greater than or equal to 15 mEq/L, a venous pH greater than 7.30, or an anion gap less than or equal to 12 mEq/L.[1]

How is the patient transitioned to long-acting subcutaneous insulin once DKA is resolved?

Once DKA has resolved and the patient can tolerate food, the patient can be transitioned to long-acting subcutaneous insulin therapy. In patients with known diabetes, the patients' usual outpatient insulin regimens can be restarted. In patients who were not previously on insulin, a weight-based regimen can be initiated at 0.5 to 0.8 units/kg/d divided between basal and bolus insulin.[1]

The insulin infusion should be continued for 1 to 2 hours after the subcutaneous basal insulin is initiated. If for any reason the patient cannot take oral nutrition, the insulin infusion can be continued until the patient is able to do so.[1,10]

What complications of treatment may occur?

Hypoglycemia and hypokalemia are the most common complications of treatment of DKA. These complications can be avoided with proper monitoring of serum glucose and potassium levels and repletion with dextrose and potassium chloride when levels decrease.[1]

Cerebral edema occurs in 0.3% to 1.0% of cases of DKA in children, but is rare in adult patients.[1] Signs of cerebral edema vary and include headache, reduced level of consciousness, seizure, incontinence, papilledema, bradycardia, increased blood pressure, and respiratory arrest.[19]

How can DKA be prevented?

For many patients, medication noncompliance or lack of education regarding proper diabetes management is the precipitating cause. For these patients, appropriate treatment includes evaluation of the underlying reason for noncompliance and diabetes education.[10] Evaluation of any socioeconomic barriers to care is also prudent.

The ADA consensus statement recommends:

1. Early contact with the health care provider
2. Emphasizing the importance of insulin during an illness and the reasons never to discontinue insulin without contacting the health care team
3. Review of blood glucose goals and the use of supplemental short-acting or rapid-acting insulin
4. Having medications available to suppress a fever and treat an infection
5. Initiation of an easily digestible liquid diet containing carbohydrates and salt when nauseated
6. Education of family members on sick day management and record keeping including assessing and documenting temperature, blood glucose, and urine or blood ketone testing; insulin administration; oral intake; and weight[1]

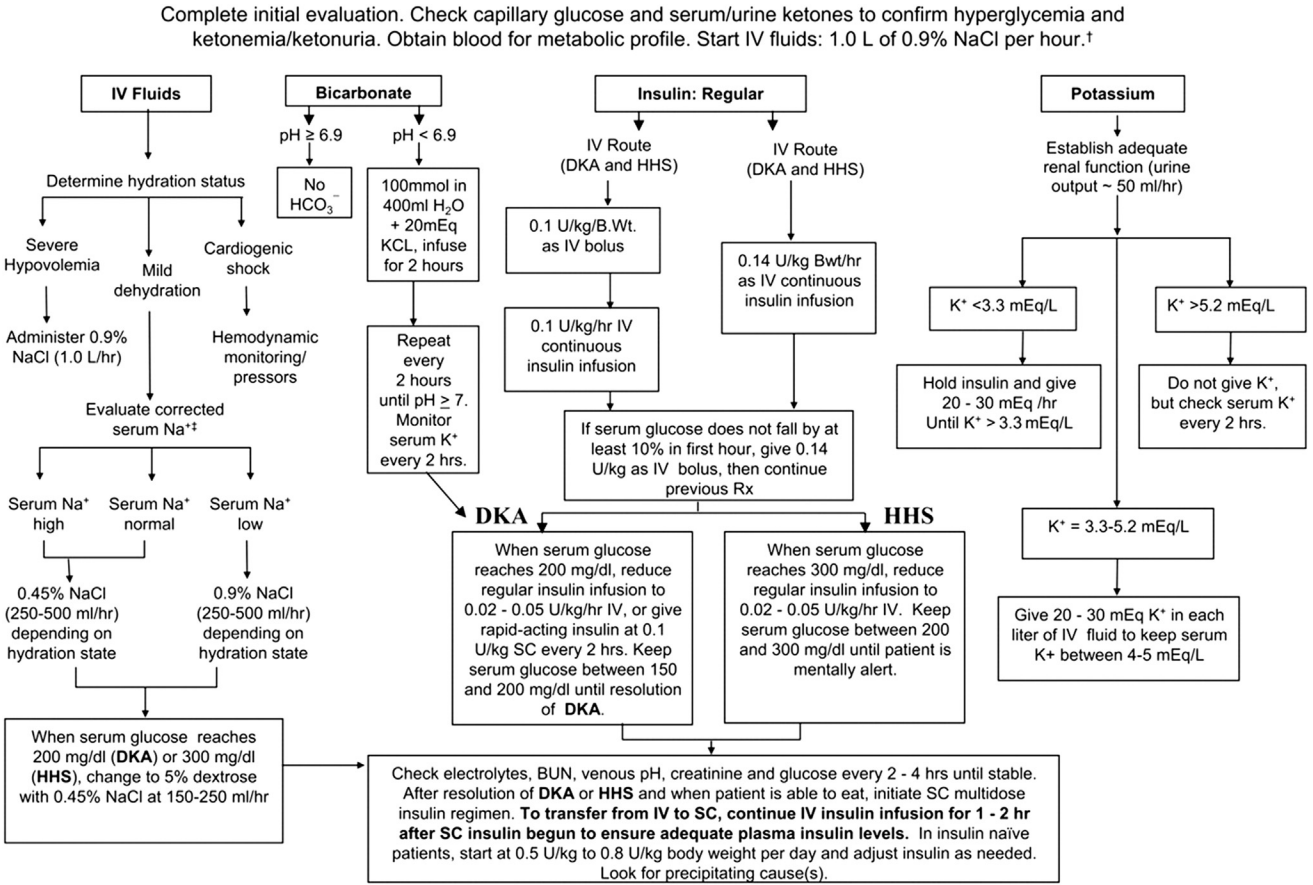

Fig. 1. Protocol for management of adult patients with DKA or HHS. BUN, blood urea nitrogen; IV, intravenous; SC, subcutaneous. † 15–20 ml/kg/h; ‡ serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose 100 mg/dl, add 1.6 mEq to sodium value for corrected serum value). (*From* Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32(7):1335–43. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.)

PERFORMANCE IMPROVEMENT

Can the implementation of hyperglycemia protocols improve outcomes in DKA?

Several studies have shown improved outcomes with the implementation of a DKA treatment protocol.

One retrospective study showed that patients treated after the implementation of the protocol for DKA and HHS decreased time to resolution of DKA by 9.2 hours. There was no difference in adverse outcomes including hypoglycemia and hypokalemia.[20]

Another retrospective study showed similar results with reduced time to resolution of DKA of 9.5 hours, and reduced hospital length of stay of 11.3 hours. In this study, a lower incidence of hypokalemia and hypoglycemia was noted.[21]

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