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Diabetic Ketoacidosis

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Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS) are the most serious and life-threatening complications of diabetes. Although significant overlap exists between these two entities, this article addresses issues specific to DKA. DKA is a syndrome characterized by hyperglycemia, ketosis, and acidosis. It occurs as the result of a relative or absolute insulin deficiency and an excess of insulin counter-regulatory hormones (ICRH) [1].

History and epidemiology

The earliest documented description of diabetes was found in a 1552 BC Egyptian papyrus [2]. In 1886, Dreschfeld provided the first description of diabetic ketoacidosis in the modern medical literature [3]. In 1971, Roger Unger described DKA as a bihormonal disorder involving insulin deficiency and glucagon excess [4].

Before the discovery of insulin by Dr. Frederick Banting in 1921, the mortality of DKA was 100%. After this landmark discovery and the institution of insulin therapy, the mortality began to decrease significantly. Currently, mortality is approximately 4% to 10% [5,6]. The incidence of DKA is between 4.6 and 8.0 per 1000 person-years among patients with diabetes [6]. DKA most commonly occurs in patients with insulin-dependent diabetes but may also occur in patients with noninsulin-dependent diabetes. The treatment of DKA episodes accounts for more than 25% of all health

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care dollars spent on direct medical care for patients with type I diabetes, and for 50% of every $2 for patients experiencing multiple episodes of DKA [7]. Annually, approximately 100,000 hospitalizations for DKA occur in the United States [6], with overall costs that exceed $1 billion per year [7].

Emergency department presentation

Precipitating factors

The most common precipitating factor in DKA is infection [8], with pneumonia and urinary tract infections accounting for 30% to 50% of cases [7]. Recent studies suggest that omission of insulin or undertreatment with insulin may be the most important precipitating factor in urban African-American populations [7,9,10]. New-onset diabetics account for up to 30% of patients presenting in DKA [6]. Other precipitating factors include cerebrovascular accident, alcohol abuse, pancreatitis, gastrointestinal (GI) bleeding, myocardial infarction, trauma, or drugs [11]. Medications that affect carbohydrate metabolism such as corticosteroids, thiazide diuretics, and sympathomimetic agents may precipitate DKA [8]. Psychological stress also causes an increase in insulin counter-regulatory hormones, and may precipitate DKA. In 2% to 10% of patients, no precipitating cause is identified [1].

History

Patients with DKA often complain of nonspecific symptoms such as fatigue and malaise. Complaints of polyuria, polydipsia, polyphagia, and weight loss are more characteristic of DKA. Nausea, vomiting and abdominal pain are also common complaints and are caused by either the acidosis itself, or to decreased mesenteric perfusion. Up to 25% of patients in DKA have emesis, which may have a coffee ground appearance. Endoscopic studies have related this finding to hemorrhagic gastritis [8]. Patients may present with depressed mental status or coma, and in these cases, the physician should attempt to illicit a history of antecedent symptoms from a family member when possible. A thorough review of systems should be performed, as specific complaints suggesting a possible source of infection or other precipitating factors may be elucidated.

The use of prescription and illicit drugs should be noted. Insulin omission or underdosing and the use of drugs that affect carbohydrate metabolism such as corticosteroids, thiazide diuretics, terbutaline, and cocaine can contribute to DKA [12,13].

Pathophysiology

The basic metabolic derangements in DKA arise secondary to a relative lack of insulin and an excess in insulin counter-regulatory hormones (ICRH).

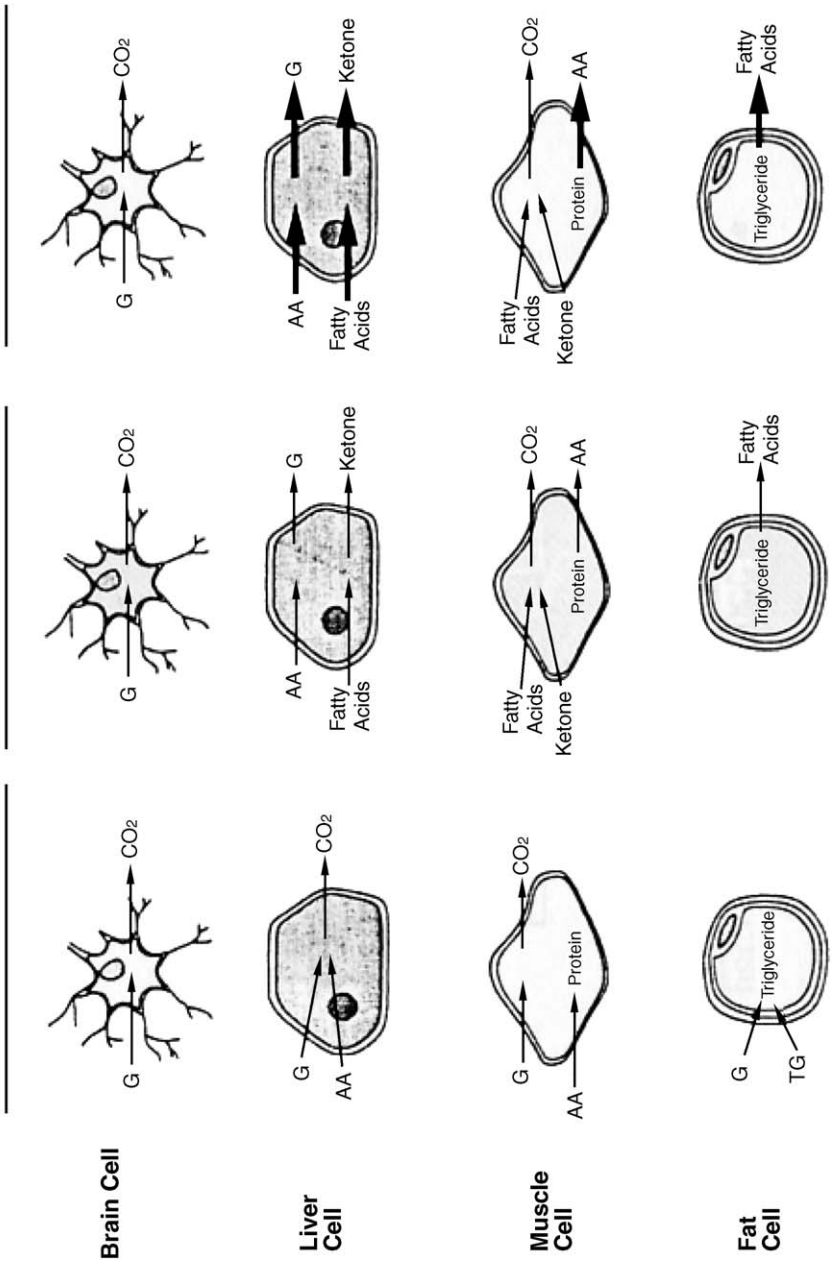
Even in the absence of changes in insulin administration, ICRHs are elevated during times of stress and may outweigh the effects of insulin. This leads to catabolic disturbances in the metabolism of carbohydrates, protein, and fat, which collectively culminate in the two cardinal features of diabetic ketoacidosis, hyperglycemia, and ketogenesis (Fig. 1).

Hyperglycemia

The hyperglycemia seen in DKA results from a combination of glucose underuse and overproduction. Insulin promotes the uptake and storage of glucose in the liver through glycogenesis (incorporation of glucose into glycogen) and lipogenesis (formation of fatty acids). Insulin is necessary for the uptake of glucose into muscle and fat cells. In the absence of adequate insulin, the body is unable to use or store circulating glucose, and ICRH levels increase. The ICRHs include glucagon, catecholamines, cortisol, and growth hormone. In DKA, glucagon becomes the primary hormone driving carbohydrate metabolism, stimulating hepatic glycogenolysis (breakdown of glycogen to glucose) and gluconeogenesis (glucose production from noncarbohydrate precursors). Although both increased hepatic glucose production and decreased peripheral glucose use occur in DKA, the major cause of the hyperglycemia is increased hepatic gluconeogenesis [5]. Hyperglycemia leads to glycosuria, osmotic diuresis, and dehydration. As a result of the osmotic diuresis, large amounts of sodium, chloride, and potassium are lost in the urine, resulting in the dehydration and electrolyte abnormalities commonly seen in DKA [5].

Ketogenesis

In the presence of insulin, triglycerides are incorporated into fat cells, and breakdown and release of triglycerides from fat cells are inhibited. In DKA, the combined relative insulin deficiency and ICRH excess promote the breakdown of triglycerides and the release of free fatty acids into the blood. Insulin deficiency is primarily responsible for the mobilization of free fatty acids, while the presence of glucagon is primarily responsible for accelerated fatty acid oxidation. Glucagon exerts its effects by acting on the carnitine palmitoyltransferase system of enzymes responsible for the transport of fatty acids into the mitochondria [14] and by inhibiting conversion of acetyl CoA to malonyl CoA by acetyl CoA carboxylase, the first intermediate in the lipogenesis pathway. Because lipogenesis is blocked, fatty acids are unable to enter the citric acid cycle and instead enter the mitochondria, where they are oxidized further to ketone bodies [7]. The major ketone bodies are acetoacetate and β-hydroxybutyrate, with acetone contributing a minor component. Ketone bodies are weak acids, but as they accumulate, they overwhelm the body's buffering capacity, and metabolic acidosis ensues [1].



Differential diagnosis

Other causes of ketosis and acidosis should be considered in patients presenting with DKA. Both starvation ketosis and alcoholic ketoacidosis (AKA) can be distinguished from DKA by clinical history and a blood glucose that ranges from mildly elevated (rarely greater than 250 mg/dL) to hypoglycemic. In patients with starvation ketosis, the serum bicarbonate level is usually not lower than 18 mEq/L, while patients with AKA may exhibit a profound acidosis [8]. AKA usually is seen in the setting of alcohol abuse with recent decreased consumption of alcohol [15].

Other causes of elevated anion gap metabolic acidosis should be considered, including lactic acidosis, chronic renal insufficiency, and ingestion of drugs such as salicylate, methanol, ethylene glycol, and paraldehyde [8] (Fig. 2). Drug ingestion history should be sought, including use of metformin, which, in rare cases, may cause lactic acidosis [16]. Some authors question the causality of the relationship of metformin use with lactic acidosis [17,18]. In the appropriate clinical situation, measurement of serum lactate, salicylate, and blood methanol level may be helpful. If concern for ethylene glycol (antifreeze) ingestion exists, the urine can be examined for calcium oxalate and hippurate crystals. Paraldehyde ingestion is suggested by characteristic strong unpleasant odor on the breath [8].

In the hyperglycemic patient, the diagnosis of HHS always must be considered. Table 1 shows a comparison of the laboratory findings in HHS and DKA.

Emergency department evaluation

Physical exam findings

The general appearance of patients with DKA is one of fatigue and dehydration. Tachycardia and hypotension may be present as a result of volume depletion, sepsis or both. The patient may be tachypneic with Kussmaul respirations. This pattern of deep, sighing respirations is an attempt to compensate for the metabolic acidosis and may or may not be accompanied by an increased respiratory rate. Patients may be normothermic or hypothermic despite accompanying infection. Hypothermia is caused primarily by peripheral vasodilation [8]. A fruity odor often is appreciated on the patient's breath because of the presence of exhaled acetone. Patients may have a depressed sensorium, and, in severe cases, may present

Fig. 1. Substrate utilization in the fed and fasting states and in diabetic ketoacidosis in insulin-insensitive tissue (brain cells) and in insulin-sensitive tissue (live, muscle, and fat). *Abbreviations:* G, glucose; AA, amino acid; TG, triglyceride. (*Adapted from* Cahill GF. Pathophysiology of diabetes. In: Hanwi GJ, Danowski TS, editors. Diabetes mellitis: diagnosis and treatment. New York: American Diabetes Association; 1967. p. 1–6; with permission.)

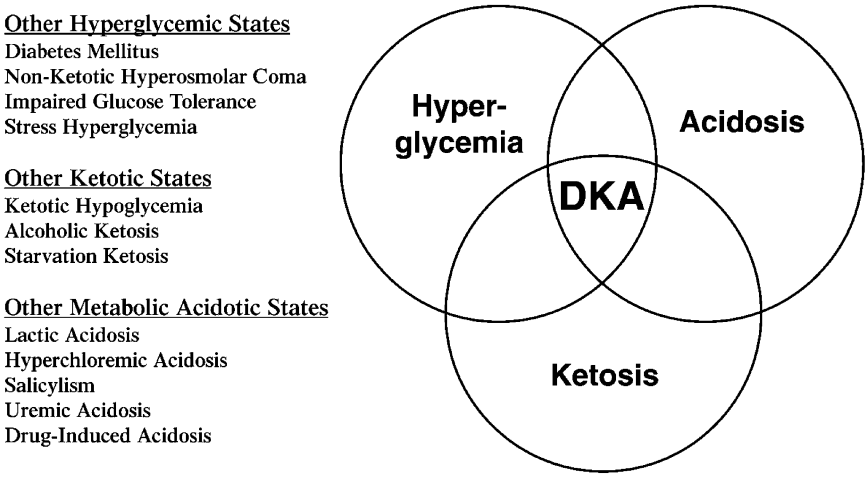


Fig. 2. The triad of DKA (hyperglycemia, acidemia, and ketonemia) and other conditions with which the individual components are associated. (*From* Kitabchi AE, Wall BM. Diabetic ketoacidosis. Med Clin North Am 1995;70(1):9–37; with permission.)

comatose. Skin examination reveals poor turgor, and mucous membranes are typically dry secondary to dehydration. The abdomen is often diffusely tender. Careful palpation for localizing tenderness should be performed, as an intra-abdominal pathology may be the precipitating factor for DKA.

The physical examination should include a thorough attempt to find a precipitating cause. Fewer than 10% of patients with DKA have no identifiable precipitant of the disease [1]. The sinuses should be palpated for

Table 1
Diagnostic criteria for diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome

	DKA			
	Mild	Moderate	Severe	HHS
Plasma Glucose (mg/dL)	> 250	> 250	> 250	> 600
Arterial pH	7.25–7.30	7.00–7.24	< 7.00	< 7.30
Serum bicorbonate (mEq/L)	15–18	10 to < 15	< 10	> 15
Urine ketones[a]	Positive	Positive	Positive	Small
Serum ketones[a]	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)[b]	Variable	Variable	Variable	> 320
Anion gap[c]	> 10	> 12	> 12	Variable
Alteration in sensorial or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

[a] Nitroprusside reaction method.
[b] Calculation: 2 [measured Na (mEq/L)] + glucose (mg/dL)/18.
[c] Calculation: (Na) – (Cl + HCO_3) (mEq/L).
From Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crisis in diabetes. Diabetes Care 2004;27:S94–102; with permission.

tenderness and the oral cavity explored for signs of dental infection. The ears should be examined for signs of otitis media or externa. The skin should be examined thoroughly for signs of infection such as abscess, cellulitis, or decubitus ulcers. A rectal examination should be performed looking for possible perirectal abscess or occult GI hemorrhage. In the female patient with abdominal pain, pelvic examination should be performed. A complete neurological examination should be performed on patients with altered mental status or localizing neurological complaints.

Laboratory evaluation

Serum glucose, ketones, electrolytes, serum urea nitrogen (BUN), and creatinine always should be ordered in suspected DKA. Although the serum glucose usually is elevated above 250 mg/dL, euglycemic DKA has been reported in up to 18% of cases [19]. Normoglycemia also may occur in patients who took insulin before presentation or have impaired gluconeogenesis caused by liver failure or alcohol abuse [1].

Hyperglycemia exerts an osmotic affect in the serum, shifting water from the intracellular to the extracellular space, creating a dilutional effect and resultant hyponatremia. The serum sodium therefore may be low despite total body water loss. The corrected serum sodium can be calculated by adding 1.6 mEq/L to the sodium for every 100 mg/dL glucose over the norm. (Table 2) Lipids also dilute the blood in a similar fashion, causing pseudohyponatremia [7,8]. Newer autoanalyzers remove triglycerides before this assay, eliminating this artifact in hyperlipidemia, but not hyperglycemia [19].

Initial serum potassium values are usually normal to high despite significant total body potassium depletion. There is a shift of intracellular potassium to the extracellular space as a result of insulin deficiency, hypertonicity, and acidemia [8]. Insulin carries glucose intracellularly with potassium and magnesium. Therefore, insulin deficiency contributes to the serum hyperkalemia. To buffer the serum acidosis, hydrogen ions move from the extracellular space to the intracellular space in exchange for

Table 2
Useful formulas in diabetic ketoacidosis

Anion gap	$[Na - (CL + HCO_3)]$
Correction of serum sodium	Measured [Na] $+ \frac{[1.6 \text{ glucose (mg/dL)} - 100]}{100}$
Serum osmolality (mOsm/L)	2 [Na + K] (mEq/L) + glucose (mg/dL)/18 + BUN(mg/dL)/2.8
Effective serum osmolality	2 [Na (mEq/L)] + glucose (mg/dL)/18
Total body water deficit (L)	0.6 × wt(kg) × [1–140/serum sodium]
Correction of serum potassium during acidemia	[K] + (0.6 mEq/L per 0.1 drop in pH)

potassium ions. To correct for the effects of acidemia on serum potassium, add 0.6 mEq/L to the measured serum potassium for every 0.1 drop in pH on the arterial blood gas (ABG) (see Table 2) [20,21].

The serum bicarbonate level is decreased to varying degrees depending on the severity of the DKA: (see Table 1) 15 to 18 mmol/L in mild DKA, 10 to 14 mmol/L in moderate and less than 10 mmol/L in severe DKA [8].

Diabetic ketoacidosis causes an elevated anion gap metabolic acidosis secondary to increased β-hydroxybutyrate and acetone levels. Rarely, a well-hydrated patient with DKA may have a pure hyperchloremic acidosis and no anion gap [19]. To calculate the anion gap, subtract the serum chloride and bicarbonate from the measured serum sodium (see Table 2). A superimposed metabolic alkalosis from vomiting or diuretic use may obscure the severity of ketoacidosis. Traditionally, an ABG has been considered part of the standard initial work-up. Recent studies have shown that the ABG rarely influences emergency department (ED) management and that the venous pH correlates sufficiently with the arterial pH [22].

Leukocytosis is often present and may be secondary to hemoconcentration, ketosis, or infection. This is a nonspecific finding and may be associated with other precipitating factors of DKA such as pancreatitis and myocardial infarction. The total white blood cell count is generally less than 25,000/mm^3 in the absence of bacterial infection [5]. An elevation in band form neutrophils has been demonstrated to indicate infection with 100% sensitivity and 80% specificity [23].

Amylase is elevated in most patients with DKA. In one study, 79% of patients in DKA had hyperamylasemia, with 48% having pancreatic type amylase [24]. This is typically subclinical and may represent effects of hypertonicity or hypoperfusion [25]. If patients have persistent abdominal pain after the treatment of DKA, consider further evaluation. Most laboratories are not equipped to differentiate between pancreatic and salivary isoenzymes [19]. Lipase is a more sensitive and specific indicator of pancreatitis, although this also may be elevated in DKA [8].

A urinalysis should be performed on all patients to screen for urinary tract infection. Urine ketones and glucose will be present.

A pregnancy test should be performed on all females of childbearing age. Other laboratory evaluation should be performed based on the review of systems and physical examination findings.

Emergency department management

The management of DKA should include intravenous fluid hydration, insulin administration, and electrolyte replacement. The presence of infection or other precipitating factors will determine whether other specific treatments are necessary. Admission and frequent monitoring are indicated to minimize the possibility of iatrogenic complications from the treatment of

DKA. Serum glucose should be checked hourly, and serum electrolytes should be repeated every 2 to 4 hours to assess the efficacy of therapy.

Intravenous fluids

The primary goal in the initial management of DKA is to restore intravascular volume and improve tissue perfusion. This will decrease ICRH levels and glucose concentration [1]. Fluid replacement alone may decrease serum glucose concentration by as much as 23% through increased renal perfusion and loss of glucose in the urine [1,26].

The use of intravenous fluid replacement in the management of DKA is supported by well-designed trials that have adequate power, and meta-analysis of the literature further supports the conclusion [11]. Although all authors agree that fluid replacement is essential in DKA, there is no uniformly accepted formula for administration. Initial intravenous fluids should be given rapidly to achieve hemodynamic stability, then decreased to a rate that allows for replacement of the total deficit over a 24-hour period. The total body water (TBW) deficit in these patients is usually 5 to 8 L. See Table 2 for TBW deficit calculation. The goal in fluid administration is to replace approximately 50% of the TBW deficit in the first 8 hours and the remainder in the subsequent 16 hours. The initial fluid of choice is normal saline (0.9% sodium chloride) with 1 to 2 L administered in the first hour. The subsequent choice for fluid replacement depends on the patient's hydration status, serum electrolytes levels, and urinary output [8]. The 2004 Position Statement of the American Diabetes Association (ADA) recommends that, after the initial fluid bolus, the corrected serum sodium should be calculated and used to determine further fluid replacement. If the corrected serum sodium is high or normal, replacement with 0.45% NaCl, 4 to 14 mL/kg per hour (depending on the state of hydration), is recommended. If the corrected serum sodium is low, continued replacement with 0.9% NaCl, 4-14 mL/kg/h, (depending on the hydration status) is recommended [8].

One approach is to start with 0.9% NaCl 1 to 2 L bolus, followed by an infusion rate of 0.9% NaCl 500 mL per hour until hemodynamically stable. Then the rate is decreased to 250 mL per hour and can be switched to half-normal saline to replace the large free water deficit [1].

When the blood glucose level falls below 250 mg/dL, a solution of 5% dextrose should be added to the intravenous fluids. This allows for continued administration of insulin to treat the ketosis and acidosis without causing hypoglycemia. The serum glucose should be maintained between 150 and 200 mg/dL until the ketoacidosis has resolved [8]. Dextrose combinations may be increased to 10% or 20% if glucose levels remain below 100 mg/dL. One efficient and cost-effective method is to use two bags of fluid with the same electrolyte content but different glucose concentrations [1,27]. One bag contains no dextrose, and the other contains

20% dextrose. The rates of infusion can be adjusted to deliver anywhere from 0% to 20% dextrose.

Special care should be taken to avoid overhydration in children, patients with cardiac or renal compromise, and elders with DKA. The lung sounds and oxygenation should be assessed frequently. In children, mental status should be evaluated frequently, as deterioration in mental status may be the first sign of cerebral edema [8]. This will be discussed further in the section on complications.

Insulin

Insulin therapy will improve the hyperglycemia, ketosis, and acidosis that occur in DKA [1]. Insulin therapy inhibits gluconeogenesis and ketone production in the liver and decreases lipolysis. The use of insulin by intravenous infusion is supported by randomized, controlled trials that have adequate power, and meta-analysis of the data further supports this conclusion [11].

Insulin therapy is secondary to intravenous fluid replacement and should be withheld initially in patients with hypotension and hypokalemia. In hypotensive patients, the administration of insulin can lead to vascular collapse secondary to rapid shifts of fluid into the intracellular space. Insulin should not be initiated until the blood pressure is stabilized with fluid administration [1]. Hypokalemic patients should not receive insulin until potassium has been administered, as the insulin-mediated movement of potassium into the intracellular compartment will worsen the hypokalemia. Insulin therapy should not be initiated until serum potassium is over 3.3 mEq/L [8].

A standard insulin regimen consists of regular insulin intravenous drip at 0.1 U/kg per hour. Some authors recommend an initial intravenous bolus of regular insulin 0.10 to 0.15 U/kg [8], but there are no data to support any clinical benefit [11]. Because insulin adsorbs to intravenous tubing, 50 mL of the infusion should be run through the pump before beginning the infusion [28]. The blood glucose level should be monitored hourly, with a goal of decreasing the glucose by approximately 50 to 75 mg/dL per hour [8]. If serum glucose does not decrease appropriately, and adequate hydration has been ensured, the insulin drip may be doubled every hour [8]. If serum glucose is not falling appropriately, consider inadequate intravascular volume replacement or the development of renal failure as potential causes.

Once the blood sugar falls below 250 mg/dL, glucose should be added to the intravenous fluids as previously discussed. The insulin drip should be continued until resolution of ketosis and improvement in the acidosis. Ketosis should be monitored by serum β-hydroxybutyrate. Urinary ketones are measured by the nitroprusside reaction, which measures acetoacetate and acetone but not β-hydroxybutyrate [1]. With treatment of DKA, β-hydroxybutyrate is converted to acetoacetate, and urinary measurements

may give the false impression that ketosis is worsening [8]. Criteria for the resolution of DKA also includes glucose less than 200 mg/dL, serum bicarbonate at least 18 mmol/L, and a venous pH greater than 7.3 [8]. In a study using an extended insulin regimen, all patients had complete resolution of their ketosis by 7 hours after achieving normoglycemia [29]. This suggests that using 7 hours of continuous insulin infusion after normoglycemia would allow for complete resolution of ketosis [1].

Once ketosis has resolved, the patient should be given his or her first dose of subcutaneous insulin. Two hours after this first dose, the insulin drip may be discontinued. It is important that the insulin drip be continued for 2 hours after the initiation of subcutaneous insulin, because hyperglycemia may recur rapidly with interruptions in insulin administration [1].

In mild DKA, regular insulin can be given subcutaneously or intramuscularly every hour. Patients should first receive a priming dose of regular insulin 0.4 to 0.6 U/kg, half as an intravenous bolus and half as either subcutaneous or intramuscular injection [8]. This should be followed by 0.1 U/kg per hour subcutaneously or intramuscularly. In the critically ill patient with DKA, insulin never should be given subcutaneously because of decreased medication absorption in the hypotensive patient [7].

Potassium

The use of electrolyte replacement in the management of DKA is supported by well-designed trials that have adequate power, and meta-analysis of the data further support the conclusion [11].

Potassium is the major electrolyte lost in DKA. Despite total body potassium depletion, mild-to-moderate hyperkalemia is common. This is secondary to an extracellular shift of potassium caused by insulin deficiency, hypertonicity, and acidemia [8]. During the treatment of DKA, serum potassium levels are decreased by insulin-mediated movement of potassium into the intracellular compartment and to a lesser extent by volume expansion and resolution of acidemia [5]. There is also ongoing potassium loss through a continued osmotic diuresis. The potential development of significant hypokalemia is the most life-threatening electrolyte abnormality that may occur during the treatment of DKA [8]. Before potassium administration, adequate urine output must be ensured. To prevent hypokalemia, the ADA recommends potassium replacement once serum levels fall below 5.5 mEq/L [5,8]. Generally, 20 to 30 mEq potassium in each liter of fluid is sufficient to maintain the serum potassium in the goal range of 4.0 to 5.0 mEq/L [5,8]. Others recommend withholding potassium until serum levels drop below 5.0, then giving 20 mEq/L if serum potassium is between 4 and 5 mEq/L, 30 to 40 mEq/L if serum potassium is between 3 and 4 mEq/L, and 40 to 60 mEq/L if serum levels are less than 3 mEq/L [1]. Tables 3 and 4 summarize approaches to potassium replacement in adult and pediatric patients, respectively.

Table 3
Potassium replacement in adult diabetic ketoacidosis

Initial potassium	Replacement
K $<$ 3.3 mEq/L hold insulin until K $\geq$ 3.3 mEq/L	*KCl 40 mEq in first hour, then 20–30 mEq/h to keep serum K between 4–5 mEq/L
K $\geq$ 3.3 but $<$5.0 mEq/L	*KCl 20–30 mEq/L of IVF to keep serum K between 4–5 mEq/L
K $>$ 5.0 mEq/L	Do not give K but check potassium levels every 2 hours

Abbreviations: K, potassium; KCl, potassium chloride; mEq, milliequivalents; IVF, intravenous fluids.

* Kitabchi et al recommend replacing one third of the potassium as potassium phosphate to avoid excessive chloride administration and to prevent severe hypophosphatemia.

Adapted from Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. Diabetes Care 2001:24(1):131–53.

Bicarbonate

The use of bicarbonate for managing DKA is not well supported in the literature [11]. The potential disadvantages of bicarbonate therapy include worsening hypokalemia, production of paradoxical central nervous system (CNS) acidosis, worsening of intracellular acidosis owing to increased carbon dioxide production, and prolongation of ketoanion metabolism [5].

Studies have shown no benefit of bicarbonate therapy for managing DKA [30–32]. These studies have looked at patients with serum pH ranging from 6.9 to 7.1. Because studies have not been done in patients with a pH of less than 6.9, some authors continue to advocate the use of bicarbonate in these severely acidemic patients. If acidosis is severe (pH less than 7.0), bicarbonate may be used to treat the possible adverse hemodynamic effects caused by severe acidemia. These include negative inotropism, CNS

Table 4
Potassium replacement in pediatric diabetic ketoacidosis

Initial potassium	Replacement
K $<$ 2.5 mEq/L, hold insulin until K $\geq$ 3.3 mEq/L	[a]KCl 10 mEq in first hour, recheck serum K after one hour
K 2.5–3.5 mEq/L	[b]KCl 40–60 mEq/L of IVF until K $>$ 3.5 mEq/L
K 3.5–5.5 mEq/L	[b]KCl 30–40 mEq/L of IVF to keep serum K between 3.5–5 mEq/L
K $>$ 5.5 mEq/L	Do not give K, but check potassium levels every hour until $<$ 5.5 mEq/L

Abbreviations: K, potassium; KCl, potassium chloride; mEq, milliequivalents; IVF, intravenous fluids.

[a] Kitabchi et al recommend replacing one third of the potassium as potassium phosphate to avoid excessive chloride administration and to prevent severe hypophosphatemia.

[b] Fluid should be run at 1.5 times maintenance for smooth rehydration.

Adapted from Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. Diabetes Care 2001:24(1):131–53.

depression, peripheral vasodilation, and insulin resistance [1]. If bicarbonate is used, it should be given as an isotonic solution over a 1-hour period. This can be done by adding 1 to 2 ampules (44 to 88 mEq sodium bicarbonate) to a liter of 0.45% NaCl [1,5,8].

Phosphate

Phosphate replacement has no benefit for most patients with DKA [5]. In certain groups of patients, phosphate replacement may be indicated to avoid cardiac dysfunction, skeletal muscle weakness, and respiratory depression [8]. These include patients with cardiac dysfunction, anemia, respiratory depression, and those with serum phosphate levels less than 1.0 g/dL [8]. Hypophosphatemia causes the depletion of 2,3-diphosphoglycerate (2,3-GPD), resulting in a left shift of the oxyhemoglobin curve, resulting in decreased tissue oxygenation [33]. Replacement of phosphate in patients with impaired oxygen carrying capacity may enhance tissue oxygen delivery. When phosphate replacement is indicated, 20 to 30 mEq/L potassium phosphate can be added to fluids [8]. Replacement of phosphate in patients with levels less than 1.0 g/dL is indicated and supported by randomized controlled trials with adequate power [11].

Emergency department management of diabetic ketoacidosis in the pediatric population (younger than 20 years of age) [8]

Intravenous fluids

Caution must be used with fluid replacement in pediatric DKA patients given the possible risk for cerebral edema associated with rapid fluid administration. In the first hour, intravenous fluid should be isotonic saline at a rate of 10 to 20 mL/kg per hour. This may need to be repeated in the severely dehydrated patient, but initial re-expansion should not exceed 50 mL/kg over the first 4 hours of therapy. Further fluid replacement should be calculated to replace the fluid deficit over 48 hours. In general 0.45 to 0.9% NaCl (depending on serum sodium concentration) at a rate of 1.5 times maintenance requirements (approx 5 mL/kg per hour) will accomplish a safe rehydration. Once serum glucose reaches 250 mg/dL, fluid should be changed to 5% dextrose and 0.45 to 0.75% NaCl with potassium [8].

Insulin

An initial intravenous insulin bolus is not recommended in pediatric patients. Regular insulin infusion at a dose of 0.1 U/kg per hour is recommended. Insulin therapy should not be started until adequate

potassium levels are ensured to avoid cardiac arrhythmias associated with hypokalemia [8].

Bicarbonate

There are no randomized studies assessing the use of bicarbonate in pediatric patients with DKA with a pH of less than 6.9. Caution should be used when administering bicarbonate, as an association between bicarbonate use and cerebral edema has been reported [34]. Despite the decrease in use of bicarbonate in pediatric patients with DKA over the last 10 years, however, there has not been a corresponding reduction in the incidence of cerebral edema [35]. The use of bicarbonate should be reserved for children with severe circulatory failure caused by profound acidosis. The ADA recommends the use of bicarbonate if the pH remains less than 7.0 after the initial hour of hydration. If given, bicarbonate can be administered as 1 to 2 mEq/kg added to NaCl with any required potassium to produce a solution that does not exceed 155 mEq/L [8].

Complications of diabetic ketoacidosis

Most complications of DKA are related to the treatment. The most common complications include hypoglycemia, hypokalemia, hyperglycemia, and hyperchloremia [8]. Less common complications include cerebral edema, fluid overload, acute respiratory distress syndrome, thromboembolism, and acute gastric dilation.

Hypoglycemia

Hypoglycemia may occur secondary to overzealous administration of insulin [8]. The occurrence of hypoglycemia during the treatment of DKA often is associated with high-dose (1 U/kg per hour) insulin therapy but not with low-dose (0.1 U/kg per hour) insulin therapy. The risk of hypoglycemia can be reduced by adding dextrose to the intravenous fluid therapy when the blood glucose falls below 250 mg/dL [1,8]. This allows the continued administration of insulin to resolve ketoacidosis while decreasing the risk of hypoglycemia.

Hypokalemia

Hypokalemia may develop secondary to treatment with insulin and bicarbonate [8]. The occurrence of hypokalemia is less common with low-dose insulin regimens [5].

To avoid hypokalemia, insulin should not be administered until the serum potassium level is known. Potassium should be replaced as discussed in the treatment section.

Hyperglycemia

Hyperglycemia often occurs secondary to interruption or discontinuation of intravenous insulin therapy without proper administration of subcutaneous doses of insulin [8].

Hyperchloremia

Patients may develop a nonanion gap metabolic acidosis as a result of excessive saline administration. Chloride replaces ketoanions lost as sodium and potassium salts during osmotic diuresis. These abnormalities are usually transient and clinically insignificant except in cases of acute renal failure or extreme oliguria [8].

Cerebral edema

Cerebral edema is a rare but frequently fatal complication of DKA that primarily occurs in pediatric patients. In the largest reported series, 95% of cases occurred in patients younger than 20 years, with one third occurring in patients younger than 5 years [36]. The incidence of cerebral edema in children with DKA is between 0.7% and 1% [8,34,37]. It is more common in patients with newly diagnosed diabetes [36,37] and is the most common cause of death in young children with diabetes [38]. The mortality rate according to different series has varied widely, with reports between 24% and 90% [37,39].

The clinical presentation of cerebral edema is characterized by deterioration in the level of consciousness, with lethargy, decrease in arousal, and headache [1,8]. The timing of the development of cerebral edema is variable, with most cases occurring 4 to 12 hours after starting treatment. There have been several case reports of cerebral edema occurring before the initiation of therapy [39].

The pathophysiology of cerebral edema is understood poorly. Many mechanisms have been proposed, but a clear understanding remains elusive. Possible contributing factors include: (1) hypoxia, (2) the osmotically driven movement of water into the CNS when plasma osmolality declines too rapidly during the treatment of DKA, and (3) the direct effect of insulin on the plasma membrane of brain cells, which may promote cellular edema [1,8,39].

When cerebral edema develops, the treatment is aimed at reducing intracranial pressure. The data on effective treatments are limited to case reports. In these reports, mannitol has been used to lower intracranial pressure, and the authors recommend that it be administered within 5 to 10 minutes of initial neurological deterioration for maximum effect [39–41]. The dose of mannitol is 1 to 2 g/kg over 15 minutes. Intracranial pressure monitoring and hypoventilation started immediately after cerebral edema is suspected have been reported to improve outcome [39,42–44]. The role of

dexamethasone and diuretics has not been established [11,39]. Further study is needed in this area.

Preventive measures that might decrease the risk of cerebral edema in high-risk patients are:

- Gradual replacement of sodium and water deficits in patients who are hyperosmolar (maximal reduction in osmolality of 3 mOsm/kg H_2O per hour)
- Avoidance of bicarbonate administration unless absolutely necessary
- The addition of dextrose to the intravenous fluid therapy once blood glucose reaches 250 mg/dL [8]

Fluid overload

Patients with underlying cardiac disease or renal insufficiency who receive excess fluid or excessively rapid administration of fluid may develop congestive heart failure. Administer intravenous fluids at a slower rate and frequently monitor fluid input and output in patients with underlying cardiac disease or renal insufficiency [1].

Acute respiratory distress syndrome

During the course of treatment for DKA, patients may develop cardiogenic and noncardiogenic pulmonary edema from excessive fluid replacement. ARDS is a rare but potentially fatal complication of DKA [1,5]. Patients with pulmonary rales and increased alveolar-to-arterial gradient may be at an increased risk of developing pulmonary edema and ARDS and should have continuous pulse oximetry monitoring [1,5,8,45]. In high-risk patients, lower rates of fluid administration should be used [5].

Thromboembolism

Diabetes mellitus is a hypercoagulable state. Subclinical endothelial injury, hypofibrinolysis, and platelet hyperaggregation are the main factors responsible for coagulation activation in diabetes mellitus [46–48]. In DKA, this hypercoagulable state is enhanced. In a study of 34 patients with DKA, hemostatic markers were measured during DKA and 1 week after resolution of DKA. During DKA patients were found to have coagulation system and platelet activation and endothelial injury. There was also a relative hypofibrinolysis during DKA [47].

Acute gastric dilation

Acute gastric dilation is a relatively uncommon but potentially lethal complication of DKA. In the patient with abdominal distension, other causes of intra-abdominal pathology should be excluded. A nasogastric tube

can be placed as a diagnostic and therapeutic tool. Metoclopramide 10 mg intravenously every 6 hours may be helpful [1].

Disposition

No randomized prospective studies have evaluated the optimal site of care for patients with DKA. The decision concerning the site of care should be based on clinical prognostic indicators and availability of hospital resources [7].

Select patients with mild DKA may be discharged after treatment and observation in the ED. A study in the pediatric population found that 94% of patients with an initial pH of at least 7.20 or a bicarbonate concentration of at least 10 mEq/L had resolution of their metabolic acidosis within 3 hours of initiating therapy and were able to be discharged from the ED [49,50]. Patients must be alert and able to tolerate oral intake to be discharged from the ED.

Patients with moderate-to-severe DKA require admission to a bed where frequent monitoring is possible, hourly glucose measurements can be obtained, there is a rapid turnaround time for laboratory services, and nurses are able to administer intravenous insulin infusions. In most cases this requires admission to a step-down or intensive care unit (ICU). Admission to a ward bed may be possible if the hospital has a general ward unit where the following are in place:

- A protocol for managing DKA
- An on-site blood glucose monitoring system
- Available nursing coverage that allows for frequent patient monitoring and hourly glucose measurements
- A rapid turnaround of laboratory values [5,7]

Indications for admission to a step-down or ICU include: (1) pregnancy, (2) hypotension refractory to initial rehydration, (3) oliguria refractory to initial rehydration, (4) mental obtundation, and (5) sepsis [7].

Summary

In summary, DKA is a common complication of diabetes, and patients frequently present to the ED. The care of patients with DKA requires frequent and intensive monitoring. The following points should be remembered when assessing and treating these patients.

1. Perform a thorough history and physical examination in search of a precipitating cause.
2. A patient may present with DKA with a near normal glucose. This is more common in patients who have taken insulin recently, have

decreased food intake or impaired gluconeogenesis as can be seen in liver disease.
3. Consider other causes of anion gap metabolic acidosis.
4. Initial therapy consists of intravenous fluid administration. It is prudent to wait for adequate rehydration and serum potassium levels before starting insulin or potassium replacement therapy.
5. Frequent monitoring of glucose and electrolytes should guide further treatment.
6. Caution should be used in fluid administration in patients with cardiovascular and renal disease.
7. If abdominal pain does not resolve with initial treatment, consider evaluating for intra-abdominal pathology.
8. Treatment of rare complications such as cerebral edema requires further studies before the development of standards of care.

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