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AHC Media

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is an acute metabolic disorder characterized by markedly increased circulating ketone bodies leading to ketoacidosis in the presence of prolonged hyperglycemia due to an absence of insulin. DKA may present in subjects with Type 1 diabetes mellitus (T1DM) with an absolute or relative insulin deficiency or in patients with Type 2 diabetes mellitus (T2DM) due to relative insulin deficiency. DKA commonly occurs at the onset of T1DM but also may occur from withdrawal or omission of insulin therapy due to psychiatric, social, or economic reasons or due to increased insulin requirements during an acute illness.[1]

The use of continuous subcutaneous insulin infusion pumps using rapid-acting insulin also has been associated with a significant increase in incidence of DKA when compared to conventional therapy with multiple daily subcutaneous insulin injections.[2-15] The occurrence of DKA in patients using pumps is attributed to the exclusive presence of rapid-acting insulin in the pump, which, if interrupted, leaves no reservoir of basal insulin for blood glucose control, as well as to patients' reluctance in adjusting the basal rates and bolus dosages via pump in the presence of an acute illness. Moreover, pump failure may also occur due to occlusion of insulin pump infusion sets or inappropriate handling of the pump and lack of selection of an appropriate site (extensive scarring, lipoatrophy, or lipohypertrophy at the site).[5-15] DKA due to relative insulin deficiency occurs in T2DM, frequently at the onset of an acute disorder such as infection, trauma, myocardial infarction, congestive heart failure, and steroid therapy, as well as due to lack of appropriate dose adjustment in pregnancy and other conditions.[1] Finally, the FDA issued an advisory regarding the occurrence of DKA in subjects with T2DM following initiation of sodium/glucose cotransporter 2 (SGLT2) inhibitors.[16]

Epidemiology

Hospitalizations for DKA are increasing in the United States. A report by the Centers for Disease Control and Prevention analyzing data regarding hospital admissions between 1988 and 2009 in the United States describes a marked increase in the number of hospital discharges with DKA as the first listed diagnosis from 80,000 in 1988 to 140,000 in 2009.[17]

The age-adjusted hospital discharge rate for DKA per 10,000 overall population increased by 43.8% during this time period as well. The rise in the hospital discharge rate may be attributed to improved testing for diagnosis, availability of better management tools and protocols promoting improved survival, and an increase in the prevalence of diabetes over the period of analysis.[17] Thus, despite the rise per overall diabetic population, both the crude and age-adjusted hospital discharge rates for DKA per 1000 subjects with diabetes declined by 43.7% and 38.4%, respectively. Moreover, the age-adjusted hospital discharge rates

EXECUTIVE SUMMARY

- Diabetic ketoacidosis typically occurs at the onset of Type 1 diabetes mellitus, but also may occur from withdrawal or omission of insulin therapy in patients due to psychiatric, social, or economic reasons, as well as increased insulin requirements during acute illness.
- Patients on continuous subcutaneous insulin infusion pumps using rapid-acting insulin have an increased incidence of DKA.
- Patients with Type 2 diabetes mellitus have been reported to develop DKA with mild-to-moderate glucose elevations following initiation of sodium/glucose cotransporter 2 (SGLT2) inhibitors: canagliflozin, dapagliflozin, and empagliflozin.
- Initiate treatment with IV normal saline, 1 to 2 L over the first hour.
- Initiate IV insulin after initial fluid administration and after verifying serum potassium is above 3.3 mEq/L.
- Monitor serum glucose hourly with point-of-care testing for the initial 4 hours.
- Monitor and replace serum potassium during insulin infusion.

for diagnosis of DKA per 1000 subjects with diabetes declined among both men and women, as well as among whites and blacks, with a greater decrease among blacks than in whites (60.5% vs 45.0%).[17] Although clinicians often associate DKA with T1DM patients, DKA also occurs in T2DM patients, though not as frequently as in subjects with T1DM. In studies of first-time DKA, about 65-70% of patients have previously documented T1DM and about 30-35% are estimated to have T2DM.[18-23]

DKA is a serious and potentially life-threatening metabolic complication of diabetes mellitus, although mortality due to complications of DKA is rare in both children and adults. In 2009, the rate of mortality in patients presenting with hyperglycemia crisis (both DKA and hyperosmolar hyperglycemic non-ketotic syndrome) was reported to be 0.02% in patients with diabetes who were ≤ 45 years of age and 0.014% among older adults with diabetes.[24] Among children, cerebral edema was reported in 0.3-1% of DKA episodes and accounted for 57-87% of all DKA deaths.[25-27] Previously, elderly patients at extreme ages were at the greatest risk for complications from DKA, with increasing mortality with each passing decade.[28-34]

However, the mortality rate in the elderly has declined significantly recently due to the advent of newer insulin formulations; well-established management protocols with appropriate insulin administration (IV or IM); close monitoring of fluid status and metabolic parameters, including glycemia, serum electrolytes, and arterial blood gas; and markedly improved tools available for management of accompanying acute disorders.[31]

Pathogenesis

Insulin plays a major role in fuel homeostasis via its effects in the liver, muscle, and adipose tissue. Insulin promotes fuel storage in the liver by stimulation of glycogen synthesis and conversion of free fatty acids into triglyceride.[34,35] It also decreases fuel expenditure by inhibiting gluconeogenesis, glycogenolysis, and lipolysis, including triglyceride breakdown, resulting in a decline of circulating free fatty acids required as a substrate for ketogenesis (*see Figure 1*).[34-36] Glucagon is a counter-regulatory hormone with properties to oppose the effects of insulin on all fuel stores.[36] Insulin, free fatty acids, and ketones inhibit glucagon secretion, whereas amino acids, catecholamines, and cortisol stimulate its secretion. Glucagon stimulates hepatic glucose production by promoting both glycogen breakdown and gluconeogenesis. Additionally, other counter-regulatory hormones, such as catecholamines, cortisol, and growth hormones, complement the effects of glucagon on carbohydrate, protein, and lipid metabolism (*see Figure 2*).[34-36] Lack of insulin and increase in glucagon and other counter-regulatory hormones stimulate lipolysis and release free fatty acids, which are then converted to ketone bodies in the liver (*see Figure 3*).[34-36]

Acetoacetate and B-hydroxybutyrate are the two major ketone bodies produced by the liver during insulin deficiency and a rise in counter-regulatory hormones. Accumulation of these ketone bodies in the circulation accounts for the induction of anion gap metabolic acidosis (*see Figure 3*). Metabolic acidosis (pH < 7.2) stimulates the cerebral respiratory center, which in turn induces deep rapid respirations known as "Kussmaul" breathing, promoting respiratory alkalosis in an attempt to restore pH toward normal.[34-39]

Glucose is the most effective fuel for the normal functioning of all tissues. However, all organs and tissues require insulin for glucose entry, with the exception of the central nervous system, renal medulla, and red blood cells. Tissues are unable to utilize glucose during absolute or relative lack of insulin in T1DM and T2DM, especially in the presence of an acute disorder, and are forced to use ketones as an alternative source of energy.[34-36] Increased serum glucose concentration causes elevation in serum osmolality, leading to a shift of fluid from intracellular to extracellular compartment. Increase in osmolality stimulates the cerebral thirst center to increase fluid intake to help maintain both extra- and intravascular volumes. However, volume depletion and dehydration are exacerbated due to lack of fluid intake because of ketoacidosis-induced nausea and vomiting and lack of ability to communicate or ambulate in patients at extreme ages. Furthermore, fluid loss results in decreased renal blood flow, leading to diminished excretion of glucose, promoting greater rise in plasma glucose and, thus, osmolality.[37-39]

Patients with DKA may simultaneously manifest other acid-base disorders. The concurrent presence of other acid-base disorders is established

Figure 1. Pathogenesis of DKA

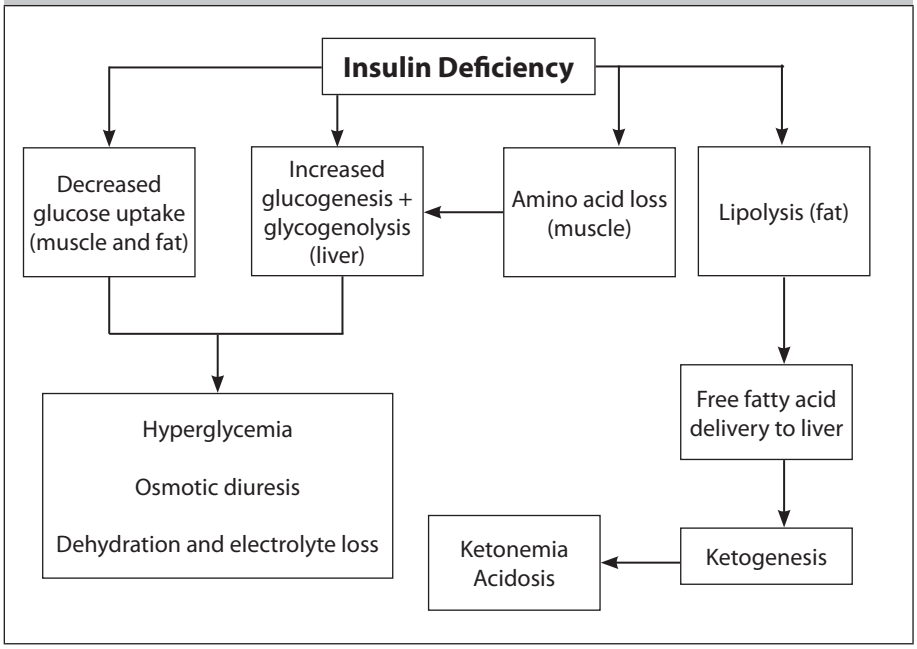
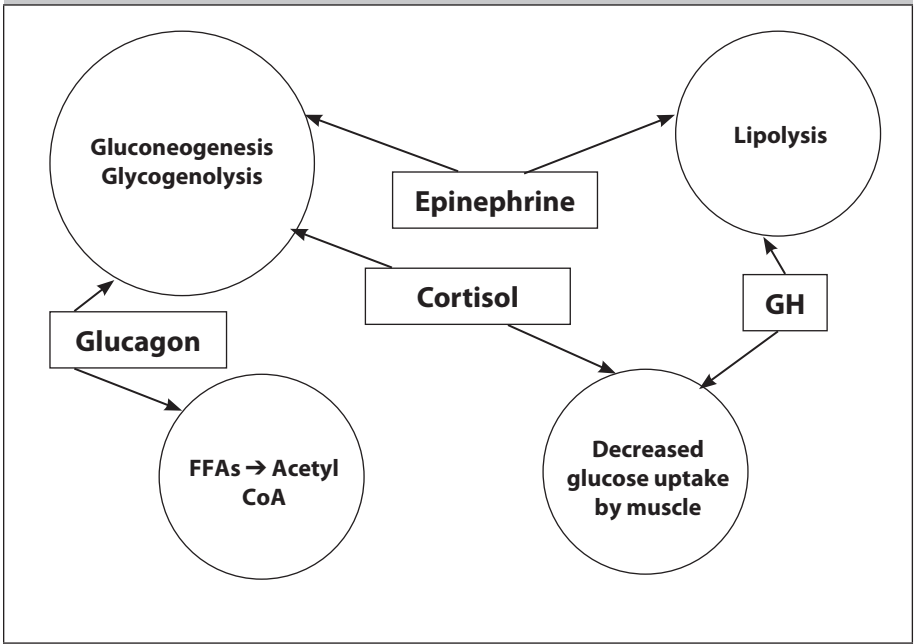


Figure 2. Counter-regulatory Hormones



While insulin is deficient, counter-regulatory hormones rise and cause effects that are opposite to insulin. The most counter-regulatory hormone is glucagon. The other counter-regulatory hormones, like epinephrine, cortisol, and growth hormone (GH), work synergestically with glucagon.

by comparing the difference (ΔAG) between the patient's anion gap and the normal anion gap to the difference (Δ HCO3-) between normal serum bicarbonate and patient's serum bicarbonate. In the presence of a pure or lone DKA, ΔAG is approximately equal to Δ HCO3-. If ΔAG is lower than Δ HCO3-, there is a greater fall in serum bicarbonate than one would expect in relation to the increase in the anion gap. This can be explained by the presence of an increase in another measured anion, leading to hyperchloremic acidosis in the presence of an anion gap metabolic acidosis of DKA. Decreased renal perfusion secondary to dehydration may lead to renal injury with induction of such hyperchloremic tubular acidosis. Thus, hyperchloremic tubular acidosis is one of the common causes of normal anion gap acidosis in the presence of DKA, because an additional fall in serum bicarbonate is due to further buffering of an acid that does not contribute to the anion gap. On the other hand, ΔAG > Δ HCO3- indicates a lesser fall in serum bicarbonate than one would expect in the presence of the rise in anion gap. This is explained by concurrent presence of metabolic alkalosis frequently induced by vomiting dehydration as well as by another process that increases the serum bicarbonate, e.g., primary hypercortisolism or hyperaldosteronism or due to compensatory metabolic alkalosis in the presence of chronic respiratory acidosis in a subject with a primary lung disorder. Finally, in a few instances, anion gap acidosis may occur secondary to accumulation of multiple measured and/or unmeasured anions, e.g., lactic acidosis due to inadequate tissue perfusion from severe dehydration or concurrent acute disorder such as septic shock or acute myocardial infarction (*see Table 1*).

Clinical Presentation

The metabolic abnormalities of DKA develop rapidly, often within 24 hours of absolute insulin deficiency. The onset of T1DM can be gradual, with progressive symptoms.[40-46] However, in clinical practice, DKA is often the initial manifestation, with a reported abrupt onset in children with T1DM; this may be attributed to lack of recognition of symptoms by children or their parents.

In adolescents and adults, DKA as an initial manifestation of T1DM, including latent autoimmune diabetes of adults (LADA), is rare.[47-52] In these subjects, hyperglycemia alone without ketosis is the frequent initial presentation and may be attributed to the patients' ability to recognize symptoms of hyperglycemia, such as polyuria, polydipsia, nocturia, and weight loss, leading them to seek prompt medical attention. Subjects with LADA are often diagnosed initially as T2DM

and are successfully managed with lifestyle intervention and oral agents for a short period. However, after the initial diagnosis, hyperglycemia usually recurs within 6-12 months and is not responsive, despite the use of a combination of oral agents, and is ameliorated only by administration of insulin.

In contrast, the onset of DKA in patients with T2DM is often preceded by symptoms and signs of poor glycemic control (e.g., polyuria, nocturia, polydipsia, weight loss) for several days or even months, unless precipitated by an acute disorder. The onset of ketonemia and acidosis is characterized by rapid occurrence of symptoms, e.g., anorexia, nausea, vomiting, abdominal pain, muscle cramps, and respiratory distress, which frequently present 24 to 48 hours prior to hospitalization. Many patients misconstrue onset of gastroenterological symptoms as an accompanying gastrointestinal disorder responsible for precipitating DKA.

Physical examination of patients with DKA shows the presence of ketotic breath, hyperventilation, tachycardia, orthostasis, abdominal pain, and occasionally hypothermia and/or impaired consciousness or even coma.[33] Change in mental status correlates more significantly with older age and increasing serum osmolality rather than the severity of acidosis. In the elderly, serum osmolality ≥ 340 mOsm/L is known to induce a markedly altered mental status, including confusion, convulsion, and coma.[53] Finally, hyperchloremic acidosis may ensue and persist during the recovery period more often and in a more profound pattern in subjects with T2DM manifesting DKA than subjects with T1DM (*see Table 2*).

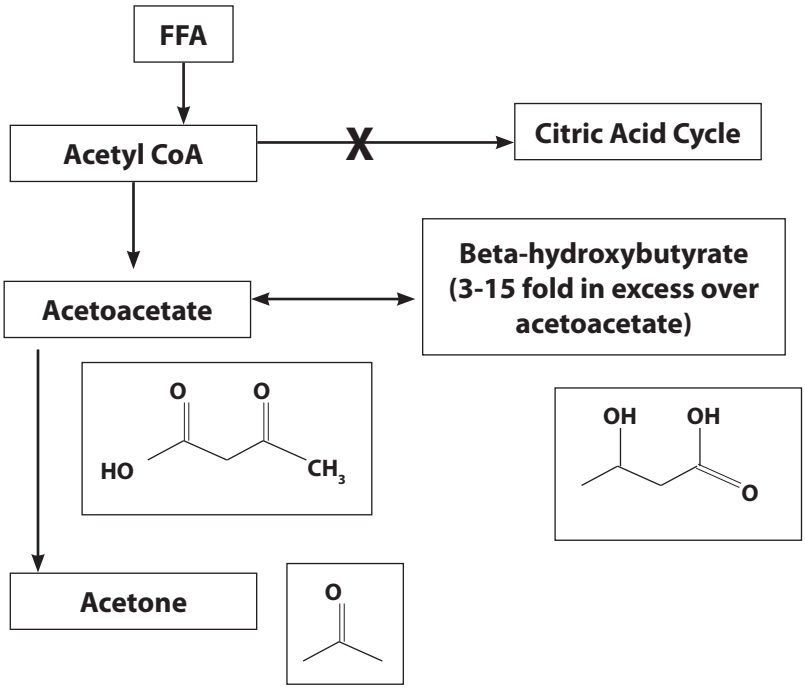
Hyperglycemia by itself does not fulfill the diagnostic criteria for DKA. High anion gap metabolic acidosis caused by elevated serum ketones, measured as beta-hydroxybutyrate, acetoacetate, or acetone, must be present in addition to hyperglycemia (≥ 250 mg/dL) to establish the diagnosis of DKA. DKA is frequently classified as mild, moderate, or severe based on the degree of acidosis and clinical manifestations (*see Table 3*).[35] Serum beta-hydroxybutyrate is present 3-5 times in excess when compared to other ketones and is the test of choice for a prompt diagnosis of DKA. Similarly, the presence of ketonemia and even ketoacidosis in the absence of hyperglycemia (≥ 250 mg/dL) does not fulfill the well-established criteria for the diagnosis of DKA. Patients partially treated with insulin prior to ED arrival may present with milder hyperglycemia but severe ketoacidosis. Ketoacidosis can also be due to alcoholic and pancreatic causes.[54-57]

Th differential diagnosis of DKA includes other forms of metabolic acidosis (*see Table 4*); specifically, ketosis and/or ketoacidosis, including:

1) DKA with laboratory findings consisting of hyperglycemia (serum glucose ≥ 250 mg/dL) and ketoacidosis (anion gap acidosis) with arterial pH ≤ 7.30 and PCO_2 ≤ 30 mmHg; and/or serum bicarbonate ≤ 18 mEq/L.

2) Alcoholic ketoacidosis manifesting with anion gap acidosis with serum glucose usually ≤ 200 mg/dL, occasionally

Figure 3. Ketone Production



DKA incites lipolysis within adipose tissue with release of free fatty acids (FFA) into the circulation, where they are beta-oxidized in the liver into acetyl-CoA. Ordinarily, acetyl-CoA would enter the Citric Acid or Krebs cycle. In DKA, many of the Citric Acid cycle intermediates (mainly oxaloacetate) have been depleted by entry into the gluconeogenesis pathway. Accumulation of acetyl-CoA leads to production of ketones and ketoacids.

Table 1. Anion Gap Acidosis and the Delta Gap

Δ AG = Δ HCO3-	Pure anion gap acidosis
Δ AG < Δ HCO3-	Anion gap acidosis + normal gap metabolic acidosis (e.g., RTA)
Δ AG > Δ HCO3-	Anion gap acidosis + metabolic alkalosis (e.g., primary aldosteronism, hypercortisolism, contraction alkalosis, and diuretic use)
Δ AG >> Δ HCO3-	Anion gap acidosis + metabolic alkalosis + primary respiratory alkalosis
Anion gap (AG) = Na = (Cl- + HCO3-)	

Table 2. DKA in T1DM and T2DM

Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
65-70% of total DKA cases	30-35% of total DKA cases
pH ≤ 7.2	pH > 7.2
BMI ≤ 27 kg/m^2	BMI > 27 kg/m^2
Shorter time to achieve ketone free urine (29 h)	Longer time to achieve ketone free urine (36 h)
Infection (21.6%) as a cause of precipitant	Infection (48.4%) as a cause of precipitant

Table 3. Classification of Severity of DKA

	Mild	Moderate	Severe
Arterial pH	7.25-7.30	7.00-7.25	< 7.00
Serum bicarbonate (meq/L)	15-18	10-15	< 10
Anion gap	10-12	12-14	> 15
Mental status	Alert	Alert/drowsy	Stupor/coma

even in the hypoglycemic range often occurring after an alcohol binge followed by starvation. As in DKA, the major circulating ketone body in alcoholic ketoacidosis is also beta-hydroxybutyrate, and the serum concentration is disproportionately greater when compared with other ketones.[54,55]

3) Pancreatic ketoacidosis as a complication of severe acute pancreatitis established by anion gap acidosis with serum glucose ≤ 200 mg/dL with occasional hypoglycemia. Significant positive correlations were documented between serum lipase levels and anion gap values as well as serum pH levels (*see Table 5*).[56,57] Moreover, the decline in ketone bodies in the circulation and rise in pH follows declining serum lipase levels during recovery.

4) Starvation ketosis is characterized by the presence of ketosis rather than ketoacidosis secondary to prolonged starvation with normal serum glucose concentration.[35,36]

Management of DKA

Management of DKA involves resuscitation, IV insulin administration, and repletion of electrolytes, and simultaneous treatment of the underlying disorder precipitating DKA.

Fluid Resuscitation. Fluid loss in patients with DKA averages approximately 6-9 L in adults (*see Table 6*). The goal is to replace the total fluid loss within 24-36 hours. Fifty percent of the fluid is administered during the first 8-12 hours.[58] One accepted approach is to rapidly infuse 15-20 mL/kg (1 to 2 L) of normal saline (0.9%) over the first hour, followed by reduced infusion rate of 250 mL/hr. Once the blood glucose decreases below 250 mg/dL, IV fluid is changed to 5% dextrose/0.45% saline.[58-63]

Fluid with electrolytes may be required to be administered orally or via nasogastric tube in patients in whom obtaining an IV site proves difficult due to volume depletion. In rural sites, especially in developing countries, these routes of administration may also be preferred in the absence of availability of equipment for IV infusion. Although the composition of lactated Ringer's is closer to that of plasma when compared to normal saline, there is no benefit to lactated Ringer's over normal saline in the treatment of DKA.[61-63] In addition, the time to recovery of glucose to desirable glucose level is longer with lactated Ringer's solution when compared to normal saline.[61-63]

Insulin Administration. Insulin lowers serum glucose by promoting glucose uptake by peripheral tissues and by inhibiting glycogenolysis and gluconeogenesis. In addition to correction of serum glucose, insulin also inhibits lipolysis, including triglyceride breakdown, thus eliminating substrates such as free fatty acids for ketogenesis and, therefore, ameliorates ketoacidosis.[64,65]

Insulin is essential in the treatment of DKA, but it must be administered after initial fluid administration and serum potassium is above 3.3 mEq/L. In the absence of fluid and electrolyte replacement, insulin may lead to a shift of fluid from extracellular space back into the cells, leading to intravascular dehydration in the presence of excess body water, resulting in persistence of hypotension. Additionally, acidosis often may not resolve simultaneously with a decline in plasma glucose because the hydration itself can induce renal tubular acidosis via suppression of plasma renin activity and aldosterone.

The objectives of insulin administration include gradual lowering of plasma glucose and amelioration of ketoacidosis. Serum glucose reduction at the rate of 10% per hour from the initial concentration is recommended to avoid adverse outcomes. A greater rapid decline in blood glucose concentration increases the risk of hyperosmotic encephalopathy (cerebral edema).[24-26] Therefore, blood glucose concentration should be monitored hourly at the bedside with a point-of-care glucose meter.

The IV route is considered to be the most optimal because it promotes direct entry of insulin into circulation and is, therefore, the most accepted and established approach of insulin administration.[64-75] This route is absolutely essential in the presence of hypotension due to severe dehydration occurring in many subjects with DKA. Absorption of insulin and its entry into circulation is hampered with any other route of administration (e.g., subcutaneous or intramuscular) and therefore is distinctly suboptimal. Moreover, IV administration is also convenient because of the ease of adjustment of the infusion rate as well as repeated administration of the bolus dose if required to obtain desirable lowering of glycemia. All types of insulin attain a similar serum profile when administered intravenously.[66,76]

Table 4. Differential Diagnosis of High Anion Gap Metabolic Acidosis

High Anion Gap Metabolic Acidosis	Normal Anion Gap Metabolic Acidosis
Common	**Low Potassium**
• Lactic acidosis • Ketoacidosis • Acute kidney injury • Chronic kidney disease • Methanol poisoning • Ethylene glycol poisoning • Salicylate poisoining	• Renal tubular acidosis • Carbonic anhydrase inhibitors • Ureteral diversions • Diarrhea • Surgical drainage or fistula • Posthypocapneic acidosi
Uncommon	**Normal/High Potassium**
• Diethylene glycol poisoning • Propylene glycol poisoning • 5-oxoproline acidosis • d-lactic acidosis	• Renal tubular acidosis • Early renal failure • Hydronephrosis • Low aldosterone • Drug induced • Addition of inorganic acid • Sulfur toxicity • Cholestyramine
	Other
	• Expansion acidosis • Cation exchange resin

Table 5. Laboratory Findings in Acute Pancreatitis

Serum lipase concentrations as well as anion gap [Sodium –(chloride + bicarbonate)] and arterial pH values in 18 subjects with acute pancreatitis divided into three groups: K_0 with neither ketonuria nor ketonemia, K_1 with ketonuria alone without ketonemia, and K_2 with both ketonuria and ketonemia.

Group	No. of Subjects	Serum lipase U/L	Anion Gap nm/L	Arterial pH
Neither ketonuria or ketonemia	5	304 ± 22	11.6 ± 1.3	7.42 ± 0.03
Ketonuria but not ketonemia	6	438 ± 64*	17.7 ± 1.4*	7.33 ± 0.03*
Both ketonuria and ketonemia	7	779 ± 110‡≠	27.6 ± 2‡≠	7.27 ± 0.02‡≠
		(23-190)$	(12-15)$	(7.35-7.45)$

* $P < 0.01$ vs K_0
‡ $P < 0.001$ vs K_0
≠ $P < 0.01$ vs K_1
$ Normal range in parenthesis

Table 6. Fluid and Major Electrolyte Losses in DKA

Water	100 mL/kg (60-110)
Sodium	6 mEq/kg (5-13)
Potassium	5 mEq/kg (4-6)

The aim of IV bolus administration is to raise the serum insulin level promptly, which is then maintained at a steady state by continuous IV infusion. Administration of insulin infusion alone delays the rise in serum insulin concentration required for prompt desirable lowering of glucose and amelioration of ketoacidosis. The initial insulin dose is based on the patient's body weight (0.1 unit/kg). IV bolus administration is followed by a continuous insulin infusion at a rate of 0.1 unit/kg/hr. IV bolus followed by infusion is the standard with which alternative insulin strategies are compared.[71,72] However, some studies have questioned the benefit of the initial bolus compared to administration of the continuous infusion alone.[70-71] A study by Kitabchi et al examined the comparative efficacy of an insulin priming dose followed by continuous insulin infusion at two different hourly rates with continuous infusion without a priming dose.[73] Patients were divided into three groups: 1) load group of 12 patients using a priming IV dose of 0.07 units of regular insulin per kg body weight followed by a continuous IV infusion with a dose of 0.07 units/kg/hr; 2) no load group of 12 patients using an IV infusion of regular insulin of 0.07 units/kg/h without a priming IV dose; and 3) twice no load group of 13 patients using an IV infusion of regular insulin of 0.14 units/kg/h (i.e., twice the dose in group 2) without a priming dose. The study concluded that the times to reach glucose < 250 mg/dL were not significantly different among the groups. However, several patients in the group not administered the priming or the bolus insulin dose required "supplemental" insulin to decrease the initial glucose levels by 10%.[71] Another study suggested that lower insulin dose (0.5-4 units/hour) may be as effective as the currently recommended dose of 0.1 unit/kg/hour. However, the duration of therapy required to achieve desirable glycemia and remission of ketoacidosis was longer at these lower insulin infusion rates.[74]

Moreover, in all of these studies,[72-74] the blood glucose levels of patients at diagnosis of DKA were only mild-to-moderately high (< 500 mg/dL) and the number of subjects in these studies was relatively small to draw appropriate and definitive conclusions. A retrospective study by Bradley and Tobias reviewed

the therapy of DKA in children admitted to the pediatric intensive care unit over a 10-year period.[75] This retrospective study compared two protocols: 1) administration of IV bolus of insulin 0.24 ± 0.27 units/kg body weight followed by continuous infusion; and 2) continuous insulin infusion alone. Patients who received continuous infusion alone required longer duration of therapy for achieving the desirable glycemic goal as well as resolution of DKA.[7]

Based on this evidence, it is prudent to implement the insulin therapy based on the severity of hyperglcyemia and/or ketoacidosis. For example, in a patient presenting with initial blood glucose of 800 mg/dL, administration of continuous IV infusion without the bolus may delay appropriate lowering of blood glucose control due to required duration of treatment. On the other hand, in a patient presenting with blood glucose of 300 mg/dL, IV bolus prior to continuous insulin therapy may not be necessary.

The rate of insulin infusion should be reduced if the decline in blood glucose is > 10% per hour and can be adjusted based on the following formula: Units of regular insulin/h = (glucose - 60) × 0.01 or 0.02. American Diabetes Association (ADA) guidelines for management of DKA recommend gradual reduction in the rate of IV insulin infusion and initiation of subcutaneous insulin administration in a multiple daily-dose schedule when the blood glucose declines to ≤ 200 mg/dL and two of the following goals are attained: serum anion gap < 12 mEq/L (or at the upper limit of normal range for the local laboratory), serum bicarbonate ≥ 15 mEq/L, arterial blood pH > 7.30, and resumption of oral intake.[1]

Maintenance insulin therapy in diabetes mellitus uses basal plus prandial dosing to replicate normal physiologic insulin secretion.[77] Basal insulin controls hyperglycemia between meals and during overnight fast, whereas rapid-acting insulin helps attain desirable postprandial glycemic excursions. The currently approved basal insulin formulations include the newer insulin analogs — insulin glargine and insulin detemir — as well as older intermediate-acting neutral protamine hagedorn (NPH) insulin.[77-80] It is important to overlap the IV insulin infusion and the subcutaneous insulin for 1-2 hours prior to stopping the IV insulin. Abrupt discontinuation of insulin infusion acutely reduces serum insulin levels and may result in recurrence of hyperglycemia and/or ketosis.[64-75,82-85]

Patients with established diagnosis of T1DM prior to onset of DKA may be reinitiated on their home subcutaneous insulin regimen on resumption of oral caloric intake.[1] In insulin-naive patients with T1DM, a multiple daily dose subcutaneous insulin injection regimen should be started at a dose of 0.5-0.6 units/kg per day, including bolus and basal insulin, until an optimal dose is established. The usual distribution of daily insulin dose is 50% basal and 50% prandial. Prandial daily dose usually is divided into three mealtime dosages. For example, a 72 kg male may require a total of 36 units — half of this dose (18 units) would be the basal dose and the other half (18 units) may be divided into three dosages of six units administered with each meal. Another alternative is to administer mealtime insulin dosage based on the amount of carbohydrate intake by educating patients about carbohydrate counting.

Treatment with a basal-prandial regimen is proactive and prevents hyperglycemia, whereas a sliding scale regular insulin regimen administered alone subcutaneously at an interval of 6 hours is suboptimal and, hence, is not recommended.[83-85] Subjects with T2DM may be discharged on the same regimen as the inpatient insulin regimen but need to be followed up promptly within 1-2 weeks to assess the need for continuing insulin therapy or reversing to their prior hypoglycemic therapy, including lifestyle modification, oral hypoglycemic agents, and/or insulin therapy.

Electrolytes

Two major depleted electrolytes in DKA include sodium and potassium (*see Table 6*). However, losses also involve other electrolytes, such as chloride, phosphate, and magnesium. Osmotic diuresis secondary to hyperglycemia is the major contributing factor to total body losses of almost all electrolytes including sodium.

Serum sodium may vary from subnormal to supernormal concentrations due to depletion as well as a shift from extracellular compartment to intracellular milieu due to hyperosmolarity. Serum sodium should be "corrected" in the presence of hyperglycemia. There is debate about the appropriate correction factor to use. Most commonly, this formula is used: Corrected Serum Sodium = Measured Serum Sodium + 0.016 × (Serum Glucose (mg/dL) - 100).

Total body potassium is depleted in DKA due to osmotic diuresis. However, serum potassium levels may be variable at the time of patient presentation. High serum potassium levels are attributed to a shift of potassium from intracellular space to extracellular space due to acidosis and lack of insulin. Normal or low serum potassium may be present despite acidosis and extracellular shift due to extreme depletion of total body potassium secondary to hyperglycemic osmotic diuresis. Administration of insulin and IV fluid facilitates intracellular influx of potassium, magnesium, and phosphate and may lead to a decline in serum concentrations of these electrolytes.[37-39,86] Additionally, hydration with normal saline improves renal blood flow, facilitating tubular exchange of potassium for sodium, promoting urinary excretion of potassium, chloride, phosphate, and magnesium.[37-39,89] Therefore, frequent and close monitoring of potassium, phosphate, and magnesium is crucial.

Maintaining normal serum potassium is critical as low levels may lead to cardiac arrhythmias and death. The average potassium deficit in DKA is 3-5 mEq/kg body weight, although it may be as high as 10 mEq/kg body weight in some subjects. Potassium must be replaced once the serum level starts declining below 5 mEq/L, with the goal of maintaining the serum potassium level between 4-5 mEq/L.[1] IV administration is preferred for potassium repletion at a rate of 10 mEq/hr. However, in circumstances involving lack of venous access due to dehydration or lack of equipment in developing or least developed countries, oral or enteral potassium supplementation may be used. In patients with nausea and inability to

Table 7. Common Precipitants of DKA

Inadequate insulin treatment or noncompliance
New onset diabetes (20-25%)
Acute illness: • Infection (30-40%) • Cerebral vascular accident • Myocardial infarction • Acute pancreatitis
Drugs: • Clozapine or olanzapine • Cocaine • Lithium • Terbutaline

Table 8. Complications in DKA

Complications Due to DKA	Complications Due to Treatment of DKA
• Vascular occlusion-MI, CVA, mesenteric, others • Acute renal failure • Pancreatitis • Erosive gastritis • Acute gastric distention	• Cerebral edema • ARDS • Hypokalemia • Fluid overload • Line infection/thrombosis • Relapse of DKA on transfer to floor • Hypoglycemia • Hyperchloremic acidosis

ingest potassium tablets, a nasogastric tube may be inserted for administration via this route.

Bicarbonate therapy for correcting acidosis in DKA has not been shown to improve patient outcomes and may actually induce potentially serious complications, such as hypokalemia, rebound metabolic alkalosis, and delay in improvement of both hyperosmolarity and ketosis.[87-89] Furthermore, in DKA patients with an initial pH < 7.0, IV bicarbonate therapy does not decrease the time to resolution of acidosis or shorten the period of hospital stay. Bicarbonate administration also has been implicated as a risk factor for cerebral edema in children.[90]

In adults, cerebral acidosis may lag behind serum acidosis with bicarbonate therapy and may cause disequilibrium between cerebral pH and serum pH, leading to worsening or persistence of altered mental status.[90,91] Finally, because of the potential adverse cardiovascular outcomes, the ADA guidelines recommend using bicarbonate only when the serum pH is < 6.9 with a prompt correction to 7.0-7.1 and/or with simultaneous presence of lactic acidosis.[1]

Once the treatment of DKA is initiated, it is important to identify an underlying acute disorder frequently responsible for induction of DKA (*see Table 7*) and institute appropriate management. Adverse outcomes due to DKA and during administration of fluids, insulin, and electrolytes should be anticipated (*see Table 8*). Dehydration may lead to vascular events such as myocardial infarction, stroke, mesenteric thrombosis, and peripheral vascular occlusion secondary to rise in serum viscosity. Cerebral edema is a rare adverse outcome occurring during the treatment of DKA in patients and is attributed to rapid glucose lowering, especially in patients at extremes of age. Treatment of DKA may result in complications such as hypoglycemia, hypokalemia, hyperchloremic acidosis, cerebral edema, acute respiratory distress syndrome, and fluid overload with generalized edema.[91]

Prevention

Prevention of DKA consists of key management principles. Diabetic educators and other providers should educate patients and their caregivers on daily diabetic management as well as during special occasions such as traveling.

Education of patients and/or their caregivers should include blood glucose goals as well as frequency of administration of rapid-acting insulin to achieve recommended glycemic goals. Finally, it is equally important to educate patients and their next of kin or caregivers that rapid-acting insulin should not be withheld during illness, even if patients lose their appetite and are unable to eat. In this situation, blood sugar should be monitored with subcutaneous insulin based on those values. Self-monitoring of blood glucose at frequent intervals is the most important maneuver, since persistent hyperglycemia is the precursor to progression to hyperglycemic crisis including DKA. Recommended blood sugar goals are preprandial capillary plasma glucose reading of 80-130 mg/dL and peak postprandial capillary plasma glucose level of < 180 mg/dL.[92-95]

Patients using an insulin pump may need to discontinue the pump during illness and administer rapid-acting subcutaneous insulin at 4-6 hours, since use of the pump is shown to be inadequate in attaining and maintaining desirable blood sugars. Therefore, all patients using insulin pumps should be educated about backup protocols for administering basal and rapid-acting insulin as well as the supplies needed to implement the protocol during illness.

Clinical indicators for seeking medical care include > 5% loss of body weight, respiration rate > 36/min, persistently elevated blood glucose, mental status change, uncontrolled fever, unresolved nausea, and vomiting.[1] Patients should be instructed and encouraged to seek early medical care in order to prevent progression of illness, hyperglycemia, and critical complications (e.g., DKA and other hyperglycemic emergencies).

Conclusion

DKA is a potentially life-threatening disorder in patients with both T1DM and T2DM. Prompt recognition of the disorder and appropriate laboratory testing, followed by efficient management with appropriate fluid resuscitation, electrolyte replacement, and adequate insulin therapy, is crucial for preventing adverse outcomes including death. DKA management requires recognizing the laboratory turnaround time and the practical aspects of administration of fluid, electrolytes, and insulin. Prevention of recurrence must be a

major goal in every patient hospitalized for DKA. This can be achieved by educating both patients and caregivers and by providing appropriate management protocols for implementation during travel and sick days. With appropriate management, mortality in adult patients with DKA is almost negligible.

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CME/CE Questions

1. Which of the following is *not true* regarding DKA?
   A. About 30-35% of cases are see in Type 2 diabetes mellitus.
   B. DKA with mild-to-moderate hyperglycemia has been reported after initiation of SGLT2 inhibitors.
   C. Continuous subcutaneous insulin infusion pumps using rapid-acting insulin also have been associated with a significant decrease in the incidence of DKA compared to conventional therapy.
   D. Mortality due to complications of DKA is rare in both adults and children.
2. Which of the following is *not* a counter-regulatory hormone to insulin?
   A. Prolactin
   B. Glucagon
   C. Cortisol
   D. Growth hormone
3. What is the most commonly reported precipitant of DKA in Type 2 diabetes mellitus?
   A. Stroke
   B. Infection
   C. Myocardial infarction
   D. Trauma
4. Fluid loss in adult patients with DKA is approximately:
   A. 1-2 L.
   B. 3-4 L.
   C. 6-9 L.
   D. 10-12 L.
5. When should IV insulin therapy be started in DKA?
   A. Immediately on diagnosis
   B. After fluid deficit has been completely restored
   C. After acidosis has been treated and arterial or venous pH is > 7.25
   D. After initial fluid bolus and serum potassium is > 3.3 mEq/L
6. What is true about the use of intravenous sodium bicarbonate in DKA?
   A. It should be used only if arterial or venous pH < 6.9.
   B. It should not be used in simultaneous presence of lactic acidosis.
   C. Its use shortens the duration of acidosis.
   D. Its use reduces the incidence of cerebral edema in children with DKA.

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