

Diabetic ketoacidosis in children and youth

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Practice Points

- Diabetic ketoacidosis (DKA) remains a common complication of Type 1 diabetes with significant morbidity.
- The pathogenesis of DKA involves profound insulin deficiency in addition to counter-regulatory hormone increases.
- DKA occurs at disease onset, its frequency is related to a number of social determinants of health, and in those with established diabetes it is linked with stress of intercurrent illness or insulin unavailability or omission.
- Treatment of DKA should be in centers with experience in this care.
- Cerebral edema remains the most important complication of DKA management.
- Most episodes of DKA can be prevented by measures developed to counter the causes.

SUMMARY Diabetic ketoacidosis (DKA) remains a common complication of Type 1 diabetes, both at the time of diagnosis of the disorder and in those with established diabetes. DKA results from profound insulin deficiency producing hyperglycemia, osmotic diuresis and ketogenesis, eventually leading to dehydration and metabolic acidosis. Provided here is a review of the approach to treatment and prevention of DKA and its complications.

Diabetic ketoacidosis (DKA) remains a common complication of children and youth with Type 1 diabetes (T1D), and has also been recognized in some adolescents with Type 2 diabetes [1,2]. DKA is a potentially life-threatening condition that remains the leading cause of hospitalization for these individuals with T1D, and is associated with considerable morbidity and a small but preventable number of mortalities.

This review will approach DKA from the standpoint that the majority, if not all, episodes

of DKA are preventable and those that do occur arise from a failure to sufficiently intervene early in order to arrest the evolution of the DKA (see 'failure hypothesis' later). The sequence will flow from:

- Pathophysiology of DKA
- Treatment of DKA
- Epidemiology of DKA and its complications
- Prevention of DKA

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Pathophysiology of DKA

Insulin is the premier anabolic hormone in humans. Under physiologic circumstances, in exquisite concert with the counter-regulatory hormones, insulin controls the balance between hepatic glucose production by its suppression of glycogenolysis, gluconeogenesis and peripheral glucose uptake in muscle and fat. It is a major determinant of lipid storage and protein deposition. Complete or near-complete deficiency of insulin, a prerequisite for the development of DKA, leads inevitably to unrestrained hepatic glucose production, poor peripheral glucose uptake, proteolysis and lipolysis. The resultant intracellular starvation is accompanied by a counter-regulatory hormone ('stress') response with increasing levels of glucagon, epinephrine, cortisol and growth hormone exacerbating the hyperglycemia and ketogenesis [2,3].

The impact of these hormonal abnormalities is resultant hyperglycemia with osmotic diuresis and dehydration when replacement of fluids fails to match losses, and ketosis then ketoacidosis as insulin deficiency fails to suppress lipolysis. The symptoms of evolving DKA begin with the classical features of polydipsia and polyuria, but are complicated by nausea, vomiting and abdominal pains (Box 1). Untreated this will progress to coma and death.

In addition to hyperglycemia, dehydration, ketosis and numerous electrolyte abnormalities occur as DKA evolves (Table 1) [1,2]:

- Potassium: multiple and complex mechanisms lead to disturbances in potassium physiology. A lack of insulin leads to the inability of potassium to enter the cells, while metabolic acidosis drives potassium out of the cells in exchange for hydrogen. Thus early in DKA, potassium levels may rise, although rarely to dangerous levels. With ongoing osmotic diuresis and dehydration, increasing potassium losses in the

urine lead to increasingly severe hypokalemia. Volume depletion also causes secondary hyperaldosteronism, which promotes further urinary potassium excretion. Potassium is also lost from the body from vomiting. Inevitably DKA is a potassium depleting state. With insulin replacement and correction of acidosis, potassium levels drop further, as insulin drives both glucose and potassium into the cells and the potassium–hydrogen exchange is reversed;

- Sodium: the presence of hyperglycemia leads to osmotic drag of water from the extravascular into the intravascular space. The impact of this is twofold: first, to dilute the concentration of the major extracellular electrolyte, sodium, as well as other analytes such as urea; and second, to maintain intravascular volume, and thereby blood pressure, until very late in the evolution of DKA. Hypotension is unusual and, when present, indicates a profound state of volume contraction;
- Other electrolytes: concentrations of chloride and phosphate tend to follow those of sodium and potassium, respectively.

The severity of DKA has been defined by the pH and bicarbonate concentrations measured in venous blood samples: mild <7.30 and <15 mmol/l, respectively; moderate <7.20 and <10 mmol/l; and severe <7.10 and <5 mmol/l.

Thus, the pathophysiology of DKA involves the complex interaction between absolute insulin deficiency and counter-regulatory hormone excess, the impact of proinflammatory cytokines, and the protean manifestations of these derangements on fluid and electrolyte homeostasis [3]. There are a limited set of circumstances under which DKA occurs: at the time of diagnosis of T1D and, importantly but less frequently, in Type 2 diabetes in children and youth; following insulin omission (e.g., in an attempt to control weight by inducing hyperglycemia and glycosuria in girls with eating and weight/shape disturbances); interruption of insulin delivery (e.g., insulin pump failure and insulin unavailability); or during intercurrent illness of sufficient severity to induce a severe counter-regulatory response.

Treatment of DKA

The major goals of DKA therapy include correction of the dehydration and acidosis, suppression of further ketogenesis, restoration of

Box 1. The clinical manifestations of diabetic ketoacidosis.

- Polyuria (enuresis and/or nocturia), polydipsia and weight loss
- Dehydration: of note, hyperglycemia is associated with ongoing polyuria until prerenal failure occurs
- Kussmaul respiration: rapid, deep and sighing breathing
- Nausea, vomiting and abdominal pain
- Progressive obtundation with eventual coma

blood glucose and electrolytes to near normal levels, identification and treatment of precipitating causes, and avoidance of complications of DKA and/or its treatment. Volume expansion leads to improved renal perfusion, increased glomerular filtration rate, increased glycosuria, decreased blood glucose and reversal of the acidosis. Insulin replacement is essential for complete restoration of metabolic homeostasis by restoring the delicate balance between insulin and the counter-regulatory hormones. The management of children and youth with DKA should occur within the context of a unit in which the physicians and nurses are experienced in this treatment [1]. This often entails transfer to an intensive care unit in a pediatric referral center. However, all physicians involved in child healthcare delivery must be competent in the diagnosis of T1D in children and youth, and the recognition and early management of DKA in these children to ensure transfer in optimal condition.

Management consists of a number of vital components that are summarized here. For greater detail the reader is referred to two international guidelines [1,2].

■ Monitoring

Hourly documentation of clinical observations, intake and output of fluids, medication usage and laboratory results is essential throughout the entire treatment period:

- Heart rate, respiratory rate, blood pressure and level of consciousness;
- Accurate fluid input and output; urinary catheterization is usually only needed in the presence of an altered level of consciousness;
- If the DKA is severe, use an ECG monitor to assess T-waves for evidence of hyperkalemia/hypokalemia;
- Capillary blood glucose (should be checked against laboratory venous glucose owing to possible inaccuracy in the presence of poor peripheral circulation and/or acidosis);
- Laboratory tests should include electrolytes, urea and blood gases every 2–4 h. In the most severe cases, electrolytes should be monitored hourly. Routine monitoring of urine or blood ketones remains controversial;
- Frequent assessment of neurological status for early signs and symptoms of cerebral edema namely, headache, inappropriate slowing of

Table 1. Fluid and electrolyte losses in diabetic ketoacidosis

Fluid/electrolyte	Average (range) loss/kg body weight
Water	70 (30–100) ml
Sodium	6 (5–13) mmol
Potassium	5 (3–6) mmol
Chloride	5 (3–9) mmol
Phosphate	(0.5–2.5) mmol

Modified from the ISPAD guidelines [2].

heart rate and/or rising blood pressure, recurrent vomiting, change in neurological status (restlessness, irritability, increased drowsiness and incontinence) or specific neurological signs (e.g., cranial nerve palsies and pupillary response);

Those monitoring children and youth under management for DKA should be instructed to immediately alert the physician of any of these manifestations.

■ Fluid & electrolyte repletion

Fluid and electrolyte deficits must be replaced. Intravenous (iv.) or oral fluids given before the child presents for treatment and prior to assessment must be factored into the calculation. iv. fluid infusion should start immediately with an isotonic solution (0.9% saline or balanced salt solutions such as Ringer's lactate). Use of colloid is not indicated.

The volume and rate of administration depends on circulatory status and the volume is typically 10 ml/kg over 1–2 h, repeated if necessary. Higher rates of administration would only be indicated in the face of circulatory collapse. Rapid infusion of fluids (iv. boluses) is rarely indicated.

Subsequent fluid management should be with a solution with a tonicity equal to or greater than 0.45% saline. We favor 0.9% saline, but others use a balanced salt solution (e.g., Ringer's lactate or 0.45% saline with added potassium). The iv. fluid infusion rate should be calculated to provide even rehydration over at least 48 h. In addition to the standard clinical assessment of the degree of dehydration, calculation of the effective osmolality may also be of value in determining guide fluid and electrolyte therapy. The joint British Diabetes Societies guidelines advise use of normal saline with premixed potassium rather than adding potassium to the Ringer's solution [4].

Given that assessment of the severity of dehydration is subjective and frequently

overestimated, particularly in those >2 years of age, the fluid infusion rate should rarely be in excess of 1.5–2 times the usual daily requirement based on age, weight or body surface area. Urinary losses should not be added to the calculation of replacement fluids.

Box 2 outlines the approach to potassium, acid base and phosphate management.

■ Insulin replacement

Correction of insulin deficiency is the third mainstay of DKA management [1,2]:

- Dose: 0.1 unit/kg/h (e.g., one method is to dilute 50 units of regular [soluble] insulin in 50 ml normal saline; 1 unit = 1 ml), commencing usually after the first hour of fluid repletion;
- Preferred route of administration is iv. Note that an iv. bolus is unnecessary and may, in fact, increase the risk of cerebral edema and should not be used at the initiation of therapy;
- The infusion of insulin should usually remain at 0.1 unit/kg/h until resolution of DKA (pH >7.30; bicarbonate >15 mmol/l), which invariably takes longer than normalization of blood glucose concentrations;
- Occasionally, a patient may demonstrate marked sensitivity to insulin. In such situations the dose can be decreased to 0.05 unit/kg/h or less, provided that the acidosis continues to resolve. Conversely, occasional patients may show evidence of severe insulin resistance and require higher infusion rates to correct the hyperglycemia.

The aim is to maintain plasma glucose concentrations in the 8–14 mmol/l range. To prevent too rapid lowering of the plasma glucose concentration and hypoglycemia, 5% glucose should be added to the iv. fluid (e.g., 5% glucose in 0.45–0.9% saline) when the plasma glucose falls to approximately 14–17 mmol/l. At times, it may be necessary to use 10–12.5% dextrose to prevent hypoglycemia:

- If the biochemical parameters of DKA (pH, bicarbonate concentration and anion gap) do not improve, reassess the patient, review fluid (rate of infusion) and insulin therapy (insulin concentration and rate of infusion), and consider reasons for impaired response to insulin, for example, infection;
- Where continuous iv. infusion is not possible, injections every 1–2 h subcutaneously or intramuscularly of a short- or rapid-acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as iv. regular insulin infusion, but should not be used in subjects whose peripheral circulation is impaired.

■ Complications of DKA and/or its treatment

The following complications may occur during DKA treatment

- Inadequate rehydration will lead to prolongation of the acidosis and hyperglycemia;
- Hypoglycemia is common where close monitoring of plasma/capillary glucose concentrations is not performed;

Box 2. Potassium, acid base and phosphate management.

Potassium

Replacement therapy should be based on serum potassium measurements

In the presence of hypokalemia, start potassium replacement immediately, otherwise, start potassium at the same time as insulin therapy. If hyperkalemic, hold off on potassium replacement until urine output has been documented. The initial potassium concentration in the infusate should be 40 mmol/l and potassium repletion should continue throughout intravenous therapy

Acid base

Unless the acidosis is 'profound', resuscitation protocols no longer recommend bicarbonate

administration. Fluid and insulin replacement without bicarbonate administration corrects ketoacidosis

Treatment with bicarbonate has not been shown to confer clinical benefit

Phosphate

Phosphate replacement has never been demonstrated to confer clinical benefit. However, some

institutions provide potassium replacement with potassium phosphate as an alternative to, or combined with, potassium chloride/acetate

Administration of phosphate may induce hypocalcemia.

Modified from the ISPAD guidelines [2].

- Hypokalemia is inevitable where insufficient potassium replacement is provided to meet ongoing urinary losses, as well as the insulin-mediated movement of potassium from the extra- to intra-cellular compartment;
- Hyperchloremic acidosis may occur, usually in the context of excess chloride replacement;
- Cerebral edema is the most serious complication of DKA management, accounting for virtually all of the mortality and much of the serious morbidity associated with DKA (see section on 'Cerebral edema' below).

DKA-related mortality in children and youth is low and dropping, except in developing countries where T1D is very uncommon and health services are inadequate. In Austria, for example, a DKA-related mortality of 0.51% was reported in the period 1979–1990, dropping to 0.08% in the 1998–2008 period [5]. In the USA, mortality of 0.23–0.25% was reported between 1982 and 1996, while in Canada it was 0.15–0.18% [6–8]. The reasons for the decline in mortality are likely multifold and may include earlier detection of DKA in many countries, more widespread use of isotonic solutions during correction of acidosis, more judicious rates of fluid and insulin infusion, and less use of bicarbonate to correct the acidosis.

■ Cerebral edema

In three relatively recent reports – two population-based surveillance studies (UK and Canada) and one retrospective, hospital-based study (USA) – cerebral edema developed in 0.5–0.9% of episodes of DKA, more commonly in younger children and those with more severe DKA, and at the time of diagnosis of T1D [7–9]. Mortality rates in these three studies were remarkably similar: 21–24% with approximately half of the remainder having severe neurological consequences.

The exact pathophysiology of cerebral edema remains uncertain, as does the best approach to management. Too rapid fluid infusion, use of hypotonic solutions, use of insulin boluses and a rapid drop in serum sodium concentrations have all been suggested as important mediators of cerebral edema, but none have proven so. Treatment of cerebral edema with mannitol infusion is still the first line of therapy, although some success has been reported with hypertonic saline use [10]. Nonetheless, the only way to

prevent cerebral edema is to prevent DKA in the first place.

■ Epidemiology & prevention of DKA

As stated previously, DKA occurs in a limited number of situations, all of which should be identified and management begun before progression to severe dehydration and acidosis occurs:

- At disease onset;
- In those with established diabetes: as a result of insulin omission (advertent or inadvertent), interruption (e.g., pump failure) or insulin unavailability;
- During intercurrent illness sufficiently severe to cause a brisk counter-regulatory (stress) hormone response.

Understanding the epidemiology of DKA in these circumstances allows for measures to be put in place to prevent them.

DKA at disease onset

Table 2 summarizes the frequency of DKA at disease onset from numerous studies published around the world. These have been collated most recently by Usher-Smith *et al.* and

Table 2. Frequency of diabetic ketoacidosis at onset of Type 1 diabetes.

Country	Time period (years)	DKA at onset (%)
Saudi Arabia	1985–1990	67.3, 66.2
Taiwan	1997–2006	65
France	–	54
Kuwait	1992–2006	49, 37.5
Bosnia and Herzegovina	1990–2005	48
Poland	1995–2005	54.7–32.9
USA	1990–2004	43.7, 32.9, 27
Italy	1987–2003	41.1–35.6
China	2004–2008	41.9
Oman	2003	41.7
Austria	1989–2002	37.2
Chile	1989–2002	37
Bulgaria	1979–2006	35.3
Lithuania	1976–2000	34.6
Turkey	1991–2008	29
UK	1987–2007	38–25.2
Germany	1991–1997	52.8–26.1
Ireland	1997–1998	25
Finland	1982–2005	22.4–19.4
Canada	1994–2000	18.6
Sweden	1995–2001	14.5–12.8

DKA: Diabetic ketoacidosis.
Data taken from [11].

modified by the authors based on additional available information [11]. In certain countries (Saudi Arabia, Taiwan and France) DKA rates at diagnosis exceed 50% (anecdotal information from some developing countries suggest few, if any, children present without DKA), while in others (Sweden, Canada and Finland) rates below 20% have been reported. Furthermore, some countries (e.g., Poland, Germany, Ireland, UK and USA) have reported either declining rates over time or fluctuations from one time to another. This is more than a fivefold difference between countries and suggests a definite opportunity to lower risk by understanding the factors associated with higher versus lower frequencies. While some of these are medical (e.g., younger age at onset, diagnostic error at first presentation to healthcare system, lower background risk of T1D in that country and amount of residual insulin secretion), most can be related to the social determinants of health and healthcare provision, including lower socioeconomic or ethnic minority status, lower parental education, lack of adequate health insurance and lack of effective pediatric diabetes healthcare teams [11–14]. In a recent report analyzing only the data from the countries listed as ‘wealthy’ by the Organization of Economic Cooperation and Development, we found a very close correlation between DKA risk at diabetes onset and income inequality, defined as the gap between each country's highest and lowest 20% income earners [13]. This analysis shows that more than 40% of the variability in DKA rates in these countries can be explained by income inequality. In those countries with the lowest income inequality (e.g., Scandinavia) DKA rates are lowest, while rates are highest in the USA, where income inequality is greatest. We have postulated that income inequality is associated with progressive porosity of the social security net providing poorer resources for public health and primary care initiatives and more for high-end diagnosis and care.

We, and others, have also demonstrated clearly that many of the children in frank DKA when diabetes is diagnosed, have seen a healthcare professional on one or more occasion in the days or weeks previously, at which time the diagnosis of diabetes has been missed [12]. In doing so, an opportunity to prevent DKA has been lost. A landmark study in Parma, Italy has demonstrated that a low-cost campaign targeting schools and primary care pediatricians can

lower the risk of DKA at disease onset from more than 70% to below 15% and perhaps even to 0% [15,16].

DKA in those with established T1D

Studies over the last 30 years or more report rates of DKA in those children and youth with established T1D of between one and ten episodes/100 patient years. Of note, the lowest rate of one per 100 patient years was reported from Germany at a time when most children with T1D were admitted annually on a routine basis for assessment and education. When this practice stopped, DKA rates rose to four per 100 patient years [17]. Our data from the province of Ontario, Canada reveals a 3.7-fold difference between regions of the province with respect to episodes of DKA per unit population, as well as a small but significant increase as these youth transition from a pediatric to adult diabetes healthcare team [6,18].

Rewers *et al.* reported their experience as follows: those children and youth experiencing one, two or more episodes of DKA after diagnosis, were more likely to be older, female, have longer duration diabetes, higher A1c levels, higher prescribed insulin dosage, more evidence of psychosocial distress and less healthcare insurance than the majority experiencing no episodes of DKA [19].

In the small group with frequently recurrent episodes of DKA, Golden *et al.* demonstrated a major reduction in the number of episodes, not by educational or psychosocial interventions, but by simply ensuring insulin injection by a responsible adult [20]. In our studies of eating and weight psychopathology, we have demonstrated insulin omission to increase rapidly with increasing age, from 2% of those in the 9–14 years age group to 12% in the 12–19 years age group, and 34% in the 16–23 years age group [21,22].

In some developing countries, access to insulin is poor or intermittent and death from DKA is much more frequent. Unavailability of insulin is scandalous given our ability to produce the hormone in limitless quantities by biosynthetic technologies.

Finally, two other situations warrant mention in which the occurrence of DKA is entirely preventable. First, in those with an intercurrent illness severe enough to produce a stress hormone response, failure to provide sufficient insulin and fluids (in the face of vomiting) will

inevitably lead to the development of ketosis and then frank DKA. Adherence to 'sick day rules' will prevent such occurrences [23]. Second, in the increasing percentage of children and youth using continuous subcutaneous insulin infusion pumps (pump treatment), interruption of the infusion of fast-acting insulin will lead to rapid insulinopenia and eventual DKA, also an easily preventable situation [24].

Thus, the major causes of DKA in children and youth with established T1D can be classified as being the result of poor education or psychosocial difficulties, once again shedding the spotlight on the social determinants of health.

Summary regarding prevention

The data provided above concerning the epidemiology and prevention of DKA have led to the enunciation of what one of us (Daneman) has termed the 'failure hypothesis', which states very simply that almost all, if not all, episodes of DKA are preventable by public health and primary care provider education and suspicion at first diagnosis, then by family and diabetes team education, support once the diagnosis has been established.

Conclusion

DKA remains a significant complication of T1D in children and youth, both at diagnosis and

during the course of their disorder. It is the most common cause of mortality and the most significant cause of hospitalization for diabetes in this age group. The only sure way to prevent DKA-related morbidity and mortality is through prevention of the episode in the first place. Public education, primary healthcare provider education and then support for the child and family will help prevent the breakdowns ('failures') that are the root causes of DKA.

Future perspective

Application of the available knowledge should be sufficient to prevent many episodes of DKA, both at disease onset and in those with established diabetes. This application will require both public health and primary care physician involvement. Similarly, attention to therapeutic guidelines will ensure best care for those with established DKA and limit complications.

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