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Review Article

Can we prevent diabetic ketoacidosis in children?

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Abstract: Diabetic ketoacidosis (DKA) is an acute potentially life-threatening complication of diabetes affecting more than 100,000 persons annually in the United States. Although major advances have improved diabetes care, DKA remains the leading cause of hospitalization, morbidity, and death in youth with type 1 diabetes (T1D). As the majority of patients presenting with DKA have established diabetes, it is important to address outpatient educational approaches directed at sick-day management and early identification and treatment of impending DKA. Teaching and reinforcement of sick-day rules involves improved self-care with consistent self-monitoring of blood glucose and ketones, and timely administration of supplemental insulin and fluids. DKA as an initial manifestation of T1D may be less amendable to prevention except with an increased awareness by the lay and medical communities of the symptoms of diabetes and surveillance in high-risk populations potentially identified by family history or genetic susceptibility. New technologies that can detect the blood ketone 3β-hydroxybutyrate (3β-OHB) instead of traditional urine ketones appears to provide opportunity for early identification and treatment of impending DKA leading to reduced need for hospitalization and potential cost-savings.

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Despite major advances in the care of diabetes, diabetic ketoacidosis (DKA) remains a leading cause of hospitalization and the leading cause of morbidity and death in children and adolescents with type 1 diabetes (T1D). There are over 150 000 annual episodes of DKA in the USA. The average cost of treating a single episode of DKA in the USA is about $11 000; the cost of all episodes combined represents about 25% of the total spent on the care of patients with T1D (1). The overall incidence of DKA varies with definition, age, and sex, ranging from 4.6 to 13.4 episodes per 1000 persons with diabetes per year in the USA (2). The majority of DKA cases have previously diagnosed diabetes and it is estimated that 50% of hospital admissions for DKA could be prevented with improved outpatient treatment and better adherence to self-care (3, 4).

Complications related to DKA are the most common cause of death in children, teenagers, and young adults with diabetes, accounting for approximately 50% of all deaths in individuals with diabetes younger than 24 yr old (5, 6). Cerebral edema is an uncommon but serious complication of DKA associated with morbidity and mortality. Estimates of the incidence of cerebral edema in DKA range from 0.4 to 3.1% (5), and recent reports from Britain and the USA have shown a mortality rate of 21–24%, and significant neurologic sequelae in 21–35% (6, 7). Cerebral edema accounts for ~60–90% of all DKA-related deaths in children (8).

It is important to try to prevent DKA in order to reduce morbidity and mortality associated with severe metabolic decompensation. This prevention can be accomplished through appropriate education, improved self-care and adherence, and consistent self-monitoring of blood glucose and ketones. DKA as an initial manifestation of T1D is less amenable to prevention, other than through surveillance in youth with a positive family history of diabetes, and increased public awareness of the symptoms of diabetes.

Epidemiology

DKA is a serious complication of diabetes that is associated with considerable mortality and morbidity. Although the mortality rate in adults diminished from 44% in the 1930s to 16% in the 1970s (9) and to 3–5% in the 1980–1990s (10), the recent rates in pediatric patients have been relatively stable at about 1% or less (6, 11). In the context of evolving T1D, DKA is frequently an indicator of a delay in the recognition of the symptoms of diabetes, whereas in the context of established diabetes, DKA is often indicative of either insulin omission or suboptimally managed intercurrent stress episodes. The latter offer opportunities for enhanced diabetes education toward DKA prevention. Given the intensity of public awareness campaigns as to the significance of diabetic symptoms and the increased effort expended in improving glycemic control after the Diabetes Control and Complications Trial (DCCT), it might be anticipated that episodes of DKA in children and adolescents with T1D would have decreased over the last two decades. However, data from Ontario between 1991 and 1999, revealed that DKA admissions remained stable (4).

DKA at diagnosis

In Europe, Australia and North America, some 15–70% of all newly diagnosed children with diabetes present with DKA (12, 13). Thus, there is wide geographic variation in the frequency of DKA at onset of diabetes; rates inversely correlate with the regional incidence of T1D, likely as a result of more experienced physicians recognizing symptoms of diabetes (8). Most commonly, rates of DKA at diagnosis are 25–30% (14–16). In addition, rates of DKA vary according to age at diagnosis of diabetes, with as many as 44% of youth <6 yr of age presenting in DKA in one study (17) and 30% presenting with acidosis and/or coma in another report (18). Recently, DKA, defined by blood bicarbonate <15 mmol/L and/or pH < 7.25 (7.3 if arterial or capillary), was found in 23.3% of a carefully analyzed US cohort (16). The prevalence of DKA decreased significantly with age from 36% in children <5 yr of age to 16% in those >14 yr, but it did not differ significantly by sex or ethnicity (16). Indeed, in the younger child who may also have a more rapid rate of beta cell loss, it is more difficult to obtain a classic history of polyuria, polydipsia, and nocturia. Thus, infants and toddlers with impending DKA may go undiagnosed, thereby increasing their duration of symptoms, leading to more severe dehydration and acidosis at presentation. For example, a dramatic 220% increase in DKA admissions was observed in the 0- to 4-yr age group between 1991 and 1999 in Ontario (4). This trend is concerning, and supports the increase in the occurrence of T1D in youth worldwide, especially in the very young (19). In a recent study of incidence trends in childhood diabetes across Europe, the 0- to 4-yr age group displayed the highest annual increase (4.8%) (20).

DKA in established diabetes

The incidence of DKA in adolescent patients enrolled in the DCCT was 2.8 per 100 patient-years in the intensive treatment group (n = 92) vs. 4.7 per 100 patient-years in the conventional therapy group (n = 103) (21). In a more recent study, incidence of DKA in children and adolescents with T1D was found to be 8 per 100 patient-years (22). The incidence of DKA in established diabetes is higher in females, peaks in early teenage years, and rarely occurs in anyone diagnosed for less than 2 yr. Individuals with earlier age of onset and lower socioeconomic backgrounds seem to be at increased risk, along with individuals who had psychopathology before diabetes onset. Research reveals several consistent themes that enable us to identify individuals at potential risk for recurrent DKA, with about 20% of individuals accounting for 80% of the hospital admissions for DKA in one report (23).

Risk factors

At disease onset

DKA at diagnosis is more common in younger children (<5 yr of age) and in children whose families do not have ready access to medical care for social or economic reasons (22, 24). Lack of health insurance is associated with higher rates (and greater severity) of DKA at diagnosis, presumably because uninsured persons delay seeking timely medical care (22). Lower income and lower parental educational achievement (father's work, education of parents) were also associated with higher risk of DKA (25). History of parental depression and diminished parental anxiety, possibly due to lower parental awareness of symptoms in offspring, may also increase DKA risk at onset (26). As expected, a lower frequency of DKA at T1D diagnosis was evident in children with a family history of insulin-treated diabetes (24).

In children with established T1D

Children whose insulin is administrated by a responsible adult rarely have episodes of DKA; 75% of episodes of DKA after diagnosis are associated with insulin omission or treatment error. The remainder are a result of inadequate insulin therapy during intercurrent illness (11). In a cohort of 1243 children with T1D followed prospectively for 4 yr in the Denver area, the incidence of DKA was 8 per 100

person-years and increased with age in girls. In younger children, the risk of DKA increased with higher A1c and higher reported insulin dose. In older children, the risk of DKA increased with higher A1c, higher reported insulin dose, underinsurance, and the presence of psychiatric disorders (22). Eating disorders, relatively common in young women with T1D, also contribute to impaired metabolic control, leading to hyperglycemia and DKA (27).

There is consistent evidence for psychosocial risk factors as predictive of recurrent DKA. Individuals from families low in warmth and support, where there are high levels of unresolved family conflict and a distinct lack of parental involvement in the adolescent's diabetes care, seem to be typical of this population (28). Objective assessment of insulin management behavior through prescription data from Scotland indicated that 28% of young adults (aged 15–25 yr) with T1D do not refill a sufficient amount of prescribed insulin to follow their treatment regimen. This behavior, indicating under-insulinization, predicts admission for DKA (29).

Individuals using continuous subcutaneous insulin infusion (CSII) are potentially at increased risk for DKA following unrecognized interruption in insulin delivery and inadequate monitoring (30). Population-based and retrospective clinical studies report a relatively low rate of DKA with pump therapy, but a higher rate with CSII compared with injection therapy, at least in some countries (30). Recent data among 1041 pediatric patients using insulin pumps in Europe revealed a risk of DKA of 6.6 per 100 patient-years (31). In a Swedish population-based study, the incidence of DKA among pump users was 3.5 per 100 patient-years compared with 1.7 per 100 patient-years among patients treated with insulin injections (32). In general, the risk of DKA appears relatively low in research settings, among adherent patients, and in patients with sufficient family support (30).

Prevention of DKA

Primary prevention

Professional and public awareness of early signs and symptoms of diabetes in children and adolescents is required to decrease the incidence of DKA in patients with new-onset diabetes; a high index of suspicion of symptomatology may lead to earlier diagnosis. Although such strategies are intuitively obvious, programs to decrease DKA at onset need to be designed and evaluated in diverse populations and age groups (11). In a program in Parma, Italy, schools and doctors' offices were provided with colorful posters with practical messages about diabetes, and local pediatricians were instructed on the use of glucose meters. Parents and pediatricians received a toll-free number to facilitate contact with the diabetes unit. In the study area, the incidence of DKA in new-onset cases aged 6–14 yr decreased from 78% in 1987–1991 to 12.5% in 1991–1997 with no cases reported after 1992. In the control region nearby, which received no information, 83% of new cases presented with DKA (33). This demonstrates that by means of an aggressive but relatively inexpensive information campaign, it is possible to reduce the incidence of DKA at onset. In another center, where tips about early symptoms of diabetes were provided to local pediatricians, a reduction from 86 to 26% of DKA at diagnosis was observed (3).

A diagnosis of DKA may be delayed in new-onset cases, especially in younger children, who may first be diagnosed with pneumonia, reactive airway disease, or bronchiolitis. Indeed, a recent study revealed that among youth diagnosed with T1D, children <3 yr old and those presenting in DKA had more medical encounters in the week prior to diagnosis compared with those without DKA, suggesting missed opportunities to prevent DKA (34). Follow-up studies suggest that DKA is more frequent (24, 35), and more severe (24), when missed at initial patient encounters. In New England, anecdotal reports include three deaths in youth from undiagnosed diabetes in 2003–2004.

Earlier diagnosis through immunologic and genetic screening of high-risk children, such as in the Diabetes Prevention Trial (DPT)-1, decreased DKA incidence at diabetes onset (36). A high level of awareness in those with positive family history of T1D also reduces the occurrence of DKA at diagnosis (24). In a recent study, children with a positive family history of T1D presented 50% less often in DKA at diagnosis than those without a family history of T1D (29 vs. 60%) (24). In addition, the DPT-1 revealed that a rising A1c even within the reference range, may predict the diagnosis of T1D, thus offering another means to avert an episode of DKA at onset (36).

Secondary prevention

DKA in established diabetes is most often the result of inappropriate management of intercurrent illness/stress or accidental or deliberate omission of insulin (Table 1). Patient and family training of sick-day management can provide the education needed to prevent or treat severe hyperglycemia and ketosis. Studies of the effects of such comprehensive diabetes management programs and telephone help lines report a reduction in the rates of DKA from 15–60 to 5–5.9 per 100 patient-years (11). It is likely that both diabetes sick-day education and 24-h telephone help lines reduce the occurrence of DKA; however, studies have not evaluated the unique contribution of each approach to decreasing the rates of DKA. Therefore, episodes of DKA after diagnosis could be reduced if all children with diabetes and their families receive comprehensive, ongoing diabetes education along

Table 1. Triggers for hyperglycemia, ketosis, and diabetic ketoacidosis

New-onset diabetes
Infection
Trauma
Surgery
Emotional stress
Errors in insulin administration
Pump failure / catheter kinking
Intentional manipulation of insulin dosing
Pregnancy
Myocardial infarction
Medications (e.g. steroids)
Substance abuse
Eating disorders
Comorbidities

with access to a 24-h diabetes telephone help line (3, 11). Sick-day rules should be reinforced periodically, especially at the start of the school year and during flu season when illness is more common. For patients receiving CSII, DKA may be avoidable with frequent monitoring of blood glucose along with urine/blood ketones, followed by appropriate intervention when needed (8). In Norway, the nationwide incidence of DKA (approximately 4 per 100 patient-years) did not change despite an increase in CSII use from 5% in 2001 to 38% in 2005 (37).

Patients who experience multiple episodes or 'recurrent' DKA are more problematic. Insulin omission has been identified as the major factor in most of these cases. There is often a trigger for insulin omission and a psychiatric social worker or clinical psychologist should be consulted to investigate any psychosocial reasons contributing to development of DKA. Insulin omission may be preventable with multidisciplinary support providing education, psychosocial evaluation, and treatment combined with adult supervision of insulin administration. When responsible adults administered insulin, episodes of DKA dropped by 90% (38). The DKA prevention program in Los Angeles, which included teaching patients and families the early warning signs of DKA, providing sick-day management guidelines, and availability of a 24-h health-care team, reduced the rate of recurrent DKA from 12 events per 100 patient-years to 4 events per 100 patient-years in 1998 (3). Again, this study did not evaluate the unique contribution of the individual components of the DKA prevention program. Dedicated outpatient diabetes treatment teams directed at adult patients can also result in significant decreases in DKA-associated readmissions and A1c values in ketosis-prone patient populations (39). When these efforts fail, attempts to prevent recurrent DKA mandate more aggressive approaches such as out-of-home placement away from dysfunctional families and even use of insulin pump therapy to provide consistent basal insulin delivery (3, 40). Multisystemic therapy involving intensive home-based psychotherapy appears to reduce DKA admissions compared to standard care for youth in poor control (41, 42).

The importance of ketone testing

Testing for ketones remains critical to the prevention of DKA, yet knowledge and practice of ketone testing are usually deficient. Diabetes education requires not only initial teaching of diabetes management to prevent metabolic decompensation but also ongoing reinforcement. Unfortunately, sick-day management is usually taught in a state of good health when practice of these principles is not needed. Thus, patients and families may have forgotten sick-day management by the time illness ensues. Sick-day management requires the patient to check blood glucose and ketones frequently.

Ketone production

Although glucose is the preferred metabolic fuel, alternative fuel sources, such as free fatty acids (FFAs) and ketones from fat breakdown, can be used if glucose is unavailable. In DKA, because of an absolute or relative lack of insulin, the insulin-dependent tissues are unable to metabolize glucose normally. The regulation of fatty acid breakdown is influenced by several hormones, in particular insulin, glucagon, and epinephrine. Low insulin levels along with high levels of counter-regulatory hormones (low ratio of insulin/glucagon) cause an increase in lipolysis, mobilizing FFAs, and promoting ketogenesis. After transport into hepatic mitochondria, FFAs are converted into acetyl-coenzyme A (CoA), which can be used for energy synthesis in the tricarboxylic acid cycle if adequate oxaloacetate is present. When oxaloacetate is being used for gluconeogenesis (as in DKA), the acetyl-CoA is instead used for synthesis of ketones. Acetoacetate (AcAc) is the primary product of β-oxidation; 3β-hydroxybutyrate (3β-OHB) results from the reduction of AcAc; and acetone results from the spontaneous decarboxylation of AcAc. Ordinarily, AcAc and 3β-OHB exist in equimolar concentrations in the blood. During DKA, however, the reduced redox potential in the hepatic mitochondria favors the formation of 3β-OHB and the 3β-OHB to AcAc ratio increases from 1:1 to 6:1, reaching as high as 10:1 in some individuals. In contrast, with recovery from DKA, the ratio again falls with conversion of 3β-OHB to AcAc.

Detection of ketones

For several decades, the only way to measure ketones was testing the urine with a dipstick test such as

Ketostix® (Bayer Diagnostics, USA) or with acetest tablets. Ketostix® measures urinary AcAc, which reacts with nitroprusside to produce a purple-colored complex. Nitroprusside does not react with 3β-OHB, the predominant ketone body in DKA. Urine strips containing glycine in addition to nitroprusside can also detect acetone.

Urine ketone testing has limitations for several reasons. Urine ketone measurements do not accurately reflect current conditions if the urine has been in the bladder for several hours (e.g. overnight) before testing. Similarly, if bottled strips are used and the bottle was first opened more than 6 months earlier (it is recommended that the date be written on the bottle when first opened), the strips can lose their accuracy. Urine ketone results can also be affected by medications, giving false-positive results in the presence of drugs containing sulfhydryl groups, like captopril. Also, obtaining a urine sample is sometimes problematic with very young children, teenagers, and people who are unable to void or who are too ill or exhausted to do the test (43).

The inability of the nitroprusside test to detect 3β-OHB and an increasing belief that blood levels of 3β-OHB might prove useful in the management and prevention of DKA prompted the development of rapid enzymatic methods for the quantification of 3β-OHB in small-volume blood samples. The first of these systems was marketed by GDS Diagnostic (Elkart, IN, USA), which provided a bench-top analyzer for use in clinical laboratories and physician offices. The GDS System determines 3β-OHB levels on a drop of blood (25 μL) in about 2 min, with a detection range between 0 and 2 mmol/L (44). More recently, a hand-held device has been developed that allows the determination of 3β-OHB from capillary blood in 10 s (initially 30 s) at home or at the patient's bedside. This system for the precise quantification of 3β-OHB levels on a fingerstick blood specimen (2 μL) has been introduced by MediSense/Abbott Laboratories (Precision Xtra®/Optium®) (Abbott Diabetes Care, Alameda, CA) and is available for clinical practice. Accuracy testing against a reference laboratory instrument demonstrates a high correlation ($r = 0.94$) with a measurement range between 0 and 6 mmol/L. Elevated ketones levels, called hyperketonemia, include values >0.6 mmol/L.

Blood ketone monitoring vs. urine ketone monitoring

The ADA previously recommended that all people with diabetes should test their urine for ketones during periods of acute illness or stress, when blood glucose levels are consistently in excess of 16.6 mmol/L (300 mg/dL), during pregnancy, or when symptoms suggestive of DKA are present. A few years ago, the ADA statement noted that 'Currently available urine ketone tests are not reliable and blood ketone testing methods are now reliable for diagnosis and monitoring treatment of ketoacidosis' (45).

Published reports on blood ketone monitoring have appeared from clinical research and from inpatient and outpatient settings. Elevations in blood 3β-OHB and urine ketones have been monitored prospectively during investigations in which CSII with lispro or regular insulin was discontinued under controlled conditions (46–48). After 5–6 h following discontinuation of CSII, moderate ketones generally appeared in the urine and blood 3β-OHB rose from 0.1–0.2 mmol/L to 1–1.2 mmol/L. Monitoring blood ketones would likely allow the earlier detection of ketosis when levels exceed 0.5 mmol/L, before ketonuria becomes evident, allowing for earlier intervention. Patients on CSII, in whom ketosis can appear rapidly in cases of pump failure or catheter occlusion, may benefit greatly (49).

Measuring 3β-OHB in a hyperglycemic patient in the acute setting can expedite diagnosis and treatment as a point-of-care tool in an emergency department (50). In this setting, sensitivity and specificity of the capillary 3β-OHB measurements in determining DKA were 72 and 82% (vs. 66 and 78% for urine ketone dipstick), respectively (51). In another study, among 50 patients who had 3β-OHB measurements in an emergency room when fingerstick glucose exceeded 11 mmol/L (200 mg/dL), 3β-OHB level of >3 mmol/L had a sensitivity of 100% and specificity of 88% for detecting DKA (52).

In the outpatient setting, blood ketone monitoring may improve self-care management during hyperglycemia, sick days, and for symptoms suggestive of DKA; however, patient adherence needs to be evaluated. Among healthy outpatients in suboptimal glycemic control, measurements of blood 3β-OHB can help distinguish ketotic patients from those with hyperglycemia alone (53). For sick-day management, the efficacy of blood 3β-OHB monitoring was evaluated in a 6-month two-centre, prospective, randomized clinical trial comparing blood 3β-OHB monitoring (Precision Xtra™) with traditional urine ketone testing. We enrolled 123 children and adolescents who were randomized, according to pump status and A1c, to receive the Precision Xtra™ system or urine ketone strips for ketone monitoring. Participants continued routine diabetes care throughout the study, which included 24-h access to an on-call physician (54). Participants received sick-day guidelines within logbooks specific for each group. Recommendations were based on blood glucose results and either blood 3β-OHB or urine ketone measurements (see Tables 2 and 3). Adherence to ketone monitoring during sick days was 90.8% for partic-

Table 2. Supplemental insulin dosages based on blood glucose and urine ketone results

		Blood glucose level mmol/L (mg/dL)		
Urine ketones	<4.4 (80)	4.4–13.8 (80–250)	13.9–22.2 (250–400)	>22.2 (400)
None/trace	Omit fast-acting analog or regular insulin when p.o. intake decreases	Usual dose	5%	10%
Small	Decrease intermediate or long-acting insulin by 20%	0–5%	10%	15%
Mod/Large	Decrease intermediate or long-acting insulin by 20%; contact health care team, especially with vomiting	0–10%	15–20%	20%

Note: % refers to percentage of total daily dosage (TDD) given as fast-acting analog or regular insulin. TDD is calculated by adding up all the insulin administered on a usual day, including the fast-acting analog or regular insulin and the intermediate/long-acting insulin. Do not include supplements added to the usual dose because of unexpected hyperglycemia. In calculating the TDD when sliding scales are used, select the sliding scale dose for blood glucose of about 8.3 mmol/L (150 mg/dL). Blood glucose and urine ketones should be monitored every 2–4 h. Supplemental insulin boosters are repeated every 2–3 h with the fast-acting analog or every 3–4 h with regular insulin. If hyperglycemia or urine ketones do not improve after two supplemental dosages, the health-care team should be contacted. Pump basal rates should be increased by 20–50% during illness along with additional bolus doses. If blood glucose level is <4.4 mmol/L and there is decreased po intake, omit the fast-acting analog or regular insulin and decrease intermediate/long-acting insulin by 20%. Contact health-care team, especially if there is vomiting. The range of dosage adjustments accounts for the need for clinical judgment based upon clinical status and anticipated oral intake of food and fluids.

ipants checking blood ketones, compared with 60.3% for those checking urine ketones. There was no difference in monitoring frequency between groups during periods of hyperglycemia alone (blood glucose ≥13.9 mmol/l), when ketone monitoring occurred in only 34% of each group. Thus, the common occurrence of hyperglycemia in youth with diabetes was often an insufficient motivation to test for ketones in the absence of illness. In this study, the need for emergency department assessment and treatment or urgent hospitalization was 50% lower in the blood ketone group compared with the urine ketone group, 38 episodes per 100 patient-years compared to 75 per 100 patient-years, respectively. At study's end, 70% of those checking ketones reported that they preferred to check blood versus urine ketones (54). Thus, blood ketone monitoring seems to be well accepted in a pediatric clinic population.

Table 3. Algorithms for supplemental fast-acting analog or regular insulin dosages incorporating blood 3β-hydroxybutyrate ketone results

		Blood glucose level mmol/L (mg/dL)	
Blood ketones (mmol/L)	<13.9 (250)	13.9–22.2 (250–400)	> 22.2 (400)
<0.6	No change	5%	10%
0.6–0.9	No change	5%	10%
1–1.4	0–5%	10%	15%
≥1.5	0–10%	15–20%	20%

Note: % refers to percentage of total daily dosage (TDD) given as fast-acting analog or regular insulin. TDD is calculated by adding up all the insulin administered on a usual day, including the fast-acting analog or regular insulin and the intermediate/long-acting insulin. Do not include supplements added to the usual dose because of unexpected hyperglycemia. In calculating the TDD when sliding scales are used, select the sliding scale dose for blood glucose of about 8.3 mmol/L (150 mg/dL). Blood glucose and ketones should be monitored every 2–4 h. Supplemental insulin boosters are repeated every 2–3 h with the fast-acting analog or every 3–4 h with regular insulin. If hyperglycemia or blood ketones do not improve after two supplemental dosages, the health-care team should be contacted. Pump basal rates increased by 20–50% during illness along with additional bolus doses. If blood glucose level should be <4.4 mmol/L and there is decreased po intake, omit the fast-acting analog or regular insulin and decrease intermediate/long-acting insulin by 20%. Contact health-care team, especially if there is vomiting. The range of dosage adjustments accounts for the need for clinical judgment based upon the clinical status and anticipated oral intake of food and fluids.

Hyperketonemia appears to be common in the setting of uncontrolled diabetes (55). Further studies are needed to confirm the impact of blood ketone testing on the prevention of DKA.

The management of elevated ketone levels

Patient and parent education remains the cornerstone for sick-day management and prevention of metabolic decompensation in youth with T1D. New technologies like a handheld blood ketone meter can improve self-care management. It provides a method to detect metabolic disturbance and correct it if appropriate guidelines are followed. First, patients, family, and general practitioners should be aware of the triggers for hyperglycemia, ketosis, and DKA (Table 1). For example, substance abuse may trigger DKA through non-adherence and comorbidities such as reactive airway disease and inflammatory bowel disease may warrant systemic steroid treatment, which may promote metabolic decompensation in the absence of supplemental insulin. Next, algorithms for management

of hyperglycemia and sick days should be explained and reinforced repeatedly. Before routine acceptance of ketone monitoring is realized, it is necessary that all patients with T1D check their glucose levels frequently. In a 1-year prospective study enrolling 300 youth with T1D (7–16 yr old) in our centre, we found that 24% of the patients checked their blood glucose twice daily or less often (56). Further, glycemic control improves significantly as the frequency of blood glucose monitoring increases. Indeed, blood glucose monitoring frequency was the sole modifiable predictor of glycemic control in this study (56). Thus, through increased blood monitoring of glucose and ketones, we have significant opportunity to improve glycemic control and prevent DKA.

Sick-day rules

The most common reason for families to report elevated ketone levels is an infection or illness; another frequent cause is failure of insulin delivery resulting from a pump mishap (pump failure, catheter kinking or slipping out, etc.). Insulin omission is also a common cause for ketosis. Ketones are checked more commonly in association with illness than with hyperglycemia alone (54). The objective of sick-day management in T1D is to minimize metabolic imbalance, avoid severe hypoglycemia with gastrointestinal illness, and prevent unchecked hyperglycemia and ketosis leading to DKA. Sick-day guidelines are taught to all families and, as age appropriate, to children and adolescents with T1D, usually at diagnosis with reinforcement at the time of illness. These guidelines should be instituted with illness, ketonuria, or hyperketonemia, when blood glucose values are elevated (>13.8 mmol/L – 250 mg/dL – on two consecutive readings), or with symptoms of DKA, such as nausea, vomiting, or abdominal pain (54, 57) (Fig. 1). The cornerstone of sick-day management includes:

(i) *Never omit insulin*: Insulin must always be administered during illness, even at times when eating is markedly diminished as infection induces insulin resistance, often necessitating increased or supplemental doses of insulin. The additional or supplemental dose is needed to manage the hyperglycemia and ketosis. Supplemental insulin dosages generally consist of 10–20% of the total daily insulin dose administrated every 2–3 h if given as fast-acting analog insulin or every 3–4 h if given as regular insulin, based on both the blood glucose and ketone results, using algorithms.
(ii) Ongoing self-blood-glucose monitoring with adult supervision at least every 2–4 h, occasionally every 1–2 h, and with results recorded in a log book.
(iii) Monitoring for ketosis every 2–4 h with results recorded in a log book.
(iv) Continuation of monitoring and supplemental insulin through the night.
(v) Increased intake of salty fluids to combat dehydration associated with hyperglycemia and possible fever. The blood glucose level determines

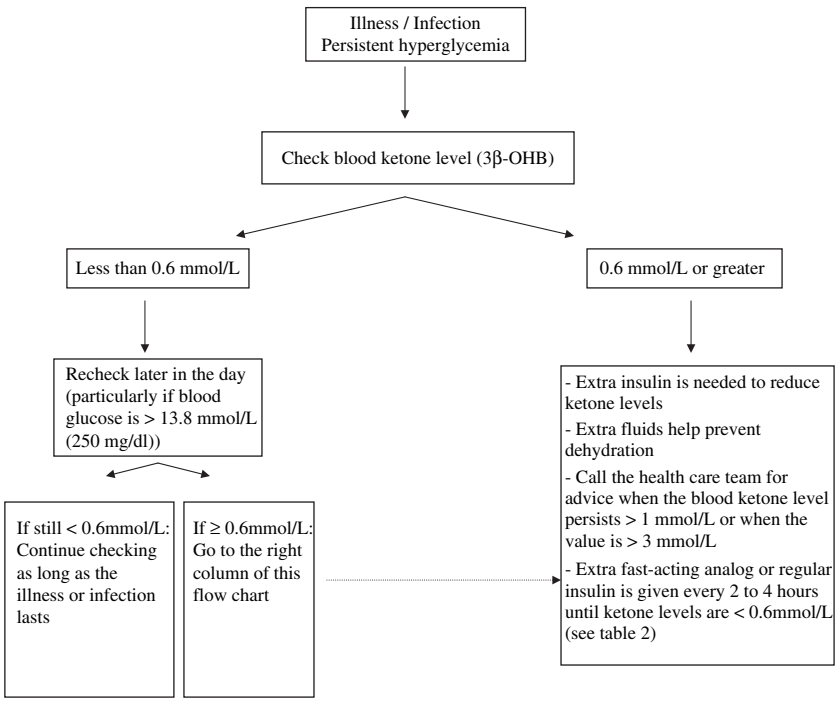

Fig. 1. Flow chart for ketone checking and treatment of illness or infection [adapted from Burdick et al., Practical Diabetology, 2004 (43)].

whether sugar-containing or sugar-free fluids should be consumed (usually sugar-free fluids if blood glucose >10 mmol/L (180 mg/dL), sugar-containing fluids if blood glucose ≤10 mmol/L).
(vi) Treatment of any underlying illness.
(vii) Anti-emetics if severe vomiting prevents adequate fluid intake, and mental status does not need ongoing monitoring.
(viii) Frequent contact with the health-care team to review clinical status.

If illness persists more than a few hours, emergency assessment may be needed.

Tables 2 and 3 provide specific guidelines based on urine ketone or blood ketone levels. Patient/families should contact their health-care team if blood ketone levels persist above 1 mmol/L or urine ketones remain large.

Conclusion

Diabetic ketoacidosis is a serious complication of diabetes and the leading cause of death in children with diabetes. Delay in the diagnosis and treatment of DKA increases morbidity and can lead to mortality, usually from cerebral edema. The initial diagnosis of diabetes or DKA may not be straightforward. Some children present with flu-like symptoms, and the diagnosis can be missed, especially during flu season. Prevention of severe metabolic decompensation through sick-day management remains a cornerstone of comprehensive diabetes treatment. Even in developed countries, children have died from DKA and undiagnosed diabetes in recent years. Increased awareness of diabetes symptoms should be reinforced among general practitioners, pediatricians, and in schools. Simple interventions like posters and educational leaflets circulated to physician offices and schools may help reduce DKA at diagnosis through earlier recognition of symptoms. In children with established diabetes, education remains the most powerful tool to prevent DKA. Identification of triggers for metabolic decompensation and knowledge of implementation of sick-day management rules should be reinforced repeatedly, especially during flu season. Screening for the risk factors for recurrent DKA may identify the child/family in need of specific interventions and attention to psychosocial factors. Monitoring 3β-OHB levels in patients with DKA can reduce the length of stay and costs (58). While blood ketone monitoring strips are costlier than urine ketone strips, there remains opportunity for overall cost savings with routine use of blood ketone testing in the ambulatory and hospitalization settings because of reduced rates of hospitalization and emergency assessments and shorter lengths of stay. In one study, the mean cost per admission was lowest for DKA precipitated by non-compliance in established T1D patients than for patients with new onset diabetes or acute illness; nonetheless, this category remains responsible for the greatest portion of the economic burden of DKA (1). Furthermore, patients with DKA resulting from insulin omission or those with recurrent DKA could potentially increase the costs of hospitalization if length of stay were increased for ongoing psychosocial assessment and management. New technologies like blood ketone monitoring and real-time continuous glucose sensing may provide opportunities to prevent or reduce the occurrence of DKA with potential cost savings in those patients and families willing to utilize such new approaches.

Conflicts of interest

LL has acted as a paid consultant and has received investigator-initiated funding from Abbott Diabetes Care. EB has declared no conflicts of interest.

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