Received: 5 September 2022 | Accepted: 6 September 2022

DOI: 10.1111/pedi.13415

ISPAD GUIDELINES

ISPAD WILEY

Sick day management in children and adolescents with diabetes

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KEYWORDS: DKA, ketones, pediatrics, sick day management, type 1 diabetes

1 | WHAT IS NEW OR DIFFERENT

This new version of the sick day guidelines gives a greater emphasis on how to manage diabetes for prevention of ketosis and management with new technologies. Continuous glucose monitoring (CGM) is being routinely used by persons with diabetes with the newer CGM technology becoming increasingly more accurate, especially for day-to-day adjustments. In this article, "glucose values" unless specifically defined, mean either fingerstick or CGM values. CGM values may need to be cross-checked with fingerstick values if required. Infections such as COVID-19, and even vaccinations for COVID-19, can precipitate persistent increases in insulin requirements for days or weeks. Anticipatory guidance to deal with predictable patterns of increased insulin requirements such as chronic conditions requiring steroid therapy or hyperglycemia associated with menstrual periods, will reduce anxiety and unnecessary morbidity. Use of electronic data sharing platforms will help families and health care teams assist with sick day management. Closed loop technologies, combining both pumps and sensors, and their interactive regulation by artificial intelligence systems (hybrid closed loop systems, automated insulin delivery, or AID), may be helpful to keep the glucose levels in the target range during sick days; particularly those systems that incorporate personalizable glucose targets and user-initiated modes to reduce or intensify insulin delivery in special situations.

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

Sick day preparation

People with diabetes, their families and/or caregivers

- Must receive education and be given guidelines preparing them for managing diabetes during illness. This education should be delivered at diagnosis, at follow-up at least annually, and opportunistically. **C**
- Should be taught to proactively adjust diabetes therapy to prevent uncontrolled or symptomatic hyperglycemia, dehydration, hyperglycemic ketosis, ketoacidosis, hypo-normoglycemic ketosis, and/or severe hypoglycemia. **E**

Management for ketosis prevention

- Never completely stop insulin! Replace insulin pen cartridge and needle, or pump cartridge, line, and catheter to ensure adequate insulin delivery. **B**
- Always monitor glucose, defined as either blood or interstitial glucose, and ketone levels at least every 1–2 h. **E**
- Monitoring blood ketones is preferred over urine ketones. Blood ketone monitoring during illness can reduce emergency room visits and hospitalizations. **B**
- Aim for glucose levels between 3.9 and 10 mmol/L (70–180 mg/dl) and blood ketones below 0.6 mmoL/L. **E**
- Adjust the insulin dose in response to blood or interstitial glucose and blood ketone levels. **E**
- Insulin doses may need to be increased considerably during illness in children who are in the partial remission or "honeymoon" phase when doses are relatively low. **E**
- Maintain hydration and seek urgent medical advice if the child is unable to drink
  - Oral fluids containing carbohydrate should be consumed if the glucose level is below 14 mmol/L (250 mg/dl); carbohydrate-free fluids should be given when glucose is above 14 mmol/L (250 mg/dl).
  - Consider timely initiation of intravenous fluids if the child is unable to drink. **E**
- Minor illnesses managed effectively at home will reduce the impact and costs on health services and the family. **E**
- Caregivers must be encouraged to seek medical review and treatment if (**E** for all below):
  - the child's condition deteriorates
  - the underlying condition is unclear
  - fever persists
  - caregiver understanding/language problems make it difficult to communicate with the family
  - the family does not have the resources to manage the illness at home
  - there are co-morbid conditions (e.g., Down syndrome, disordered eating behaviors, mental illness, epilepsy, inflammatory bowel disease, malaria, parasitic infections, etc.)
  - the child is very young (less than 5 years old)
  - parents are unable to keep glucose level above 3.9 mmol/L (70 mg/dl)

Management when vomiting and/or gastrointestinal illness is present

- Consider nausea and/or vomiting as a sign of insulin deficiency and ketosis until proven otherwise. **E**
- Hypoglycemia with hyperketonemia, which may occur in the setting of gastrointestinal (GI) illness or starvation, requires administration of insulin along with carbohydrate intake. **E**
- GI illnesses, especially viral gastroenteritis, are the most frequent cause of hypoglycemia during sick days and may require decreasing insulin doses. **E**
- Seek URGENT specialist medical review in an emergency setting if (**E** for all below):
  - weight loss suggesting worsening dehydration continues and potential circulatory compromise
  - vomiting persists beyond 2 h (particularly in young children)
  - unable to keep glucose level >3.9 mmol/mol (70 mg/dl)
  - if hypoglycemia cannot be corrected, refer for intravenous fluids with dextrose along with continued monitoring.

Management where ketosis is suspected or confirmed

- Give small amounts of liquids containing water and electrolytes every 5–10 min, carbohydrate-containing liquids if glucose level is below 14 mmol/L (250 mg/dl). Aim for 4–6 ml/kg/hour.
- Give frequent additional doses of ultrarapid, rapid-acting or short-acting insulin to treat ketosis and prevent progression to ketoacidosis and hospital admission.
- Seek URGENT specialist medical review in an emergency setting if (**E** for all below):
  - glucose level continues to rise despite extra insulin doses
  - fruity breath odor (acetone) detected or worsens
  - blood ketones remain elevated (>1.5 mmol/L) or urine ketones remain large despite extra insulin and hydration
  - the child or adolescent is becoming exhausted, confused, hyperventilating (Kussmaul breathing), or has severe abdominal pain
  - there is a change in neurologic status, mental confusion, loss of consciousness, seizures, or progression of confusion to avoid the potential for cerebral edema and/or cerebral injury
- Transport should be facilitated as soon as possible according to local circumstances.
- The diabetes team should contact local medical personnel to ensure systems are in place for initial glucose and electrolyte monitoring along with administration of intravenous fluids and insulin.

Specific advice regarding sick day management where diabetes technology (insulin pump, hybrid closed loop systems, glucose sensors) is used

- If available, continuous glucose monitoring (CGM) devices or intermittently scanned glucose monitoring (isCGM) devices can preferably be used to supplement blood glucose monitoring. **E**
- The use of insulin pumps, including both closed loop and hybrid models, can be continued in the hospital when health care teams are familiar with the technology, there is access to adequate insulin pump supplies, and/or the person and/or their caregiver can continue to safely operate the pump.

- In the presence of high glucose levels and vomiting and/or ketonaemia, closed loop should be stopped and the pump should operate in open loop or manual mode while following rules for sick day management.

3 | THE EFFECT OF ILLNESS ON DIABETES

Children and youth who have optimal diabetes management should not experience more illness or infections than their peers without diabetes. However, even routine childhood illnesses complicate diabetes management and increase the risk for diabetic ketoacidosis (DKA) or hypoglycemia (especially with gastroenteritis). While there are very few studies about intercurrent illness in type 1 diabetes (T1D), one study involving adults with T1D reported a higher risk of urinary tract, bacterial skin, or mucous membrane infections, although upper respiratory tract infections were no more frequent in adults with T1D than in controls.[1] There is some evidence of impaired leukocyte function with impaired metabolic control, and children with suboptimal diabetes management may have altered immune function, increasing susceptibility to and delayed recovery from infection.[2] One pediatric study found low IgG concentrations and reduction in complement protein 4, variant B (C4B) levels related to impaired metabolic control.[3]

Most illnesses, particularly where there is fever, raise blood glucose levels due to higher levels of circulating stress (counter-regulatory) hormones which promote glycogenolysis, gluconeogenesis, and insulin resistance.[4] Illness often increases ketone body production due to inadequate insulin levels and the counter-regulatory hormone response. In contrast, illness associated with vomiting and diarrhea (e.g., viral gastroenteritis) may lower glucose levels with the increased possibility of hypoglycemia rather than hyperglycemia. Decreased food intake, delayed gastric emptying, poor intestinal absorption, and/or overt diarrhea with more rapid transit time with gastroenteritis may contribute to hypoglycemia risk. Insulin requirements may increase during the incubation period of an infection for a few days before the onset of symptoms. Likewise, the increased need for insulin may persist for a few days after symptoms have passed. However, insulin needs are highly variable from one person to another and from one illness to the next. During a typical viral "epidemic," however, patterns may occur that facilitate making some generalizations to help advise subsequent persons/families.

Infections such as COVID 19, and even vaccinations for COVID 19, can precipitate persistent increases in insulin requirements for days or weeks. Insulin doses of up to 2.2 units/kg/day may be required to maintain normoglycemia during the peak inflammatory response, but rapid reduction of doses may be needed on recovery. In the case of COVID 19, it may be wise to ask families about respiratory symptoms in the setting of unexplained hyperglycemia in a person with previously stable diabetes.[5–8]

Some conditions are associated with insulin resistance: children with chronic conditions requiring steroid therapy will sometimes experience predictable patterns of increased insulin requirements.[9] Similarly, some women will routinely experience hyperglycemia immediately prior to and during their menstrual periods. In one study, 67% of women experienced changes in blood glucose levels or glycosuria premenstrually and 70% during the menstrual phase.[10] An exposure to a gluten-containing meal in a person with celiac disease may precipitate a period of prolonged hyperglycemia with or without abdominal pain and loose stools, and this possibility must be considered with a history of similar recurring episodes. The hyperglycemia may last overnight and require "sick day" doses of insulin.[11–14]

4 | SICK DAY DIABETES MANAGEMENT PRINCIPLES

4.1 | **Sick day guidelines should be taught soon after diagnosis** and reviewed at least annually. See below Section 5.

4.2 | Monitor glucose levels frequently

Frequent glucose monitoring facilitates optimal management during illness (with adult supervision, even in adolescents). Glucose, either blood or interstitial levels, should be monitored every 1–2 h. Insulin adjustments are guided by the results of ongoing glucose and ketone monitoring.

CGM use in children, adolescents and young adults has tremendously increased within the past years in well-resourced countries.[15] The accuracy and convenience of CGM technology has improved significantly and CGM is now more frequently being used without confirmatory blood glucose monitoring. CGM devices are more effective in detecting trends towards hyper- and hypoglycemia,[16,17] which appears very useful in sick day management, as the CGM device can signal whether the glucose is continuing to rise, fall, or is remaining stable. However, one needs to be aware of limitations and possible interference by drugs used in sick day management (e.g., acetaminophen, ascorbic acid, salicylic acid) and the specific CGM device used.[18] In this case, blood glucose measurements are still necessary, accompanied by ketone measurements in urine and/or blood. In addition, hypoperfusion from dehydration can also decrease the accuracy of CGM. Parents and adolescents should maintain attention to glucose trends, ensuring the diabetes care team has access to shared data where possible, and that parents are followers of their child's/adolescent's glucose patterns if possible.

4.3 | Monitor ketones, ideally by fingerstick blood test

Ketones are produced by the liver from free fatty acids that are mobilized as an alternative energy source when there is lack of glucose for intracellular metabolism, either from inadequate intake or inability to

utilize glucose in the setting of insulin deficiency. Starvation ketosis occurs when there is insufficient dietary carbohydrate.

There are three ketones: acetoacetate (AcAc), acetone, and beta-hydroxybutyrate (BOHB). Urine ketone strips measure AcAc and acetone (if the strip contains glycine), while laboratories and blood ketone strips measure BOHB, the predominant ketone in DKA. Home measurement of blood BOHB concentrations in children and adolescents enables earlier identification and treatment of ketosis compared to urine ketone testing and decreases diabetes-related hospital visits (both emergency department visits and hospitalizations).[19–21] Families should be encouraged to have a home blood ketone meter and test strips, and always measure ketones during sick-days. However, blood ketone strips can be unaffordable for many households, may not be covered by insurance programs, or may not be available. In these circumstances, urine ketone strips can be used for sick day management. In countries where diabetes is uncommon, or a low priority, persons/families should be encouraged to carry blood ketone strips with their meter or urine ketone strips to hospital if the child needs admission, in case the hospital does not have the facilities for ketone testing.

- Adult studies have shown that the time delay after an insulin pump stop to diagnose ketosis is significantly longer for ketonuria than for plasma ketonaemia[22] and that urinary ketone tests can remain positive more than 24 h after resolution of ketoacidosis in the majority of persons.[23]
- There can be a dissociation between urine ketone (AcAc) and blood BOHB concentrations such that urine ketone tests can still be negative or show only trace or small ketone levels when the blood BOHB concentration is already high, indicating need for treatment.[19,24]
- Following resolution of DKA, the dissociation between urine ketones and blood ketones continues as urine ketone levels remain elevated and can lead to excess insulin administration and risk for hypoglycemia if treatment is based on the urine ketone value rather than the blood ketone level.

Urine ketone strips are inexpensive but may deteriorate within a month or so after opening the bottle, so care may be needed to ensure a fresh bottle is available if the previous bottle had been opened more than a month prior. Individually foil-wrapped strips are recommended if available.

Blood BOHB monitoring can be especially useful in very young children, who cannot provide urine on demand, or in others who find giving urine samples difficult. Continuous ketone measurement that occurs alongside continuous glucose measurement is in research development, and not yet clinically available.

4.4 | Monitor and maintain hydration with adequate salt and water balance

Hyperglycemia, fever, excessive glycosuria, and ketonuria all contribute to increased fluid losses. Prevention of dehydration should be a priority during sick days.

4.5 | Do not stop insulin

Remind the family that T1D is a condition caused by lack of insulin, not glucose excess. The insulin dose may need to be increased or decreased but it should never be stopped. The most common mistake made by health care teams and caregivers who are unfamiliar with diabetes is to recommend the complete omission of insulin because "the child is ill and not eating" or "the blood glucose is low" thus increasing the risk of developing DKA.[4,24–26] Even in the fasting state, insulin is required for basal metabolic needs, which may increase during an acute illness, when counter-regulatory or stress hormone levels are elevated.

4.6 | Treat any underlying, precipitating illness

The underlying illness should be treated as recommended for any child or adolescent without diabetes (i.e., antibiotics for bacterial infections, etc.). Fever, malaise, and headache can be treated with antipyretics or analgesics such as acetaminophen or ibuprofen, unless there are allergies to these medications. Families can be advised to include acetaminophen suppositories with their sick day supplies for use when enteral intake may be difficult, such as with gastroenteritis. Acetaminophen or acetaminophen-containing cold medications can cause interference in some CGM devices[27,28]; however, some newer generation CGM sensors are not susceptible to acetaminophen interference.[18,29]

5 | PREPARATION FOR SICK DAYS

5.1 | Sick day education

All families should receive education about sick day management and have access to guidelines (either paper or electronic) on its management (Figure 1). At diabetes diagnosis, families can be overwhelmed with new information and find it difficult to retain information about sick day management.[30] For this reason the information at diagnosis should be simple, focusing on the importance of frequent monitoring and *not stopping* insulin during an illness, and contacting the health care teams early for advice. As families become more competent with their diabetes care, the sick day management education should be repeated at least annually. Intensive training in sick day rules have been shown to decrease the incidence of DKA.[31]

The health care team should tailor the education to suit the age of the child/adolescent and development stage.[32] For very young children, families should receive appropriate advice on managing gastroenteritis and the need for early intervention and possible use of mini-dose glucagon (Table 1).[33] Older teens should receive sick day management education in a format that is most appropriate to them as they become more independent in their diabetes self-management, although families should be advised to manage the diabetes tasks during illness regardless of age, as managing any intercurrent illness is challenging without support and guidance.

FIGURE 1 ISPAD sick-day management guidelines action plan

TABLE 1 Recommended dose for mini-dose glucagon

	Quantity			
Age (years)	µg	mg	cc (1 mg/cc)	Units on insulin syringe
<2	20	0.02	0.02	2
2–15	10 per year of age	0.01 per year of age	0.01 per year of age	1 per year of age
>15	150	0.15	0.15	15

Note: The doses recommended above are quite different (lower) from emergency doses given in case of severe hypoglycemia.

5.2 | Sick day supplies

Households should maintain supplies of glucose and ketone monitoring strips, insulin, and an emergency glucagon kit/supply of nasal glucagon, and have a sick day management plan either in electronic or paper format, with clear guidance on:

- glucose targets and insulin adjustments
- fluid/hydration requirements including what type of fluid to offer, how often fluid and food should be offered and how much should be consumed
- frequency of glucose and ketone monitoring and how to respond to presence of ketones
- troubleshooting insulin delivery devices and dosage recommendations in event of insulin pump failure
- mini-dose glucagon instructions
- vomiting and when to seek medical advice
- information on when and how to access health care team members.

5.3 | Communication with health care team

Health care team availability by telephone facilitates communication, allows for earlier advice and institution of sick day guidelines, and decreases or minimizes clinical decompensation and avoids emergency room use and hospitalization.[34–36]

5.4 | Immunizations and influenza

During the influenza season, health care professionals should assess families' sick day management knowledge and review sick day management plans.[37] Families should be advised of the local recommendations regarding influenza and COVID vaccination. Where influenza and pneumococcal immunizations are available and recommended, for example, in the United States, during the influenza season, health care professionals should emphasize the importance of these immunizations for persons living with diabetes.[37] Countries where multiple immunizations are available and recommended for pediatric age groups, health care professionals should encourage families to immunize their children and address any expressed barriers to the uptake of immunizations, including concerns they may have regarding managing minor side effects.

6 | DIABETES MANAGEMENT FOR MILD ILLNESS AND KETOSIS PREVENTION

6.1 | Insulin storage

The cold chain should be reviewed. If the cold chain is not maintained to the point of purchase (e.g., the pharmacy may store in a refrigerator, but it may have been exposed to high temperatures earlier, at the warehouse level), or if transport and storage are not optimal (e.g., carrying insulin home after purchase, or packing insulin in hold baggage during a flight—insulin will freeze and then thaw), then insulin potency may be affected, leading to impaired insulin action (Figure 2).[38]

6.2 | Insulin dose adjustments

Illnesses, especially when there is fever, raise glucose levels and require increasing insulin doses. Commonly, an increase of basal and prandial insulin will be required to counteract the effect of insulin resistance observed in acute illnesses, preventing ketosis. The following general guidelines may be useful for these cases:

- If there is hyperglycemia without hyperketonemia or no more than small ketonuria, usual recommendations are to give an additional, supplemental injection or bolus of rapid-acting or short-acting insulin. Begin by giving the usual dose for carbohydrate coverage and correction. Repeat correction dose if needed after 2 h.
- Basal insulin doses, whether given as a long-acting insulin analog or intermediate-acting insulin in injection-based therapy, or as a basal rate when using an insulin pump may need to be increased by 20%–30%, depending on the magnitude of hyperglycemia.
- Higher prandial insulin doses, whether ultrarapid, rapid-acting, or short-acting insulin, may be required. For mild elevation of post-meal glucose levels, increase the calculated bolus by 10%; whereas in those cases where a moderate to large post-prandial elevation is present, a 20% increase in the insulin boluses might be needed.

6.3 | Insulin delivery and injection technique

It is important to check for possible causes of inadvertent interruption of insulin delivery. It is essential that during illness, health care professionals prompt parents and caregivers to assess for adequate insulin delivery. For insulin pen users assess for:

- correct placement of pen needle, raised skin folds, and skin infection
- a broken insulin cartridge holder
- excess air in the insulin cartridge
- the dose units counter not moving or moving incorrectly, and insulin not being delivered when the dose button is depressed.

Checking for adequate insulin delivery is particularly important for insulin pump users, as ketosis will develop within hours if there is a blocked or kinked pump infusion set. See Section 9 "Specific advice regarding sick day management for children and adolescents using diabetes aid (insulin pumps, hybrid closed loop systems, glucose sensors)."

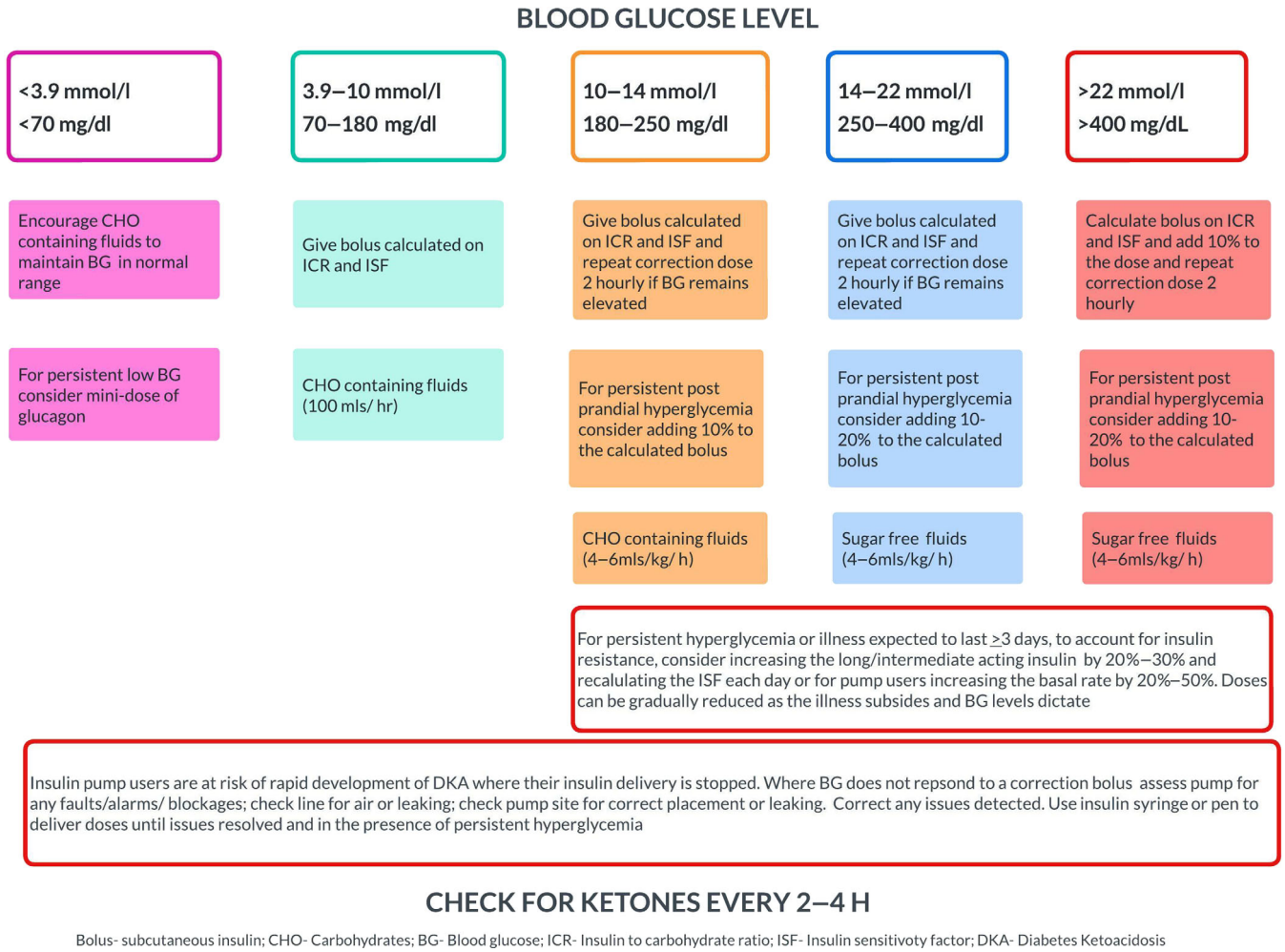

FIGURE 2 Insulin and fluids for the prevention of ketosis. Bolus refers to subcutaneous bolus, either given by injection or pump. CHO: oral carbohydrates; ICR: insulin–carbohydrates ratio; ISF: insulin sensitivity factor

6.4 | Monitor glucose and ketones during mild illnesses for DKA prevention

As explained in the "Principles of sick days management," glucose should be monitored every 1–2 h and ketones every 2–4 h. Urine glucose and urine ketones can be measured if blood glucose and/or blood ketone monitoring equipment are/is not available.[24,25] Insulin adjustments are guided by glucose and ketone levels. When CGM is used, the parents and adolescent should keep in mind that capillary glucose measurements are desirable when sick days occur, and the person is not feeling well.

Blood ketone tests or urine ketone tests when blood ketone monitoring is unavailable, help to guide sick day management.:

- Blood BOHB ≥0.6 mmoL/L is abnormal in children with diabetes.[39,40]
- Blood BOHB measurements may be especially valuable to prevent DKA in persons who use an insulin pump, as only short-rapid- or ultrarapid-acting insulin is used in this type of therapy. Elevations in blood BOHB may precede elevations in urine ketones due to interrupted insulin delivery[41] (e.g., trace levels of ketones may be observed related to fasting. These low levels should be treated with a meal and insulin dosing).
- During resolution of ketosis, blood BOHB normalizes sooner than urine ketones.[24,25]

6.5 | Monitor and maintain hydration with salt and water

Prevention of dehydration should be a priority during sick days. When vomiting, advise to take small sips of cool liquids, which are better tolerated than warm liquids. Hydration can be aided with frozen popsicles or frozen juice bars (either sugar-free in the setting of hyperglycemia, or sugar-containing when glucose is <14 mmol/mol, ~250 mg/dl).

If appetite is decreased, replacing meals with easily digestible food (e.g., rice-lentil broths, rice porridge and sugar-containing fluids) that provide energy (carbohydrates) can help prevent starvation ketosis, as long as insulin is given. It may be helpful to remove excessive

carbonation (bubbles) in some soft drinks. Carbonated fluids may alter the distribution of food within the stomach and may contribute to bloating in some persons.[42] Families should be advised to keep supplies to be used to prevent dehydration during illness.

- glucose tablets, sweets, or candies such as jelly beans or sucking candies as well as dried fruits to prevent hypoglycemia
- clean (boiled/purified as necessary) water to provide hydration
- sugar and electrolyte containing fluids such as sports drinks, homemade lemonade with sugar and salt, electrolyte mixtures, or sugar-containing soft drinks or sodas to provide hydration, glucose, and salts
- easy to digest carbohydrates such as crackers, noodles, rice, rice porridge, or yogurt

During GI illnesses, it is reasonable to advise replacing meals with small volumes of sugar-containing drinks for calories, provided with appropriate insulin coverage, along with fluids that contain electrolytes, as noted above. A simple diet can be reintroduced that may include rice, crackers, applesauce, bananas, tea, bread, yogurt, and potatoes, for example, depending on availability and local customs.

- Include sugar-containing drinks with insulin coverage.
- Give sufficient fluids to maintain hydration, keeping records of how much the child has had to drink.
- Attend to urine output and follow body weight, if available at home, every 4–6 h. Steady weight suggests adequate hydration and fluid replacement, whereas ongoing weight loss usually requires contact with the health care team to assess need for emergency room assessment or hospitalization for intravenous fluid treatment.

7 | SICK-DAY MANAGEMENT WHEN VOMITING AND/OR GASTROENTERITIS

7.1 | Vomiting

Consider nausea and/or vomiting as a sign of insulin deficiency until proven otherwise.

Nausea and vomiting can be caused by either:

- insulin deficiency resulting in hyperglycemia and ketosis and risk for DKA.
- an illness itself (i.e., gastroenteritis, food poisoning, a surgical condition such as appendicitis, other illness, etc.)
- severe hypoglycemia

When vomiting occurs in a person with hyperglycemia and when ketosis is present, extra insulin must be administered, even when there is nausea and vomiting. In fact, the vomiting may stop once extra insulin has been given, due to management of the ketosis.

If vomiting persists beyond 2 h, especially in children under 5 years old, or if hypoglycemia cannot be corrected, refer for intravenous fluids with dextrose along with continued monitoring as reviewed in the Hypoglycemia Guideline (see ISPAD 2022 Clinical Practice Guidelines Chapter 11 on Management of Hypoglycemia in Children and Adolescents with Diabetes).

For vomiting in association with gastroenteritis, consider treatment with anti-nausea medications, if available, and if there is no known allergy or other medical contraindication to such treatment. Antinausea medications can include injectables or rectal suppositories of antiemetics (e.g., ondansetron, promethazine, etc.), as oral intake of such medications may be difficult with ongoing emesis. Some children/families have had success with oral antiemetics like ondansetron if given early in the course of the illness, or just after a bout of vomiting. Such medications are contraindicated with any mental status changes. These medications also should be used cautiously with food poisoning when they may be contraindicated. Additionally, if the nausea and vomiting are due to DKA treat as per ISPAD DKA Guideline (see ISPAD 2022 Clinical Practice Guidelines Chapter 13 on Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State) as antiemetics are contraindicated.

7.2 | GI tract infections associated with hypoglycemia

GI tract infections, especially viral gastroenteritis, often cause hypoglycemia (Table 2). Occasionally, people with diabetes and families may report unexplained hypoglycemia as a prelude to viral gastroenteritis, even prior to the first bout of emesis. Additionally, hypoglycemia may continue beyond the symptomatic stage of nausea and vomiting, as malabsorption may persist for a few days as the gut heals. Frequent glucose monitoring can guide temporary insulin dose reductions; however, insulin should never be totally stopped.[24–26,43,44]

Reduce total daily insulin dose by 20%–50% during GI illnesses associated with hypoglycemia (Table 2), generally beginning with a 20% reduction of the basal or intermediate-acting insulins and a 50% reduction of the bolus dose, which may be given after eating to ensure intake of the prepared drink and/or food. Ongoing frequent monitoring is needed because an excessive dose reduction may lead to insulin deficiency and risk for ketosis and ketoacidosis.

Check ketones along with glucose levels as a guide to determine if starvation ketosis is occurring. Such ketones in association with hypoglycemia reflect inadequate energy supply and indicate a need for increased carbohydrate intake with insulin.

7.3 | Consider mini-dose glucagon for persistent hypoglycemia

If hypoglycemia persists with blood glucose levels <3.9 mmol/L (<70 mg/dl) along with nausea, vomiting, anorexia, or food refusal, a

TABLE 2 Normoglycemia/hypoglycemia

Ketones (starvation)		Blood glucose	
Blood	Urine	< 5.0 mmol/L < 90 mg/dl	5.0–10 mmol/L 90–180 mg/dl
< 0.6 mmol/L	Negative/trace	• No extra insulin • Reduce TDD insulin 20% • Oral sugar fluids and extra CHO[a] • If BG < 70 mg/dl (3.9 mmol/L)→ Hypo correction (consider mini-dose of glucagon)	• No extra insulin
0.6–0.9 mmol/L	Trace/small	• Reduce TDD insulin 15% • Give ordinary bolus • Oral sugar, fluids • Extra CHO[a]	• Oral sugar, fluids • Extra CHO[a]
1–1.4 mmol/L	small/moderate	• Oral sugar, fluids • Extra CHO[a] • Give correction bolus according to ISF when blood glucose has risen over 5–6 mmol/L (90–110 mg/dl)	• Give ordinary bolus • Oral sugar, fluids • Extra CHO[a]
1.5–2.9 mmol/L	Moderate/large	• Do not reduce TDD insulin • Oral sugar, fluids • Extra CHO[a]	• Add +5% TDD or 0.05 U/Kg to ordinary bolus • Oral sugar, fluids • Extra CHO[a]
≥ 3 mmol/L	large	• Give correction bolus according to iSF when blood glucose has risen over 5–6 mmol/L (90–110 mg/dl) • If vomiting, cannot eat or drink, consider IV Saline +5% glucose solution Risk of Ketoacidosis	• Add +5% TDD or 0.05 U/kg to ordinary bolus
Check for BG and ketones every 2 h			

Note:

- To calculate the TDD, add up all the insulin given on a usual day (i.e., short/ rapid and long/ intermediate acting) or sum daily basal rates and boluses in a pump.
- include additional boluses given for correction of hyperglycemia.
- Recalculate the ISF (Insulin Correction Factor) each day during illness to account for the increase in insulin resistance that the illness causes.
- In children and adolescent with usual low (<0.7 U/kg/day) or usual high (>1 U/kg/ day) insulin requirements, consider using the percentage (%) calculation rather than empirical 0.05–0.1–0.2 U/kg supplemental dose.
- High BG and elevated ketones indicate a lack of insulin.
- "Starvation" blood ketones" are usually <3.0 mmol/L.
- When the child is feeling sick or vomiting and ketone levels are negative or low (trace or small) with BG < 10–14 mmol/L (< 180–250 mg/dl), he/she must try to drink sugar-containing fluids in small amounts (at least 100 ml/h) to keep BG up.
- When ketone levels are elevated, priority is to give extra insulin. If BG is simultaneously low, IV saline 5% dextrose solution may be required.
- Additional doses of insulin are always short or rapid-acting. Short-acting insulin can be given intramuscularly to speed up absorption.
- The ketone level may increase slightly (10–20%) within the first hour after giving extra insulin, but afterward, it should decrease.
- Blood ketones (BHOB) normalize sooner than urine ketones.
- If the child's glucose levels are persistently elevated or the illness is expected to last ≥3 days, consider increasing long- or intermediate-acting insulin or the basal rates delivered by pump by 10–20% (even higher, up to 50% by pump at times, if needed) during the expected sick days and reduce gradually as the illness subsides. [**E**]

Abbreviations: BG, blood glucose; CHO, carbohydrate; Ordinary bolus, usual correction and/or carbs insulin; TDD, total daily dose.

[a]Extra carbohydrates if tolerated.

modified, smaller-than-usual dose of glucagon, if available, can be given, termed "mini-dose glucagon" (Table 1). Mini-dose glucagon can increase the glucose level back into a safe range as long as there are adequate glycogen stores in the liver; however, hepatic glycogen may be deficient following prolonged vomiting or fasting. Nonetheless, it is safe to try mini-dose glucagon in such circumstances.[33,45] The mini-dose is administered using an insulin syringe after reconstituting the glucagon with the diluent provided in the glucagon kit. The dose begins with 0.02 mg (equal to 2 units on an insulin U-100 syringe) for children up to age 2 years, and then increases by 0.01 mg (1 unit on an insulin syringe) per year of life up to a maximum dose of 0.15 mg (15 units on an insulin syringe). The mini-dose can be repeated after 30–60 min, if needed. If hypoglycemia persists and/or glucagon is not available, emergency services will be required for intravenous dextrose-containing fluids.

Oral medicines for symptomatic relief of gastroenteritis have no proven efficacy and are therefore not usually recommended. Infectious diarrheal illnesses are best managed in their locales when the local health care teams should be aware of the proper medications, and if any are indicated. Unknown or uncertain alternative medicines should be avoided; sick day education efforts should include discussion of safe and unsafe management efforts with a review of all medications.

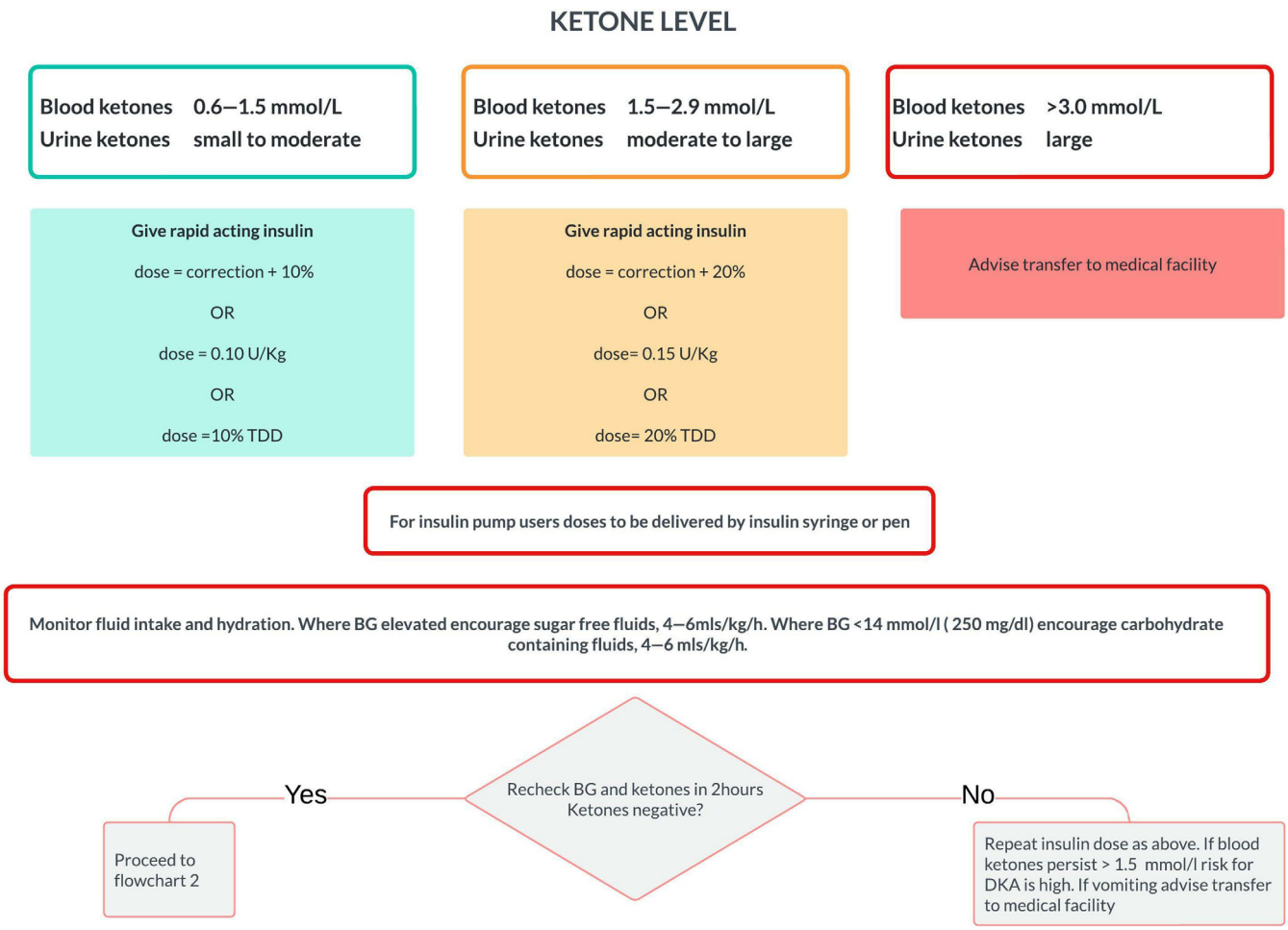

FIGURE 3 Insulin and fluids for treatment of ketosis in the home. BGL: blood glucose level

8 | TREATMENT OF KETOSIS

8.1 | Ketone monitoring

Blood BOHB levels guide treatment since increasing BOHB levels correlate with decreasing pH levels and reflect the severity of the clinical status (Figure 3). Blood ketone levels decline in response to insulin therapy. Caution should be taken when treatment decisions are based on ketonuria, as persistent ketonuria may be due to the slow clearance of AcAc. In response to insulin therapy, BOHB levels commonly decrease long before AcAc levels do. The frequently employed nitroprusside test only detects AcAc in blood and urine, and so routine urine ketone monitoring often shows prolonged ketonuria even when significant ketoacidosis and hyperketonemia have already responded to treatment.[46]

- BOHB levels lower than 0.9 nmol/L or trace urinary ketones may correspond to starvation ketosis.
- BOHB levels 1–2.9 mmol/L may be treated at home. In fact, declines in BOHB levels will be clinically evident even before declines in glucose levels in response to fast-acting insulin analogs. BOHB may rise within the first hour but will almost always have decreased 2 h after administration of extra insulin.
- BOHB levels greater or equal than 3 mmol/L or large ketonuria suggest possible ketoacidosis. The child should be transferred to an emergency department for evaluation and, if necessary, treatment for DKA. In some cases, starvation ketosis may rise to >3 mmol/L and additional biochemical assessment, including measurement of venous pH, is necessary to distinguish between DKA and starvation ketosis.

8.2 | Hydration

When ketosis is present, hydration is a cornerstone of treatment to avoid water and electrolyte deficits that may progress to acidosis and DKA.[4,24–26,43,44,46] Frequent small sips of liquids containing water and electrolytes should be given every 5–10 minutes. Suggested approximate volume of fluids may be either 4–6 ml/kg/h or 100 ml/h. For those children who have glucose levels of <14 mmol/L (~250 mg/dl), glucose containing liquids should be administered. When hyperglycemia above 14 mmol/L (~250 mg/dl) and ketosis is observed, oral hydration should where possible contain salt, but no glucose.

8.3 | Insulin adjustment

When ketosis is present, frequent additional doses of ultrarapid, rapid-acting, or short-acting insulin are required to stop ketogenesis, reduce glucose levels, and prevent progression to ketoacidosis and hospital admission.[24,25,46,47] Several methods for calculating supplemental insulin doses are practiced around the world. All of these methods consider that the dose and frequency of subcutaneous (SC) bolus insulin will depend on the severity of ketosis and the level and duration of hyperglycemia.

Supplemental doses of SC rapid-acting insulin analog (insulin lispro, aspart, glulisine, fast-acting aspart) should be repeated every 1–2 h if ketosis is severe, and every 2–4 h if ketosis is mild. Short-acting (regular) insulin repeated every 2–4 h may be used if insulin analogs are not available. Frequent glucose and ketone monitoring results will guide the frequency and extra insulin that should be used in successive insulin dosing. The most frequently used methods for treating hyperglycemia and ketosis are based on body weight, increased correction doses by 10%–20%, and doses as a percentage of total daily dose of insulin (TDD).

8.3.1 | Body weight method

One to two hours SC rapid-acting insulin analog (lispro, aspart, or glulisine) is safe for treatment of ketosis.[48–52] Fast-acting aspart insulin may be used, too.

- The dose of 0.1 to 0.15 units/kg is a general recommendation for children and adolescents with standard insulin requirements of approximately 0.7–1.0 units/kg/day. However, for children or adolescents who have low usual daily insulin requirements, or those with insulin resistance and high daily insulin requirements, the percentage calculations (see below) may be more appropriate than the empiric units/kg additional dose.
- When children or adolescents are in the "honeymoon" remission phase and insulin doses are relatively small, it may be necessary to increase supplemental insulin doses; consider providing supplemental doses (~0.05–0.1 units/kg) and assess response, as the standard supplemental dose of 10%–20% of the TDD may be insufficient to lower the glucose levels in a timely manner.

8.3.2 | Percentage increase method

Where diabetes is managed on a glucose and meal adjusted regimen, the additional insulin dose for ketosis can be calculated as a percentage increase of the dose calculated based on the insulin sensitivity/correction factor. The caregiver calculates the usual dose to correct hyperglycemia and increases the dose by 10% when mild ketosis is present and by 20% when ketosis is moderate/severe. If ketosis does not improve, one can also give 150%–200% of the calculated correction dose, repeated every 2–4 h, based on response. For example, a child has a glucose level that would typically require 5 units to correct, but in the presence of moderate ketones the caregiver would increase the dose by 20% and give 6 units.

8.3.3 | TDD Method

With this method the caregiver should calculate the TDD, defined as the total of rapid- or short-acting and long- or intermediate-acting insulins for the day (or the total of bolus and basal insulin given by a pump). This method is based on giving 10%–20% of TDD for treatment of ketosis.

9 | INSULIN PUMPS AND HYBRID CLOSED LOOP SYSTEMS

The key principles of sick day management are the same for insulin pump and hybrid closed loop users, as for those receiving insulin injections.[44,53,54] Some points to highlight for pump users are:

9.1 | Hyperglycemia and risk for DKA

People on an insulin pump use only rapid- or short-acting insulin and do not have any injected depot of long-acting insulin, so DKA can develop rapidly with either interruption of insulin delivery or during an intercurrent illness. Blood BOHB measurements may be especially valuable to prevent DKA in people who use an insulin pump. Elevations in blood BOHB may precede elevations in urine ketones due to interrupted insulin delivery.[41]

If the glucose level is 14 mmol/L (~250 mg/dl) or above, check for problems with the insulin pump or delivery system. Common problems include kinks in the catheter, air in the infusion line, leakage at connections, disconnected catheters especially at the insertion site, and insertion site inflammation. Refresh the insulin cartridge and replace the insulin needle, tubing, and catheter. Extra boluses should be given to correct hyperglycemia and ketonemia (Figures 2 and 3). Do not use an insulin pump for extra insulin in this situation for the first extra boluses; pens or injections ensure that insulin was delivered. After extra insulin has been given, the blood ketone level may temporarily increase by 10%–20% for the first hour or two but should be expected to decrease thereafter. If it has not decreased, repeat dose with insulin from a new cartridge/vial.

Use temporary basal rate increases of 20%–50% or higher until the glucose level improves and ketone levels return to normal (BOHB <0.6 mmol/L or negative to small urine ketones). Note, it may be necessary to increase the maximum hourly basal rate that the pump can deliver when using temporary basal rate increases for sick day management.

If blood ketone level is ≥3 mmol/L (or the urine ketones remain large) despite extra insulin and hydration, the risk for DKA is high and the patient should be referred to an emergency room for assessment and intravenous fluids.

9.2 | GI Illnesses and hypoglycemia

Meal insulin boluses may need to be decreased during GI illnesses, as noted above, when hypoglycemia is a concern. Basal insulin rates can also be decreased by 20%–50% when hypoglycemia is a concern, as a temporary basal rate reduction for 2–4 h or longer, as needed based on ongoing glucose and ketone monitoring. If ketones appear, the insulin dose has been decreased too much.

9.3 | Closed loop technologies

Current closed loop technologies, combining both insulin pumps and sensors, and their interactive regulation by artificial intelligence systems (hybrid closed loop systems, AID), are increasingly used in all pediatric age groups, including toddlers.[55,56] They have the potential to substantially increase time in range and improve metabolic control.[57,58] Several systems incorporate customizable glucose targets and user-initiated modes to reduce or intensify insulin delivery in special situations.[59] These tools make closed loop systems helpful to keep the glucose levels in target during sick days. However, if in doubt, it may be better to run a hybrid closed loop in manual mode during sickness. Subsequent correction boluses are increased by 10%–20% during the period of illness, according to the glucose and ketone results, and can be given by pump once the infusion set has been changed. If glucose levels are high and vomiting or illness occurs ketone measurements are important. If ketones are 0.6 mmol/L or higher or vomiting occurs, closed loop should be stopped and sick day management should run in open loop or manual mode following regular sick day rules, to ensure adequate supplemental insulin delivery.[60]

9.4 | Hospitalization

Hospitalized persons using insulin pump treatment need advice whether pump use can be continued during hospitalization. The conclusion depends on the ability of the person to safely operate the pump, availability of insulin pump supplies and the health care team's familiarity with pump treatment. Experienced pump users may be encouraged to continue their pump treatment during hospitalization as some studies have shown fewer episodes of severe hyperglycemia and hypoglycemia and that most persons could use their pump safely in the inpatient setting. Reasons for discontinuing pump treatment during hospitalization might be lack of pump supplies, malfunction of the pump, altered level consciousness, and threats of suicide.[61] Similar to insulin pump use, closed loop usage in hospitalized persons can be successful, if health care teams are up to date and familiar with these new diabetes technologies.[62] In-hospital use of HCL systems may be subject to local regulations and hospital policies.

10 | ADJUNCTIVE THERAPY

Adjunctive use of the new class of oral agents called SGLT2 (or SGLT1/2) inhibitors have been reported to increase risk for DKA in persons with T1D or type 2 diabetes. The greatest concern stems from the DKA risk, which can occur without extreme hyperglycemia (euglycemic DKA), especially in the setting of "low carb" diets or low carbohydrate intake or associated with dehydration.[63,64] Any person receiving SGLT1/2 inhibitors must receive rigorous sick day management education and strategies for mitigating DKA risk need to be discussed to avoid progression to DKA. This includes training on the use of blood ketone monitoring and counseling patients that DKA may occur without severe hyperglycemia if SGLT1/2 inhibitors are being taken. SGLT-2 inhibitors should be stopped whenever the person is feeling unwell, or ketones arise.[65,66]

11 | LOW CARBOHYDRATE DIETS

Low carbohydrate diets have recently gained increased popularity and, despite being controversial, are being used by children with diabetes. Clinical trials to assess their safety, efficacy and impact on diabetes-specific quality of life are ongoing.[67,68] Of concern is the high risk for hyperketonemia, especially in sick children; low carbohydrate or very low carbohydrate diets might lead to DKA. In addition to their potential adverse effect on growth and higher cardiovascular risk metabolic profile, occurrence of DKA is a notable risk especially during episodes of acute illness.[69] The higher risk for DKA could be mitigated by increased blood ketone monitoring.[70] In the future, newer technologies like ketone sensors might improve ketone monitoring.[71–73]

CONFLICT OF INTEREST

Jamie R. Wood has research grants unrelated to the current manuscript from the following: AstraZeneca, Novo Nordisk, Boehringer Ingelheim, and MannKind. Sabine E. Hofer has received lecturing honoraria from Eli Lilly, Sanofi, Medtronic, Pfizer, Insulet and Vertex. Ragnar Hanas has consulting activities unrelated to the current manuscript with Abbott, AstraZeneca and NovoNordisk. Warren Lee has consulted for NovoNordisk previously, and received speaking honoraria from Eli Lilly, Sanofi, Medtronic, Merck. None of these activities have conflicts with the current manuscript. The other authors have declared no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13415.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Phelan H, Hanas R, Hofer SE, et al. Sick day management in children and adolescents with diabetes. *Pediatr Diabetes*. 2022;23(7):912-925. doi:10.1111/pedi.13415