

## ISPAD Clinical Practice Consensus Guidelines 2009 Compendium

# Sick day management in children and adolescents with diabetes

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### The effects of illness on diabetes

Children whose diabetes is under good metabolic control should not experience more illness or infections than children without diabetes [E]. Adult patients with type 1 diabetes in one study had a higher risk of urinary-tract, bacterial skin, or mucous-membrane infections, but upper respiratory-tract infections were no more frequent than in controls (1) [B].

There is some evidence of impaired leukocyte function in poorly controlled diabetes [C] (2). Children

with poor metabolic control may have altered immune function, increasing susceptibility to and delaying recovery from infection. One pediatric study found low IgG concentrations and reduction in C4B (complement protein 4, variant B) levels to be related to impaired metabolic control (3)[C].

Many illnesses, especially those associated with fever, raise blood glucose (BG) levels because of higher levels of stress hormones promoting gluconeogenesis and insulin resistance [C] (4). Illness increases ketone body production due to inadequate insulin levels.

Illness associated with vomiting and diarrhea (eg gastroenteritis) may lower BG with the possibility of hypoglycemia rather than hyperglycemia. Decreased food intake, poor absorption and a slower emptying of the stomach during gastroenteritis may contribute to the hypoglycemia.

Sometimes there are increased insulin requirements during the incubation period of an infection for a few days before the onset of the illness [E]. The increased need for insulin may persist for a few days after the illness has passed, due to insulin resistance [E].

### General principles:

- **Never stop insulin [A]**
- **The insulin dose may need to be increased or decreased [A].**

- ◇ The most common mistake made by health care providers and caregivers who are unfamiliar with diabetes is to advise the omission of insulin because the child is ill and not eating, thus increasing the risk of diabetic ketoacidosis (DKA).
- ◇ More frequent monitoring is required of blood glucose (BG) and ketones. All levels mentioned in this chapter refer to plasma glucose as most meters are calibrated to display this value.
- ◇ If episodes of hyperglycemia, ketosis, and vomiting recur, with or without infection, it should be recognised that this may be due to omission or inadequate administration of insulin. Insulin omission is particularly problematic during adolescence.

- **More frequent monitoring**

#### Blood glucose

- ◇ Frequent BG monitoring facilitates optimal management during illness (with adult supervision even in adolescents)
- ◇ BG should be monitored at least every 3–4 hours including through the night and sometimes every 1–2 hours

#### Ketones

Ketones are produced by the liver from free fatty acids that are mobilized as an alternative energy source when there is a lack of glucose for intracellular metabolism. Starvation ketones are produced when the blood glucose is low. Ketones are also produced when insulin is lacking to initiate the transport of glucose from the blood stream into the cell. Ketones accumulate because of increased lipolysis, increased ketogenesis and decreased ketone body utilization

due to low insulin levels. Urine strips measure acetoacetate (AcAc) while blood strips measure beta-hydroxybutyrate (BOHB). In acute ketoacidosis, the ketone body ratio (BOHB:AcAc) rises from normal (1:1) to 10:1 or more (5). 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 (5).

- Urinary or, when available, blood ketone tests, may help to guide sick day management
- Blood ketone testing (measuring BOHB) provides additional information to urine ketone testing (6)[E]:
  - ◇ Blood BOHB >0.5 mmol/l is abnormal in children with diabetes (7, 8)[C, B].
  - ◇ Adult studies have shown that the time delay after a pump stop to diagnosis of ketosis is significantly longer for ketonuria than for plasma ketonemia (9)[C], and that a urinary ketone test can remain positive more than 24 hrs after resolution of an episode of ketoacidosis in over half of patients studied (10) [C].
  - ◇ There may be dissociation between urine ketone (AcAc) and blood BOHB concentrations, which may be increased to levels consistent with DKA when a urine ketone test is negative or shows only trace or small ketonuria (11) [C].
  - ◇ Home measurement of blood BOHB concentrations in children enables earlier identification and treatment of ketosis, when compared to urine ketone testing, and decreases diabetes-related hospital visits (both emergency department visits and hospitalizations) (8) [B].
  - ◇ Blood BOHB measurements may be especially valuable to prevent DKA in patients who use an insulin pump as only rapid- or short-acting insulin is used in this type of therapy. Elevations in blood BOHB may precede elevations in urine ketones due to interrupted insulin delivery, which can rapidly lead to ketogenesis and ketosis [E].
  - ◇ During resolution of ketosis, blood BOHB normalizes sooner than urine ketones (5). Monitoring BOHB potentially prevents late hypoglycemia from over treatment with insulin based upon the persistence of ketonuria [E].
  - ◇ Blood BOHB monitoring may be especially useful in very young children or when urine specimens are difficult to obtain.

Households should maintain readily available supplies and information for sick day management including:

- written information on management and important contact numbers/addresses of health care team

Table 1. How to Calculate the Amount of Extra Insulin on Sick Days Adapted from (7, 8, 13–15) [E]. No data are available from clinical trials

Ketones		Blood glucose		
Blood ketones mmol/l	Urine ketones	<5.5 mmol/l <100 mg/dl	5.5–10 mmol/l 100–180 mg/dl	10–14 mmol/l 180–250 mg/dl
<0.6	Negative or trace	Do not give extra insulin. May need to consider minidoses of glucagon (see Table 2) if <4 mmol (70 mg/dl)	No need to worry.	Increase dose of insulin for next meal if BG is still elevated
0.6–0.9	Trace or small	Check BG and ketones again in two hours. Starvation ketones. Extra carbohydrates and fluid are needed.	Starvation ketones. Extra carbohydrates and fluid are needed.	Give extra 5% of TDD or 0.05 U/kg
1.0–1.4	Small or Moderate	Starvation ketones. Extra carbohydrates and fluid are needed.	Starvation ketones. Extra carbohydrates and fluid are needed. Give ordinary bolus dose.	Give extra 5–10% of TDD or 0.1 U/kg
1.5–2.9	Moderate or large	High levels of starvation ketones. Check BG meter. Recheck BG and ketones. Extra carbohydrates and fluid are needed.	High levels of starvation ketones. Extra carbohydrates and fluid are needed. Give 5% of TDD or 0.05 U/kg. Repeat when blood glucose has risen.	Give extra 10–20% of TDD or 0.1 U/kg. Repeat dose after 2 hours if ketones do not decrease.
≥3.0	Large	Check BG and ketones every hour. Very high levels of starvation ketones. Check BG meter. Recheck BG and ketones. Extra carbohydrates and fluid are needed.	Very high levels of starvation ketones. Extra carbohydrates and fluid are needed. Give 5% of TDD or 0.1 U/kg. Repeat when blood glucose has risen.	Give extra 10–20% of TDD or 0.1 U/kg. Repeat dose after 2 hours if ketones do not decrease.

**There is an immediate risk of ketoacidosis if the blood ketone level is  $\geq 3.0$  mmol/l. Insulin treatment is needed urgently! Consider evaluation of patient at emergency department.**

• To calculate the Total Daily Dose (TDD), add up all the insulin given on a usual day (ie. rapid-/short-acting + intermediate/long-acting) or sum of basal rate and boluses in a pump. Do not include additional boluses given for unexpected hyperglycemia. • High blood glucose and elevated ketones indicate a lack of insulin. “Starvation blood ketones” are usually below 3.0 mmol/l. • When the child is feeling sick or vomits, and the BG is below 10–14 mmol/L (180–250 mg/dl, see table), he/she must try to drink sugar-containing fluids in small portions to keep the BG up. When ketone levels are raised, priority is to give extra insulin, and this will be difficult if BG is low. • Extra insulin may be given as rapid-acting insulin analogues or short-acting regular insulin, but rapid-acting if available is preferred. • 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 after that it should decrease [E].

- Sick day foods and hydration supplies
- Sufficient glucose and ketone monitoring supplies, additional insulin and glucagon kit

#### Loss of appetite

- Replacing meals with easily digestible food and sugar-containing fluids provides energy and helps prevent further ketosis. Necessary sick day management supplies include the following:
  - ◇ glucose tablets, sweets or candies such as jelly beans, dried fruit, etc to prevent hypoglycemia
  - ◇ clean (boiled/purified), cool water to provide hydration
  - ◇ sugar and electrolyte containing fluids such as sports drinks, electrolyte mixtures, Lucozade®, Kool-Aid® to provide hydration, glucose and salts

#### Maintaining hydration

- Hyperglycemia, fever, excessive glycosuria and ketonuria increase fluid losses
- Sick day cabinets should contain supplies as above to prevent dehydration
- Liquids for hydration should contain salt and water and not just plain water if there are ongoing losses like vomiting or diarrhea. If appetite is decreased or the BG is falling below  $\sim 10$  mmol/l (180 mg/dl), sugar-containing fluids should be considered to avoid starvation ketosis (eg. Sports/electrolyte drinks, pediatric electrolyte mixtures, diluted fruit drinks, colas, ginger ale etc). It is best to shake the bubbles out of the sugar containing soft drinks, to minimize indigestion [E]. Carbonated fluid does not affect the rate of gastric emptying, but alters the distribution of a meal within the stomach, causing a retention within the proximal part (12) [B].
- Elevated levels of ketones, whether associated with low BG (starvation) or high BG (insulin deficiency), contribute to nausea and vomiting, leading to decreased food and fluid intake, further elevated levels of ketones, and dehydration and ketoacidosis
- Especially in young children with diabetes, intravenous fluids may be required if nausea, vomiting or diarrhea are persistent.

#### Specific medical advice

- The underlying illness should be treated as it would be for a child without diabetes.
- Treating fever, malaise and headache with antipyretics such as paracetamol or acetaminophen or ibuprofen is acceptable but not mandatory

- ◇ Sick day cabinet supplies can include enteral and rectal preparations for fever management (anti-pyretics such as Paracetamol, Acetaminophen, Ibuprofen as oral preparations or suppositories like acetaminophen with emesis)
- ◇ Unknown or uncertain alternative medicine co-prescription should be avoided

- Vomiting may be caused by either
  - (i) the illness itself (i.e. gastroenteritis, unclean food or food poisoning, surgical condition or other illness)
  - (ii) low BG
  - (iii) lack of insulin resulting in high BG and ketosis.
- Unless food poisoning is suspected, consider treatment of vomiting with single injection or rectal administration (such as Phenergan suppositories) of anti-emetic to help oral intake of carbohydrate, unless concerns about mental status exist. However, in the case of high BG and an excess of ketones, priority should be given to administering extra insulin. In this situation, the vomiting often stops once insulin therapy is begun, due to reversal of ketosis [E].
- Oral medicines for symptomatic relief of vomiting or diarrhea have no proven efficacy and are therefore not usually recommended [E].
- In some communities specific endemic or epidemic illnesses have to be considered (eg. dengue hemorrhagic fever (DHF), malaria etc). Monitoring and clinical manifestations of these may be complicated in diabetes patients.

#### Infections associated with hyperglycemia, with or without ketosis

##### Additional Insulin

- Additional doses of short/rapid-acting insulin are required with careful monitoring to reduce BG, prevent ketoacidosis and avoid hospital admission
- The dose and frequency of injection will depend on the level and duration of hyperglycemia, and severity of ketosis
- If there is hyperglycemia with negative or small amounts of ketones, usual recommendations are to give an additional 5–10% of TDD (total daily dose) (or 0.05–0.1 U/kg) as short/rapid acting insulin administered. This may be repeated every 2–4 hours based upon BG monitoring results (see Table 1)
- If there is hyperglycemia and more marked ketonuria (moderate to high), usual recommendations are to give an additional 10–20% of TDD (usually not more than 0.1 U/kg) as short-/rapid-acting insulin. This dose should be repeated every 2–4 hours; based upon frequent glucose and ketone results (see Table 1).

- The additional dose recommendation of 0.05 to 0.1 U/kg is a general recommendation for children with standard insulin requirements of approximately 1 U/kg/day. However, for children who have low requirements or adolescents with insulin resistance and high insulin requirements the % calculations should be used rather than the 0.1 U/kg empiric additional dose [E].
- When patients in remission phase are ill (during “the honeymoon phase”) there may be a need to increase insulin up to ~1 unit/kg/day very quickly. [E]
- During illness it also may be necessary to increase basal insulin doses, whether by injection therapy or when using an insulin pump. With a pump, temporary basal rate increases of 20% to as high as 50 or 100% may be used until the blood glucose begins to normalize and the ketones clear [E].

**Example:** A sick child has BG 14–20 mmol/l (ie. 250–360 mg/dl) with moderate urinary ketones and/or blood ketones of approximately 1.5 mmol/l. Advise 10–20% of total daily insulin dose (or 0.1 U/kg) as short/rapid acting insulin every 2–4 hours until BG falls to <14 mmol/l (<250 mg/dl). Thereafter any additional doses might be 5–10% of total daily dose. Check urine ketones at every voiding. If available, check blood ketones, and recheck hourly if elevated ( $\geq 0.6$  mmol/l).

- ◇ After extra insulin has been given, the blood ketone level may temporarily increase by 10–20% for the first hour or two, but should decrease thereafter [E].
- ◇ Urine ketones often stay elevated for many hours because of the body’s conversion of blood BOHB into acetoacetate which then can be measured in urine (5). Acetone can be stored in fat tissue during ketosis, and, along with conversion of BOHB to acetoacetate may contribute to persistent urine ketones despite interruption of ketogenesis with insulin administration (5).

**When ketone testing is not available**

It is strongly recommended that some form of ketone testing be available, and urine strips are a cheap

investment. However, in some countries they may not be available.

In these situations it must be emphasised that during intercurrent infections, BG testing is very important in helping to avoid ketoacidosis and to prevent hospital admission (E).

It is helpful to provide written advice on how much additional insulin to give for particular levels of BG (as in Table 1) or when body weight is not available to advise on particular extra doses of insulin according to the child’s age and usual TDD (16) [E].

**Infections associated with hypoglycemia**

- ◇ These infections are often associated with nausea and vomiting, with or without diarrhea. Advise replacing meals with frequent small volumes of sugary drinks and maintain careful BG monitoring
- ◇ Do not give non-sugar fluids in this situation
- ◇ Give sufficient fluids to maintain hydration. Keep records of how much the child has had to drink
- ◇ Attention to urinary output and measurement of body weight at home every 4–6 hours can serve as a guide to fluid needs. Steady weight suggests adequate hydration and fluid replacement.
- ◇ Reduction of total daily insulin dose by 20–50% may be required. However, if the doses are lowered too much, there is a risk of developing insulin deficiency leading to ketosis and ketoacidosis [E].
- ◇ Check ketones regularly to see that the child has sufficient carbohydrate/sugar intake. Ketones associated with gastrointestinal illnesses and hypoglycemia usually reflect inadequate energy supply rather than insulin deficiency (i.e. starvation ketones)
- ◇ If hypoglycemia (< 3.5–4 mmol/L, 65–70 mg/dL) and nausea or food refusal persists, an injection of glucagon may reverse the hypoglycemia and enable oral fluid intake to be re-established (“mini-glucagon treatment”) (17, 18) (see Table 2). Repeat after 1 hour or more if needed.

If hypoglycemia persists and glucagon is not available, emergency services will be required.

Table 2. Recommended Dose for Mini-dose Glucagon (15) (E) (17, 18) (C)\*

Age (yrs)	Quantity			
	mcg (µg)	Mg	Mls (1 mg/ml)	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 that the doses recommended above are quite different from emergency doses given in case of severe hypoglycemia.

Table 3. Management of Sick Days and hyperglycemia with insulin pump

If urine ketones are negative/small or blood ketones <0.6 mmol/L.	If urine ketones are moderate/large or blood ketones ≥0.6 mmol/L, or the pump is not working.
<ul style="list-style-type: none"> <li>● Give a correction bolus with the pump*.</li> <li>● Test the BG hourly.</li> <li>● Drink extra low carbohydrate fluids.</li> <li>● If BG is lower after 1 hour, recheck again in 1 to 2 hours and decide if another correction bolus dose is needed (use the unused bolus rule**).</li> <li>● If the BG is not lower after the first bolus proceed to give an injection with a syringe or pen (see column 2).</li> </ul>	<ul style="list-style-type: none"> <li>● There may be a pump delivery problem or a significant illness developing. Give insulin injection by pen or syringe appropriate for the degree of hyperglycemia and ketonuria/ketonemia (as in Table 1 above or using the individual correction bolus*)—then problem solve any mechanical or catheter difficulties.</li> <li>● Continue to give bolus doses with a pen or syringe until the situation is under control.</li> <li>● Replace the insulin in the pump, and the infusion set and cannula. Resume basal rate, using temporary basal rate of approximately +20% until BG is lowered.</li> <li>● Monitor the BG hourly.</li> <li>● Drink extra high carbohydrate fluids if the ketones are elevated and BG is low and extra low carbohydrate ‘diet’ fluids if BG is elevated with or without elevated ketones.</li> <li>● If after 2 hours there is no improvement, liaise with diabetes pump team.</li> <li>● If after 2 hours the BG is improved, use the unused bolus rule to decide if an additional bolus is needed**. Pump use can be resumed.</li> <li>● If BG remains high, ketones persist, or nausea, vomiting or abdominal pain develop, contact the diabetes pump team or proceed to immediate hospital assessment.</li> </ul>

\*Correction boluses to correct hyperglycemia can be given at any time or added to meal boluses. A useful guide to estimate correction doses is to employ the ‘100’ rule (the total daily dose is divided into 100 to estimate the number of mmol/L that the PG will fall by giving 1 unit of insulin) (19, 20). [C, C and E] For mg/dl, use the ‘1800 rule’, i.e. divide 1800 by the total daily dose. For example, for a patient on 50 units of insulin per day, the BG should fall by approximately 2 mmol/L (36 mg/dl) for each additional 1 unit of insulin. This calculation can also be used to estimate a negative correction to correct for hypoglycemia (in a patient on 50 units of insulin a day, giving 1 unit less at meal times should allow the PG to rise by 2 mmol/L (36 mg/dl)).

\*\*Correction doses given for hyperglycemia should take into consideration the residual effect of any previous meal or correction bolus dose. A useful guide is to use the ‘unused bolus rule’, also called ‘insulin on board’ (approximately 30% of a rapid-acting insulin bolus is absorbed each hour). The correction dose should be reduced accordingly. For example, if 5 units had been given as a meal bolus 2 hours previously, 60% would have been absorbed and the remaining 40% or 2 units would still be exerting an effect. This should be subtracted from any correction dose. Many pumps have a built-in algorithm for this type of calculation.

### Specific advice regarding sick day management on insulin pumps

The key points of sick day management, mentioned previously, are the same for pump users as for those on insulin injections. Patients on pumps use only rapid- or short-acting insulin and do not have any injected depot of long-acting insulin. Therefore, diabetic ketoacidosis can develop rapidly. Episodes of hyperglycemia must be taken very seriously, especially if associated with positive urine and/or blood ketones.

If the BG level is 14 mmol/L (250 mg/dL) or above, the following steps should be taken:

- Immediately check for problems with the pump or delivery system and change the infusion set, tubing and reservoir of insulin.

- Check for ketones in the blood or urine.
- Proceed as directed in Table 3, depending on ketone result. In case of ketosis, extra insulin should always be given with a pen or syringe, not with the pump (as malfunction may be the cause of ketosis)
- To overcome insulin resistance, the basal rate and/or correction boluses may need to be increased during the period of illness.

Meal insulin boluses may need to be decreased when the hyperglycemia has been corrected, as patients may be eating less and their gastrointestinal absorption may be poor during the illness. Hypoglycemia should be treated in the usual way. The basal insulin rate may also need to be decreased if the BG still tends to be low, provided the ketones continue to be negative.

## Recommendations

- The diabetes care team should provide clear guidance to patients and families on how to manage diabetes during intercurrent illnesses to avoid the complications of:
  - ◇ ketoacidosis
  - ◇ dehydration
  - ◇ uncontrolled or symptomatic hyperglycemia
  - ◇ hypoglycemia
- Never stop insulin
- The insulin dose may need to be increased or decreased.
- When vomiting occurs in a child with diabetes, it should always be considered a sign of insulin deficiency until proven otherwise
- In a child with an intercurrent illness, URGENT specialist advice must be obtained when (23):
  - ◇ the underlying condition is unclear
  - ◇ weight loss continues, suggesting worsening dehydration
  - ◇ vomiting persists beyond two hours (particularly in young children)
  - ◇ BG continues to rise despite extra insulin
  - ◇ parents are unable to keep BG above 3.5 mmol/l (60 mg/dl)
  - ◇ ketonuria is heavy and increasing/persistent or blood ketones are >1–1.5 mmol/l
  - ◇ the child is becoming exhausted, confused, hyperventilating, dehydrated or has severe abdominal pain
  - ◇ the child is young (< 2–3 years) or has another disease besides diabetes
  - ◇ patients/relatives are exhausted, for example, due to repeated night time waking
  - ◇ language problems make it difficult to communicate with the family

Emergency hospital presentation must be considered if the situation does not improve rapidly or if specialist advice cannot be obtained

  - ◇ There is an immediate risk of ketoacidosis if the blood ketone level is  $\geq 3.0$  mmol/l. Insulin treatment is needed urgently! Consider evaluation of patient at emergency department.
- Patients on pumps use only rapid- or short-acting insulin and do not have any injected depot of long-acting insulin. Therefore, diabetic ketoacidosis can develop rapidly. Episodes of hyperglycemia must be taken very seriously, especially if associated with positive urine and/or blood ketones.

Further advice for patients and families can be found in references (16, 24–25)

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