The International Society of Pediatric and Adolescent Diabetes guidelines for management of diabetic ketoacidosis: do the guidelines need to be modified?


The current version of the International Society of Pediatric and Adolescent Diabetes (ISPAD) guidelines for management of diabetic ketoacidosis (DKA) is largely based on the Lawson Wilkins Pediatric Endocrine Society/European Society of Pediatric Endocrinology (LWPES/ESPE) consensus statement on DKA in children and adolescents published in 2004. This article critically reviews and presents the most pertinent new data published in the past decade, which have implications for diagnosis and management. Four elements of the guidelines warrant modification: (i) The definition of DKA; (ii) insulin therapy; (iii) water and salt replacement; and (iv) blood β-hydroxybutyrate measurements for the management of DKA.

Definition of DKA

The current biochemical criteria for the diagnosis of DKA are: hyperglycemia (blood glucose >11 mmol/L or 200 mg/dL), venous pH <7.3 or bicarbonate <15 mmol/L, and the presence of ketonemia or ketonuria (3). These diagnostic criteria have limitations because serum pH and bicarbonate concentrations...
are relatively non-specific and can be affected by the degree of respiratory compensation or the coexistence of a separate acid–base disturbance (4). Although serum bicarbonate concentration is less susceptible than pH to abrupt changes in ventilation, nonetheless, like pH, it is a non-specific measure. Nausea and vomiting, which are common in patients with DKA, can result in metabolic alkalosis secondary to loss of protons (5), and an acute increase in the blood lactate concentration (from poor tissue perfusion) can lower serum bicarbonate concentrations. The presence of ketonemia or ketonuria is qualitative (6), and neither the concentration of blood nor urine ketones is specified in the current definition. All of the commercially available testing methods rely on the nitroprusside reaction to produce a purple color in the presence of ketone bodies; acetone is detected only if the reagent contains glycine in addition to sodium nitroprusside, and none of the tests detect β-hydroxybutyrate (BOHB), the predominant ketone body in DKA. It must also be noted that urine ketone tests using nitroprusside-containing reagents give false-positive results in the presence of several sulfhydryl drugs (e.g., captopril). False negative readings have been reported when test strips have been exposed to air for an extended period of time or when urine specimens are highly acidic, such as after consumption of a large amount of ascorbic acid (6). The relative proportions in which the ketone bodies are present in blood vary according to the redox state of the cell. Normally, BOHB and acetoacetate (AcAc) are present in serum in approximately equimolar amounts; however, in DKA the ratio of BOHB:AcAc may vary from 1.3:1 to 5.5:1 ['nitroprusside negative' patients with ratios >7:1 have been reported in association with lactic acidosis (4)]. The average ratio is approximately 3:1 (standard deviation 0.9 and coefficient of variation 30%) (7–10). Reliance on qualitative measurement of plasma or urine AcAc concentration alone, which typically represents 15–40% of the total ketone body concentration, therefore, grossly underestimates the severity of ketonemia. The concentrations of AcAc and BOHB directly reflect the rate of ketone body production (11), which is accompanied by equimolar production of hydrogen ions (12). It would seem logical, therefore, to include quantitative measurement of BOHB in the diagnostic criteria for DKA.

A retrospective review of records from 129 hospitalized children <16 yr (mean age 10.8 ± 0.4 yr) admitted for DKA compared simultaneous measurements of BOHB performed in the Clinical Chemistry Laboratory and serum bicarbonate concentrations (8). The relationship between bicarbonate and BOHB was curvilinear: the BOHB values that corresponded with a bicarbonate concentration of 18 and 15 mmol/L were 3.0 and 4.4 mmol/L, respectively. When these BOHB levels are used for the diagnosis of DKA, there is discordance with at least one of the conventional diagnostic criteria (bicarbonate, pH, or glucose) in 15% of children. These data suggest that diagnostic confirmation of ketonuria or ketonemia with a quantitative measurement of serum BOHB concentration would be very useful to evaluate patients presenting with suspected DKA. Non-specific tests of acid–base status such as pH and bicarbonate concentration have been central to the diagnosis of DKA, presumably because of their widespread availability in hospital emergency departments and, until relatively recently, BOHB was a research test. However, the widespread use of open-channel automated chemistry analyzers now makes it possible for virtually any laboratory to rapidly measure serum BOHB levels. Point-of-care (POC), also referred to as near patient BOHB measurement, is now also readily available, and is increasingly being used for the evaluation and management of patients with suspected hyperglycemia emergencies. It must be noted, however, that POC devices have limited precision and accuracy above a BOHB concentration of approximately 3 mmol/L (13). Despite this limitation, POC BOHB measurement should, nonetheless, be useful for diagnostic purposes as well as for managing the response to treatment. The diagnosis of DKA can be made with confidence in a patient with hyperglycemia (blood glucose >11 mmol/L or 200 mg/dL), a venous pH <7.3, and a serum BOHB value >3 mmol/L.

Insulin therapy

Between the 1950s and early 1970s, insulin doses of 25–100 U/h were given to adults with DKA by the intravenous (IV), intramuscular (IM), or subcutaneous (SC) route. Prospective randomized studies, however, subsequently showed no advantage of high-dose compared with lower doses (see reference 14). In 1973, Alberti et al. reported the results of low-dose IM insulin in the management of adult patients with mild to moderate DKA. An initial average bolus dose of 16 U followed by 5–10 U of IM regular insulin per hour was effective in correcting hyperglycemia and metabolic acidosis (15). Subsequently, a series of randomized prospective studies by Kitabchi et al., and others (10), convincingly demonstrated the efficacy of low-dose insulin protocols for the treatment of DKA in adults. Even lower doses, referred to as ‘very low dose’ insulin therapy [1 U/h (range 0.5–4 U/h)], together with fluid and electrolyte replacement and variable dextrose administration aiming to decrease blood glucose by ≤50 mg/dL/h, has been successfully used to treat severe DKA in adults (16).

Several reports also attest to the successful use of low-dose insulin in the treatment of DKA in children; however, most of these reports included
small numbers of patients, and failed to compare one treatment against the other (17–19). Two prospective studies involving small numbers of children with DKA compared low-dose with high-dose insulin treatment (20, 21). For example, Burghen et al. compared two doses of regular insulin: 0.1 and 1 U/kg/h of regular insulin in 32 children (6.2–15.8 yr), 16 in each group. As in adults, low-dose insulin treatment was as effective as high-dose treatment; however, plasma glucose reached 250 mg/dL in the high-dose group in 3.4 ± 0.4 h as compared with 5.4 ± 0.5 h in the low-dose group. It was also observed that a priming dose of insulin was not necessary when the IV route of insulin administration was used. Despite a slower rate of decline of plasma glucose concentrations, the authors concluded that the low-dose insulin protocol was as effective as the high-dose for the treatment of DKA in children and had a lower potential for hypoglycemia and less frequent hypokalemia (22).

On the basis of the best data available at the time, consensus guidelines for the management of children with DKA recommended the use of a continuous IV insulin infusion at a dose of 0.1 U/kg/h (1, 3). The studies on which the consensus guidelines were based do not, however, provide evidence that a dose of 0.1 U/kg/h is superior to lower doses of insulin for the treatment of DKA in children. Although 0.1 U/kg/h is widely used for treatment of DKA in children and adolescents, a recent report has convincingly shown that lower initial insulin doses (for example, between 0.03 and 0.05 U/kg/h) can adequately normalize BOHB levels associated with DKA (23). However, clinical judgment must guide the required dose in individual patients who may not respond to the lower doses for various reasons.

Although the cause of cerebral edema is unknown, it is by far the greatest risk for morbidity and mortality. The role of therapeutic interventions in its pathogenesis continues to be controversial. Described associations include: insulin administered within 1 h of starting fluid replacement (24), a greater insulin dose within 2 h of commencing fluid therapy (24), and rapid decline in blood glucose levels after starting insulin treatment (25). The latter observation has not been substantiated in other studies (24, 26, 27).

Most children presenting with DKA have adequate tissue perfusion and investigators have argued that it is prudent to correct hyperglycemia, acidosis, and dehydration slowly over 48 h (28–30). Despite the ongoing controversy regarding the role of the rate of change in plasma effective osmolality on risk of development of cerebral edema, it has been suggested that assuming a rapid decrease in the effective plasma osmolality (equal to the plasma glucose concentration in mmol/L plus twice the plasma sodium concentration in mmol/L) increases the risk of cerebral edema, it would be desirable to gradually reduce the serum effective osmolality. To insure a slow fall in effective osmolality, the plasma sodium concentration has to rise by nearly 1 mmol/L for every 2 mmol/L decrease in the plasma glucose concentration (30). However, the dose of insulin is only one of several factors that influence the rate of fall of plasma glucose concentration. Other factors include the initial degree of compromise of renal function caused by dehydration, rate of infusion of IV fluid, and the timing and amount of dextrose administration. Given the proven risk for hypoglycemia and unproven but possible association between insulin treatment and cerebral edema, it has been proposed that lower insulin doses, i.e., 0.05 U/kg/h, rather than the current standard of 0.1 U/kg/h, may be safer while still effectively correcting the abnormalities associated with DKA (31).

Meanwhile, in the decade since publication of the consensus statement, treatment outcomes using lower doses of IV insulin have been published (23, 31–33). These data must be cautiously interpreted owing to the limitations of retrospective observational studies. Nonetheless, in the absence of Randomized controlled trials (RCTs), these studies show that lower doses of IV insulin can be successfully used to treat DKA. Key features of these studies are summarized below and in Table 1. In a retrospective observational study involving pediatric centers in the Greater Manchester Region in the UK, Puttha et al. compared outcomes from five pediatric centers that treated 41 episodes of DKA with IV insulin at a dose of 0.05 U/kg/h (low dose) with 52 episodes treated with 0.1 U/kg/h (standard dose) (31). Comparable data were only available at 6 h following admission. The decline in blood glucose levels 11.3 mmol/L (95% confidence intervals, 8.6–13.9) vs. 11.8 mmol/L (95% confidence intervals, 8.4–15.2) and increase in pH [0.13 (0.09–0.18) vs. 0.11 (0.07–0.15)] were similar at 6 h. These changes were comparable between doses in relation to: severity of initial acidosis, children with newly diagnosed diabetes, or age less than 5 yr. After adjustment for other clinical and biochemical covariates, insulin dose was unrelated to the change in pH and blood glucose concentrations at 6 h after admission. Glasgow Coma Scores (GCS) ≤13 were more frequent in the standard dose group. The authors concluded that low dose (0.05 U/kg/h) insulin was as effective as 0.1 U/kg/h in correcting the main biochemical abnormalities in the initial (<6 h) treatment of DKA in children with type 1 diabetes.

In a retrospective non-randomized study that included all children with DKA admitted to the pediatric intensive care unit (ICU) at the Royal Children’s Hospital, Melbourne during the period 2000–2005, Al Hanshi and Shann compared the effects of infusing insulin at 0.05 U/kg/h (n = 33) as compared with 0.1 U/kg/h (n = 34) (32). Compared
<table>
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<th>Study</th>
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<th>Results and conclusions</th>
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<tr>
<td>Puttha et al. (31)</td>
<td>To compare 0.05 U/kg/h IV insulin infusion for initial treatment of DKA with 0.01 U/kg/h.</td>
<td>Retrospective observational; data from five centers: 41 vs. 52 episodes.</td>
<td>At 6 h, fall in BG and rise in pH similar: 11.3 vs. 11.8 mM and 0.13 vs. 0.11.</td>
<td>Changes comparable between doses in relation to: severity of initial acidosis, newly diagnosed or aged &lt;5 yr. After adjustment for other clinical and biochemical covariates, insulin dose was unrelated to change in pH and BG levels at 6 h after admission. Safety comparisons (especially abnormal Glasgow Coma Score) inconclusive.</td>
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<td>Al Hanshi et al. (32)</td>
<td>To compare insulin infusion at 0.05 vs. 0.1 U/kg/h in children admitted in ICU.</td>
<td>Retrospective observational; 34 children received 0.1 vs. 0.05 U/kg/h in 33 children; 0.05 U/kg/h children younger (25 vs. 62 months).</td>
<td>Assessed parameters 12 h after commencing insulin infusion.</td>
<td>More gradual reduction in effective plasma osmolality over first 12 h because PG decreased more slowly and plasma sodium concentration increased faster. Both groups had satisfactory improvements in acidosis and ketosis, and had similar length of stay in ICU. Smaller dose may make it easier to gradually lower effective plasma osmolality.</td>
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<td>Kapellen et al. (33)</td>
<td>To compare insulin infusion at 0.025 U/kg/h vs. standard 0.1 U/kg/h (0.05 U/kg/h &lt;5 yr).</td>
<td>Retrospective, observational; 23 treated in ICU of center A, mean age 8.9 yr (low dose) vs. 41 in ICU of center B, mean age 13.5 yr, (standard dose).</td>
<td>Follow-up to 48 h. Time to normalize pH (≥7.3) and BG; occurrence of hypoglycemia (&lt;56 mg/dL, 3.1 mM) or hypokalemia (&lt;3.2 mmol/L.</td>
<td>Standard dose resulted in slightly shorter duration of acidosis (8 vs. 6.5 h) and faster normalization of BG, &lt;11 mmol/L (18 vs. 10.5 h). Similar low rates of hypoglycemia during first day. Center B, one case of cerebral edema with cerebral infarction. In first 12 h, patients in center B received twice as much fluid as in center A; 70% of patients in center A and 17% in center B received HCO₃. Cumulative insulin dose until pH normalized 0.21 vs. 0.48 U/kg, center A vs. B, respectively.</td>
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<td>Noyes et al. (23)</td>
<td>To assess clinical application of near patient testing device for capillary BOHB measurement in evaluating a new endpoint for IV insulin. Starting insulin dose 0.03–0.05 U/kg/h (median 0.045, range 0.02–0.1).</td>
<td>Prospective study of 40 DKA episodes in 25 subjects 1–14 yr. Evaluated two treatment endpoints in same subjects: (i) pH &gt;7.3 + urine ketone free; (ii) pH &gt;7.3 + two successive hourly BOHB values &lt;1 mmol/L.</td>
<td>35 of 40 episodes, ICP completed without significant variation; 28 episodes followed to negative urine ketones. Endpoint A reached after 17 h (4–39); endpoint B was reached after 28 (14–64) h. Median lag was 11 (1–36) h. For 59 paired venous samples (excluding samples with lab BOHB &gt;6 mM) POC and laboratory BOHB y = 0.92x − 0.05, r² = 0.94, mean bias −0.25 mmol/L.</td>
<td>Serial measurements of BOHB allow a new simple earlier endpoint for IV insulin therapy.</td>
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BG, blood glucose; BOHB, β-hydroxybutyrate; DKA, diabetic ketoacidosis; ICU, intensive care unit; IV, intravenous; ICP, integrated care pathway; PG, plasma glucose.
with the 34 children who received 0.1 U/kg/h, those who received 0.05 U/kg/h were younger (median age 25 vs. 62 months) and had a more gradual reduction in the effective plasma osmolality over the first 12 h of treatment. The more gradual decline in plasma osmolality was attributed to a slower decrease in plasma glucose concentration and a faster increase in plasma sodium concentration. Acidosis and ketosis improved satisfactorily in both treatment groups, and length of stay in the ICU was similar. An accompanying editorial pointed out that the authors used analysis of covariance methods to compare the two groups on laboratory values obtained approximately 12 h after initiation of treatment, controlling for age and laboratory values at presentation (34). This analytical method, according to the editorialists, is not optimal for between-group comparisons of repeated laboratory values when treatment group is not independent of pretreatment laboratory values, and advised cautious interpretation of the results (34).

Another recent retrospective, observational study compared treatment of DKA with a regimen of low dose (0.025 U/kg/h) vs. a standard insulin dose (0.1 U/kg/h; 0.05 in children <5 yr) (33). A chart review was performed of the first 48 h after onset of DKA in all cases of children and adolescents, n = 64, (0–18 yr) with type 1 diabetes and DKA treated in the intensive care unit at two pediatric centers (Children’s Hospitals of Chemnitz and Leipzig, Germany) from 1998 to 2005 (Table 1). Patients’ ages, initial blood glucose concentrations, venous pH and bicarbonate concentrations were similar at the two centers. Treatment with 0.1 U/kg/h resulted in a shorter duration of acidosis (6.5 vs. 8 h) and significantly faster normalization of blood glucose concentration (10.5 vs. 18 h). Similar low rates of hypoglycemia (blood glucose <3.1 mmol/L) were observed on the first day of treatment. Interpretation of the results of this study is further confounded because treatment strategies between the two centers did not only differ with respect to the amount of insulin administered but also in the frequency of sodium bicarbonate administration and in the amount of fluid administered in the first 4 h of treatment.

A study performed at Royal Hospital for Sick Children, Edinburgh, analyzed 35 episodes of DKA in 25 subjects (aged 1–14 yr). Although the purpose of this study was to examine the advantages of monitoring blood BOHB levels (as compared with urine ketones) during DKA therapy and to evaluate a new end-point (venous pH > 7.3 and two successive hourly BOHB measurements <1 mmol/L) for IV insulin therapy in DKA management, it is notable that the starting dose of IV insulin in this prospective study was 0.03–0.05 U/kg/h (23) and the median IV insulin infusion rate was 0.045 U/kg/h (range 0.02–0.1). In the 28 patient episodes followed to negative ketonuria, venous pH > 7.3 and two successive hourly BOHB measurements <1 mmol/L, was reached after 17 h (median, range 4–39 h), whereas the end-point pH > 7.3 and urine ketone free was not reached until 28 h (14–64 h) after starting treatment.

Notwithstanding the important limitations of retrospective, non-randomized observational studies, in aggregate the above studies suggest that it may be safe and effective to treat most children with DKA with an insulin infusion of 0.05 U/kg/h. There remains some concern, however, about whether patients with severe DKA (pH < 7.1 or HCO3 < 5 mmol/L) will respond equally well to the lower dose regimen. A prospective randomized controlled trial with different insulin doses will be required to show whether there are real and clinically significant differences between insulin dose regimens with respect to metabolic outcomes, occurrence of cerebral edema, duration of hospital stay, and costs.

**Water and salt replacement**

There has been a longstanding controversy concerning the optimal fluid treatment regimen for pediatric DKA. Much of this debate has centered on how to prevent cerebral edema, the most feared complication of DKA in children (35, 36). At the center of the controversy is the potential role of fluid therapy in the pathogenesis of cerebral edema. Clinically overt, life-threatening cerebral edema is infrequent, occurring in 0.5–1% of episodes of DKA, which makes it a difficult disorder to study (37, 26). Cerebral edema that is either asymptomatic or only mildly symptomatic has now been documented to occur during treatment in most children with DKA (38–41).

Some investigators have suggested that cerebral edema is the result of osmotic shifts caused by rapid IV rehydration (42–45, 28) and have recommended conservative (slower) fluid therapy. However, properly controlled retrospective studies have not detected associations between osmotic changes during treatment and risk of cerebral edema (26, 27, 46), leading to the conclusion that there is little or no convincing evidence of an association between the rate of fluid or sodium administration used in the treatment of DKA and the development of cerebral edema (47). Indeed, recent data suggest that cerebral hypoperfusion and the effects of reperfusion during DKA treatment may play a role in the development of cerebral injury and edema (26, 48–50). Conservative rates of rehydration, therefore, could delay restoration of normal cerebral perfusion and be harmful, and use of fluids with low sodium content may exacerbate this problem by decreasing the volume of fluid retained in the vascular compartment, whereas...
Table 2. Overview of fluid regimens used in the FLUID Trial (adapted from reference 51)

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<tr>
<td>Assumed fluid deficit</td>
<td>10% of body weight</td>
<td>10% of body weight</td>
<td>5% of body weight</td>
<td>5% of body weight</td>
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<tr>
<td>Initial fluid bolus</td>
<td>10 cc/kg of 0.9% saline</td>
<td>10 cc/kg of 0.9% saline</td>
<td>10 cc/kg of 0.9% saline</td>
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<tr>
<td>Additional fluid bolus</td>
<td>10 cc/kg of 0.9% saline</td>
<td>10 cc/kg of 0.9% saline</td>
<td>No additional bolus</td>
<td>No additional bolus</td>
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<tr>
<td>Deficit replacement</td>
<td>1/2 deficit + maintenance fluids over initial 12 h; remaining deficit + maintenance fluids over next 24 h</td>
<td>1/2 deficit + maintenance fluids over initial 12 h; remaining deficit + maintenance fluids over next 24 h</td>
<td>Deficit + maintenance fluids evenly over 48 h</td>
<td>Deficit + maintenance fluids evenly over 48 h</td>
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<tr>
<td>Fluid used for deficit replacement</td>
<td>0.45% saline</td>
<td>0.9% saline</td>
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FLUID, Fluid Therapies Under Investigation in DKA.
Protocol A1 more rapid rehydration with 0.45% saline; protocol A2 more rapid rehydration with 0.9% saline; Protocol B1 slower rehydration with 0.45% saline; and protocol B2 slower rehydration with 0.9% saline.

isotonic saline may slow the repair of intracellular dehydration. Conversely, more rapid rates of fluid infusion might increase vasogenic edema associated with cerebral reperfusion, especially if prior ischemia affected integrity of the blood–brain barrier (51). A recent pilot randomized study compared two rates of deficit replacement in children with DKA: protocol A replaced two-thirds of an assumed 10% fluid deficit over the first 24 h and the remaining one-third over the next 24 h (in addition, half the urine volume was replaced while the serum glucose remained >250 mg/dL); protocol B assumed a 7% fluid deficit and replaced the deficit evenly over 48 h (36). In this comparison, the rate of fluid infusion did not substantially affect magnetic resonance imaging (MRI) measures of cerebral edema.

Lack of high quality data from randomized controlled trials has hampered the formulation of evidence-based definitive therapeutic recommendations (51), and there continues to be substantial variability in DKA management (51, 52) as evident from a recent poll of 20 hospitals participating in the Pediatric Emergency Care Applied Research Network (PECARN), cited by Glaser et al. (51). According to currently used protocols at the pediatric referral centers participating in PECARN, a 40-kg child with DKA could receive IV fluid at rates as low as 114 mL/h or as high as 215 mL/h. There is also disagreement about the optimal sodium content of rehydration fluid. Some centers use 0.45% saline, others use 0.9% saline, and yet others a combination.

It is important to note that a single major pediatric referral center in the USA recently reported the outcomes of 3712 episodes of DKA in children and adolescents during the period 1999–2011. Cerebral edema occurred in 0.5% of cases and the overall rate of death or disability was 0.08% (53). This vast experience and good outcomes comparable to those reported in other large studies, using the so-called ‘Dallas protocol’, warrants serious consideration as an alternative, simplified fluid therapy strategy. Briefly, in the ‘Dallas protocol’, after an initial fluid bolus of 20 mL/kg of normal saline, 0.675% saline (3/4 normal saline, 115.5 mmoL sodium) is infused at 2–2.5 times the calculated maintenance rate of fluid administration, regardless of the degree of dehydration, and decreased to 1–1.5 times the maintenance rate after 24 h, or earlier if acidosis resolved, until urine ketones are negative (54, 53).

The PECARN sponsored ‘Fluid Therapies Under Investigation in DKA’ (FLUID) study in the USA, currently in progress, is a randomized controlled clinical trial to investigate the impact of fluid rehydration regimens on neurological and neurocognitive outcomes in children with DKA (Table 2). The study will determine the effects of rehydration rate and fluid sodium content on neurological status during DKA treatment, the frequency of clinically overt cerebral edema and long-term neurocognitive outcomes (51). It is anticipated that the results of this study will provide definitive therapeutic recommendations concerning the optimal fluid treatment regimen for pediatric DKA. The 2009 version of the ISPAD guidelines state that ‘no treatment strategy can be definitively recommended as being superior to another based on evidence’ (3), and this view is reiterated in the current revision of the ISPAD guidelines to be published in September 2014.

**Blood BOHB for the management of ketoacidosis**

POC, also referred to as near patient, capillary blood measurement of BOHB using a meter has been available for more than a decade (55), and
several studies have examined the utility of POC BOHB measurements for the prevention, diagnosis, and management of DKA. The package insert states ‘the test strips are not intended for use in the diagnosis or screening of diabetes mellitus, but are to be used as an aid in monitoring the effectiveness of diabetes control programs’. BOHB measurements at home and in the clinic are now widely used (and frequently preferred by patients to urine AcAc testing) to guide the management of marked hyperglycemia and sick days, especially in patients who use insulin pumps when there is a concern about failure of insulin delivery (56) (see reference 57).

Ham et al. measured the precision and bias of bedside BOHB measurement in the acute care setting (58). As compared with a hospital laboratory measurement, a Bland–Altman analysis (a method used to analyze the agreement between two different assays) showed that meter values >4 mmol/L are less accurate when compared with a reference method (58). Similarly, in a study in which a laboratory technologist simultaneously measured BOHB in venous whole blood samples by a reference method and with a ketone meter good correlation was found up to 3 mmol/L; however, at higher BOHB concentrations, accuracy deteriorated (high AcAc concentrations affect the assay resulting in lower BOHB measurement compared with a reference method) (59). Because any meter value >1.5 mmol/L indicates significant ketosis and potential for DKA, lack of accuracy >4 mmol/L should not prevent the meter from being used to detect DKA. Furthermore, meter BOHB values steadily decreased during treatment of DKA as pH and bicarbonate concentration increased and acidosis resolved, leading the investigators to conclude that the meter may be useful in monitoring therapy of DKA (58). Likewise, near patient BOHB levels were significantly lower than laboratory BOHB levels at presentation of DKA; however, from approximately 12 h onward the two methods gave similar results leading to the conclusion that IV insulin therapy can be stopped and SC insulin commenced when the venous pH is ≥7.3 and two successive BOHB values are ≤1 mmol/L (Fig. 1) (23). Three studies have shown that when blood BOHB values (as compared with urine ketone measurement) are used as an endpoint to define resolution of DKA, time to recovery is significantly reduced, with mean differences reported of 17.4 (60), 4.6 (61) and 11 h (23). An earlier treatment endpoint would be expected to decrease time spent in the ICU and cost of care. One study showed that the time spent in the ICU was reduced by a mean of 6.5 h and estimated substantial total cost savings per subject (61).

The evidence indicates that the currently available BOHB meter is accurate up to 3–4 mmol/L. Therefore, a value >3 mmol/L in the patient whose venous pH is <7.3 and plasma glucose is >200 mg/dL confirms the diagnosis of DKA. During treatment, when the venous pH is ≥7.3 and a meter BOHB is <1 mmol/L (within the meter’s accurate range), one can confidently conclude that DKA has resolved. It has been suggested that initial measurement of pH, pCO₂, and bicarbonate are
necessary to confirm the diagnosis of DKA and assess its severity, but real-time POC measurements of BOHB may be able to replace repeated measurements of these parameters in the management of DKA (13).

Conclusions

Controversy persists concerning the appropriate starting dose of insulin for the treatment of DKA. Notwithstanding the important limitations of small retrospective, non-randomized observational studies, the available data suggest that it may be safe and effective to treat most children with DKA with an insulin infusion of 0.05 U/kg/h. The longstanding controversy continues concerning the optimal fluid treatment regimen for pediatric DKA, and a lack of high quality data from randomized controlled trials has hampered the formulation of definitive evidence-based therapeutic recommendations. The 2009 version of the ISPAD guidelines stated that ‘no treatment strategy can be definitively recommended as being superior to another, based on evidence’ (3). This view is reiterated in the current revision of the ISPAD guidelines to be published in September 2014. The guidelines, once again, indicate that there is no strong evidence for a more protracted replacement regimen being safer or more efficacious. Data suggest that diagnostic confirmation of qualitative measurements of ketonuria or ketonemia with a quantitative measurement of serum BOHB concentration may be useful in the evaluation of patients whose clinical presentation is indicative of DKA. Also, quantitative serial measurements of serum BOHB concentrations at the bedside are useful to monitor the response to treatment and as a criterion for resolution of DKA. In addition to the topics discussed in this article, hyperglycemic hyperosmolar state (HHS) and a mixed picture of these hyperglycemic crises, the use of standard monitoring of BOHB for management of established DKA and impending DKA.

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DKA: do the guidelines need to be modified?


