Daniel L. Metzger, MD, FAAP, FRCPC

A PROVINCIAL PROTOCOL FOR THE TREATMENT OF DIABETIC KETOACIDOSIS IN CHILDREN

Although the pathophysiology and tenets of treatment for DKA have long been established, the mortality rate for pediatric DKA is still estimated at 1% to 5%. The primary cause of DKA-associated mortality is cerebral edema.

ABSTRACT: *Despite advances in our understanding of the pathophysiology and clinical management of diabetic ketoacidosis (DKA) in children, there remains a 1% to 5% mortality rate associated with this condition. This is due primarily to the development of cerebral edema during treatment. At highest risk are children under 5 years of age, those newly diagnosed with diabetes, and those with an initial pH <7.1. The pathogenesis of cerebral edema remains controversial; however, overzealous administration of free water may be a key contributing factor. This article introduces a straightforward protocol that was developed to guide the clinician in treating DKA in children. The protocol consists of an algorithm for calculating safe fluid-replacement rates, recommendations for the composition of rehydration fluids, and a plan for monitoring the clinical status of the patient. The rationale for each step of the management plan is explained in footnote format. This protocol is being promoted in an effort to decrease the incidence of DKA-related cerebral edema and mortality in British Columbia.*

Insulin-dependent (type I) diabetes mellitus (IDDM) develops in 1 of every 5000 to 10 000 Canadian children yearly; the point prevalence of diabetes is estimated to be around 1 in 800 children aged 0 to 14 years.[1] In British Columbia, there are 753600 children in this age group.[2] Therefore, roughly 50 to 100 new cases of childhood diabetes will be diagnosed annually in our province, and there are an estimated 900 children aged 0 to 14 years with IDDM in BC.

The diagnosis of IDDM is relatively straightforward, requiring only a *random* blood glucose of ≥11.1 mmol/L in the presence of typical symptoms (polyuria, polydipsia, weight loss, enuresis), with or without ketonuria.[3] Note that neither a fasting blood glucose nor an oral glucose tolerance test is required for diagnosis, and performing these unnecessary tests serves only to delay treatment of this potentially serious condition. Despite widespread efforts at educating the public about the signs and symptoms of diabetes, many newly diagnosed children still present to their family physicians or local emergency rooms in diabetic ketoacidosis (DKA).

Although the pathophysiology and tenets of treatment for DKA have long been established, many researchers still estimate the mortality rate for DKA among children to be approximately 1% to 5%, a figure that does not appear to have decreased significantly in the past decades.[4-9] Our own observations in the BC pediatric population would suggest that this estimate is valid. The Division of Vital Statistics reported four diabetes-related deaths in the 0- to 19-year age group in BC for the years 1987–1994,[10] and there have been at least two DKA-related fatalities since then.

The primary cause of DKA-associated mortality is cerebral edema (CE).[4-9] Once established in the child with DKA, CE is associated with a ~90%

Dr Metzger is a pediatric endocrinologist in the Endocrinology & Diabetes Unit at British Columbia's Children's Hospital and a clinical assistant professor of pediatrics at the University of British Columbia.

BRITISH COLUMBIA'S CHILDREN'S HOSPITAL
DIABETIC KETOACIDOSIS PROTOCOL[a]

0. Establish diagnosis: blood glucose (BG) ≥ 12 mmol/L, ketonuria, capillary pH ≤ 7.35.[b]

1. Measure body weight (BW) in kilograms . . . . . (1) _____ kg

2. Establish extent of dehydration (BP, tears, urine output, skin turgor) as cc/kg:[c]

	infants:	children:
• mild:	5% = 50 cc/kg	3% = 30 cc/kg
• moderate:	10% = 100 cc/kg	6% = 60 cc/kg
• severe:	15% = 150 cc/kg	9% = 90 cc/kg

. . . . . (2) _____ cc/kg

3. Calculate total free water deficit: multiply (1) × (2) . . . . . (3) _____ cc

4. Give normal saline (0.9NS) fluid push **only if patient is orthostatic or shocky**:[d]
   • recommended amount: 10–20 cc/kg BW over 1–2 h . . . . . (4) _____ cc

5. Calculate remainder of free water deficit after fluid push: subtract (4) from (3) . . . (5) _____ cc

6. Calculate maintenance fluid requirements for the next **48 h**:[e]
   ⇒ 200 cc/kg for the first 10 kg BW
   \+ 100 cc/kg for the next 10 kg BW
   \+ 40 cc/kg for the rest of BW . . . . . (6) _____ cc/**48 h**

7. Calculate total amount of fluid still to be given over 48 h: add (5) and (6) . . . . . (7) _____ cc/**48 h**

8. Calculate hourly rate of fluid replacement: divide (7) by 48 . . . . . (8) _____ cc/h

9. Make up and start a Regular human insulin drip at 0.1 unit/kg BW/h:[f]
   • no bolus necessary
   • piggyback with IV fluids
   • put 50 units insulin in 500 cc 0.9NS, 25 units in 250 cc, etc.
   • run at 1 cc/kg BW/h . . . . . (9) _____ cc/h

10. Adjust fluid replacement rate for insulin drip rate: subtract (9) from (8) . . . . . (10) _____ cc/h

Notes and Rationale:

[a]Please note that this protocol is designed as an algorithm for treating the majority of cases of DKA in infants, children and adolescents. **It cannot replace careful clinical observation and judgement in treating this potentially very serious condition.** If you have questions or problems related to the management of DKA or diabetes, please feel free to contact the BCCH Pediatric Endocrinologist on call (over).

[b]Mild hyperglycemia, even with ketonuria and mild acidosis, can often be managed without IV fluids or IV insulin, particularly in the older child or known diabetic who is not vomiting or seriously dehydrated.

[c]Rapid, deep mouth-breathing (Kussmaul respiration) often dries out the oral mucosa, which makes the child appear more dehydrated that s/he really is. The other clinical signs noted above are more accurate.

[d]Large fluid boluses are potentially dangerous[k] and should be administered slowly and with caution, unless the patient is truly shocky. Only very rarely will a larger (30–40 cc/kg BW) fluid bolus will be required to maintain perfusion.

[e]Since most patients develop DKA over days, slow metabolic repair is generally safest. Overhydration may contribute to cerebral edema.[k] Nonetheless, DKA in children often resolves in less than 48 h.

[f]This relatively high dose of insulin is chosen to inhibit ketogenesis and gluconeogenesis and should be maintained...

Fig 1. The DKA protocol (also see overleaf).

mortality rate; most survivors are severely neurologically impaired.[7] Other potential causes of fatality include shock, electrolyte abnormalities, concurrent illness/infection, and cerebrovascular thrombosis.[7]

The exact pathogenesis of CE remains unknown, but it is apparently much more common in children than in adults.[7] Serial cranial CT scans in children treated for DKA suggest that subclinical brain swelling may be a common (~10%) occurrence during the treatment of DKA in children,[11] and that it may in part exist prior to initiation of therapy.[12] The most widely accepted hypothesis suggests that, as the body becomes dehydrated from chronic hyperglycemia, the neurons form osmoprotective molecules, so-called idiogenic osmoles, to prevent intracellular loss of fluid.[9] As the dehydration is repaired during the course of treatment of DKA, these molecules may persist and lead to a relative intracellular hypertonicity compared to the intravascular space. This results in a net fluid shift from the circulation into the neurons, leading to brain edema. Altered membrane sodium–hydrogen ion transport and disruptions in the blood-brain barrier due to hyperosmolality and acidosis are also hypothesized to play a role in the pathogenesis of CE.[8] Because the phenomenon of CE is still incompletely understood, the optimal treatment of DKA in children remains unknown and the subject of ongoing controversy.

> "Neither a fasting blood glucose nor an oral glucose tolerance test is required for diagnosis [of IDDM], and performing these unnecessary tests serves only to delay treatment."

Risk factors for CE

From the clinical point of view, certain patient-related risk factors have been identified for the development of CE in DKA:[7]

- New diagnosis (i.e., first episode of DKA).
- Age <5 years (and especially <2 years).
- Initial pH <7.1.

Some experts speculate that the smaller the children and the more ill they appear, the more aggressive the fluid resuscitation they are likely to receive. As discussed below, this may add to their risk of developing CE.

Some, but not all, retrospective studies have identified various approaches to or consequences of clinical management that are *statistically* linked to the development of CE. In general, these are related to overzealous administration of fluids or to a precipitous decline in the serum hypertonicity:

- Free-water administration of >4 L/m² body-surface area in the first 24-hour period.[4]
- Administration of fluids at a rate exceeding 2.5 × the maintenance rate.

11. Determine type of fluid to use as replacement:
- Sodium: patient's Na^+ >145 mmol/L: use 0.9NS[g]
  patient's Na^+ ≤145 mmol/L: use 0.45NS
- Potassium: patient not urinating: add no K^+
  patient urinating: add KCl 20–40 mmol/L[h]
  may give K^+ as half chloride—half phosphate for the first 8 h[i]
- Dextrose: patient's BG >15 mmol/L: add no dextrose
  patient's BG ≤15 mmol/L: add 5.0–12.5% dextrose
  aim to keep BG ~10–15 mmol/L without changing insulin rate[f]
- Bicarbonate: $NaHCO_3$ is **not** recommended, regardless of pH[j]

12. Start replacement fluid type determined in (11) at rate determined in (10).

13. Close neurological observation and frequent rousing of the child with fingerpokes to detect any changes consistent with cerebral edema. Severe headache, change in sensorium or in BP, dilated pupils, bradycardia, posturing and incontinence are signs of impending deterioration. Rapid intervention (intubation, mild hyperventilation, mannitol bolus 1 g/kg BW IV) is imperative.[k]

14. Follow laboratory parameters:
- follow BG by meter every 30–60 min: **does the child respond to the poke?**
- follow Na^+, K^+, Cl^-, HCO_3^-, capillary pH every 2–4 h[f, g, h]
- follow Ca^{2+} and P_i if giving phosphate[i]
- check all urine for glucose and ketones

15. Reevaluate appropriateness of replacement fluid type frequently, anticipating the need to add or increase K^+, dextrose, etc.

...When the patient's BG begins to fall, dextrose is added to the IV fluid in a concentration sufficient to keep the BG in the 10–15 mmol/L range. This allows for a buffer against hypoglycemia and a too-rapid fall in the osmolarity.

[g]To correct the serum Na^+ for hyperglycemia, add 0.3 mmol/L Na^+ for every 1.0 mmol/L glucose above 5 mmol/L. As the hyperglycemia resolves, the serum Na^+ should normally rise; failure of this to occur could indicate excess free water administration. A high uncorrected serum Na^+ in the face of hyperglycemia indicates severe dehydration and hyperosmolarity. Such patients should be rehydrated with extreme caution, using fluids with higher osmolar content (e.g. 0.9NS).

[h]Serum K^+ levels are usually normal at diagnosis and fall precipitously with treatment. An IV fluid K^+ concentration of 20–40 mmol/L is usually required to keep the serum K^+ >3.0 mmol/L. Oral/nasogastric KCl boluses (0.5–1 mmol/kg BW) may also be administered.

[i]While there is no proven benefit to replacing phosphate, it has the theoretical advantage of repleting the severe phosphate deficit of DKA and ameliorating the hyperchloremia which inevitably occurs during DKA treatment. If phosphate is given, however, then serum calcium and phosphate levels should be monitored closely.

[j]The acidosis of DKA is due to both ketone bodies and lactic acid, and it resolves with fluid and insulin replacement. There is **no** proven benefit to giving $NaHCO_3$, but it does have a number of deleterious effects, including hypokalemia, metabolic alkalosis, and delayed clearance of ketones. Its use in DKA is **not recommended**, regardless of the patient's pH.

[k]Subclinical brain swelling is common in children with DKA. Cerebral edema accounts for more than half of the ~1–5% mortality rate of DKA in children. At highest risk are newly diagnosed diabetics, those aged <5 years, and those with pH <7.1. The etiology of cerebral edema remains unclear, but overhydration has been implicated in several studies. Resuscitation is successful in only 50% of cases. Most experts suggest limiting fluids to <4 L/m² body surface area, or to <2.5× maintenance fluid rate, in the first 24 h.

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Fig 1. The DKA protocol (cont'd).

- Too-rapid lowering of "corrected" serum sodium
  $[Na^+ + 0.3(glucose - 5.5)]$.[4-6]
- Too-rapid correction of the "active" serum osmolality
  $[2(Na^+ + K^+) + glucose]$.[6]

Provincial protocol

In response to concerns raised by the Office of the Chief Coroner of British Columbia, the physicians of the Endocrinology & Diabetes Unit of British Columbia's Children's Hospital have developed a provincial protocol for the treatment of DKA in children (Figure 1). A laminated copy of this document was distributed to all pediatricians, emergency medicine physicians, and emergency room medical directors registered in this province in November 1996. Because of the positive feedback we have received about its usefulness, we are making it generally available through its publication in the *BCMJ*. It is also available from the author and on the Internet at **<http://www.childhosp.bc.ca/edu/dkawarn.htm>**.

As stated in the first footnote (see Figure 1), this protocol "is designed as an algorithm for treating the majority of cases of DKA in infants, children and adolescents. It cannot replace careful clinical observation and judgment in treating this potentially very serious condition." We urge clinicians to consult with a specialist in pediatric diabetes if they are caring for a sick child (especially an infant) with DKA.

> "This protocol . . . cannot replace careful clinical observation and judgment in treating this potentially very serious condition."

The protocol consists of two major sections. The left-hand side is a straightforward algorithm for calculating the rate of fluid resuscitation, determining the appropriate composition of the replacement fluid, and monitoring the clinical status of the patient. The right-hand side explains in footnote format the rationale behind each of the recommendations of the management plan.

Consistent with more recent recommendations,[5,7,9] we have designed the protocol to aim for complete fluid replacement at an even rate over a 48-hour period. This is somewhat more conservative than many earlier published protocols, which typically replace 50% of the fluid deficit in the first 8 hours and the remainder over the next 16 hours. We believe that this more judicious approach to fluid management will put the child in DKA at lesser potential risk for developing CE as a result of treatment. Compared with adults, children generally have more vigorous homeostatic (hypothalamic,

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Endocrinology & Diabetes Unit

DIABETIC KETOACIDOSIS WORKSHEET

DATE: TIME:										
HR										
RR										
BP										
neuro ✓ OK?										
blood glucose (BG)	meter									
	lab									
NURSE'S INITIALS										
capillary pH										
HCO_3^-	capillary									
	venous									
base excess										
Na^+										
K^+										
Cl^-										
anion gap ⇒ $(Na^+ + K^+ - Cl^- - HCO_3^-)$										
"corrected" sodium ⇒ $Na^+ + [0.3(BG-5)]$										
"active" osmolality ⇒ $2(Na^+ + K^+) + BG$										
Ca^{2+}										
P_i										
PHYSICIAN'S INITIALS										
urine glucose										
urine ketones										
NURSE'S INITIALS										

Fig 2. The DKA worksheet.

cardiovascular, renal, and adrenal) mechanisms for compensating for severe dehydration and acidosis. As a result, in our experience few children actually require the full 48-hour period to achieve resolution of their metabolic derangement. Once the child is alert and no longer acidotic, he or she can be switched to subcutaneous insulin and allowed to eat and drink.

"Mild hyperglycemia, even with ketonuria and mild acidosis, can often be managed without intravenous fluids or insulin, particularly in the older child or known diabetic who is not vomiting or seriously dehydrated."

Several other points should be noted about the protocol that may differ from similar protocols for treating adults with DKA.

1. All calculations for fluid replacement are based on the child's *measured* body weight; it cannot be stressed how important it is that this be determined at the outset.
2. Children who are acidotic and mouth-breathing are not always as dehydrated as they appear on first glance;[9] other objective signs of dehydration (decreased skin turgor, absence of tears, orthostasis) should be sought.
3. When absolutely necessary, the volume given as a "fluid push" should be limited to 10–20 mL/kg over 30 to 60 minutes, which is usually sufficient to treat orthostasis and decreased perfusion.
4. The use of sodium bicarbonate is discouraged, regardless of pH or serum bicarbonate level. Its use has not been demonstrated to improve outcome, and there is now good evidence that bicarbonate may actually prolong ketone-body formation.[13]
5. Frequent clinical monitoring of the patient is of utmost importance. Many studies[7] have identified a critical premonitory phase of rapid neurological deterioration (headache, incontinence, decreased arousal, bradycardia, blood pressure instability) prior to the development of respiratory arrest. In this situation, prompt, aggressive intervention with intravenous mannitol and intubation may be lifesaving.

A copy of the worksheet used by physicians and nurses at BCCH to monitor the patient's clinical and biochemical progress is shown in Figure 2.

One final note: mild hyperglycemia, even with ketonuria and mild acidosis, can often be managed without intravenous fluids or insulin, particularly in the older child or known diabetic who is not vomiting or seriously dehydrated.

Unfortunately, no therapeutic intervention or management plan has been proposed that completely eliminates the risk of CE in children treated for DKA. Until this occurs, the medical practitioner is advised to keep alert to the warning signs and symptoms of diabetes in childhood; this will allow earlier diagnosis and treatment, and will ultimately prevent most cases of DKA and its related mortality.

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