2018-2019

DKA TREATMENT PROTOCOL
Barbara Davis Center for Childhood Diabetes, University of Colorado & Children's Hospital Colorado

Diabetic ketoacidosis (DKA) is a life-threatening condition. One in 100 children with DKA dies in the USA. Those with severe DKA have a much higher mortality and risk of complications. Meticulous attention to the details of therapy and the child's clinical course can decrease this risk. A patient who is unresponsive to vocal commands or presents with hypotension is rare and requires immediate critical care in a hospital. Urgent critical care and diabetes consultation should be obtained.

In Colorado and the Rocky Mountains Region, the Barbara Davis Center for Childhood Diabetes at the University of Colorado and Children's Hospital Colorado offer acute care to patients with DKA and advice to any provider encountering a child with DKA. Please feel free to contact immediately our physician on call regarding treatment of any child with possible or confirmed DKA.

During working hours Barbara Davis Center physicians can be reached for advice at 303-724-2323. After hours a physician can be reached through the answering service at 303-388-2626.

For admission or transfer of a patient to Children's Hospital Colorado, contact the Emergency Department Transfer Center at 720-777-8838.

On call physicians may also be contacted for physician to physician consultation through Children's Hospital Colorado One Call at 720-777-3999.

The Barbara Davis Center is an outpatient diabetes treatment center and a research facility. It is part of the University of Colorado, School of Medicine, and provides diabetes care for Children's Hospital Colorado. It is located on the Anschutz Medical Center campus at 1775 Aurora Court (Colfax and Aurora Court – two blocks west of Colfax & I-225).
http://www.barbaradaviscenter.org.

I. DKA Definition:

A state of absolute or relative insulin deficiency resulting in hyperglycemia, dehydration and accumulation of ketone bodies in the blood with subsequent metabolic acidosis (pH < 7.30; serum bicarbonate < 15 mmol/L). The severity of DKA is defined by the venous pH. Severe DKA is defined by a pH <7.15 and usually will require treatment in the ICU. Moderate DKA is defined by a pH of 7.15-7.25 and can usually be treated on the ward. A pH >7.25 is mild DKA and **usually** can be treated in the ED over a 4-6 hour time period, or on the floor, if admission is otherwise required.

II. Causes of DKA:

A. Initial presentation of type 1 diabetes mellitus
B. Missed insulin injections or insulin pump failure
C. Inadequate insulin dosage in a known diabetic patient
D. Emotional stress/ trauma/surgery without adequate insulin adjustment
E. Intercurrent illness/infection without appropriate insulin adjustment

III. Clinical Presentation

A. History (key points)
1. Classic triad = polydipsia, polyuria, and weight loss (polyphagia is unusual in children)
2. Vomiting/abdominal pain
3. Increased, difficult, or deep respirations
4. Symptoms of infection/flu (may be similar to those of DKA)
5. Illness in family members or close friends
6. In a known diabetic:
*when and how much insulin was last taken?
*missed shots?
*emotional stress as clues to missed shots?

B. Physical exam
1. Vital signs
2. Hydration status/peripheral perfusion/hypovolemic shock?
3. Acetone-fruity breath
4. Kussmaul respirations
5. Neurologic status
6. Signs of infection

C. Initial labs-stat
1. For diagnosis: blood glucose and urine ketones.
A simple urine dipstick and/or a meter glucose level in an ED or office may make a diagnosis and save a life. If abnormal, obtain consultation. "THINK ABOUT DIABETES - DO A UA!"
2. Serum glucose, electrolytes including Na+, K+, HCO3 and BUN, venous pH and PC02. [Arterial PC02 less than 20 mmHg may be an important predictor of cerebral edema in severe DKA. (pH <7.0).
3. Serum osmolality*, calcium, phosphorus.
*serum osmolality should be calculated in all, and measured in severe DKA and/or dehydration; however, this will give a slightly low value because serum Na+ will be factitiously low:
serum Osmolality (mOsm/L)=2(Na+K) + glucose/18 + BUN/2.8

Na correction for glucose:
Corrected Na= measured Na + (serum glucose-100)(1.6)/100

4. Appropriate cultures and/or UA if infection is suspected from H&P. Delay chest film until hydration is normalized.

D. Follow-up lab

1. **First four hours** (or until glucose and electrolytes stable): **q1hour** serum glucose, electrolytes, and venous pH in severe DKA.
2. **When glucose and electrolytes stable**: **q2 hour** venous pH and electrolytes until the HCO3 is above 17 mEq/L. Note: continue to check bedside blood glucose q1hour while on insulin drip.
3. Other studies (osmolality, calcium, phosphorus, etc.) as indicated.
4. **Flow sheet of I & O, lab values**; catherterization may be necessary in the critically ill child, but ask to void hourly for I&O.

IV. Management

Theory: Any treatment plan for DKA should be based on the underlying pathophysiology. Hyperglycemia and ketoacidosis induce important alterations in organ physiology. Hyperglycemia causes an osmotic diuresis and eventually leads to dehydration, electrolyte depletion, and hypertonicity. Metabolic acidosis is partially compensated by hyperventilation and hypocapnia. These effects in turn cause changes in renal, CNS, and cardiovascular system functioning.

Considering the above, the first therapeutic step is to restore extracellular fluid volume which has been depleted through osmotic diuresis and vomiting. Insulin must be given to allow normal carbohydrate utilization and to stop ketogenesis. Serum hyperosmolality should be normalized gradually and intracellular stores of potassium replenished. Severe acid/base disturbances need to be corrected both for homeostatic reasons and to permit optimally effective insulin action. Normal glycogen and fat stores, and protein synthesis also need to be restored over time.

Medications which may alter mental status should be given with extreme caution. Agitated patients may have impending circulatory collapse or CNS catastrophe, which may be precipitated or masked by medications that alter mental status, e.g., Ativan or Haldol.

V. Complications in treating DKA

A. Dehydration/shock

In the presence of severe dehydration, the tendency is to want to correct the dehydration very rapidly – which can be VERY DANGEROUS (see cerebral edema below). However, decreased vascular volume and impending circulatory collapse also must be addressed and continued excessive urine output needs to be considered during the first several hours of therapy. Five percent albumin (10 ml/kg over 30 min) or other colloid should be given if severe shock is present or if there is still evidence of shock one hour after receiving saline (crystalloid). Measured replacement is suggested below in section VI (B). In patients with severe dehydration or in patients with severe mental status changes, intravascular pressure monitoring to follow hydration status is indicated.

Disposition for ED, ICU, or Ward should not be made until initial laboratory values return.

B. Criteria for ICU Admission

1. Severe DKA, including long duration of symptoms, impaired circulation, depressed level of consciousness.
2. Children at increased risk for cerebral edema.
3. Under the age of 5.

C. Hypokalemia - Hyperkalemia:

Correction of acidosis results in intracellular movement of K+. Resultant hypokalemia may lead to muscular weakness (including diaphragmatic fatigue in an already exhausted patient) which may result in a respiratory arrest. **(Hypokalemia or hyperkalemia may lead to cardiac arrhythmias or cardiac arrest.)**

D. Hypoglycemia

While on a continuous IV infusion of insulin, the patient is at risk for hypoglycemia. Hourly glucose measurement and addition of dextrose to the IV solution when blood glucose falls to < 250 mg% should prevent the problem. It is appropriate to use 10% dextrose if glucose levels are <150 mg/dl on D5 and HCO3 not yet >17 mg% and, therefore not yet appropriate to discontinue IV insulin. For acute hypoglycemia, the insulin infusion may be discontinued for 15 minutes, then recheck the serum glucose and restart insulin with a higher concentration of dextrose. If the patient can tolerate oral glucose, 2-4 ounces of juice may be given as well.

E. Cerebral edema

The major cause of death in childhood DKA. Children, in contrast to adults, develop cerebral edema if their rehydration is undertaken too rapidly, even in the hyperosmolar state. The etiology of cerebral edema is still unknown, but may result from unfavorable osmotic gradients (excessive free water) and /or cerebral anoxia. Recent evidence suggests a greater likelihood if the serum sodium concentration fails to rise as the serum glucose falls. Mahoney, et al. found: cerebral edema to be more likely with an arterial pH <7.1, and PC02 <20, and in children receiving more than 50 cc/kg of fluid in the first 4 hours of treatment. Usually seen in patients who are less than 15 years old who are severely dehydrated, very acidotic, and very hyperosmolar. Newly diagnosed patients who are < 5 years old seem to be at greatest risk.

Clinically the patient may complain of headaches or have a change in mental status hours after therapy for DKA has begun. In some there is a premonitory period when development of cerebral edema could be suspected if there is a change in arousal or behavior, severe headache, incontinence, pupillary changes, seizures, bradycardia, or disturbed temperature regulation. Early intervention before respiratory arrest is essential. Most often, the patient's lab values are improving as she/he appears to be worsening clinically.

Treatment includes **decreasing fluids** (<70cc/kg/day or 0.75 X Maintenance) and giving **Mannitol** (1 gm/kg over 30 minutes), elevating the head of the bed, **intubation and hyperventilation** until a pCO2 level of 30-35 mmHg is reached may be necessary, although many already have a pC02 less than 30 mmHg due to hyperventilation. Hypocapnea causes cerebral vasoconstriction. Mannitol may need

to be repeated depending on the clinical condition of the patient. Dexamethasone should not be given.

Treatment **should <u>not</u> be delayed** until after the radiographic studies have been obtained. The absence of demonstrable cerebral edema or CT scan does not preclude the diagnosis.

VI. General Management (cookbook)

A. Mistakes and how to avoid them

There are **two major mistakes** one can make in diagnosing and managing DKA:

1) Failure to recognize the problem (e.g., the diagnosis of new onset diabetes, cerebral edema, hypokalemia, etc.), and
2) Failure to react to the situation, whether the problem is due to the natural course of the disease, or secondary to therapy.
    a. Keep a **flow sheet** for fluids, insulin, vital signs, lab values, etc.
    b. Record all **intake and output** meticulously.
    c. EKG monitor for K+ changes if severe acidosis or elevated K^+.
    d. Urinary catheter only if unconscious. If conscious, ask patient to void every hour. In the young child, weigh the diapers hourly.
    e. IV access for frequent blood draws separate from fluid administration line(s) when hydration allows.
    f. **Check pupils and sensorium** hourly (for cerebral edema).

B. Fluids

1. **Initial volume expansion** =10 to 20cc/kg (300-600cc/m2) of a physiologic solution (such as normal saline or lactated Ringers solution) over the first one to two hours. This may need to be repeated if the patient is severely dehydrated and/or if urine output is massive. However, **the initial bolus re-expansion must be included in the calculations of the total fluid dose for the first four hours of treatment, which should never exceed 40 cc/kg.**

2. **24 hour fluid therapy**

a. **Replacement:** Use estimates of dehydration based on physical exam varying from **5 to 10% of body weight for mild to severe losses. Deficits should be replaced evenly over 48 hours.** Remember to subtract the quantities given in the first hours of re-expansion from the 24 hour totals. Follow urine output to be certain initial estimates are adequate. Total fluid replacement should not exceed 4 L per square meter per 24 hours.

b. Maintenance

body weight (kg)	24 hour fluid maintenance requirements
up to 10	100 ml/kg
10 to 20	1000 ml + 50 ml/kg over 10 kg
>20	1500 ml + 20 ml/kg over 20 kg

c. Special additional losses

Additional replacement may be required where there is severe vomiting, etc.

3. **Monitoring fluid requirements.** In the severely dehydrated child, or the one with

mental status compromise, monitoring fluid administration with a CVP and/or arterial pressure monitoring may be required to ensure adequate fluid replacement.

C. Insulin

1. **No insulin should be given until a blood glucose level has been obtained.** Blood sugar can be checked at the bedside with a glucose meter
2. Insulin therapy should **be started 1 hour after the initial rehydration bolus but should not be delayed for more than 2 hours after starting IV hydration.**
   The serum glucose level falls fairly rapidly during volume re-expansion with or without insulin. **An initial IM or IV insulin bolus should not be given** since this increases the rate of initial glucose fall without decreasing the time required to correct the acidosis.
3. Continuous **IV regular insulin is given at a dose of 0.1u/kg per hour.** Because insulin will bind to the walls of the IV tubing, the tubing is first washed with 20 ml of the insulin solution. IV insulin provides a relatively smooth decline in blood glucose levels with a predictable time to expect a blood sugar of 300mg%.
4. Aim to have blood glucose level decrease by 50-100 mg %/hr.
5. **When blood glucose falls to < 250mg% add dextrose to the IV solution.** The IV solution can be changed to ¾ or ½ normal saline at this time.
6. Aim to keep glucose between 150-300 mg % by addition of 5 to 15% Dextrose. Unless a patient is truly hypoglycemic, however, the insulin drip should not be decreased to less than 0.05u/kg/hr as <u>insulin is essential for preventing continued ketogenesis, IV insulin should not be discontinued until the HCO3 is >17 mEq/L.</u>

D. Electrolytes

<u>1. **Potassium**</u>: K+ is a special problem because high urinary losses occur in association with normal serum levels caused by the intracellular exodus of K+ in the presence of acidosis. Vomiting may also contribute to hypokalemia. **Total body potassium is usually depleted, but serum levels may be normal or high. As acidosis is corrected, K+ is driven back into the cells and there is usually a fall in serum K+ in spite of large K+ replacements. Low or high serum potassium levels can be a cause of cardiac arrhythmias, which can be fatal.**

a. **<u>Potassium must never be given until the serum potassium level is known</u>.**
b. Once the serum potassium is known to be normal or low, and <u>after voiding is observed</u>, **generally after the first hour of fluid resuscitation, all IV fluids should include 20-40 mEq/L of potassium.** If the serum potassium is high, it is best to wait to add K+ to the IV until the K^+ begins to decrease. The potassium may be in the form of KCl, KAc, K2H PO4 or a combination of these supplements, no more than half of the potassium replacement should be given as PO4. **Do not give K+ as a rapid IV bolus or cardiac arrest may result. Severe hypokalemia may lead to respiratory arrest due to muscle dysfunction.**
c. EKG strips (Lead II) may give the best indication of total body K+ deficit or change.

2. **Sodium**: Initial serum Na+ is frequently low for several reasons: 1) Depletion secondary to urinary losses/vomiting, 2) Hyperglycemia creates an osmotic dilution of extracellular solute so that for each 100 mg% increase in glucose above a 100 mg% baseline, there is an expected decrease of 1.6 mEq/L of Na+, 3) Hyperlipidemia displaces water in the lab method used, causing serum Na+ to be factitiously low .

Laboratory hyponatremia will correct with resolution of hyperglycemia and ketonemia. Total body Na+ deficit is approximately 10 mEg/kg based on a dehydration estimate of 10%. Because of the factitious Na deficit, the sodium deficit is not usually calculated. It is important to follow the serum sodium during therapy to make certain the level is rising. A falling serum sodium may be associated with cerebral edema and impending herniation. Usually initial treatment with isotonic saline, or lactated Ringers followed by ½ or 3/4 physiologic saline will adequately replace Na+ deficit.

3. Phosphorus: Uncontrolled diabetes causes an increased urinary excretion of phosphorus.

a. Serum phosphorus may, like potassium, be elevated initially in diabetic acidosis, only to fall rapidly during therapy.
b. Hypocalcemic tetany has occurred with excessive phosphorus administration.
c. Clinical problems due to low phosphorus are not proven, but there is some evidence that neurologic disturbances may respond to raising the serum phosphorus level when it is very low (<1mg/dl) (normal adult phosphate =3-5mg/dl).
d. On theoretical grounds, a low phosphorus may lead to a low red cell 2, 3 DPG causing a shift of the 02 dissociation curve to the left, creating a relative tissue hypoxia.
e. Treatment may be administered as KH2 PO4 at 10-20 mEq/L in IV solutions (see potassium therapy above).

4. Calcium: Hyperglycemia also causes increased urinary calcium loss. Because of the large calcium reservoir in bone, serum calcium usually remains normal. Excessive phosphorus administration may result in hypocalcemia due to suppressed PTH.

E. Osmolality: Hyperosmolality always accompanies DKA. During treatment, serum osmolality may decrease more rapidly than CNS osmolality, resulting in fluid shifts into the CNS. This may cause life threatening cerebral edema. Excessive, rapid fluid administration may increase the risk for cerebral edema.

1. Serum osmolality should not be rapidly decreased or CNS damage may result.
2. **If the serum osmolality is very high (greater than 320 mOsm/L), the elevated blood glucose and dehydration should be corrected cautiously with special attention to neurological status. However, severe dehydration must be steadily corrected to prevent circulatory collapse.**
3. **An 18 mg% rise in blood glucose yields a 1 milliosmol rise in serum osmolality.**
4 The **osmolality can be calculated by: 2(Na+K) + glucose/18+BUN/2.8. Measured or calculated serum osmolality should be followed if the initial osmolality is >320 mOsm/L.**

5. Hyperosmolar, non-ketotic coma is different than diabetic ketoacidosis. It should not be treated as outlined in this paper. Fortunately, this condition is rare in childhood. When it occurs in a pediatric aged patient attention still needs to be given not to decrease the osmolality too rapidly. **Children, in contrast to adults, develop cerebral edema if their rehydration is undertaken too rapidly, even in hyperosmolar non-ketotic state.**
6. Overweight or obese children may make estimation of dehydration difficult. A measured serum osmality should always be obtained in the overweight patient with either DKA or hyperosmolar, non-ketotic conditions.
7. **Monitoring intravascular pressure, cardiac rhythm, and osmolality is essential for patients with HHS**.

F. Acid-base: The cause of the acidosis is ketogenesis from insulinopenia. Correction of this will reverse the acidosis.

Published reports confirm that bicarbonate therapy is not necessary even in severe DKA (pH <7.1).

Arguments against the use of bicarbonate revolve around 4 issues:

1) Bicarbonate therapy causes a paradoxical CNS acidosis and decreases CNS oxygenation. Bicarbonate crosses the blood-brain barrier slowly, but the CO2 formed (from HCO3 + H+ --> H2O + CO2) crosses rapidly into the CNS forming H2CO3, thereby **accentuating rather than reducing the CNS acidosis.**
2) Use of bicarbonate will lead to a more rapid initial correction of acidosis with resultant intracellular movement of K+ and hypokalemia. Potassium replacement requirements are 2 to 3 times greater in patients treated with bicarbonate.
3) Rapid infusion of bicarbonate and correction of acidosis may shift the oxygen dissociation curve to the left, thereby decreasing oxygen delivery to the tissues.
4) Several reports (including Glazer, et al, NEJM 344:264, 2001) have found a greater likelihood of cerebral edema when HC03 is given.

G. Ketones: Acetoacetate and a small amount of acetone are measured by the urinary "dipstick" reactions as used by the clinician or laboratory. Beta-hydroxybutyrate is not measured by this method and is usually the major ketoacid in DKA. As treatment is begun, B-OH butyrate is oxidized to acetoacetate so ketonuria may appear to worsen initially. Urinary determinations are markedly affected by hydration status and urine output. A bedside meter, the Precision Xtra, is now available which can be used to estimate serum B-OH butyrate levels. Serum B-OH levels >3.0 mmol/L are usually indicative of severe DKA (nl = <0.6mmol/L) Serum ketones usually disappear at or about the same time the venous pH reaches a level of 7.30. Following bedside B-OH butyrate levels may be helpful. They can be extremely useful, if available at home, in determining if an ill child requires ED therapy. Repeating urine ketones is not necessary.

VII. Following the patient

1. Use a flow sheet.
2. VS q one hour until stable.
3. Accurate record of hourly fluid intake and output.
4. Neurologic checks every hour (at least pupil size and sensorium) until metabolically stable.
5. Lab tests: Bicarbonate (bicarbonate < 10 mm/L), glucose, K+ every hour for 4 hours, hourly pH until pH >7.1; then every 2-4 hours until HCO3>17.
   Also do a blood sugar at the bedside with each blood draw.

VIII. The next day, or when ketoacidosis is resolved and the patient is ready to eat, routine diabetes care can be initiated or resumed**. IV dextrose must be discontinued when the insulin infusion is discontinued and subcutaneous insulin must be given.**

A. **Diet**: **Order a constant carbohydrate diet appropriate for age** - 1000 calories for 1st year of life. Add in 100 calories/year for each year thereafter up to 2500 K Cal/24 hours. **May need to increase this by 25-50% if significant weight loss has occurred.** The diet is given as 3 meals and 3 snacks, the dietitian will provide the same grams of carbohydrate at each meal and snack. The dietary staff will help to determine the appropriate caloric content of the diet. An "ADA" diet is *not* necessary: however, concentrated sweets should be avoided.

B. **Insulin:** The half life of IV insulin is 6 minutes in blood and 30 minutes in tissue so insulin infusion need not be discontinued until subcutaneous insulin is given.

1. Subcutaneous insulin dose

a. known diabetic - return to usual dose the morning after the acidosis is corrected. Do not waste a day using a sliding insulin scale. The usual dose may need to be supplemented with additional rapid acting insulin (lispro, aspart or glulisine insulin) since there is some insulin resistance following an episode of DKA.

b. new diabetic - start on insulin analogs.

Consultation with the BDC physician on call is <u>required.</u>

Use MDI (Multiple Daily Injection) regimen with a long-acting insulin such as Lantus (insulin glargine) or Levemir (insulin detemir) once a day (0.25-0.35 units/kg/day) and a rapid acting insulin such as Humalog (lispro), Novolog (aspart) or Apidra (glulisine) given 15 minutes before meals using carbohydrate counting or a sliding scale. Total Daily Dose (TDD) should be approximately 0.5-1.0 units/kg/day.

The long acting insulins cannot be mixed with rapid acting insulins and must be given by a separate injection due to pH incompatibility.

c. monitoring insulin therapy: obtain glucose levels before meals, 2-3 hours after lunch at bedtime and at 2 AM AND anytime there are hypoglycemic symptoms.

C. **Potassium**: Since patients are often total body K+ depleted, continued supplementation with oral K may be necessary for several days.

SUMMARY OF SUGGESTIONS FOR THE MANAGEMENT OF KETOACIDOSIS

A. At the onset:

ALL DKA PATIENTS REQUIRE DIABETES CONSULTS!

1. Weigh the patient prior to starting treatment.
2. Do pulse and blood pressure and capillary filling time on the patient yourself as an estimate of shock rather than relying on someone else's values.
3. Administer plasma or other colloid to a patient in shock.
4. Do not administer more than 20 cc's/kg as total bolus without careful consideration of fluid status and neurological status. More than 40cc's/kg should never be given in the first 4 hours.
5. Start insulin treatment after the blood sugar and urine ketones are determined and initial resuscitation fluid bolus has been given.
6. Always know the blood glucose prior to starting insulin therapy.
7. Know the blood pH and serum potassium prior to starting potassium therapy.
8. Ask the lab to check for lipemic serum when the sodium level is very low.
   Na correction for elevated glucose: Na = lab Na + (1.6)(serum glucose-100)/100
9. Determine osmolality in a patient with a very high blood glucose (above 800 mg/dl), or severe dehydration and aim to decrease the osmolality gradually (10 m0sm/hr).
   The osmolality can be calculated by:
   2(Na+K) + glucose/18+BUN/2.8

B. During the treatment:

10. Have the nurses run 50 ml of insulin solution through the IV tubing and buretrol prior to starting insulin therapy.
11. Keep an **accurate flow sheet** including lab values, precise intake and output records.
12. Check blood glucose levels every one hour initially and then every two hours with the goal to decrease the value at a rate of 50 to 100 mg/dl/hour.
13. **Add glucose to the IV when the blood glucose level falls below 250 mg/dl** so that insulin therapy can be continued to help stop hepatic ketone formation and promote hepatic glucose uptake. The IV fluid at that time may be changed to 1/2 or 3/4 physiological saline. **Usually 1.5 times maintenance fluid rate is appropriate at that time, but calculation of deficit, ongoing loses, and maintenance requirements should be done.**
14. Check neurologic status at regular intervals as a sign of possible early cerebral edema.

C. When ready to discontinue IV therapy:

15. Make sure the HCO3 is above 17 prior to discontinuation of IV fluids.
16. Make sure the sodium and potassium are normal prior to discontinuation of IV fluids.
17. Discontinue IV insulin when the subcutaneous insulin is administered.
18. **Stop the IV glucose when the insulin drip is stopped** so that the blood glucose levels do not become high and cause diuresis.
19. Weigh the patient prior to discharge to have a baseline for possible future problems and calculation of insulin dose.
    For previously diagnosed patients:
20. Oral fluids should be tolerated prior to discharge.
21. Make sure the patient is checking in with a diabetes care provider at a set time after discharge. There are specific transfer of care instructions in EPIC.
22. Make an appointment for the patient to see their diabetes-care-provider in the week after treatment, so that education and changes in therapy can be given to help prevent future similar episodes.

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