Guidelines for the Management of Diabetic Ketoacidosis

I. Definition of Diabetic Ketoacidosis

D	Hyperglycemia	Blood sugar > 200 mg/dl
K	Ketonemia/ketonuria	
A	Acidosis	pH < 7.3 or HCO_3 < 15 mEq/L

II. Pathophysiology

Insulin deficiency has three main effects:

1. Loss of insulin-dependent glucose transport into peripheral tissues
2. Increased gluconeogenesis in the liver
3. Increased breakdown of fat, protein, and glycogen

Thus, insulin deficiency results in hyperglycemia (from increased hepatic glucose production and decreased peripheral uptake) and acidosis (primarily derived from hepatic fatty acid oxidation into ketoacids).

Hyperglycemia above the renal threshold (>180-200 mg/dL) results in glycosuria. This produces an osmotic diuresis that drags solutes (Na, K, Cl, PO_4) along with it, leading to dehydration and electrolyte losses. With significant dehydration, there may be poor perfusion of peripheral tissues leading to lactic acidosis, which further aggravates the existing ketoacidosis.

III. Assessment

A. History

The classic symptoms of new-onset diabetes mellitus are polyuria, polydipsia, and polyphagia accompanied by weight loss. There may be a history of weakness, malaise, or lethargy. Often the acute crisis will be precipitated by an acute infection or stress. Nausea, vomiting, abdominal pain, altered breathing, or progressive obtundation may precipitate the visit to the Emergency Department. In children known to have diabetes, DKA is usually preventable. It is often precipitated by poor compliance with the home management routine or failure to increase insulin doses with an intercurrent illness.

B. Physical Exam

1. Airway -- may be compromised in patients with extreme obtundation. Consideration should be given to intubation and mechanical ventilation if the patient is not making adequate respiratory compensation for the metabolic acidosis.

2. Breathing -- typically deep, hyperpneic (Kussmaul). Breath sounds should be clear; rales/rhonchi may suggest intercurrent infection or pulmonary edema (which can be seen in the correction of DKA).

3. Circulation -- particular attention should be paid to pulse, blood pressure, capillary refill, and any orthostatic changes. Children with DKA are hyperosmolar, so that intravascular fluids are spared at the expense of cellular fluids. Therefore, the clinical examination underestimates the degree of dehydration.

4. Mental status -- A full neurological examination must be performed on all patients presenting in DKA, so that a baseline may be established to which subsequent examinations may be compared. Acute deteriorations in mental status may herald cerebral edema (see section on cerebral edema).

5. Abdomen -- many patients in DKA complain of abdominal pain, often due to persistent vomiting or ketosis. Tenderness tends to improve with treatment; pain which remains or worsens should prompt consideration of other disease processes (e.g., appendicitis).

C. Initial laboratory tests

The laboratory confirmation of the diagnosis of diabetes mellitus requires only a fingerstick blood sugar and urinalysis to confirm the hyperglycemia, glycosuria and ketonuria, but in DKA additional laboratory tests are useful in assessing the severity of illness and guiding treatment.

1. Electrolytes -- The sodium is typically low, as a result of urinary losses, hyperglycemia, and hypertriglyceridemia (artefactual hyponatremia). For every 100 mg/dL glucose above 200 mg/dL, the measure Na should be reduced by 1.6 mEq/L.

$$Na_{corrected} = Na_{measured} + 1.6 \times \frac{[Glucose] - 200}{100}$$

Potassium may be low, normal, or elevated, but the total body stores are always depleted. Bicarbonate values are usually low, consistent with metabolic acidosis. BUN and Creatinine are usually elevated with dehydration. Glucose is invariably elevated in DKA.

2. Venous blood gas -- will document metabolic acidosis. Arterial blood gas should also be considered in the appropriate setting of severe clinical decompensation.

3. Calcium, Phosphorus -- Phosphate levels are usually low due to urinary losses. Replacement of phosphate in the rehydration fluids may precipitate tetany in patients with low calcium levels. If the initial calcium and phosphorus levels are close to normal, there is no need to keep repeating them.

4. CBC w/ differential -- Elevated WBC counts and "left shifts" are often seen with the acute stress of DKA and do not necessarily indicate an acute infectious process. Furthermore, significant infection may be present even in the absence of fever.

5. Additional laboratory tests will depend on the clinical situation.

IV. Goals of Therapy

In planning treatment, it is important to consider the important complications of DKA:

A. Cardiovascular collapse

1. From dehydration
2. Treatment involves intravascular fluid expansion with ISOTONIC fluids (saline)

B. Overwhelming acidosis

1. From ketoacid production and lactic acid accumulation
2. Volume expansion and tissue reperfusion to correct lactic acidosis
3. Prompt initiation of insulin to stop fatty acid oxidation and ketone production
4. Consider use of sodium bicarbonate in patients with arterial pH < 6.9 and/or evidence of myocardial depression

C. Hypokalemia

1. Insulin therapy is associated with rapid intracellular movement of potassium
2. Adequate potassium replacement in rehydration fluids and frequent monitoring with blood tests and EKG's

D. Cerebral Edema

1. Hypertonic dehydration in DKA is associated with the production of osmotically active particles in the brain (taurine, inositol -- formerly "idiogenic osmoles") that act to prevent neuronal cellular dehydration.
2. Correction of hyperosmolar state leads to fluid influx into the brain. Rapid rates of rehydration or correction of hyperosmolarity may lead to cerebral cellular swelling and brain herniation. It usually occurs 6-18 hours into therapy, just as the patient appears to be clinically and biochemically improving. *This is the most common cause of mortality in children with DKA !!!*
3. Much of the etiology and pathophysiology of cerebral edema is still unknown, but the risk should be minimized by attention to the following:

    a. Slow fluid replacement (over 48 hrs) with isotonic fluids
    b. Frequent monitoring and slow rise of calculated CORRECTED Na values
    c. Close neurologic surveillance for early signs of increased ICP (headache, lethargy, slurred speech, obtundation) and rapid evaluation & action

V. Treatment

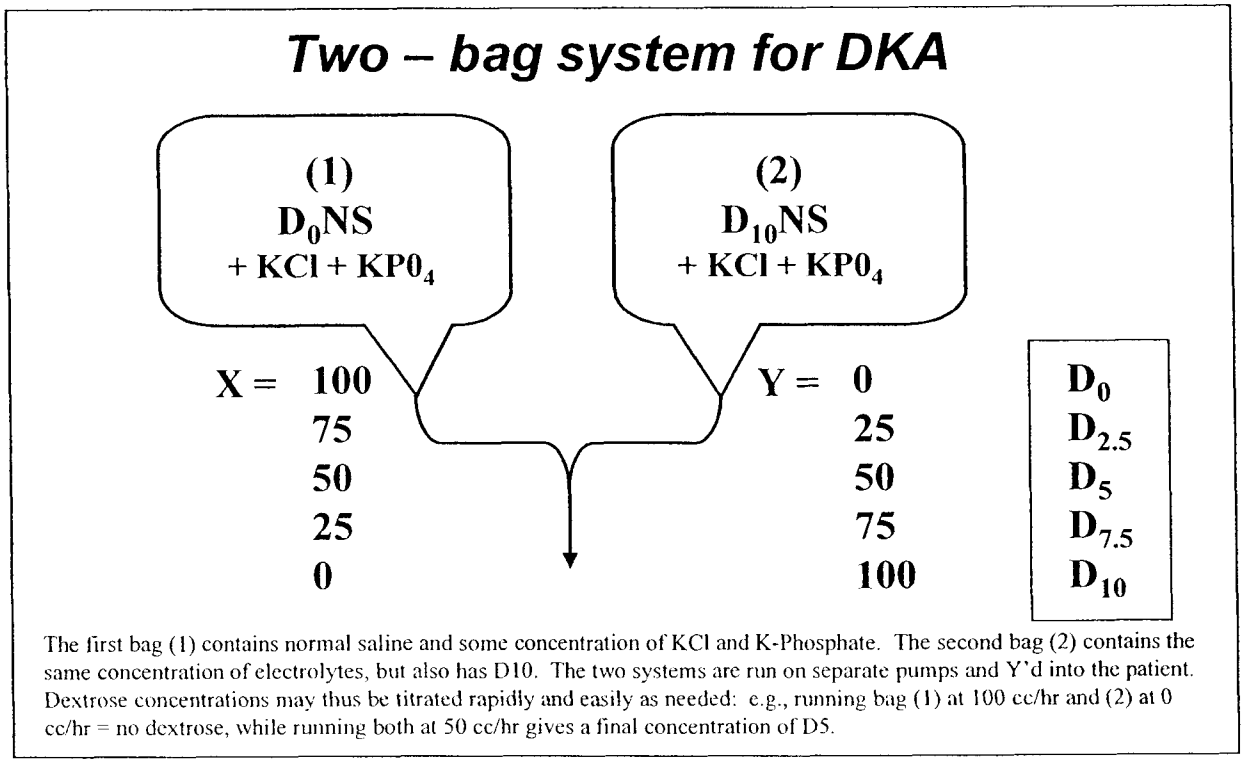
A. Initial Resuscitation

Obviously, adequate airway patency and breathing should be assessed first, and immediate interventions made as needed. Initial fluid resuscitation should always be with normal saline, 10-20 cc/kg. Remember, rapid fluid replacement is potentially dangerous, so thoughtful consideration of fluid needs should guide treatment, not "automatic" reactions. After each 10-20 cc/kg aliquot, pulse, blood pressure, orthostatic changes, intake/output, perfusion, and blood glucose should all be reassessed. The aim is not to completely normalize the vital signs but to improve them.

B. Insulin

The initial dose is usually 0.1 Units/kg/hour. For profound hyperglycemia (BG > 1000) or hyperosmolarity, lower rates (0.05-0.75 Units/kg/hr) may be preferable. The goal is to lower the serum glucose by 50-100 mg/dL/hr.

When the blood sugar falls below 250 mg/dL, dextrose should be added to the rehydration fluids. A "two-bag" infusion system, in which one bag contains D_{10} (+electrolytes) and the other D_0 (+electrolytes), is convenient for titrating the slow, steady decline in serum glucose.



The first bag (1) contains normal saline and some concentration of KCl and K-Phosphate. The second bag (2) contains the same concentration of electrolytes, but also has D10. The two systems are run on separate pumps and Y'd into the patient. Dextrose concentrations may thus be titrated rapidly and easily as needed: e.g., running bag (1) at 100 cc/hr and (2) at 0 cc/hr = no dextrose, while running both at 50 cc/hr gives a final concentration of D5.

C. Acidosis

The most important steps in treating acidosis are the prompt institution of insulin and adequate fluid resuscitation for tissue reperfusion. Sodium bicarbonate should be considered if:

1. Arterial pH < 6.9
2. There is evidence of cardiovascular dysfunction, such as poor contractility or peripheral vasodilation

The dose may be calculate by the formula

Dose (mEq) = weight (kg) x 0.3 x (15 – [HCO_3])

Alternatively, a reasonable dose is 1-2 mEq/kg. Bicarbonate should always be given as a SLOW infusion over 1-2 hours, not as a bolus. Rapid pH changes may precipitate hypokalemia or cause a paradoxical CNS acidosis (which may worsen the patient's mental status). Failure of the acidosis to improve in response to bicarbonate suggests inadequate volume status, respiratory compromise, or severe systemic infection (sepsis).

Recent evidence has called into question the utility of bicarbonate administration, and most studies show that bicarbonate use does not hasten resolution of DKA or shorten hospitalizations.

D. Rehydration fluids

Dehydration in DKA is predominantly intracellular. Clinical estimates of percent dehydration are often highly inaccurate. Therefore, CLOSE MONITORING OF INTAKE/OUTPUT AND FREQUENT REASSESSMENT OF FLUID NEEDS is critical. Calculations should aim to restore the fluid deficit slowly and evenly over 48 hours. The fluid replacement rate must be titrated to the clinical setting; i.e., the calculated Na rate should RISE with treatment. *A FALL IN THE CALCULATED SODIUM SHOULD PROMPT AN IMMEDIATE DECREASE IN THE FLUID RATE.* Resuscitation fluids should be subtracted from the fluid deficit. Replacement of fluids for urinary losses is not needed, because urinary losses are usually negligible after the first several hours of treatment. *THE RESUSCITATION FLUID SHOULD ALWAYS BE NORMAL SALINE.* Thereafter, normal saline and ½ normal saline can be used, although we prefer normal saline. Hypotonic fluid replacement increases the risk of cerebral edema. In profound hypernatremia, 2/3 or 3/4 NS may be considered after the hyperglycemia has been corrected.

E. Electrolyte replacement

1. Sodium – Total body Na deficit of 8-10 mEq/kg as a result of osmotic diuresis. Calculation of deficits and replacements are generally not needed. The initial rehydration fluids in DKA should almost always be normal saline to protect against cerebral edema, changed to ¾ or ½ normal saline as needed later.

2. Potassium -- Total body K deficit of 8-10 mEq/kg as a result of osmotic diuresis. However, serum K+ may be normal or even elevated, because acidemia causes a H+/K+ exchange that moves K+ out of the cells into the intravascular space. Serum K+ falls with therapy, because of correction of acidemia and the direct action of insulin on cellular K+ uptake. Potassium should be added to the replacement fluids as soon as the absence of renal failure is shown:

K+ < 3.0 mEq/L	--	60 mEq/L
K+ = 3.0 - 6.0 mEq/L	--	40 mEq/L
K+ > 6.0 mEq/L	--	hold K

   Occasionally, replacement rates as high as 80 mEq/L may be needed. Rates > 80 mEq/L should be given via central venous access. Potassium replacement rates greater than 0.5 mEq/kg/hr should be avoided. Serum potassium levels should be known before insulin is given. Formal EKG should be considered in patients with serum potassium levels < 3.0 or > 6.0 mEq/L.

3. Phosphate -- To correct phosphate depletion, and to prevent hyperchloremia (which often occurs during treatment of DKA), the potassium is generally replaced as:

   Potassium Chloride + Potassium Phosphate, in a 1:1 ratio

   This method offers the advantage of replacing phosphate, which improves oxygen and energy delivery, through the formation of ATP and 2,3-DPG.

   Calcium should be monitored when receiving supplemental phosphate.

   ** If potassium phosphate is not available, standard KCl may still be given **

VI. Monitoring

Treatment of DKA requires frequent eyes-on, hands-on, brain-on reassessment. DKA should never be "auto-pilot" or managed from the call room. Frequent bedside review of clinical data, including vital sign changes, perfusion, mental status, I/O's, and labs, is essential.

A. Neurological reassessment should be performed q 1hr
B. Blood glucose should be measured q1hr while on an insulin infusion
C. Electrolytes q2hr until calculated Na and K are normal and measured $HCO_3 > 15$, then q4hr until infusions are d/c'd. More frequent monitoring may be necessary if the calculated Na falls at any time.
D. BUN/Creatinine, calcium and phosphorus no more frequently than q4-6hrs unless clinically indicated.
E. Serial measurements of arterial pH may be necessary in intubated patients, those with extreme life-threatening acidosis, or after bicarbonate therapy. These patients should have intra-arterial catheters placed and be monitored in the ICU. Serial VBG's may be discontinued once $HCO_3 > 15$.
F. All patients should be on telemetry.
G. Central venous catheters should be considered in patients with evidence of impaired renal function, pulmonary edema, or in other situations of complicated fluid management.
H. Intracranial pressure monitors ("bolts") should be considered in any patient with cerebral edema and neurologic deterioration. Immediate brain imaging and neurosurgical consultation are required in this setting.

VII. The High-Risk Patient

Patients with the following characteristics may require ICU admission:

A. Age < 3 years
B. Significantly altered or deteriorating mental status
C. pH < 7.2
D. Glucose > 1000 mg/dl
E. Na (calculated) > 160 or any patient with falling (calculated) Na
F. K < 3.5 mEq/L on admission
G. Severe hyperosmolality ($S_{osm} > 350$ mOsm)
H. Other organ system dysfunction that complicates treatment

VIII. Transition to Subcutaneous Insulin

A. When dehydration, acidosis and hyperglycemia are corrected (glucose < 300 mg/dl, pH > 7.3, HCO_3 > 15), and patient is clinically hydrated it is time to begin feeding the patient and plan for subcutaneous insulin. The patient should be changed to subcutaneous insulin after tolerating oral nutrition well, and at a time of a major meal (breakfast or dinner).

B. Subcutaneous insulin may also be started directly in new onset DM, if the patient is not in ketoacidosis.

C. Guidelines for initial doses as follows:

1. Total dose for day = 1.0 unit/kg/day
2. AM: 2/3 of total dose with 1/3 as Humalog and 2/3 as Lente (if child is <6yo, use NPH instead of Lente)
3. PM: 1/3 of total dose with 1/2 as Humalog and 1/2 as Lente (if child is <6yo, use NPH instead of Lente)

The insulin drip should be discontinued 30-60 min after the first dose of subQ insulin

4. Adjust AM and PM doses daily based on fingerstick glucose levels until glucose levels come into the normal range (70-120mg/dl). This may require as much as 1.5 u/kg/day (or more!) in the hospital

IX. Summary

The mortality rate of DKA in children, despite all that we know, continues to be 3-5%. One must never be lulled into a "cookbook" approach to DKA. This reference serves as a *guideline*, not a protocol, for therapy. It does not replace an understanding of the pathophysiology underlying DKA, vigilant surveillance, and active modification of the treatment to prevailing circumstances.