Diabetic Ketoacidosis (DKA): Treatment Guidelines

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Summary: Diabetic ketoacidosis (DKA), resulting from severe insulin deficiency, accounts for most hospitalization and is the most common cause of death, mostly due to cerebral edema, in pediatric diabetes. This article provides guidelines on management to restore perfusion, stop ongoing ketogenesis, correct electrolyte losses, and avoid hypokalemia and hypoglycemia and the circumstances that may contribute, in some instances, to cerebral edema (overhydration, rapid osmolar shifts, hypoxia). These guidelines emphasize the importance of monitoring glycemia, electrolytes, hydration, vital signs, and neurologic status in a setting where response can be rapid if necessary (e.g., mannitol for cerebral edema). Most important is the prevention of DKA in established patients by close supervision of those most likely to omit insulin, or during illness, and a high index of suspicion for diabetes to prevent deterioration to DKA in new patients, particularly those under age 5, who are at greatest risk of complications.

Introduction

Diabetic ketoacidosis (DKA) is the most common cause of hospitalization of children with diabetes and of death in the pediatric years in this group. Most deaths can be attributed to intracerebral crises.[1] From 20 to 40% of newly diagnosed patients are admitted in DKA, depending on the adequacy and availability of medical services to diagnose the diabetes early. Recurrent DKA in established patients has been reduced in frequency by the intervention of multidiciplinary teams.[2,3] Unfortunately, there is no evidence of a decrease in case fatality below the 1-2% achieved by the early 1970s, despite improvements in fluid and insulin therapy and more careful monitoring.[1,3] Thus, a major goal of diabetes management is to prevent DKA by a high index of suspicion with early symptoms of diabetes and close supervision of established patients.

This article provides guidelines to serve as a checklist and reminder, particularly for those who do not regularly treat DKA or hyperosmolar coma in diabetes. Guidelines cannot be written for all circumstances and for rigid adherence. It should be obvious that a diagnosis does not carry with it the assumption that either the patient or the treatment regimen will follow the book. This article is a supplement to, not a substitute for, clinical judgment.[4]

Cause

DKA is always caused by insulin deficiency, either relative or absolute. Many previously undiagnosed patients have been seen in physicians' offices or emergency rooms where an adequate history and laboratory study could have made the diagnosis before they became critically ill. A high index of suspicion is particularly important for infants and young children. An interesting phenomenon is the occasional marked delay in diagnosis seen in medical families and in

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the siblings or offspring of people with diabetes, reflecting denial. A simple urine test may turn out to be lifesaving by preventing the initial episode of ketoacidosis, particularly in the high-risk infant and preschool child.[1]

In the established patient, DKA results from:

- Failing to take insulin, the most common cause of recurrent DKA, particularly in adolescents.[5]

- Acute stress, which can be trauma, febrile illness, or psychological turmoil, with elevated counterregulatory hormones (glucagon, epinephrine, cortisol, growth hormone).

- Poor sick-day management, typically not giving insulin because the child is not eating or failing to increase insulin for the illness, as dictated by blood glucose monitoring. Home testing of urine for ketones with test strips may be misleading and result in delayed institution of sick-day management; the strips can deteriorate and give false-negative readings. Nitroprusside tablets are less convenient but very stable and reliable (6).

Definition

The combination of hyperglycemia (greater than 12 mmol/L), hyperketonemia (large serum ketones-acetone or betahydroxybutyrate) or large ketonuria, with acidosis (venous pH <7.3 or serum bicarbonate <15 mmol/L). Occasionally, DKA can occur with normoglycemia when there is vomiting, reduced intake of carbohydrate, and continued insulin therapy.[7] There are also pediatric instances of coma in which ketosis is mild but the blood glucose level very high (often referred to as hyperosmolar nonketotic coma); this occurs typically in very young patients, in those with brain disorders that may affect thirst responses, and in older adolescents with new-onset noninsulin-dependent diabetes. These treatment guidelines also apply to these variants.

Presentation

- *Hyperglycemia*: Insulin deficiency results in decreased glucose uptake with tissue starvation resulting in proteolysis and lipolysis providing amino acids and glycerol for gluconeogenesis, enhanced by counterregulatory hormone response to both the precipitating and tissue starvation stress; in the liver, insulin deficiency results in glycogenolysis and enhanced gluconeogenesis, also stimulated by counterregulatory hormones.

- *Dehydration and thirst:* Results from osmotic diuresis due to hyperglycemia and hyperketonemia, hyperventilation, and vomiting as part of the primary precipitating illness or resulting from the ketosis; since dehydration is usually hyperosmolar and mostly intracellular, dehydration may be underestimated by clinical examination.

- *Acidosis*: Due to ketonemia from overproduction of ketones, which cannot be metabolized in the absence of insulin, and lactic acidosis from tissue hypoperfusion.

- *Rapid deep respiration (Kussmaul):* Compensatory response to the metabolic acidosis, contributing to dehydration.

- *Coma:* Results from hyperosmolality, not acidosis; calculated osmolality greater than 320 mosm/L is associated with coma (8).

- *Hyperosmolality:* Largely due to hyperglycemia; calculated as

$$\text{Na (mmol/L)} \times 2 + \frac{\text{glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}$$

or

$$\text{Na (mmol/L)} \times 2 + \text{glucose (mmol/L)} + \text{urea (mmol/L)}$$

- *Hyperlipidemia:* Due to counter-regulatory-hormone-stimulated lipolysis and hypoinsulinemia.

- *Electrolyte disturbances:* Spuriously low Na level due to osmolar dilution by glucose and sodium-free lipid fraction. Corrected Na (i.e., for normal glucose level) can be estimated as measured

$$\text{Na} + \frac{(\text{glucose in mmol/L} - 5.6)}{2}$$

Na deficit is estimated at 10 mmol/kg body weight. Potassium may be spuriously normal because of acidosis-related exudation from tissues and obligatory urinary losses; estimate total K deficit at 5 mmol/kg. Potassium deficits in newly diagnosed patients may be greater than in established patients because of the longer duration of polyuria before admission.

Other Findings

- BUN: elevated as a result of dehydration.

- Creatinine: may be falsely elevated due to interference in the autoanalyzer methodology from ketones.

- Serum ketones: dilutions for nitroprusside testing of no value; betahydroxybutyrate will be most abundant and is not measured by nitroprusside, but betahydroxybutyrate assay is available in many laboratories.

- Elevated WBC with shift to the left is a stress response that is not helpful for diagnosing intercurrent infection.

- Elevated serum amylase level is salivary, not pancreatic; acute pancreatitis may occasionally be seen with DKA, in which case serum lipase level will also be increased.

- Abdominal pain and tenderness, with ileus, are usually nonspecific and improve with improvement of the metabolic state (if not, these need to be evaluated as with any other acute abdominal problem).

- Increased blood pressure and heart rate are due to constricted circulatory volume and stress state.

- Retrosternal or neck pain with dysphonia, dyspnea, or subcutaneous emphysema can occur from pneumomediastinum due to alveolar rupture from hyperventilation or retching. Typically, however, pneumomediastinum is asymptomatic (9).

Treatment

Basic rules in dealing with DKA are:

1. Admit patients only to a unit in which neurologic status and vital signs can be monitored frequently and blood glucose level measured hourly.

2. Personally evaluate the patient early on admission and frequently thereafter.

3. Keep good records, including rationalization for decisions, and a flow sheet.

4. Develop a relationship with a pediatric diabetes specialist you trust and call him or her with any questions, including whether the patient needs to be transferred to a specialized unit.

The patient who does not have persistent vomiting, with a pH >7.25, can be treated and observed in the emergency room over a few hours without hospital admission.

The goals of treatment are:

1. Restore perfusion, which will increase glucose use in the periphery and reverse the progressive acidosis.

2. Stop ketogenesis by giving insulin, which will reverse proteolysis and lipolysis, and stimulate glucose uptake and processing, normalizing blood glucose concentration.

3. Correct electrolyte losses.

4. Avoid the complications of treatment insofar as possible, including intracerebral complications, hypoglycemia, and hypokalemia.

Fluid Therapy

- Can generally assume 10% dehydration (100 mL/kg), up to 15% in infants.

- Provide 20 mL/kg 0.9% NaCl in first one to two hours to restore peripheral perfusion.

- In the patient with shock or preshock give 5% albumin, 20-25 mL/kg, as initial hydration.

- Calculate maintenance in usual fashion (e.g., 1,000 mL for first 10 kg + 500 mL for next 10 kg + 20 mL/kg over 20 kg).

- Calculate remainder of replacement after the loading dose based on 10% dehydration, and maintenance for administration over the subsequent 22 to 23 hours.

- If osmolality (calculated or measured) is >320 mosm/L, correct in 36 hours and if >340 mosm/L, correct in 48 hours.

- After initial 0.9% NaCl bolus, continue rehydration/maintenance with 0.45% NaCl. Some prefer to continue with Ringer's lactate or acetate solution; however, hyperosmolar patients should be changed to 0.45% NaCl after the initial bolus of 0.9% NaCl. During rehydration the measured Na can increase to the level of the corrected Na as glycemia declines and then decline to normal levels if the corrected level was elevated.

- Provide K (20-40 mmol/L or up to 80 mmol/L as needed) as half KCL, half KPO4 (to replenish low phosphate levels and to decrease the risk of hyperchloremia) or as half KPO4 and half K acetate (which, like lactate, is converted to bicarbonate to help correct acidosis) after serum K reported as less than 6 mmol/L or urine flow is established.

- Bicarbonate is rarely indicated. There is no evidence that bicarbonate facilitates metabolic recovery. It should be

given when there is absence of hyperventilation; never give bicarbonate by push, for this can produce dangerous hypokalemia. Safe administration to avoid risk of hypokalemia is to give 1-2 mmol/kg body weight or 80 mmol/m2 body surface area over 2 hours.[10] Reduce NaCl concentration in the fluids to allow for added Na ion unless Na level in the serum is subnormal.

Insulin

- Insulin can be started immediately at the time of the initial fluid expansion or it can be held until the fluid expansion is completed for a more realistic starting glucose level.

- The most widely used system is 0.1 U/kg hourly as a continuous infusion, using a pump.

- It may be more convenient in some settings to administer 0.I U/kg IV and 0.1 U/kg IM with subsequent doses of 0.1 U/kg IM or SC hourly. In adults, there did not seem to be any difference whether insulin was administered intravenously, intramuscularly, or subcutaneously after the first couple of hours of treatment.[11]

- There is no evidence that low-dose insulin as currently used results in any less frequency of hypoglycemia, hypokalemia, or cerebral edema than the earlier treatment with much higher doses. The principal advantages of low-dose therapy given as continuous IV or hourly injections are that there is frequent contact with the patient and hourly blood glucose determinations are done.

- During initial fluid expansion, a high blood glucose level may drop 10-15 mM/L, even without insulin infusion.

- High blood glucose levels should drop 3-8 mmol/L/hr (but not > 12 mmol/L/hr), and if they do not, the dose should be increased. This is rarely necessary.

- · When the blood glucose level falls to 15 mmol/L or >12 mmol/L/hr, 5-10% dextrose should be added to the intravenous fluids.

- If the blood glucose level falls below 8 mmol/L with 10% dextrose solution running, the insulin dose should be reduced to 0.05 U/kg/hr.

- Do not stop insulin or reduce it below 0.05 U/kg/hr, for a continuous supply of insulin is needed to prevent ketosis and permit continued anabolism.

Monitoring

- A flow sheet is essential to record the measures noted in Table 1 at hourly intervals.

- The nursing personnel must have clear guidelines on when to call the attending physician, such as findings listed in Table 2.

- ECG monitoring should be done and hourly potassium measurements made if the initial potassium level is <3 or >6 mmol/L.

- Mannitol in quantities sufficient to give 1-2 g/kg body weight should be kept at the bedside for the first 36 hours

Table 1

MONITORING TREATMENT OF DKA

Clinical	Interval
Vital signs	20-30 minutes
Coma score (e.g., Glasgow)	20-30 minutes
Laboratory	
Glucose	Hourly bedside; in the laboratory with electrolyte assay, or 1-2 hourly if outside bedside monitor range
Potassium	Hourly if abnormal (<3 or >6 mM/L)
Sodium, potassium, CO_2 or HCO_3, venous pH, osmolality	Admission, 2, 6,10, 24 hrs. (or 2-4 hourly until osmolality normal)
BUN	Admission, 12, 24 hrs.
Betahydroxybutyrate (if available)	Admission, 6,12, 24 hrs.
Ketonuria	Admission, 4-6 hourly
Calcium, phosphorus (optional)	Admission, 12, 24 hrs.
Fluids	
Type and rate Intake (include oral and reduce IV intake accordingly) Output	
Insulin	

Table 2

SIGNS AND SYMPTOMS OF INTRACEREBRAL CRISIS DURING TREATMENT OF DKA

- Decreasing sensorium
- Sudden and severe headache
- Incontinence
- Vomiting
- Combativeness; disorientation; agitation
- Change in vital signs (hypothermia, hypotension or hypertension, tachycardia or bradycardia or arrhythmia, gasping respirations, or periods of apnea)
- Ophthalmoplegia
- Pupillary changes (asymmetry, sluggish to fixed)
- Papilledema
- Posturing; seizure

(see below under complications).

- Resist the convenience of catheterization for monitoring output. The occasional older patient may have bladder atony while ketoacidotic and require

initial catheterization, but it is rare to need an indwelling catheter.

- Failure of measured serum Na level to rise with falling blood glucose concentration or an actual decrease in serum Na may indicate impending cerebral edema. Hydration should continue slowly and with 0.9% NaCl solution.

Complications

Hypoglycemia

- Infrequent with hourly blood glucose monitoring.

- With the presence of an intravenous line, severe hypoglycemia is best treated with intravenous glucose. Glucagon can produce ketosis and nausea with vomiting, particularly in children.

Persistent Acidosis

- Defined as persistence of a bicarbonate value less than 10 mmol/L after eight to ten hours of treatment.

- Usual cause is inadequate insulin effect, indicated by persistent hyperglycemia. Check insulin dilution and rate of administration, consider inadequate absorption if insulin is being given by subcutaneous or IM injection or resistance due to unusually high counterregulatory hormones, as with concomitant febrile illness.

- May need to switch to IV administration if patient is not receiving insulin IV. If receiving IV insulin, solution should be changed every six hours.

- Extremely rare causes are lactic acidosis due to an episode of hypotension or apnea or inadequate renal competency in the handling of hydrogen ion as a result of an episode of renal hypoperfusion.

Hypokalemia

- Extracellular K concentrations fall as a result of treatment, with potassium reentering cells.

- If initial serum K <3 mmol/L, K must be put into the initial expansion fluids without waiting for demonstration of renal function and insulin should be delayed or stopped until after the initial bolus fluids are infused.

Intracerebral Complications

Intracerebral complications comprise the most serious and frequent complications of DKA and can occur despite adherence to the guidelines above. There is no evidence for reduction in the frequency of intracerebral complications with the advent of low-dose insulin use by continuous infusion or the shift to more isotonic initial fluids. Although the classic picture is one of metabolic and clinical improvement with sudden deterioration, there may be up to several hours of decreasing sensorium and change in vital signs, as noted in Table 2, and some children will be admitted in coma and not recover. An occasional patient will develop intracerebral complications even before treatment, raising the suspicion of cerebral thrombosis.

In more than half of patients who develop intracerebral complications, there is a sufficient warning period to permit administration of mannitol to reduce edema and, if indicated by respiratory distress, intubation/hyperventilation to reduce intracerebral blood flow. When this is accomplished

before respiratory arrest, there is a greater than 50% chance of survival in the normal state or with disability that does not preclude independence.[1] Computerized tomographic (CT) scans should not be depended upon to determine the need for intervention; this decision should be made on clinical grounds. Initial CT scans, even after respiratory arrest, often appear normal or show only localized basilar edema. The dose of mannitol is I g/kg body weight intravenously, over 15 minutes, repeated as necessary.[l3]

Particularly susceptible to intracerebral complications are previously undiagnosed patients and children under 5 years of age.

Mucor Infection

Opportunistic infection with mucormycosis is a rare and frequently fatal complication of recurrent ketoacidosis, involving the respiratory tract and sinuses with erosion into the brain.[l2]

Transition

- IV fluids can be stopped l-2 hours after substantial consumption of oral fluids without vomiting.

- Subcutaneous insulin injection can be started when the patient no longer needs IV fluids.

- Wait until the presupper or prebreakfast time to restart intermediate-acting insulin. Until then, give regular insulin 0.25 U/kg subcutaneously (sc) every ~6 hours and do not stop the insulin infusion until 60-120 minutes after first sc dose.

  -Give the established patient the usual morning or afternoon insulin dose unless this was inappropriate. The infusion can be stopped an hour later if still running.

  -The new patient can be given 0.5 U/kg intermediate-acting insulin and stop infusion an hour later. If blood glucose level is >220 mg/dL, can combine this with 0.1 U/kg of regular. Various other starting regimens are used.

- Do not keep patient in the hospital simply to adjust insulin dosage, for food, activity, and psychosocial environment are not normal.

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