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Management of Diabetic Ketoacidosis in Children and Adolescents

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Contents

Abstract 209
1. Diagnosis of Diabetic Ketoacidosis (DKA) 210
2. Complications 210
   2.1 Cerebral Edema 210
   2.2 Other Complications 211
3. Management of DKA 211
   3.1 Fluid Therapy 211
   3.2 Electrolyte Therapy 212
   3.3 Insulin Therapy 212
   3.4 Bicarbonate Therapy 213
   3.5 Management of Cerebral Edema 213
      3.5.1 Mannitol 213
      3.5.2 Hypertonic Saline 213
4. Future Possibilities for Medical Management 213
   4.1 Subcutaneous Insulin: Treatment of DKA 213
   4.2 Bumetanide 214
5. Conclusion 214

Abstract

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus. While it can occur in all types of diabetes mellitus, it is seen most often in patients with type 1 diabetes, either at presentation or as a result of non-compliance with medical therapy. DKA is characterized by hyperglycemia, acidosis, dehydration, and electrolyte abnormalities, which result from a deficiency of insulin and an excess of counter-regulatory hormones.

Therapy is aimed at repleting fluids, and correcting acidosis and electrolyte disturbances by administration of intravenous fluid and intravenous insulin. Rapid correction should be avoided as it may result in untoward effects, including cerebral edema. Frequent monitoring of neurologic status and metabolic parameters aids in avoidance or early detection of complications. While much is still not understood about the most serious complication, cerebral edema, recent studies suggest that its development may be tied to a loss of cerebral autoregulation and a vasogenic mechanism of edema formation. Treatment of cerebral edema includes fluid restriction and administration of mannitol. Once DKA has resolved, subcutaneous insulin is initiated with careful consideration of its pharmacokinetics to avoid a period of insulin deficiency and metabolic decompensation.

Diabetic ketoacidosis (DKA) is the result of a relative or absolute deficiency of insulin, and increased levels of the counter-regulatory hormones glucagon, cortisol, and catecholamines. Glucagon seems to be particularly important in the pathogenesis of ketoacidosis. Individuals with glucagon and insulin deficiency (i.e. patients post pancreatectomy or with cystic fibrosis-related

diabetes mellitus) rarely develop DKA, and DKA takes longer to develop when insulin is withdrawn.[1,2]

Blood glucose levels rise because there is increased production of new glucose (gluconeogenesis) and failure to store glucose that is absorbed through the gut. In addition, glycogenolysis, as a result of both insulin deficiency and elevations of counter-regulatory hormones, contributes to hyperglycemia. With insulin deficiency, there are minimal glycogen stores in the liver or other tissues. Hyperglycemia induces an osmotic diuresis and obligate loss of salt as well as water. Loss of sodium and potassium in adults may amount to up to 20% of total body stores;[3] there are sparse data quantitating these losses in children. Without insulin, there is a breakdown of fat with the release of free fatty acids. Free fatty acids are converted to ketones through glucagon-dependent hepatic pathways. The released ketoacids are excreted by the kidney as long as there is sufficient hydrogen exchange. With decreasing fluid volume as a result of osmotic diuresis and loss of salt necessary for hydrogen exchange, blood levels of ketoacids rise and acidosis develops. Pulmonary compensation for the metabolic acidosis is not sufficient, leading to increasingly severe acidosis.

DKA is the presenting manifestation of type 1 diabetes mellitus (T1DM) in about 25% of children and of type 2 diabetes mellitus in 5–25%.[4] DKA in children with established T1DM can be the result of non-compliance with insulin therapy, insulin pump failure, or intercurrent illness. DKA in the setting of an intercurrent illness can often be avoided with close home monitoring of blood glucose and urine or blood ketone levels and administration of supplemental insulin as needed. In one study, home-meter monitoring of blood 3-hydroxybutyrate levels significantly decreased hospital visits compared with urine ketone monitoring.[5]

This article reviews the management of diabetic ketoacidosis in children and adolescents. Reference to adult data is made where data in children are limited.

1. Diagnosis of Diabetic Ketoacidosis (DKA)

The diagnosis of DKA can be missed as it can resemble other, more common, pediatric illnesses such as severe dehydration due to gastroenteritis. DKA should be considered in any child or young adult with mental status changes. The presence of DKA is supported by a history of polyuria, polydipsia, weight loss, rapid breathing with fruity-smelling breath, and vomiting.

The diagnosis of DKA is based on biochemical evidence of hyperglycemia (serum glucose levels >200–250 mg/dL), acidosis and ketosis (venous pH <7.25–7.30 and/or serum bicarbonate levels ≤15 mEq/L), with serum concentrations of ketones (β-hydroxybutyrate plus acetoacetate) >31 mg/dL and/or ketonuria >80 mg/dL. DKA may be characterized as mild (venous pH 7.2–7.3, serum bicarbonate level 10–15 mEq/L), moderate (venous pH 7.1–7.2, serum bicarbonate level 5–10 mEq/L), or severe (venous pH <7.1, serum bicarbonate level <5 mEq/L).

2. Complications

Consideration of the complications of DKA is important in the management of DKA to ensure that they are neither missed nor exacerbated.

2.1 Cerebral Edema

Cerebral edema is the most serious complication of DKA in children. It is most common in young children newly diagnosed with T1DM, and is rare in individuals >20 years of age.[6] Most children with DKA will exhibit some degree of neurologic dysfunction. A high index of suspicion for clinically symptomatic cerebral edema is warranted because, although uncommon (occurring in only 0.5–1% of children with DKA), it is the major cause of morbidity and mortality.

Diagnosis should be made on clinical grounds as computed tomography (CT) scans can be negative early in the course of cerebral edema in up to 40% of cases.[7] Early signs include headache, confusion, and lethargy. Cushing's triad is a late sign; however, a slowed heart rate and wide pulse pressure should be investigated immediately as a sign of cerebral edema. A retrospective study of 24 children with cerebral edema showed a relatively quick decline in mental status in these patients, occurring at an average of 9 hours after initiation of treatment for DKA with a bimodal peak at 3 and 14 hours. Neurologic deterioration was seen as late as 30 hours after the initiation of therapy. The mean time between when a patient exhibited early signs of neurologic dysfunction and collapse was 3 hours. Thus, an early diagnosis is critical in being able to intervene before the progression to irreversible damage, necessitating hourly assessments of neurologic status. These authors prospectively made a diagnosis of cerebral edema in an additional 17 patients with DKA, with a sensitivity of 92% and specificity of 96% when the patients met the following: (i) one diagnostic criterion (abnormal motor or verbal response to pain, decorticate or decerebrate posture, cranial nerve palsy, abnormal neurogenic respiratory pattern); (ii) two major criteria (altered mentation, sustained heart rate deceleration, incontinence); or (iii) one major and two minor criteria (vomiting, headache, lethargy, diastolic blood pressure >90 mmHg, age <5 years).[7]

The pathogenesis of cerebral edema is not well understood, making prevention of this complication difficult. It has been postulated that certain elements of treatment (high doses of insulin, rapid administration of hypotonic fluid, administration of

intravenous bicarbonate) may cause cerebral edema, but cerebral edema is evident in many patients before treatment is initiated.[8] A compilation of risk factors associated with cerebral edema in children, including prolonged illness, greater initial dehydration and hypocapnia, and persistent hyponatremia,[8] does not clearly delineate a causal mechanism. Recent studies using radiologic techniques to study the brain in children during treatment of DKA suggest that the development of cerebral edema may be linked to a loss of cerebral autoregulation and a vasogenic mechanism of edema formation.[9-11] These findings suggest the need for close monitoring of blood pressure and fluid status in the treatment of DKA in order to prevent the development of cerebral edema.

2.2 Other Complications

Other complications of DKA are rare. Although cerebral edema accounts for 90% of neurologic complications, other possible etiologies should be considered in a patient with an encephalopathy without cerebral edema (i.e. no evidence on CT scan and no response to osmotherapy). These include subarachnoid hemorrhage, basilar artery stenosis, dural sinus thrombosis, cerebral venous thrombosis, meningo-encephalitis, infarction, and thiamine deficiency.[12]

Abdominal pain and vomiting are common complaints among patients with DKA. While elevations of amylase and lipase levels (up to 3 times the upper limit of normal) are common, pancreatitis is rare in children, suggesting that pancreatic enzymes should only be checked in patients with persistent abdominal pain after correction of acidosis.[13] Diabetes is associated with a prothrombotic state in adults and children.[14] There have been reports of deep vein thrombosis in children with DKA and femoral intravenous lines.[15,16] Cases of rhabdomyolysis,[17] pulmonary edema, and rhinocerebral mucormycosis have been reported in children with DKA.

3. Management of DKA

Figure 1 provides an overview of the management of DKA. Because common management practices may be linked to the development of cerebral edema, the use of these interventions must be employed judiciously. There are often competing factors in an individual patient. For example, the administration of bicarbonate may be important for quickly correcting peripheral acidosis in the setting of cardiac impairment but may paradoxically worsen intracranial acidosis and lead to CNS hypoxia. High initial fluid volumes may increase intracranial pressure in the setting of impaired cerebral autoregulation, but too little fluid may result in shock and cerebral hypoperfusion. In such circumstances, clinical judgment must be employed and, thus, strict guidelines cannot be created.

3.1 Fluid Therapy

Assessment of the fluid deficit in children with DKA is difficult. In a prospective study of 37 children, no clinical sign reliably

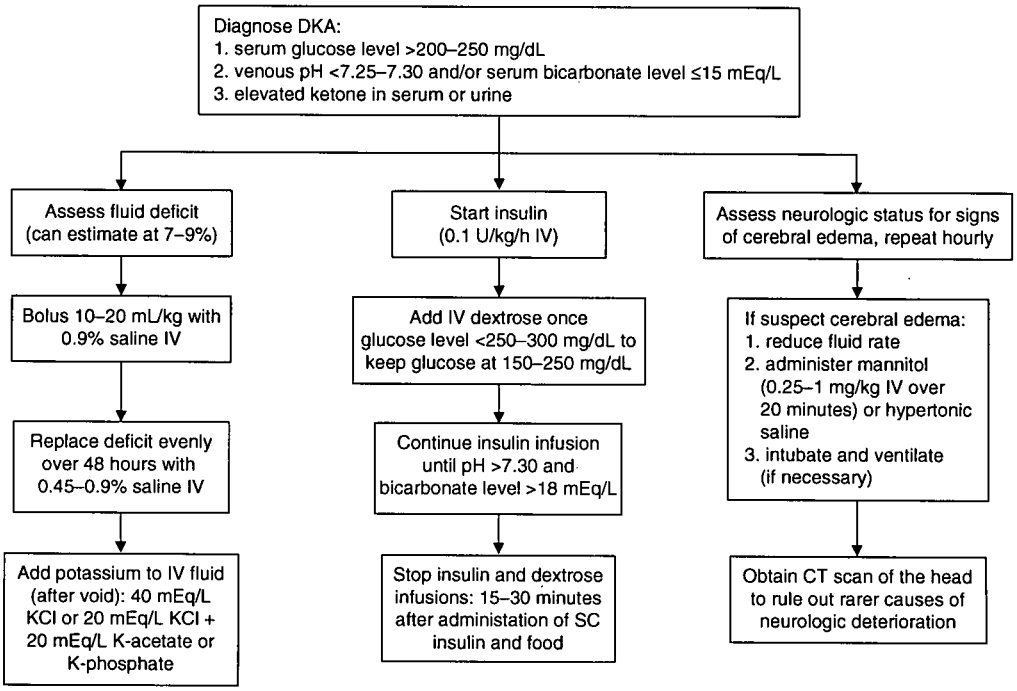

Fig. 1. Management of diabetic ketoacidosis (DKA). **Cl** = chloride; **CT** = computed tomography; **K** = potassium; **IV** = intravenous; **SC** = subcutaneous.

correlated with the degree of dehydration as measured by comparing admission and discharge bodyweights. The average fluid deficit was 8.7%. It was suggested that an initial estimate of 7–9% dehydration for all patients was appropriate.[18] The International Society of Pediatric and Adolescent Diabetes (ISPAD) has recently recommended using an estimate of 5–7% dehydration in patients with moderate DKA and 7–10% in patients with severe DKA.[19]

Fluid therapy should be administered as an initial 0.9% saline bolus of 10–20 mL/kg, followed by deficit replacement with 0.45–0.9% saline administered evenly over the next 48 hours. Again, given the difficulties in assessing the fluid deficit, replacement at a rate of 1.5–2 times the daily maintenance rate has been suggested as a rough guideline.[20] Generally, urinary losses are not replaced. The 2004 position statement by the American Diabetes Association recommends that if the corrected serum sodium[1] is high or normal, 0.45% saline should be used and if it is low 0.9% saline should be administered.[21] Rapid fluid resuscitation and a rapid decrease in osmolality have been associated with the development of cerebral edema (see also section 3 introduction).[22,23] We suggest frequent monitoring of serum sodium levels with the goal of correcting the sodium at a rate no greater than 1–2 mEq/L per hour.

3.2 Electrolyte Therapy

Although the serum potassium level at presentation in patients with DKA is often normal or elevated, the total body potassium level is low and should be replaced. Initial increased serum potassium levels reflect an extracellular shift of potassium due in part to the concurrent acidosis and extracellular hypertonicity secondary to hyperglycemia. Total body depletion results mainly from urinary loss of this extracellular potassium due to osmotic diuresis. Administration of potassium at 40 mEq/L is generally sufficient. However, replacement should be performed carefully with avoidance of hyperkalemia (serum potassium level >5.5 mEq/L) and hypokalemia (serum potassium level <3 mEq/L), both of which may have deleterious effects on cardiac function. If the initial potassium level is greater than 5.5 mEq/L, replacement should be held to avoid transient hyperkalemia. Frequent monitoring of serum potassium levels is necessary, and ECG monitoring may also be helpful. Potassium replacement can be given as potassium chloride alone or in combination with potassium phosphate or potassium acetate. The latter two options may be better in certain situations to avoid hyperchloremic metabolic acidosis resulting from a chloride load, especially if 0.9% normal saline is being used as fluid therapy. The total phosphate level is also depleted, but replacement is not necessary, unless depletion is severe (serum phosphate level <1 mg/dL); low serum phosphate levels are well tolerated and replacement does not improve outcome.[24]

3.3 Insulin Therapy

Short-acting (regular insulin) and ultrashort-acting (lispro, aspart, glulisine) insulin preparations differ in their absorption when administered via the subcutaneous route. Regular insulin aggregates into subcutaneous hexamers that are absorbed into the circulation only after dissociation, resulting in a delayed action (onset of action 30–60 minutes, peak 2–4 hours, duration 4–6 hours). Insulins aspart, lispro, and glulisine do not self-associate and thus have an onset of action that is quicker (onset 5–15 minutes, peak 0.5–2 hours, duration 3–4 hours). However when given intravenously, all four insulins have equivalent pharmacokinetics and can be used interchangeably in the treatment of DKA.[25-28] For this reason, regular insulin is the logical choice for intravenous therapy. The longer-acting insulins (neutral protamine Hagedorn [NPH], glargine, and detemir) have reduced solubility at physiologic pH and if given intravenously would have unpredictable pharmacokinetics and actions, and thus should not be used by the intravenous route.

Insulin (0.1 U/kg/h administered intravenously) should be started after establishing that the serum potassium level is not dangerously low. An initial insulin bolus is not recommended, as it does not lead to a more rapid correction of acidosis than a steady intravenous infusion. Additionally, it may be harmful as it may lead to a more rapid drop in serum glucose levels and osmolality and, thus, potentially cause an increased risk of cerebral edema (see also section 2.1).[23] A recent case-control study in the UK has linked early insulin therapy to the development of cerebral edema and the ISPAD has recommended that insulin therapy be delayed for 1–2 hours from the start of fluid management.[19,22] Because insulin adsorbs to the plastic intravenous tubing, a volume (about 50 mL) of the infusion should be run through the tubing before initiating therapy.

Insulin should be administered intravenously until the ketosis and acidosis improves (venous pH >7.30 and serum bicarbonate level >18 mEq/L). Urine ketones (acetoacetate) will take longer to disappear than serum measures of acidosis and do not need to be cleared before starting subcutaneous insulin. Correction of acidosis leads to improvement in the redox ratio of the body so that betahydroxybutyrate, which may initially be in excess compared with acetoacetate (ratios as high as 1 : 8 have been reported), is converted to acetoacetate, the measured urine ketone. With adequate hydration and insulin therapy, acetoacetate and betahydrox-

1 Corrected serum sodium = measured sodium + (1.6 × glucose [mg/dL] − 100)/100.

ybutyrate are metabolized and acidosis is corrected by the generation of bases; however, during the correction phase, appearance of acetoacetate generated from betahydroxybutyrate may maintain apparent ketonuria.[29-31] Acidosis often does not correct until several hours after the serum glucose level is in the normal range and, thus, dextrose (5% increasing to 12.5% as necessary) should be added to the intravenous solutions when the serum glucose level is <250–300 mg/dL, with the goal of keeping the serum glucose level in the range of 150–250 mg/dL. It is preferable to add glucose to the intravenous fluid rather than to decrease the insulin infusion, as insulin is necessary to suppress ketosis. When ketoacidosis has resolved, a short-acting subcutaneous insulin with a longer-acting preparation is given in combination with a snack or meal. Intravenous insulin should be continued to allow time for the subcutaneous insulin to act (30–60 minutes for regular insulin; 15 minutes for insulin aspart, insulin lispro, and insulin glulisine).

3.4 Bicarbonate Therapy

Bicarbonate therapy is generally not recommended. The acidosis associated with DKA will improve with fluid and insulin therapy. Studies have not shown that bicarbonate therapy improves outcomes in children with severe DKA.[32]

Bicarbonate therapy must be used judiciously as it may be linked to the development of cerebral edema (see also section 3 introduction). Bicarbonate administration may cause a paradoxical worsening of CNS acidosis. This is thought to be due to the fact that bicarbonate ions do not readily cross the blood brain barrier (BBB), but are actually reformed and actively secreted by cells of the BBB.[33] Bicarbonate and hydrogen ions are in chemical equilibrium with carbon dioxide and water. Carbon dioxide does cross the BBB and can recombine with water in the CNS and form carbonic acid. Additionally, peripheral correction of acidosis leads to a decreased respiratory rate and an increase in carbon dioxide (that can cross the BBB and cause worsening of cerebral acidosis).

There is conflicting evidence regarding the causative role of bicarbonate therapy in the development of cerebral edema. While the use of bicarbonate therapy has declined greatly in the past 10 years, the incidence of cerebral edema has remained the same.[34] Also, a recent case-control study in England did not find that bicarbonate therapy significantly contributed to the risk of cerebral edema.[22] In summary, it is not clear whether the use of bicarbonate is detrimental in itself or is a marker of other factors.[34]

Bicarbonate therapy is generally reserved for children with a risk of cardiac dysfunction due to profound acidosis (pH <6.9) or with severe hyperkalemia. If given, it should be dosed as 1–2 mEq/kg, mixed as one ampule of sodium bicarbonate in 1 liter of 0.45% saline, and administered intravenously over 1 hour.

3.5 Management of Cerebral Edema

Once the diagnosis of cerebral edema is made, there is a lack of clarity regarding the best treatment. The European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society (ESPE/LWPES) consensus statement recommends a reduction in the rate of fluid administered, the early administration of intravenous mannitol (0.25–1.0 g/kg over 20 minutes) or, alternatively, of 3% hypertonic saline (5–10 mL/kg over 30 minutes), either of which can be repeated after 2 hours, and, if necessary, intubation and ventilation.[35,36] Although high-dose dexamethasone has been used for the treatment of other types of cerebral edema, there is no evidence supporting the use of this agent in the management of cerebral edema associated with DKA.[37,38] Hyperventilation of intubated young patients with DKA has been shown to both improve and worsen outcomes.[39,40] Thus, intubation is warranted only when there is respiratory distress.

3.5.1 Mannitol

Although large prospective trials using mannitol in the treatment of cerebral edema are lacking, early administration has been associated with an improvement in cerebral edema in case reports. Mannitol is recommended as the first line of therapy after fluid restriction in recent consensus statements from the American Diabetes Association (ADA) and ESPE/LWPES.[20,35,36,41,42]

3.5.2 Hypertonic Saline

While mannitol is generally accepted as the mainstay of therapy for DKA-related cerebral edema, hypertonic saline has been used with success in other situations involving cerebral edema. Hypertonic saline offers the benefit of causing less diuresis than mannitol allowing for maintenance of intravascular volume. A retrospective study of 67 children with cerebral edema resulting from various etiologies who received therapy with either mannitol, hypertonic saline, or both showed that the group that received mannitol alone fared the worst in terms of duration of the comatose state and mortality.[43] Hypertonic saline has also been used successfully in case reports in children with cerebral edema in the setting of DKA.[44]

4. Future Possibilities for Medical Management

4.1 Subcutaneous Insulin: Treatment of DKA

When continuous intravenous insulin therapy was introduced for the management of DKA, direct comparison with regular

insulin injections given at 4–6 hourly intervals demonstrated that continuous intravenous insulin therapy was equivalent in outcome and easier to manage. Given the rapid onset of action of the newer insulin analogs (aspart and lispro), several recent studies have successfully substituted insulin delivered subcutaneously for intravenous insulin infusion in the treatment of DKA.

In a study of 60 children and adolescents with DKA randomized to receive either 0.1 U/kg/h of intravenous regular insulin or 0.15 U/kg of subcutaneous insulin lispro every 2 hours, Della Manna et al.[45] found that the correction of glucose levels was identical. While correction of acidosis was faster in patients receiving intravenous insulin, correction in both groups occurred less than 12 hours after normalization of glucose levels.

Several small, prospective, randomized clinical trials in adults with DKA have shown no differences in the rate of resolution of hyperglycemia and acidosis between subcutaneous and intravenous insulin regimens.[46-48] Insulin delivery via subcutaneous insulin pumps, although reported only anecdotally, theoretically would have a similar effect. These therapeutic options offer the largely economic advantage of enabling management of DKA outside of the intensive care unit. However, the risk of cerebral edema or other complications remains a concern and resources for rapid intervention must be available.

4.2 Bumetanide

While the mechanism of cerebral edema in DKA is still largely unknown, stimulation of the sodium-potassium-chloride cotransporter on the cells of the BBB has been found to be important in cerebral edema associated with ischemic stroke. A recent study by Lam et al.,[49] using the streptozotocin rat model of diabetes, suggests that this cotransporter is also important in the development of cerebral edema in DKA. In this study, the cotransporter was found to be stimulated by ketoacids. Treatment of rats with DKA and evidence of cerebral edema with bumetanide, an inhibitor of the sodium-potassium-chloride cotransporter, reversed the experimental cerebral edema.

5. Conclusion

DKA is the major cause of severe morbidity and mortality in children with T1DM. Careful fluid, electrolyte, and insulin management as well as close monitoring may prevent the most common and serious complication – cerebral edema. If cerebral edema is suspected, prompt intervention is necessary to prevent irreversible neurologic damage. Newer techniques for the prevention of cerebral edema are currently theoretical but could potentially reduce this complication in the future.

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