Diabetic ketoacidosis in children: review of pathophysiology and treatment with the use of the “two bags system”

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Abstract

**Objectives:** to review diabetic ketoacidosis, including the “two bags system”, a method of administering liquids in order to provide a smoother correction of the hyperglycemic and ketotic states.

**Methods:** review of recent publications (last 7 years) from a Medline search and chapters published in pediatric textbooks that discuss the etiology, therapy, and complications of diabetic ketoacidosis. The management approach incorporates the findings of these publications as well as the clinical experience at the Children’s Hospital of Philadelphia and Duke University Medical Center.

**Results:** the pathology of the type 1 Diabetes Mellitus involves the progressive destruction of the β-cells of the pancreas, causing insulin deficiency. Insulin is essential in the metabolism of carbohydrates, protein and fat. Insulin deficiency may lead to diabetic ketoacidosis which has three components: 1) hyperglycemia, which causes glycosuria and consequently dehydration; 2) lipolysis which, causes ketonemia/ketonuria; and 3) acidosis, that is caused by the dehydration and the high serum levels of ketones. Diabetic ketoacidosis is a serious condition and, if not treated appropriately, can cause coma and death. In children cerebral edema is the major complication of the therapy for diabetic ketoacidosis. Careful replacement of insulin, fluids, glucose and electrolytes is essential.

**Conclusions:** the literature presents different ways to manage DKA in pediatrics, without a consensus on the cause of the most important complication (cerebral edema), and consequently without a consensus on the best approach. The use of the two saline bags in patients in DKA allows fast adjustments in the dextrose concentration of the infusion fluids, simplifying and reducing the costs of the treatment of diabetic ketoacidosis.


**Introduction**

Diabetes mellitus type 1 (DM1) is an autoimmune disease that affects thousands of children around the world. The incidence of DM1 is of 1 case per 2,500 children aged less than 5 years and of 1 case per 300 people until 18 years of age. DM1 also presents an important regional and racial variation, for an incidence of 30 to 40 cases per 100,000 children in Finland and of less than 1 case per 100,000 in children from the Eastern hemisphere. In this sense, studies carried out in São Paulo indicated an incidence of 3.6 per 100,000.1

The pathology of DM1 involves the progressive destruction of pancreatic beta cells, resulting in insulin deficiency and subsequent alterations. The clinical status of hyperglycemia associated with an increase in the production of ketones is known as diabetic ketoacidosis (DKA).
Hyperglycemia may lead to glycosuria and dehydration, whereas the excess production of ketones may intensify the metabolic acidosis resulting from dehydration. DKA, in turn, if not treated properly may lead to coma and death. In children, cerebral edema represents the most dire complication of the treatment for DKA.

In this review we will discuss various aspects of DKA, including a different approach to administering fluids that is aimed at a more subtle correction of hyperglycemia and ketosis. The objective of this paper is not to present a specific “recipe” for the treatment of patients with DKA. We understand that there is a great diversity in the presentation of DKA and in responses to therapy for DKA and, also, that different centers and specialties have reported different ways to manage DKA. Our objective is, rather, to present a general review regarding DKA and, at the same time, give emphasis to the two bag system, which makes the treatment for DKA simpler, faster, and more cost-effective.

**Definition**

The literature does not present a consensus regarding the definition of DKA (5). DKA occurs when the metabolic acidosis presents an arterial pH lower than 7.3 or serum bicarbonate lower than 15 mEq/dl, and, moreover, in the presence of a worsening increase in the concentration of ketones in blood and, consequently, in urine. In DKA, the glycemia is usually high (above 240 mg/dl) but it may also present normal.

**Incidence**

Twenty-five percent of children newly diagnosed with diabetes mellitus present ketoacidosis, out of which 15% present a serious clinical status. In patients with established diabetes, including adults and children, DKA occurs in 0.2 to 8.0% of patients per year. Mortality due to episodes DKA is higher in adults due to the presence of abnormalities in other organs of the body. A mortality rate of 2 to 5% is reported for adults and of 1 to 3% for children.

**Predisposing factors**

Diabetic ketoacidosis is progressive and, consequently, the longer and the more severe the period of insulinopenia, the more serious the clinical status of DKA.

In children who have not been diagnosed with diabetes mellitus, the interval of time between the onset of symptoms and medical intervention is the most important factor that will determine seriousness of patient clinical status. Since the process of destruction of pancreatic beta cells is slow, children normally present loss of weight, hyperphagia, polydipsia, and polyuria for a few weeks, and sometimes months. The ability of relatives to perceive these changes in the child and the ability of the pediatrician to establish a correct and fast diagnosis are fundamental.

In children with established diabetes mellitus, the inadequate use of insulin is the most common cause of DKA. The lack of insulin can either be real or relative. Real lack of insulin occurs when the child or the parents are not following medical recommendations by not administering daily routine doses of insulin. Relative lack of insulin occurs when the patient requires a higher dose of insulin and the dosage has not been corrected appropriately. In this sense, situations of infectious clinical status are associated with an increase in the resistance to insulin. In these situations, it is necessary to indicate a more intense monitoring of the glycemia and of the presence of ketones in urine. If the presence of ketones is not monitored during situations of infectious clinical status, a loss of appetite may disguise the onset of diabetic ketoacidosis since there will not be an increase in glycemia.

To teach the patient and relatives how to proceed when facing infections and alterations in the ingestion of carbohydrates is a fundamental part of the endocrinologist’s work in the follow-up of diabetes patients. In general, DKA usually follows a lack of insulin, since the variations in diet are not associated with the production of ketones, unless when associated with a reduction in the daily dosage of insulin.

**Pathophysiology**

The main causes for metabolic alterations in DKA are: 1) the loss of glucose transport, which depends on insulin, into peripheral tissues, such as muscle and fatty tissues; 2) increase in hepatic glyconeogenesis and glycogenolysis; 3) disinhibition of the break down of fat, proteins, and glycogen (Figure 1). Consequently, a status of insulin deficiency will lead to hyperglycemia, due to a reduction in the peripheral use of glucose and an increase in the hepatic production of glucose, and to acidosis, due to the production of ketones by the liver. In addition, hyperglycemia can cause glycosuria and, consequently, polyuria, thus worsening DKA. The loss of fluids results in loss of electrolytes and dehydration. In case of a serious dehydration, there will be a decrease in the peripheral circulation of blood and an increase in the production of lactic acid, thus contributing to worsen metabolic acidosis (Figure 2).

Other hormones are also involved in DKA (Figure 3). In this sense, the lack of insulin induces the release of glucagon by the pancreas; whereas the stress and the reduction of glucose available for the intracellular environment stimulates the release of growth hormone, cortisol, and catecholamines. These hormones lead to an increase in the resistance to insulin and a reduction in the use of glucose by peripheral
control of their diabetes have a weak metabolic balance; consequently, the stress that follows an infection may break this balance. Likewise, patients who have not been diagnosed with diabetes mellitus can also be able to maintain a relatively good clinical status despite a progressive loss in the ability to produce insulin. With an infection, however, there is an increase in the metabolic needs of patients and a temporary resistance to the effects of insulin and, consequently, the metabolic balance will suddenly be broken and DKA fully manifested.

History of abdominal pain, vomiting, and nausea can also occur with frequency and can be a consequence of an infectious process or of a metabolic imbalance, since a high concentration of ketones in serum can cause the referred symptoms.

**Physical examination**

At diagnosis, children with DKA present depressed, weak, and dehydrated. Kussmaul’s respiration, characteristic of DKA, can be observed in serious cases of acidosis. Cardiovascular shock can occur in cases of extreme dehydration.

Abdominal examination of patients should be carried attentively since the presentation of DKA can be similar to that of acute appendicitis.

A complete neurological examination is necessary in order to follow up the progress of the clinical status and to diagnose complications, such as cerebral edema, that may follow with therapy.

**Electrolytes**

Metabolic acidosis and polyuria can cause the loss of several electrolytes (Na, K, Cl, PO₄, and CA).

**Sodium:** if the amount of sodium is reduced, the measurement of serum sodium may not give a precise indication of the proportion of the deficiency. Errors in measurement of serum sodium occur due to the osmotic pressure of glucose. In order to obtain the real measurement of sodium (corrected sodium), it is necessary to use the following formula: for every 100 mg/dl of glucose above 100, the corrected sodium should be increased in 1.6 mEq/l; or: corrected sodium = [Na] + 1.6 \{([glucose] - 100)/100\}. Let us consider the following example: a child presents with glucose of 900 mg/dl and sodium of 133 mEq/l. Initially, the patient seems to have serum sodium levels near the lower limits of normality. The corrected sodium indicates, however, that the child actually presented with levels of serum sodium above the upper limits of normality. Using the formula, the corrected sodium is equal to 133 + 1.6 \{(900 - 100)/100\} = 145.8 mEq/L.
Potassium: polyuria and acidosis can cause a decrease in levels of potassium. In order to compensate the extracellular acidosis, the cells exchange H⁺ ions for K⁺ ions, thus losing a significant amount of potassium. When serum levels of potassium increase, the patient starts excreting the potassium through the urine. Consequently, patients who present with DKA can have low, normal, or high levels of potassium in plasma. With the correction of metabolic acidosis, however, the cells will begin to release H⁺ ions and recover K⁺ ions and, thus, the levels of potassium in plasma will decrease approximately 0.6 mM for every 0.1 unit of increase in pH.

Table 1 - Common complications in children with DKA, causes and treatment

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Cardiovascular shock</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Severe acidosis</td>
<td>Dehydration and ketones</td>
</tr>
<tr>
<td>Hypopotassemia</td>
<td>Ionic exchange between intra and extracellular media and polyuria</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>Osmotic pressure (?)</td>
</tr>
</tbody>
</table>
Table 2 - Indicators of risk for complications during treatment of DKA

<table>
<thead>
<tr>
<th>Alterations in mental status</th>
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<tbody>
<tr>
<td>Arterial pH &lt;7.1</td>
</tr>
<tr>
<td>Serum glucose &gt;1000 mg/dl</td>
</tr>
<tr>
<td>Na &gt;155 mEq/L</td>
</tr>
<tr>
<td>K &lt;3.5 mEq/L</td>
</tr>
<tr>
<td>Aged &lt;5 years and especially &lt;1 year</td>
</tr>
<tr>
<td>If corrected sodium does not increase with treatment</td>
</tr>
</tbody>
</table>

Cerebral edema in this population. The problem of studies that have demonstrated a relation between the use of bicarbonate and cerebral edema is that the patients who were given bicarbonate were also patients who presented a more severe clinical status. Consequently, it is difficult to establish whether the use of bicarbonate was the cause of cerebral edema or if the patients were going to develop cerebral edema independently of the treatment.

A classical symptom of cerebral edema is arterial hypertension associated with bradycardia. Other symptoms are mental alterations, sudden onset of severe headaches, incontinence, vomiting, disorientation, ophthalmoplegia, changes in the appearance of the pupil (asymmetry, slow reaction to stimulation with light, fixation), papilledema, seizures, and different variations in vital signs.7,17

The treatment for cerebral edema consists of rapidly increasing the osmotic pressure of plasma. Mannitol (0.25 - 0.5 g/kg) should be used in all patients suspected with cerebral edema. While the cause of cerebral edema is still not well understood, most studies have shown that the best indication for a good recovery is early therapy with mannitol. The use of imaging methods for the confirmation of the diagnosis only increases the interval of time between the onset of symptoms and the start of therapy with mannitol, thus also increasing the risks of unfavorable results. It is important to inform neurosurgery services as soon as possible in these cases. The use of hyperventilation is controversial.7,14,17

DKA therapy

**Objectives of the therapy**
- To correct the loss of fluids
- To correct insulin deficiency
- To prevent complications

**Laboratory exams**
Routine measurements of serum glucose, electrolytes, calcium, and phosphorus should be carried out. Serum osmolality can be calculated using the formula (2[Sodium] + [urea]/2.8 + [glucose]/18) and should be followed-up in more serious cases. Depending on the clinical status of the patient, the venous pH should be calculated beforehand. If it is above 7.1, it is a sure indication that the arterial pH is even higher. In the case of patients with a more serious clinical status or with a venous pH below 7.1, the measurement of arterial pH is required. It is important to remember that during the first hour of therapy the pH will worsen - especially the venous pH - as a result of the ‘washing out’ of lactic acid in peripheral tissues following rehydration.

A leukogram can be helpful for the investigation of infections as the cause of metabolic decompensation. Due to the resulting stress, cases of leukocytosis are common during DKA. However, a shift to the left is more common in cases of concomitant infections. Urine examinations can also be helpful in order to establish diagnosis. These examinations should be carried out regularly as a means to follow-up the evolution of patient clinical status, since the concentration of ketones in urine should reduce after the administration of adequate insulin therapy.

**Treatment**

**Fluids**
At the beginning of treatment, a rapid venous infusion of saline should be provided (10 to 20 ml/kg). If the patient remains in shock, more saline should be administered by rapid infusion. Greater amounts of fluid should be administered carefully due to the risk of developing cerebral edema.1,5,21-26

After the stabilization of the clinical status, the administration of maintenance fluid volumes can be initiated. The degree of dehydration and possible fluid deficit should be calculated. In general, it is estimated that patients have a dehydration of 10% of their body weight.21,23 The use of clinical parameters for calculating the degree of dehydration may lead to a misevaluation since, in DKA, the dehydration is hyperosmolar. The amount of saline administered during the stage of patient stabilization should be subtracted from the total volume, and the remaining volume should be divided in order to be administered during the following 48 hours. To this resulting volume, it is necessary to add the maintenance fluid volume. The final result will indicate the total volume of fluids to be administered per hour. The two bag system should be started in order to rehydrate the patient and control the glycemia.

**The two bag system**
This system was developed during the use of hyperglycemic or hyperinsulinimic clamps in a research. Its main objective is to provide the medical staff with a faster and more practical method for glycemic control.4
Conventional DKA treatment methods require different solutions based on glycemia, since the concentration of glucose to be administered varies. In the two bag system, two different saline solutions are prepared, one with glucose at 10 or 12.5% and another without glucose. The saline concentration of each solution varies according to each clinical case.

Figure 3 illustrates the two bag system. By calculating the total volume to be administered per hour, the relation between the solution with and without glucose should be changed accordingly based on glycemia. At our services, we prefer to use different NaCl concentrations based on patient age and calculated sodium. Other services have reported using simply a saline solution to ensure an increase in corrected sodium.23

By using the two bag system, alterations in the concentration of the glucose being administered can be made instantaneously; otherwise, it would be necessary to prepare a new solution with a calculated concentration of glucose. With the two bag system, it is possible to administer different glucose concentrations by simply changing the relation between the two solutions.

The concentrations of NaCl, KCl, and K₂PO₄ of each saline solution and the concentration of glucose administered can be adapted according to different protocols for different services.

**Controlling glycemia with the two bag system**

The glycemia should be monitored every hour by analysis of capillary blood. The decrease in glycemia should not be greater than 50 mg/dl/h after the first two hours of treatment. Moreover, the total decrease, after the first six hours, should not be greater than 600 mg/dl. The intravenous administration of glucose is based on the glycemia at presentation and on the glycemia measured at every hour.

If the glycemia at presentation is higher than 800 mg/dl, intravenous administration of glucose should be started when the capillary glycemia is lower than 500 mg/dl. However, if the glycemia at presentation is lower than 800 mg/dl, intravenous administration of glucose should start when the capillary glycemia is lower than 350 mg/dl. Table 3 presents the concentration of glucose in intravenous solution and the capillary glycemia at presentation and at every hour. The values presented are based on our experience; different values can be obtained at different services.

Let us consider the example: a child weighing 30 kg and 10% dehydrated receives 20 ml/kg of saline solution by rapid infusion. The maintenance fluid volume (based on weight) is of 70 ml/h. The loss of fluids is of 3.0 liters and the patient had been given 600 ml of replacement. In this case, there is still 2.4 liters to be administered. By dividing the administration of this volume into 48 hours, the patient should be given a volume of 50 ml/h. Adding the volume of replacement of fluids to the maintenance fluid volume, the total volume administered is of 120 ml/h. If the glycemia at presentation was of 935 mg/dl and the present glycemia is of 427 mg/dl, it would be necessary to administer 90 ml/h

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### Table 3 - Demonstration of the amount of glucose administered based on glycemia at presentation (more than or less than 800 mg/dl) and on glycemia per hour

<table>
<thead>
<tr>
<th>Glucose at presentation</th>
<th>% of total fluid (maintenance + deficit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;800 mg/dl</td>
<td>&lt;800 mg/dl</td>
</tr>
<tr>
<td>Present glucose</td>
<td></td>
</tr>
<tr>
<td>&gt;501 mg/dl</td>
<td>&gt;350 mg/dl</td>
</tr>
<tr>
<td>401-500 mg/dl</td>
<td>301-350 mg/dl</td>
</tr>
<tr>
<td>301-400 mg/dl</td>
<td>251-300 mg/dl</td>
</tr>
<tr>
<td>201-300 mg/dl</td>
<td>201-250 mg/dl</td>
</tr>
<tr>
<td>&lt;200 mg/dl</td>
<td>&lt;200 mg/dl</td>
</tr>
<tr>
<td>Solution without glucose</td>
<td>Solution with glucose</td>
</tr>
<tr>
<td>100%</td>
<td>zero</td>
</tr>
<tr>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>zero</td>
<td>100%</td>
</tr>
</tbody>
</table>

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**Figure 4 - Illustration of the two bag system**
Diabetic ketoacidosis in children... - Collett-Solberg PF

Sodium bicarbonate is administered in slow, intravenous dosages of 1 to 2 mEq/kg. Two to four hours time should be allotted for complete administration of the dosage.

**Laboratory follow-up**

The serum glucose of patients should be measured at every hour. The amount of electrolytes should be observed at every 2 to 4 hours depending on the status of the patient at presentation and on clinical evolution. With the exception of more serious or rare cases, it is not necessary to repeat the examinations for serum levels of calcium, phosphorus, or the leukogram.

**Conclusions**

The best treatment for diabetic ketoacidosis is prevention. Practically all cases of DKA in established diabetic children could have been avoided by regular follow-up of the patient. The correction of metabolic or hydration disorders in cases of DKA should be carried out using conservative and slow methods, with the exception of more extreme cases. The use of insulin is fundamental for the correction of metabolic ketoacidosis. The status of patients with type 2 diabetes mellitus, in turn, can be significantly improved simply by the administration of fluids.

Though it is still not proven that the decrease in corrected sodium can cause cerebral edemas, the indication of an association between these two elements should be enough to call for careful follow-up in these situations. As stated previously, the objective of this review is not to present new regimens for the treatment of DKA, but rather to present a new way to turn the control of DKA more practical and more adaptable to different services.

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**References**


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