Current perspectives for treating children with diabetic ketoacidosis

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Abstract

Objective: To review current concepts of physiopathology, diagnosis and treatment of diabetic ketoacidosis (DKA) in childhood, as well as preventive measures to avoid cerebral edema.

Sources: The authors selected articles from MEDLINE with the keywords diabetes, ketoacidosis, hyperglycemia and cerebral edema, and priority was given to studies including children and that contained complete texts published in English, Portuguese or Spanish. Chapters of books published in Brazil describing the treatment of DKA in pediatric intensive care unit were also reviewed. Based on the reviewed literature and on the author's experience, the most efficient and recommended measures for DKA management are presented.

Summary of the findings: Normal saline solution (NaCl 0.9%) has been increasingly used for fast replacement and hydration, as a substitute to diluted (hypotonic) solutions, as well as contraindication of sodium bicarbonate to repair metabolic acidosis in DKA. Regular insulin should be used as continuous infusion (0.1 IU/kg/h) without the need of a loading dose. For fast corrections of glucose oscillations, a practical scheme using two bags of electrolytic solutions is presented. Cerebral edema, its physiopathological mechanism and current treatment are reviewed.

Conclusions: Use of continuous infusion of regular insulin associated with adequate water and electrolyte replacement using isotonic solutions, besides being an effective treatment for DKA, preserves plasma osmolarity and prevents cerebral edema.

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Introduction

Diabetic ketoacidosis (DKA) is a frequent cause of admission in emergency rooms or pediatric intensive care unit (PICU), and even nowadays it has high morbidity and mortality rates. After insulin was discovered and introduced in the treatment of DKA, it has been possible to reduce its mortality from 100% (early 20th century) for the current 2-5%.[1-12] Despite all available therapeutic options, DKA is still the main cause of death in children and adolescents with type 1 diabetes mellitus (DM1). Most fatal cases are related to the development of cerebral edema, which is present in 0.5-2% of

patients with DKA, with mortality rate between 40-90% and able to produce sequelae in 10-25% of survivals.[1,2,3,13,14] Other causes of morbidity and mortality are hypokalemia, hyperkalemia, hypoglycemia, infections and changes in the central nervous system (CNS).[1,2,9,11]

According to DKA definition, there must be metabolic acidosis (pH < 7.3 and/or HCO_3 < 15 mEq/L) secondary to ketosis (ketonemia and ketonuria), hyperglycemia (over 200 mg/dL) and several dehydration degrees in patients with diabetes mellitus (DM).[1,2,9,10] Hyperglycemia in this situation is usually high, but not necessarily so. Small or partially treated

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children, as well as pregnant adolescents, may present DKA with almost normal blood glucose levels (euglycemic ketoacidosis).[1,2,9] In DKA, there is relative or absolute insulin deficiency, associated with increased counter-regulatory hormones, changing carbohydrate, protein and lipid metabolism.[1-12]

In small children, it is often hard to characterize the classical and characteristic signs of DM, such as polyuria, polydipsia and weight loss. Many of those symptoms can be attributed to other more prevalent diseases, delaying diagnosis. Even in developed countries, between 15-70% of new cases of DM in childhood are diagnosed based on a DKA crisis.[1-12] Prevalence of DKA is inversely associated with effectiveness of the health system and with prevalence of diabetes in the community.[1,3] Adolescents and young adults with type 2 DM can also present DKA at diagnosis, therefore it is not considered a characteristic disorder of DM1.[1-12]

Although a significant part of patients have DKA as an initial manifestation of DM, exclusion and/or identification of one or more triggering factors is needed. It is crucial to perform a thorough and detailed anamnesis and clinical examination, associated with a minimal amount of laboratory investigation, with the aim of identifying possible triggering factors. The fact that morbidity and mortality of DKA are associated with type of intervention and treatment used over the first hours has been well documented.[1,3,11,13-15]

In patients with previously diagnosed DM, DKA is usually associated with inadequate use of insulin. Adolescents have problems adhering treatment and diet, as well as psychological factors associated with eating disorders that could trigger up to 20% of cases of recurrent DKA.[1-3,9,10] In patients submitted to insulin pump therapy, its inappropriate interruption, even if transient, leads to DKA due to low serum levels of insulin common to this type of therapy.[2]

Among the most common precipitating factors of DKA are infections (30-40% of cases).[1-3,13,14] Insulin resistance is associated with increased levels of stress hormones (adrenalin, glucagon, hydrocortisone and growth hormone) and some cytokines (for example, interleukin-1) that are also increased in infections.[2,10] High doses of glucocorticoids, atypical antipsychotics, diazoxide and some immunosuppressive drugs have been reported as KDA precipitants in patients without previous diagnosis.[2] Other causes of KDA are pancreatitis and trauma.[9,15] As a general rule, possible triggering factors should be assessed in all patients with KDA and only after they are discarded the irregular treatment should be considered as causal factor. In 2-10% of cases, it is not possible to identify the precipitating factor.[9,15]

Physiopathology

Clinical manifestations and laboratory changes in DKA (Figure 1) occur as a consequence of interactions of absolute or relative insulin deficiency and increased counter-regulatory

hormones (glucagon, catecholamines, cortisol and growth hormone). Therefore, counter-regulatory hormones are usually increased in situations of infection and stress, which often precipitate DKA in diabetic patients, whereas hyperglycemia, dehydration, hyperosmolarity, electrolytic and acid-basic disorders perpetuate release of counter-regulatory hormones.[1-13]

Ketoacidosis

Insulin is an anabolic hormone, promoting synthesis and/or storage of carbohydrates, fats, proteins and nucleic acids. Insulin action allows energy generation through use of glucose by muscles, adipose tissue and liver cells. When insulin is absent, there is lipolysis with increased fatty acid mobilization for hepatic gluconeogenesis and release of ketone bodies. Excessive production of ketones exceeds the buffer capacity of organic alkalis, resulting in metabolic acidosis. Consequently, according to acidosis intensity, DKA can be quantified into mild (pH 7.3-7.2), moderate (7.2-7.1) and severe (< 7.1).[1,2,9,15] A characteristic of metabolic acidosis in DKA is increased anion gap (normally between 10 and 12), which is obtained by the following formula: anion gap = Na - $(HCO_3 + Cl)$.

In DKA, ketosis is primarily caused by increase in β-hydroxybutyrate and acetoacetate. Beta-hydroxybutyrate is the ketone found in higher circulating levels during DKA, with a β-hydroxybutyrate:acetoacetate ratio of 3:1 during early disease stages. Ketonemia tests are generally performed qualitatively or semi-quantitatively in relation to acetoacetate. Considering that, during ketoacidosis correction, β-hydroxybutyrate is transformed into acetoacetate, ketonemia test can be positive for some time, even with proper treatment. Therefore, persistence of positive ketonemia does not necessarily mean that DKA treatment is being ineffective.[9] Anion gap could thus be used as an indirect indicator of ketone body levels, since reduction in anion gap value represents reduced ketone body levels, which represent treatment efficiency.[1,2,9,10,12]
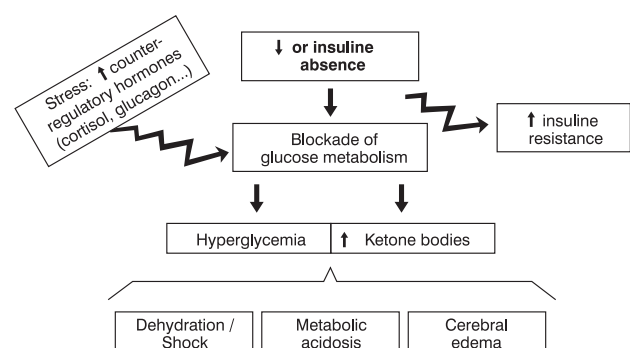

Figure 1 - Metabolic consequences of insulin deficiency in the genesis of diabetic ketoacidosis

Hyperglycemia

In case of insulin deficiency (or absence) associated with the action of counter-regulatory hormones, cells cannot capture and metabolize glucose, causing muscle and hepatic glycogenolysis and subsequent hyperglycemia.[9] Blood glucose levels higher than 180 mg/dL exceed the maximum capacity of glucose reabsorption in the proximal tubule, causing glycosuria and osmotic diuresis. Osmotic diuresis leads to polyuria with loss of free water and electrolytes, promoting polydipsia. In If adequate water ingestion is maintained, dehydration will be mild and blood glucose will stabilize between 300- 400 mg/dL. In some cases, blood glucose can reach levels of up to 800 mg/dL, especially when there is severe dehydration with reduction in glomerular filtration rate.[9,15,16] Although hyperglycemia is the rule in DKA, there may be cases of DKA with normal blood glucose levels. This phenomenon occurs in patients partially treated with insulin and without receiving fluids with carbohydrates and/or in situations with long periods of vomiting and no ingestion of carbohydrates.[1,2,9,12,16]

Dehydration

Osmotic diuresis associated with vomiting and insufficient ingestion causes dehydration of several degrees in DKA, while shock is a rare event in this situation.[1] As dehydration progresses, there is reduction in the intravascular volume and consequent progressive loss of glomerular filtration rate. Reduction in glomerular filtration rate causes reduction in diuresis and glucose loss, resulting in worsening of hyperglycemia. Blood glucose levels close to 600 mg/dL indicate that glomerular filtration rate is reduced in approximately 25%, whereas glucose of 800 mg/dL suggests a 50% reduction in glomerular filtration rate, as a consequence of severe dehydration.[1,2,9,10]

Hyperosmolarity

Plasma osmolarity can be estimated using the calculation $[(Na + K) \times 2] + (blood glucose/18)$. It is easy to note that, with blood glucose at 180 mg/dL, contribution of glucose in plasma osmolarity will be minimal (around 10). However, in case of blood glucose increases to, for instance, 720 mg/dL, osmolarity impact caused by hyperglycemia will be 40. Under these circumstances, there is movement of free water from the intracellular to the extracellular space (intracellular dehydration). Maintenance of this hyperosmolar state stimulates cells' (especially neurons) production of substances with intracellular osmotic activity (idiogenic osmoles) to preserve intracellular water. In case of sudden fall in blood osmolarity (quick fall of blood glucose or reduction in plasma sodium), this will cause the shift of water into the intracellular space, favoring occurrence of cerebral edema.[14-16] It has been demonstrated that hypernatremia can be a protective factor of cerebral edema in patients with DKA.[16]

Electrolytic disorders

Polyuria caused by osmotic diuresis may induce dehydration with several degrees of associated electrolytic changes: hyper- or hyponatremia, hypokalemia, hypophosphatemia and hypocalcemia.

Sodium

In DKA, there may be dilutional hyponatremia associated with increased osmolarity caused by hyperglycemia. A reduction in the blood sodium level of 1.6 mEq/L is estimated for each 100 mg/dL of glucose above the limit of 100 mg/dL. Other factors, such as increase in serum lipids with low sodium content, action of antidiuretic hormone, urinary sodium loss related to osmotic diuresis and elimination of ketone bodies, may enhance hyponatremia.[1,2,9,11] Hypernatremia, despite being less frequent, has been observed in the presence of DKA. Increase in serum sodium, since it maintains plasma osmolarity, seems to be a protective factor in the development of cerebral edema in DKA, because there is reduction in blood glucose levels.[16] Therefore, in the light of current knowledge, hyponatremia should be avoided and treated in children with DKA. Moderate hypernatremia (between 150-160 mEq/L) could be accepted and considered protective in children with DKA who have more marked hyperglycemia (higher than 600 mg/dL).[16]

Potassium

Glycogenolysis and proteolysis caused by insulin deficiency promote output of cell potassium into the extracellular fluid. Many factors influence reduction in serum potassium in DKA: urinary excretion along with ketoacids, increased aldosterone caused by dehydration, vomiting and potassium input in the cell along with glucose when insulin infusion is started. However, at DKA diagnosis, serum potassium may be normal or increased, because acidosis causes potassium shift from the intracellular environment into the extracellular space.[1,2,9] Nevertheless, even if this occurs, it should be stressed that total body potassium is reduced. Therefore, normal or reduced potassium dosage at the beginning of DKA indicates need of early replacement, since the treatment tends to reduce serum levels of this ion.[1,2,9,11]

Calcium

As a result of acidosis correction during DKA treatment and improvement in glomerular filtration rate, there is a tendency to hypocalcemia. Use of phosphate in the treatment of patients with DKA is also associated with hypocalcemia.[1,2,9]

Phosphorus

During DKA, similarly to what occurs with potassium, there is initially hyperphosphatemia secondary to metabolic acidosis. As a result of urinary losses of phosphorus due to polyuria, hypophosphatemia is common, which will cause a reduction in erythrocyte 2,3-DPG levels. Low 2,3-DPG levels

can lead to reduction in oxygen supply to tissues due to displacement in hemoglobin dissociation curve; however, this effect does not usually have clinical repercussion in DKA.[1,2,9]

Clinical and laboratory diagnosis of diabetic ketoacidosis

Polyuria, polydipsia, enuresis, weight loss and polyphagia characterize DM. When it progresses to DKA, there are nauseas, vomiting, progressive anorexia, abdominal pain, fatigue and signs of dehydration: dry skin and mucosa, reduced skin turgor, tachycardia and reduced perfusion according to degree of dehydration. It is estimated that deficit in extracellular fluid in DKA is between 5-10% of body weight. However, as previously stated, hypotension (hypovolemic shock) is a rare and late finding in children with DKA, often associated with sepsis or cerebral edema.[1,2,9,16] In case of changes in sensorium (sleepiness, clouding of consciousness), hypothesis of cerebral edema should be immediately considered, since it has high mortality rates.

There is also tachypnea (hyperventilation to compensate metabolic acidosis), ketotic breath (sweetish odor due to ketosis) and fever (which can be associated with infectious, bacterial or viral process).[1-11]

DKA should be suspected in every patient who has depression of sensorium with or without clinical signs of acidosis; capillary blood glucose screening and/or tests for ketonuria should always be performed in initial assessment.[1-11]

Laboratory criteria to define DKA are pH (venous or arterial) lower than 7.30 and/or bicarbonate lower than 15 mEq/L, blood glucose higher than 200 mg/dL and presence of ketonemia and ketonuria.[1,2,9] It should be stressed that arterial gas analysis is painful, has a higher risk, and the data we intend to evaluate (pH, bicarbonate and base deficit) are equivalent in both arterial and venous blood. Besides blood glucose, ketonemia and venous gas analysis, serum values of lactate, sodium, potassium, ionic calcium, chlorine, phosphorus, urea, creatinine, hematocrit and hemoglobin should be initially monitored, as well as glycosuria and ketonuria. If there is suspicion of infection, specific exams should be required according to clinical status.[1,2,9,11] Leukocytosis with left shift is a frequent finding in patients with DKA, and there is no strong association with presence of infection.[1,2,9] Serum amylase is often high in DKA, which is not usually an indicator of pancreatitis. This hypothesis should be investigated in the presence of suggestive clinical signs and markedly high amylase levels.[1,2,9]

In many patients with DKA, there are case reports of patients submitted to urgent exploratory laparotomy, which lately proved to be unnecessary. This conduct may add significant morbidity and mortality in DKA management. Therefore, it should be stressed that presence of abdominal pain associated with vomiting and often with signs of peritoneal irritation (positive Blumberg's sign) may occur in DKA, mimicking acute abdomen due to infection, acute appendicitis, pancreatitis, cholecystitis or other causes. Under these situations, before indicating surgical treatment using exploratory laparotomy, the patient should be better investigated and DKA should be corrected, waiting a few hours for resolution of abdominal pain. Such conduct should not evidently be established in the presence of severe infectious status, sepsis or clear evidence of associated abdominal disease.

Treatment

DKA is a life-threatening situation in which the treatment should be performed by an experienced medical team in intensive care unit (ICU) or hospital ward and trained to receive this type of patients. This situation does not allow improvisations or attitudes based on empirical evidence. Therefore, it is recommended that every service has its own protocol adjusted to local operational resources and difficulties. Another important principle in the treatment of patients with DKA is individualization of therapy, with careful monitoring of fluids, electrolytes and control of serum glucose as a priority.[1,2,9,16] The criteria used for the treatment of DKA are listed below:[1-17]

Correction of dehydration and electrolytic disorders

Volumetric replacement in DKA follows the same principles of other situations of dehydration or shock: an initial stage of rapid expansion (1-4 hours) followed by a slower stage of rehydration and replacement of losses (20-22 hours).[1,2,9,16] Some retrospective and multi-centered studies concluded that in DKA there is a strong association between cerebral edema and administration of large amounts of fluids.[13,14] However, it should be stressed that those studies do not allow concluding that cerebral edema exclusively occurred due to excess of infused fluids or because it is a most severe group of patients, which requires more amount of volume replacement. As long as such doubt is not clarified, we have followed the current recommendations for volume replacement in patients with dehydration and/or shock: volume expansion in the early stage followed by a moderate maintenance during the late stage.[9]

Expansion stage (1-4 hours)

It is essential to quickly obtain two or more peripheral venous access. Expansion stage should be immediately started with NaCl 0.9% (normal saline solution, NSS), 20 mL/kg at every 20 minutes, which can be repeated until circulatory stability is obtained. Let us consider a child with DKA, weighing 20 kg, with clear signs of dehydration. It should, in this case, be given a first expansion with 400 mL of SS for 20 minutes. This volume obviously cannot be infused in such a short period of time through a single peripheral vessel. For that reason, it is recommended that, in DKA, two or three

peripheral accesses should be punctured, so that the volume calculated is replaced within predicted time.

DKA usually requires two to three volume expansions of 20 mL/kg with NSS until dehydration signs are reverted. This fast replacement with SS reestablishes blood volume and improves renal perfusion, which increases glomerular filtration, resulting in glucose-induced osmotic diuresis, with reduction in blood glucose and plasma osmolarity.[1,9,17] In the treatment of DKA, expansions with NSS, since it is isotonic in relation to plasma (NSS: Na = 154 mEq/L), promote higher increase in blood volume than the diluted solutions, causing a slower reduction in the osmolarity.[1,9,17] Therefore, even in situations of DKA in which initial serum sodium is higher than 150 mEq/L, hypotonic solutions are not used.

Rehydration stage (20-22 hours)

As soon as the signs of blood volume depletion (tachycardia, hypoperfusion, hypotension, etc.) are reverted, fast expansions with NSS are suspended and maintenance stage is started.[1,2,9,16,17] This stage should include maintenance volume (1,800-2,000 mL/m^2/day) along with volume for replacement of further losses, in cases of persistent vomiting and diarrhea. In patients with marked hyperglycemia, even receiving adequate treatment, it should be assumed that they will continue to have increased urinary losses. In such case, it is recommended an increase of up to 30-50% in maintenance water supply, which corresponds to an infusion of up to 2,500-3,000 mL/m^2/day.[1,2,9,14,16] To avoid hyperhydration, periodic assessments should be performed with the aim of reducing water supply to maintenance values.

Some authors suggest initial use of NaCl 0.45% (Na = 75 mEq/L) in cases in which serum sodium exceeds 150 mEq/L, or when calculated plasma osmolarity is higher than 340 mOsm/L.[12,15] Due to the reasons described above, even in those cases, we prefer to maintain infusion of isotonic NSS until blood glucose is around 300 mg/dL, when 5 g of glucose should be added for each 100 mL.[1,9,16,17]

It is estimated that there is a potassium deficit of 4-6 mEq/kg in DKA, which is more evident after acidosis correction and due to insulin action (which promotes input of glucose and potassium into the cell).[1,2,9,18] In the presence of diuresis, potassium should be added (40 mEq/L) in the rehydration solution and adjustments should be performed according to laboratory data. In severe cases of hypopotassemia (levels lower than 2.5 mEq/L), replacement can be performed using 0.4-0.6 mEq/kg/h for 6 hours. Until recently, there has been a recommendation to administer part of potassium as phosphate, but randomized studies did not show benefits in phosphate replacement, since clinical effects of hypophosphatemia are rare. Phosphate replacement should only be started in patients with respiratory depression and in those with serum level < 1.0 mg/dL. In those cases, 1/3 of potassium is administered as potassium phosphate.[1,2,9]

Correction of metabolic acidosis in patients with DKA occurs with volumetric replacement, especially due to insulin action, which reverts formation of ketoacids. Metabolic acidosis, as stated above, is a marker of severity. Differently from what was previously believed, it has been demonstrated that acid pH alone is not a determining factor that increases risk of death or organic failure.[9,19-22] On the other hand, administration of sodium bicarbonate in DKA has been associated with cerebral edema and death.[1,2,13-15] Use of sodium bicarbonate may cause many side effects, such as hypokalemia, worsening of hyperosmolarity, increased intracellular acidosis due to CO_2 production, paradoxical acidosis in the CNS, left shift in hemoglobin dissociation curve with reduction in oxygen supply to tissues, slower reduction of ketonemia and possible association with development of cerebral edema.[1-14]

Recent consensus reports by the American Diabetes Association for children with DKA consider use of bicarbonate when pH is lower than 6.9 and persists after the first hour of hydration. In these cases, 1-2 mEq/kg of sodium bicarbonate should be administered in 1-2 hours.[1,2] In our services, we have avoided infusion of sodium bicarbonate in DKA, even in the presence of pH lower than 7.0.

Oral diet should be started with the patient awake, without vomiting and with improved acidosis. Parenteral hydration solution should be maintained as along as continuous insulin is necessary.[1-12]

Insulin therapy

Administration of insulin promotes glucose input into the intracellular space, reverts catabolic status and suppresses lipolysis and ketogenesis, correcting blood glucose and acidosis.[1,2,10,18,22-24]

Despite the fact that some authors recommend an infusion of a loading dose of regular insulin (0.1 IU/kg) in patients with DKA, we have chosen to directly start continuous infusion of 0.1 IU/kg/h of regular insulin diluted in NSS.[1,2,9,11,23] As previously mentioned, adequate replacement of blood volume induces improvement in renal perfusion, resulting in reduced blood glucose. If, associated with this fact, we administer a loading dose of regular insulin, we can induce a marked reduction in blood glucose and osmolarity (main factor associated with cerebral edema).[1,9,23]

In our services, we use a dilution of regular insulin at 0.1 IU/mL (250 mL of SS adding 25 IU of regular insulin), which is infused at a speed of 1 mL/kg/h (0.1 IU/kg/h) using an infusion pump. Due to insulin adherence to plastic, we use the first 50 mL of the solution to wash the catheter.[9]

In general, glucose infusion is started in the treatment of DKA when blood glucose reaches 250-300 mg/dL. To do so, glucose is added to the NSS to obtain a 5% concentration (50 g/L, or 100 mL of glucose at 50% for each liter of NSS). An infusion of 2,000 mL/m^2/day of a solution wit 5% glucose provides a glucose infusion rate between 2.5-3.5 mg/kg/min.

Such variation occurs because body weight and surface do not have an absolutely linear correlation. Therefore, besides the calculation of amount of supplied fluid (mL/m^2/day), glucose infusion rate (mg/kg/min) should be calculated based on glucose concentration in the solution, patient's weight and infusion rate.

DKA treatment initially aims at correcting acidosis and maintaining blood glucose between 150-250 mg/dL during infusion with continuous insulin. Use of continuous insulin infusion may provide reduction in blood glucose between 50-100 mg/dL at every hour.[1,9,23] In cases in which reduction in glucose levels is lower than 50 mg/dL/h, insulin infusion should be increased to 0.15-0.2 IU/kg/h. If reduction in blood glucose is faster than 100 mg/dL/h during continuous insulin infusion, administration of intravenous glucose should be increased and may reach up to 5 mg/kg/min.[1,9,23]

Acidosis and ketonemia are the main markers of insulin and glucose insufficiency in the cell metabolism during DKA. Blood glucose correction is faster than acidosis correction. Therefore, in patients who have major reduction in blood glucose, but who maintain positive acidosis and/or ketonemia, continuous insulin infusion should not be reduced. In these cases, it is necessary to increase glucose infusion, sometimes using 10% glucose.[1,2,9,23]

Continuous insulin infusion should only be reduced when there is need of glucose infusion higher than 5 mg/kg/min to maintain blood glucose between 150-200 mg/dL. Such phenomenon may occur in: (a) patients with recently diagnosed DM who still have some endogenous insulin production and higher insulin sensitivity; and (b) patients with residual long-acting insulin levels (for example, users of insulin glargine or detemir). In this situation, we reduce insulin infusion rate to 0.05 U/kg/h and maintain glucose infusion (between 3.5-5 mg/kg/min).[1,2,9,22-24]

Therefore, by adding glucose to hydration solution (NSS) and in the presence of continuous insulin infusion, it is common to perform frequent adjustments in glucose infusion rate, due to higher or lower blood glucose reduction. Changing solutions is often needed, which demands time and cost. Some authors propose using a system with two bags (Figure 2), which have identical electrolytic content (NaCl = 150 mE/L and KCl = 40 mEq/L), being different in relation to the glucose concentration (0 and 10%), placed in the shape of an "Y" in a single venous access in the patient.[25] Variations in supply of infused glucose would only occur when adjusting dripping of each bag, maintaining previously estimated water and electrolyte supply. This system allows quick adjustments according to blood glucose, and it is possible to infuse solutions with concentrations between 0-10% of glucose, so that therapy can be individualized to the needs of any patient.[25]

Continuous insulin infusion can be suspended when blood pH is higher than 7.30, serum bicarbonate is ≥ 18, anion gap
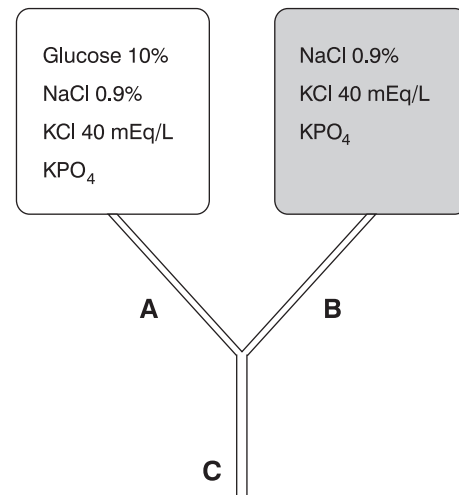

Figure 2 - Diagram of two parallel bags to infuse hydration solution in patients with DKA

is between 8 and 12, and the patient is under conditions of being fed through the digestive system (Figure 3).[1,2,9,11]

One hour before suspending continuous insulin infusion, a subcutaneous regular insulin bolus of 0.1 IU/kg should be administered. Subsequent doses of insulin should be defined according to previous insulin regime for each patient. In patients whose DM diagnosis was established based on current DKA status, an initial daily insulin regime between 0.6-0.7 IU/kg/day is recommended, divided into long- and short-acting insulin, which is administered in two or three applications before meals.[1,2,9] From the practical perspective, suggestion is to perform transition of intravenous insulin to NPH insulin at times close to the patient's meals, preferentially in the morning. In cases in which the patient fulfils the criteria for suspension of continuous insulin at different times, such as at night, for example, intravenous infusion can be maintained for a few extra hours, with adjustments in glucose infusion rate as needed.

A new option in this transition of regular intravenous insulin into subcutaneous insulin is the use of insulin glargine (Lantus). Insulin glargine is a slow-release and long-acting insulin, mimicking the effect obtained when using insulin infusion pump therapy. In a study including children with DKA, progression of a group treated with traditional regular intravenous (IV) insulin was compared with another group that was given 0.3 IU/kg of insulin glargine over the first 6 hours of treatment associated with regular IV insulin infusion. Addition of that low and stable dose of insulin glargine allowed suspension of continuous IV insulin infusion earlier, reduction in total amount of insulin administered, faster correction of acidosis and earlier ICU discharge.[26]
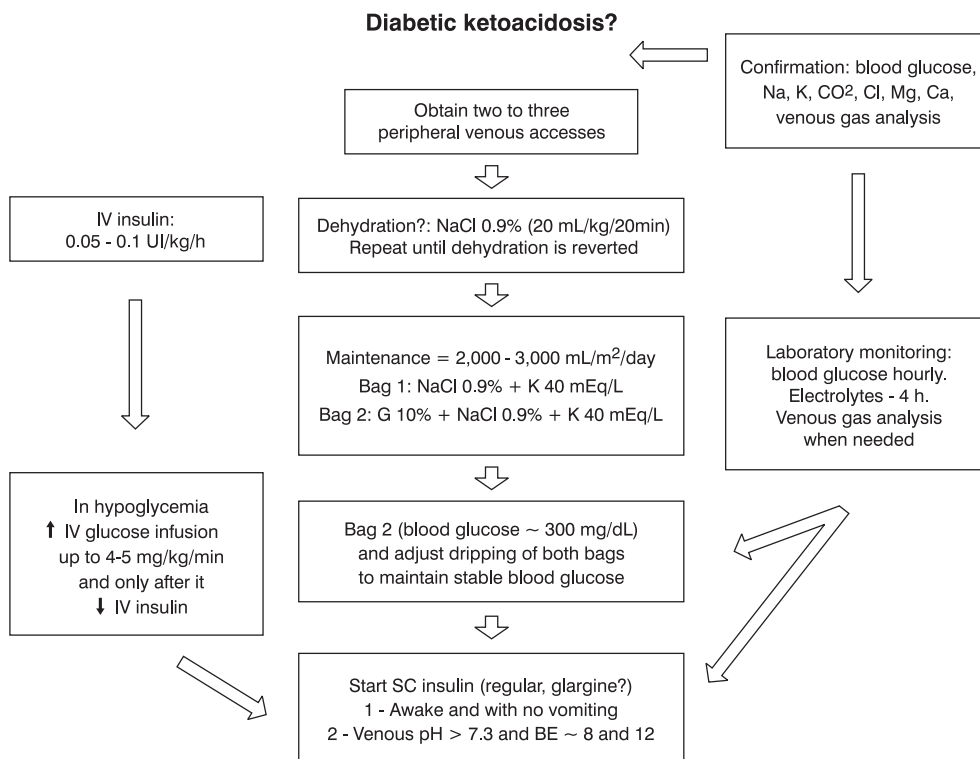
Diabetic ketoacidosis?

Confirmation: blood glucose, Na, K, CO_2, Cl, Mg, Ca, venous gas analysis

Obtain two to three peripheral venous accesses

IV insulin: 0.05 - 0.1 UI/kg/h

Dehydration?: NaCl 0.9% (20 mL/kg/20min) Repeat until dehydration is reverted

Maintenance = 2,000 - 3,000 mL/m^2/day
Bag 1: NaCl 0.9% + K 40 mEq/L
Bag 2: G 10% + NaCl 0.9% + K 40 mEq/L

Laboratory monitoring: blood glucose hourly. Electrolytes - 4 h. Venous gas analysis when needed

In hypoglycemia ↑ IV glucose infusion up to 4-5 mg/kg/min and only after it ↓ IV insulin

Bag 2 (blood glucose ~ 300 mg/dL) and adjust dripping of both bags to maintain stable blood glucose

Start SC insulin (regular, glargine?)
1 - Awake and with no vomiting
2 - Venous pH > 7.3 and BE ~ 8 and 12

Figure 3 - Suggested flowchart in the treatment of children with diabetic ketoacidosis

Complications

Electrolytic disorders (hypopotassemia, hypo- or hyper-natremia, hypophosphatemia, etc.) and hypoglycemia (mentioned above) are among the main complications in the treatment of DKA. Hyperchloremic acidosis is also a frequent complication, resulting from excess of chlorine replacement, present both in sodium chloride and in potassium chloride, used in initial management of patients. In general, it is manifested after some days of DKA and does not require specific treatment, spontaneously progressing in the presence of normal renal function.

Cardiac arrhythmias

These are caused by electrolytic disorders (hypo- or hyperpotassemia, hypocalcemia, hypomagnesemia), and rarely occur in DKA.[7,9]

Aspiration of gastric content

As major changes in the sensorium occur and many patients have recurrent vomiting, there may be pulmonary aspiration of gastric content. This complication should be prevented by careful supervision of patients at an adequate hospital setting.

Pulmonary edema

It is not a common complication. There is an increase in oxygen demand, and there may or may not be radiological changes compatible with pulmonary edema. Many factors can be involved: low oncotic pressure, increased pulmonary capillary permeability and neurogenic pulmonary edema. Treatment includes oxygen therapy, use of diuretics and ventilatory support when indicated.[9,27-29]

Cerebral edema

It is practically restricted to the pediatric age group, with prevalence of 1-2% in children with DKA, being more prevalent in children 5 years and younger and in the first DKA diagnosis. It is a much feared complication of DKA, since it has mortality rate between 40-90%, whereas part of survivors will have sequelae. There is evidence that many patients with DKA have some degree of subclinical cerebral edema even before starting treatment.[3,13,14,16,30-33]

Clinical manifestations of cerebral edema are usually sudden, and there may be fast progression to brain herniation, even when clinical status is recognized and aggressively treated.[31] Cerebral edema usually occurs within 4-12 hours after beginning treatment and at the moment acidosis, dehydration and hyperglycemia, as well as the patient's general status, are improving. Initial signs and symptoms are headache and reduced level of consciousness, which quickly progress to deterioration of sensorium, dilated pupils, bradycardia and respiratory arrest. In some cases, it can be preceded by a period of change in behavior associated or not with

headache and vomiting.[1-3,13,14,17,31,32] In up to 40% of children with clinical status of cerebral edema, initial brain tomography may be normal.[1]

Physiopathology of cerebral edema in DKA has not been completely clarified, and is more frequently associated with fast decline in plasma osmolarity, excess of fluids (higher than 4,000 mL/m^2/day), administration of bicarbonate, low pCO$_2$, high plasma urea, brain hypoperfusion and direct action of ketones in release of brain inflammatory interleukin. Fast reductions in concentration of serum sodium and plasma osmolarity during treatment, associated with presence of idiogenic osmoles in CNS cells, are the main mechanism in cerebral edema genesis.[1-3,13,14,16,17,29-32] It is believed that vasogenic cerebral edema is prevalent, which is more responsive to treatment.[1,32]

Treatment of cerebral edema can be performed using infusions of mannitol 0.25-0.5 g/kg/day at every 2-4 hours, or using 3% hypertonic saline solution (5-10 mL/kg/every 30 min), maintaining plasma sodium between 150-160 mEq/L. In cases with early diagnosis, before occurrence of changes in pupil and heart rate, mannitol often promotes significant improvement, and intubation and ventilatory support are not required. When ventilatory support is used, pCO$_2$ should be controlled between 30-35 mmHg, besides maintaining head of the bed elevated at 30 º and normovolemia. In cases of herniation, mortality rate is high, even starting treatment. Therefore, frequent and judicious monitoring of the patient's consciousness status over the first hours of treatment is crucial and, in the presence of any acute deterioration, mannitol should be immediately administered.[1,3,9,16,17,32]

Prevention

Despite improvement in diagnostic and therapeutic resources, there has been no reduction in mortality due to DKA over the past 2 decades.[1-3,13,14,17] Therefore, the main objective of managing patients with insulin-dependent DM should de prevention of DKA episodes through a high suspicion index with rigorous monitoring of symptoms.[1,2,9,12]

Prevention of recurrent DKA episodes, especially in adolescents, demands an efficient participation and surveillance by the family and health team. Recurrent DKA episodes should be considered as failure in long-term treatment. Efficient DKA prevention comprehends:[1,2,9,12,18] (a) recognition of early signs of diabetes decompensation; (b) identification of events that may precipitate increase in insulin supply; (c) early intervention; and (d) aggressive intervention at the family core of patients with recurrent DKA episodes.

DKA prevention when diagnosing new cases of DM involves physicians' knowledge of the disease's initial manifestations, as well as a high suspicion index. Early diagnosis of diabetes and beginning of treatment avoid progression to DKA.[1] It is also important to stress that whenever a diagnosis of DM is established, we should also characterize whether DM is insulin-dependent or not. In children and adolescents, at first, all cases are insulin-dependent. In this situation, all patients with DM should be treated from the start using insulin therapy. Use of oral hypoglycemic agents is not indicated, since they are dependent upon existence of pancreatic insulin secretion to be effective. Unfortunately, there are still cases of patients with recently diagnosed DM that progress to DKA when oral hypoglycemic agents are used. In these cases, DKA could be prevented by correct diagnostic and therapeutic guidance of insulin-dependent DM.

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