# EMERGENCIES IN CHILDHOOD DIABETES

**Saleh Adi MD,** Division of Endocrinology, Department of Pediatrics, The Madison Clinic for Pediatric Diabetes, University of California San Francisco, San Francisco, California. abousteif7@gmail.com

**Updated March 13, 2019**

## INTRODUCTION

Diabetes Mellitus, after asthma, is the second most common chronic condition in children. It can be diagnosed at any age and the incidence has been rising. Type 1 Diabetes (T1D) is by far the most common type of diabetes in children and its incidence has been increasing slowly but steadily. By definition T1D is an autoimmune condition caused by immune-mediated destruction of beta cells, with resultant development of pancreatic auto-antibodies (Type 1a). However, 10-15% of patients with a clinical phenotype of T1D do not have detectable antibodies and are classified as having Type 1b. Besides autoimmunity, beta cell loss can be caused by absence or loss of the pancreas, cystic fibrosis, and drug-induced diabetes. In these cases, the management of diabetes is very similar to the management of autoimmune T1D. Type 2 Diabetes (T2D) in children is characterized by progressive loss of beta cell function due to severe insulin resistance and often requires insulin therapy. The incidence of T2D has also been increasing in children, commensurate with the rise of obesity. Therefore, the key to treating most children with diabetes is replacement of insulin and most of the emergencies in children with diabetes are associated with either inadequate or excess insulin administration.

## NEW ONSET DIABETIC KETOACIDOSIS (DKA)

### Clinical Recognition

The onset of T1D can be insidious because the immune-mediated loss of β-cells is typically slow, occurring over several months to years before hyperglycemia is manifest. The earliest signs of hyperglycemia begin with polyuria, followed shortly by polydipsia. A typical scenario in children is that of a few weeks' history of increasing fatigue, intermittent polyuria and polydipsia, a recent viral illness and/or travel followed by exacerbation of these symptoms. If not recognized at this stage, hyperglycemia further impairs β-cell function and insulin secretion, which eventually leads to increasing lipolysis to provide free fatty acids as an alternative substrate for energy generation. Oxidation of free fatty acids leads to accumulation of acetoacetic and β-hydroxybutyric acids (ketones). When the level of ketones exceeds the child's capacity to buffer the acidosis, the blood pH begins to decrease to below 7.3. In addition, the osmotic diuresis caused by the hyperglycemia leads to dehydration and lactic acidosis which further contributes to the acidosis and to increasing insulin resistance, all leading to a vicious cycle and rapid worsening in the hemodynamic status and development of severe DKA. The severity of DKA is divided into mild (pH 7.2-7.3, or bicarbonate <15 mmol/L), moderate (pH 7.1-7.2, or bicarbonate <10 mmol/L), and severe (pH <7.1, or bicarbonate <5 mmol/L). The younger the child the faster the progression towards DKA, and the more severe

the acidosis can be, with ensuing classic signs of dehydration, Kussmaul breathing, and potential obtundation and even coma.

**Diagnosis**

The diagnosis of new onset DKA relies on a high index of suspicion because most children presenting with new onset T1D have no family history of T1D. In addition, infants and toddlers may not have the classical series of symptoms that usually precede presentation with DKA and may present with non-specific symptoms such as increased irritability, difficulty sleeping, or poor feeding. Because the initial hyperglycemia can be exacerbated by a viral illness, these non-specific symptoms can be attributed to the viral illness and not to diabetes. Therefore, a careful review of the history of the illness and the presenting symptoms is essential for making the right diagnosis. Important clues include increased number of daily diapers or parental description of "heavy diapers especially in the morning", the presence of diaper rash in infants or vaginal yeast infection in older girls, increased frequency of using the bathroom during school, nocturnal enuresis in a child who has already been trained, increased appetite yet continued weight loss, deterioration of performance in sports or school, and the presence of a sweet fruity smell from the child.

Once suspected, new onset T1D is easily confirmed by obtaining a basic metabolic panel which includes glucose and bicarb measurements. A glucose level >200 mg/dl, with symptoms of hyperglycemia confirms the diagnosis of diabetes, while a lower than normal bicarb level suggests the presence of DKA, which can be confirmed by measuring urine or serum ketone levels.

**Treatment**

Once diagnosed, new onset DKA in children is best managed if possible in a pediatric specialty center with expertise in treating children with DKA. This is due to the fact that a) fluid replacement in children must be calculated with greater precision based on body weight and surface area, and be provided in a manner that minimizes the risk of rapid shifting in osmolality between intra- and extracellular spaces, which can occur more easily in children because of their relatively immature hemodynamic and cerebral autoregulatory processes. Rapid shifting of fluids can lead to cerebral edema, the most serious complication of DKA especially in younger children presenting with new onset T1D; b) children, especially pre-pubertal children, are far more sensitive to insulin, requiring much smaller doses than what is usually needed in adults; and c) even within the pediatric population, the approach to managing DKA in infants and toddlers is quite different than in older patients. Adolescents in peak puberty present a different challenge because of their often-severe resistance to insulin. For these and other reasons, we strongly recommend that children in DKA get transferred to a center with pediatric intensive care with the ability to provide close monitoring and management according to childhood specific treatment protocols. If initial stabilization of the child is required before transfer, it should be done in consultation with a pediatric intensivist and/or endocrinologist if possible.

The first steps in the treatment of DKA are shown in Table 1.

| **Table 1. The First Steps in the Treatment of DKA** |
|---|
| 1) Determine current weight and height (or length) of the child, to calculate body surface area. |
| 2) A careful physical examination looking for signs of infection, the presence of acanthosis nigricans, and assess the neurological status and degree of dehydration. |
| 3) Initial blood sampling for laboratory measurements of electrolytes and glucose, BUN, creatinine, a blood gas, ketones, and a complete blood count. |
| 4) Provide oxygen if needed. |
| 5) Obtain samples for culturing if evidence of infection exists. Antibiotics should be considered if the child is febrile. |
| 6) Establish peripheral intravenous access. Central line access is rarely needed |

FLUID REPLACEMENT

All children presenting with DKA have some degree of dehydration, and must receive fluid replacement immediately. When thinking of fluid replacement, a few important principles should be kept in mind:

a) Estimating total fluid deficit in a child with DKA can be difficult: High concentrations of glucose in the extracellular space pulls water out of the cells and the osmotic diuresis maintains a relatively large urine output even when severe fluid depletion has occurred. Therefore, intravascular volume and urinary volume are not good indicators of the degree of total fluid deficit. A decreased urine excretion in the face of hyperglycemia is often a late sign of severe dehydration. Therefore, it is a good practice to start with an assumption of 10% dehydration in patients with severe DKA and 5-7% dehydration with moderate DKA.

b) Serum sodium is often falsely low due to dilution of the extracellular fluid (ECF) caused by high glucose concentration in this compartment. Corrected, true sodium concentration can be calculated by adding 1.6 x current measured serum glucose – 100 to the measured serum sodium. Serum urea nitrogen and hematocrit levels are more reliable indicators of the status of the ECF and can be used for monitoring changes in the ECF after fluid replacement.

c) While fluid repletion is essential, caution must be taken as to the speed of fluid administration. Rapid fluid infusion can result in rapid changes in the differential osmolality between the ECF and intracellular space, leading to a shift of water into the cells which is the main cause of cerebral edema. Naturally, when the peripheral circulation is compromised, resuscitation should be provided as quickly as possible using normal saline (or Ringer's lactate solution). Once adequate circulation and tissue perfusion have been established, it is essential to slow down the rates of fluid replacement. Additional boluses of fluids should be given over 1-2 hours whenever possible. Subsequently, fluid administration for deficit replacement must be provided evenly over the next 48 hours, and should not include replacement of ongoing urinary losses. At this stage, normal saline can be used for the initial 6 hours, followed by half normal saline, with

added potassium.

d) Fluid administration will result in a significant decrease in glucose concentration. Once serum glucose has decreased to 250-300 mg, a glucose-containing solution (5-12.5% dextrose) can be added to the saline solution as part of the fluid replacement. This is aimed at slowing down the rate of decrease in serum osmolality and to provide sufficient substrate for administering insulin (see below).

INSULIN

A major component of the acidosis in DKA is caused by the accumulation of ketones which is the result of absent or insufficient insulin secretion or action. While rehydration improves the hyperglycemia and acid-base status, it is insufficient to correct the pH back to normal. Insulin administration is essential for restarting glucose metabolism and halting fatty acid oxidation and further ketone production.

Because children's sensitivity to insulin varies markedly, starting with an intravenous insulin infusion provides the ability to titrate rapidly in response to changes in serum glucose, primarily to avoid hypoglycemia and relative rapid drops in serum glucose. Most children can start at a rate of 0.05-0.1 unit/kg/hour. Smaller children often require the lower end of this range; However, it is not surprising to occasionally see a toddler requiring up to 0.8 unit/kg/hour in the presence of a concomitant infection.

Insulin infusion rates can be titrated down if serum glucose concentrations are decreasing, but only if acidosis is correcting and the anion gap is closing. If not, it is important to keep the insulin infusion rates higher and increase the glucose infusion rate to raise serum glucose above 200 mg/dL. Failure to provide adequate insulin delays normalization of the acid base status.

POTASSIUM REPLACEMENT

An important consideration is potassium (K) replacement. Most children presenting with new onset DKA have a relative depletion of intracellular potassium even if initial serum K is in the normal range. Once hydration is provided and insulin is started, K shifts from the ECF into the intracellular space resulting in hypokalemia and potential arrythmias. Thus, K should always be added into the fluids administered for the slow phase of rehydration. On the contrary, it has been established that administration of bicarbonate should not be routine, and in fact may be harmful to the CNS, except in extreme cases with severe acidosis (pH <6.9) and severe hypokalemia.

LABORATORY MONITORING

Initial laboratory monitoring should include a CBC, a chemistry panel (Na, K, Cl, bicarb, BUN, Creatinine, glucose, Ca, Phosphate, Mg), and a venous blood gas. The chemistry panel and

blood gas should be done hourly initially, and can be reduced in frequency to every 2-4 hours after significant improvement in the clinical and the acid base status of the child. After complete resolution of the acidosis, laboratory monitoring can be less frequent, and should focus on serum K and phosphate. Assessment of serum glucose must continue at intervals of 3-4 hours and additional rapid acting insulin is provided when serum glucose values exceed 200 mg/dl.

Additional laboratory testing, which can be done after stabilization and resolution of the DKA, includes pancreatic auto-antibodies, thyroid function tests, serum total IgA level, and a tissue transglutaminase antibody measurement to screen for Celiac disease. Pancreatic auto-antibodies against the following 5 antigens should be included: Islet cells, GAD 65, Zn-T8, IA-2 (or ICA 512), and insulin. TSH and Free T4 should be done only after complete resolution of the acute phase of the illness and any concomitant infection to avoid falsely abnormal values.

**Follow-Up**

After recovery from the DKA and normalization of pH and anion gap, the child can be transitioned from intravenous to subcutaneous insulin administration. It is essential to recognize that subcutaneous insulin takes time to begin and reach peak action, which means that intravenous insulin should be continued for a few hours after the first injection of insulin. Ideally, iv insulin should be continued until 1-2 hours after the first injection of SQ rapid acting insulin (Aspart or Lispro), or 4 hours after the first injection of long acting insulin (Glargine or Detemir).

Although it is obviously important to differentiate between children with new onset T1D and T2D because of the implications for long term therapy, the initial management of DKA in both populations should not be different. With increasing rates of obesity in children, more youth are presenting with T2D at younger ages. It is thought that children who develop T2D at a younger age do so because of more progressive beta cell failure than in adults. Thus, the initial DKA at presentation with T2D is physiologically and biochemically similar to DKA in new onset T1D, with the main targets of therapy being fluid and insulin replacement. Measuring pancreatic auto-antibodies and documentation of careful family history, will eventually aid in differentiating T1D from T2D, especially in children who are overweight or obese.

**RECURRENT DKA**

When DKA occurs in a child with an established diagnosis of diabetes, it is almost always due to insulin omission (for a variety of reasons), inadequate administration of insulin, or relative insulin insufficiency due to inadequate adjustment of insulin dosing in the context of conditions that cause temporary insulin resistance, such as generalized or localized infections.

With wider use of insulin pumps, one of the most common causes of recurrent DKA, especially in young children, is unrecognized pump failure. Patients treated with an insulin pump receive only rapid acting insulin as a continuous infusion with superimposed boluses for meals and for correcting high blood glucose, without the use of long acting insulin. When pump failures occur, delivery of rapid acting insulin stops, and ketones can begin to accumulate within 2-4 hours. If

unrecognized and uncorrected within this time frame, mild-moderate DKA can result, with varying degrees of symptomatology, from minor nausea and stomach ache, to vomiting, headache, and acidosis.

Pump failures are often mechanical, ranging from a kinked or clogged catheter of the infusion set, to presence of air bubbles in the tubing (which can interrupt delivery of insulin for several hours, especially in small children), dislodging of the infusion set, or simply a spontaneous pump malfunction. Other common causes include use of ineffective insulin that has been degraded or contaminated, injection of insulin (by a pump or syringes) into a severely hypertrophied area, which interferes with insulin absorption, errors in programming the pump, and running out of insulin or battery in the pump, especially at night.

Management of DKA in these cases is similar to new onset DKA, often associated with faster recovery and return to baseline once insulin administration is initiated. It is important in such cases to work with the child and family to identify and remedy the cause of the DKA. Whenever possible, the treating physician should communicate with the diabetes provider(s) to arrange for prompt follow up with emphasis on specific training to avoid recurrence in the future.

Another common cause of recurrent DKA in adolescents is intentional insulin omission. Particular attention should be given to adolescents with history or evidence of eating disorders and recent weight loss, as they may be more sensitive to insulin than anticipated. Psychological evaluations and therapy should be arranged upon discharge of these patients.

**DKA WITHOUT HYPERGLYCEMIA IN T1D**

These cases are actually more challenging than those presenting with hyperglycemia, and are more prone to mismanagement. A typical scenario is that of a young child with T1D, who has not been eating well for at least one day due to a gastro-intestinal infection with or without vomiting and diarrhea. In young children, a greater proportion of the daily insulin is given for carbohydrate consumption, up to 75% of total daily dose. Therefore, a child who is not eating even for one day will miss significant amounts of insulin and begin the process of lipolysis very quickly and become ketonemic. The lack of food consumption is associated with euglycemia. Fluid loss in euglycemic DKA is modest because of the absence of an osmotic diuresis. If fasting is prolonged with extended consumption of glycogen stores, hypoglycemia can develop, along with ketonemia and acidosis.

A careful history review with the parents will clarify these scenarios and direct the management of DKA towards earlier start of intravenous glucose infusion and insulin administration to block further production of ketones. In these cases, even if the child is able to take some fluids orally, intestinal absorption is generally not optimal and should not be relied upon. With adequate intravenous hydration with intravenous or SQ insulin, the DKA can resolve fairly quickly.

These scenarios are not limited to small children and can certainly occur in older children and even adolescents with poor oral intake due to a GI illness, prolonged fasting, or severe

carbohydrate restriction. The management principles are similar and rely on providing glucose which in turn allows for more insulin dosing. The latter can be provided by intravenous infusion, SQ intermittent dosing, or even with an insulin pump if the child already has one, as long as there is adequate peripheral tissue perfusion to ensure appropriate absorption of insulin.

An emerging cause of euglycemic DKA is the use of a new class of drugs, the SGLT-2 inhibitors. Although still rare in children, some older adolescents with T1D or T2D are prescribed SGLT-2 inhibitors, which primarily cause forced glucosuria, preventing a rise in blood glucose, even when insulin boluses for food are omitted. Management of these cases is similar to what is described above in this section, and patients should be counseled against use of SGLT-2 inhibitors without further consultation with a pediatric endocrinology team.

One final note is in regard to patients who are using a continuous glucose monitor (CGM). With significantly improved accuracy of CGM devices, more and more pediatric patients are using CGM, which can be used for treatment decisions. However, in the presence of moderate to severe dehydration and impaired tissue perfusion, CGM readings may not be accurate and should not be relied upon in an emergency setting.

**DKA IN PATIENTS WITH T2D**

As stated above, generally speaking, when children develop T2D at such a young age, they are likely to have lost significant endogenous beta cell function. Most children with T2D are either treated with metformin alone, insulin alone, or a combination. Those who require insulin have little endogenous insulin and can develop DKA in the same way children with T1D do, and their DKA should be treated in the same way. Children on metformin or metformin + insulin, may have some insulin secretion capacity, but do not have the ability to increase their insulin production at times of physiological stress which exacerbates their insulin resistance. Therefore, if they do present with DKA, this is an indication of relative insulin insufficiency and they should also be treated similarly to children with T1D. These scenarios include a special group labelled ketosis-prone T2D, who can be effectively treated with metformin alone, but have a tendency to develop DKA despite sufficient insulin production capacity at baseline conditions.

Because of their general insulin resistance, children with T2D presenting with recurrent DKA generally have concomitant hyperglycemia and rarely present with DKA and euglycemia except when treated with SGLT-2 inhibitors as described above.

A special group that is being recognized more often lately are children with monogenic diabetes, who can eventually progress towards partial insulin insufficiency and can present for the first time with either new onset or recurrent DKA. In particular, maturity onset diabetes of the young (MODY) type 1 and 3 are the most common. They usually have negative pancreatic auto-antibodies, their phenotype is not suggestive of insulin resistance, and there is a strong family history of non-type 1 diabetes in several generations. Once again, when presenting in DKA their management follows the same principles.

## HYPOGLYCEMIA

Hypoglycemia is the most common acute complication of diabetes in children and represents the greatest challenge in managing children with diabetes. Surprisingly, the definition of hypoglycemia in children remains controversial and somewhat nebulous, and varies for different ages.

### Clinical Recognition

While in the general population, a blood glucose (BG) level of <70 mg/dL is considered low (hypoglycemia) and results in clinical symptoms, children with diabetes spend significant time with BG levels above 200 mg/dL, thus shifting upward the brain threshold for exhibiting signs and symptoms of hypoglycemia. Conversely, recent episodes of hypoglycemia can shift downward the threshold for exhibiting and recognizing hypoglycemia. Recent consensus statements from the American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) have defined hypoglycemia in a child with diabetes as any BG level that results in symptoms or signs of impaired cognitive function. These hypoglycemic levels frequently change as the range of BG levels shift up or down over time, even within short periods of time.

In the context of diabetes, any level of hypoglycemia (resulting in symptoms) can be considered an emergency because of the potential for the BG level to drop further within minutes. Therefore, any BG <70-80 mg/dL is generally considered a “hypoglycemia alert” and should be managed urgently. This is particularly true in children with diabetes because of their higher sensitivity to both insulin and physical activity, resulting in more rapid drops in BG levels.

The current consensus is that a true emergency is considered a BG <54 mg/dL (3 mMol/L), a level that indicates a clinically important hypoglycemia that is likely to be associated with defective counter-regulatory response and impaired cognitive function. At these levels, a child is at a much higher risk for more severe cognitive impairment**,** with or without loss of consciousness or seizure, and requiring external assistance (severe hypoglycemia).

### Pathophysiology

By far the most common cause of hypoglycemia in children with diabetes is excess insulin. Most children are treated with intensive insulin therapy with a basal/bolus regimen, by multiple daily injections or via an insulin pump. Boluses of rapid acting insulin are determined for each meal based on current BG value at the time before the meal and on the amount of carbohydrates (carbs) to be consumed in that meal. This requires fairly accurate carb counting, followed by entry of the estimated carbs and the BG number into a dose calculator, which can be a simple sliding scale hard copy sheet, a smart phone app, or a smart insulin pump. This process involves multiple steps, which naturally presents opportunities for estimation and transcription errors, leading sometimes to over-dosing of insulin.

A common scenario, especially in young children, is refusal to eat or to finish a meal after a bolus had been given, or vomiting shortly after a meal. A history of repeated episodes of vomiting and/or repeated hypoglycemia after meals in an adolescent should alert the provider to the possibility of an eating disorder.

The second frequent cause of hypoglycemia in children is exercise. Patients and caregivers are trained on adjusting insulin dosing to compensate for the enhanced sensitivity to insulin during and after any physical activity. These include lowering doses of long acting insulin or rapid acting insulin, lowering a bolus amount for the meal before or after exercise, or consuming extra carbs which are not dosed for. For patients on insulin pumps, a temporary basal rate reduction for several hours beginning before the activity is planned is often necessary. Omission of such adjustments can lead to hypoglycemia which can occur during or up to few hours after the exercise.

**Management**

Most hypoglycemic episodes in children should be managed in a timely manner, at the patient location, such as home, school, or sports fields, to avoid extended brain deprivation of glucose and prevent acute and long-term sequelae. Parents of children and persons with diabetes who are taking insulin or insulin secretagogues (sulfonylureas), should be trained to recognize the signs and symptoms of hypoglycemia and how to manage hypoglycemia.

Once a child exhibits signs of hypoglycemia, treatment should be initiated after measuring the BG regardless of level. If the child is cooperative and able to take anything by mouth, simple and fast absorbing carbohydrates should be given. Examples include glucose tablets, clear juice, soda, regular sugar, cake frosting, and a variety of candies. In late adolescents, like in adults, 10-20 grams of carbs can be given to treat any hypoglycemia, and can be repeated 15 minutes later if needed. However, in smaller children, it is imperative to recognize that smaller amounts of carbs should be used to prevent a rebound hyperglycemia. As little as 2-4 grams are often sufficient in toddlers to raise the BG 30-60 mg/dL.

If a child is combative, unconscious, or seizing, oral treatment should not be attempted, as this carries the risk of aspiration or injury. Instead, glucagon should be given intramuscularly as soon as possible. For most children, a dose of 0.5 mg (half the amount provided in glucagon emergency kits) is effective in raising BG to >100 mg/dL, but up to 1.0 mg can be given to older adolescents. Although rare, a dose of glucagon can be repeated within 30 minutes if the BG level does not rise above 100 mg/dL.

**HYPERGLYCEMIC HYPEROSMOLAR STATES**

The hyperglycemic hyperosmolar state (HHS) is very rare in children, but is worth reviewing because of the associated high mortality rate, which approximates 20%. As the name indicates, HHS is characterized by severe hyperglycemia, hyperosmolarity, and dehydration in the absence of ketoacidosis. Treatment of HHS is directed at replacing the usually severe fluid

deficit and slowly correcting the hyperglycemia, osmolality, and electrolyte disturbances with low-dose insulin infusion similar to treating DKA.

**Pathophysiology**

HHS is typically initiated by severe hyperglycemia caused by both relative insulin deficiency and elevation of counter regulatory hormones, which cause a decrease in peripheral glucose utilization and increase glucose production, respectively. The resulting severe hyperglycemia leads to polyuria and severe dehydration, with subsequent decrease in glomerular filtration and glucose clearance, which further exacerbates the hyperglycemia and hyperosmolality. The absence of ketones in HHS is attributed to the relative but not absolute deficiency of insulin, and the higher insulin to glucagon ratio than that in DKA.

As in adults, HHS occurs in children with T2D, but it can also be the first presentation of new onset T1D, caused by use of beverages with high carbohydrates, such as regular soda or juice, to alleviate the accompanying polydipsia. Other common precipitating factors of HHS are infections, cystic fibrosis, and use of certain anti-psychotic medications.

**Diagnosis**

The progression of HHS is typically slower than DKA, resulting in delayed diagnosis and presentation with more severe hyperglycemia, dehydration, and altered mental status. Diagnostic criteria for HHS include a BG >600 mg/dL (33.3 mmol/L), absence of appreciable acidosis (pH>7.30 and bicarb >15), anion gap <12, and an effective serum osmolality >320 mmol/kg. Recent consensus guideline recommended calculating the effective serum osmolality as [2 (serum Na)] + [glucose in mmol/L]. This is based on the fact that altered mental status is usually manifest at serum Na >160 mmol/L, or calculated effective serum osmolality >320 mmol/L.

**Treatment**

The main objectives of treating HHS are very similar to treating DKA: restoration of circulatory volume and tissue perfusion; correction of hyperglycemia and electrolyte imbalance; and identification and treatment of the precipitating event(s). Because HHS is rare in children, most published guidelines are based on experiences with adults. Therefore, practical management of HHS in children follow the same guidelines as for DKA, including estimation of fluid deficit, careful replacement of the deficit after initial management of shock if present, keeping in mind that fluid administration results in significant decrease in BG concentration and drop in serum osmolality. Once osmolality stops declining, insulin infusion can be started while fluid replacement continues, with the goal of maintaining BG at 250-300 mg/dL.

**GUIDELINES**

Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, Lee WW, Mungai LN, Rosenbloom AL, Sperling MA, Hanas R; ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. International Society for Pediatric and Adolescent Diabetes. Pediatr Diabetes. 2014 Sep;15 Suppl 20:154-79

Jones TW. On behalf of the ISPAD hypoglycemia guidelines writing group. Defining relevant hypoglycemia measures in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2018; 19:354-355.

**REFERENCES**

Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic Crises: Diabetic Ketoacidosis (DKA), And Hyperglycemic Hyperosmolar State (HHS). In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000- 2018 May 17

Spanakis EK, Cryer PE, Davis SN. Hypoglycemia During Therapy of Diabetes. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000- 2018 Jun 18.

Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol. 2016 Apr;12(4):222-32.

Dayna E. McGill & Lynne L. Levitsky. Management of Hypoglycemia in Children and Adolescents with Type 1 Diabetes Mellitus. Current Diabetes Reports (2016) 16(9): 88.

Dhatariya KK, Vellanki P. Treatment of Diabetic Ketoacidosis (DKA)/Hyperglycemic Hyperosmolar State (HHS): Novel Advances in the Management of Hyperglycemic Crises (UK Versus USA). Current Diabetes Reports. 2017 May;17(5):33.

Yau M, Sperling M. Treatment of Diabetes mellitus in Children and Adolescents. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000- 2017 Sep 25

Bialo SR, Agrawal S, Boney CM, Quintos JB. Rare complications of pediatric diabetic ketoacidosis. World J Diabetes. 2015 Feb 15;6(1):167-74

Jefferies CA, Nakhla M, Derraik JG, Gunn AJ, Daneman D, Cutfield WS. Preventing Diabetic Ketoacidosis. Pediatr Clin North Am. 2015 Aug;62(4):857-71