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Diabetic Ketoacidosis In Children: From Early Recognition To Optimal Management

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Abstract: Diabetic ketoacidosis is an acute complication of diabetes associated with severe metabolic impairment. The condition is commonly encountered in the pediatric diabetic population and necessitates prompt response by the parents and the healthcare team. Education about the condition and the various clinical features helps in providing expedited care to the children.
Aim: To objectively review the latest methodology for treatment guidelines for the management of diabetic ketoacidosis in pediatric patients.
Materials and methods: This review is a comprehensive search of PUBMED from the year 2015 to 2025.
Conclusion: Diabetic ketoacidosis is a medical emergency that is involved with mortality and morbidity in pediatric patients. Management of patients with DKA requires expeditious and accurate diagnosis and treatment regimen establishment. It is essential to be up to date with the latest therapy guidelines and treatment modalities to minimize the risk of loss of life and the economic costs associated with prolonged hospital stays for managing complications.

Keywords: Diabetic Ketoacidosis; Children; Management; Pediatric patients; Cerebral Edema

Introduction

Diabetes ketoacidosis (DKA) is an acute metabolic state that is caused by insulin deficiency in diabetes mellitus. It is most associated with type 1 diabetes, but can be seen with other types of diabetes. DKA can be potentially fatal as it accounts for approximately 3-5% mortality. It is caused by acidosis when the ketone levels are not compensated for by the body's buffering capacity. The symptoms of the condition develop rapidly. [1]

Pathophysiology

DKA is primarily seen due to an absolute or relative insulin deficiency in type 1 diabetes mellitus (T1DM), which is caused by autoimmune degeneration of the β-cells of Langerhans islet cells and associated increase of counter-regulatory hormones that are stimulated by stress, such as glucagon, growth hormone, catecholamines, and cortisol. It is also caused by uncontrolled T1DM. [2] Other causes include the presence of concurrent illness such as pneumonia, influenza, gastroenteritis, pregnancy, inadequate administration of insulin, myocardial infarction, stroke, or cocaine use. Younger individuals who undergo recurrent DKA episodes might have underlying eating disorders or might be using an insufficient quantity of insulin because of fear of weight gain.[3]

Certain drugs, such as SGLT2 inhibitors- gliflozin, have been associated with the development of diabetic ketoacidosis, wherein the blood glucose level is not significantly elevated – euglycemic DKA. It is an uncommon adverse effect but can be observed in patients being administered SGLT2 inhibitors, who also receive insulin. It can be triggered by events such as severe acute illness, extensive exercise, dehydration, surgery, low-carbohydrate diets, or excessive alcohol intake.[4] Perry et al hypothesized that SGLT2-inhibitor-induced ketosis is caused by volume depletion, in combination with relative insulin deficiency and glucagon excess.[5] The mechanism for DKA is based on insulin deficiency in the body.[6] This state of deficient insulin, along with a corresponding increase in glucagon, results in increased conversion of glycogen to glucose via glycogenolysis and gluconeogenesis by hepatic tissue.[7] Osmotic diuresis takes place as the high concentration of glucose in urine causes increased secretion of water and other electrolytes, such as sodium and potassium, in the urine. This results in polyuria, dehydration, and polydipsia. The absence of insulin leads to lipolysis in the liver, which results in the formation of acetyl-CoA from free fatty acids.[8]

This acetyl-CoA gets metabolized into ketone bodies in conditions where the body is under severe energy deficiency, like starvation. In insulin-deprived states, the ketone bodies act as an energy source but consequently decrease the blood pH- metabolic acidosis. This acidosis is countered by the buffering mechanisms of the body, such as hyperventilation (characteristic Kussmaul respiration in DKA). As in diabetes, there is either insufficient insulin production- T1DM or insufficient insulin response- type 2 DM, the patients are likely to develop DKA.[8] This results in adult patients experiencing a shortage of total body water of up to 6 liters or 100 mL/Kg, with additional deficits seen in electrolytes such as sodium, potassium, calcium, chloride, and phosphate. The glucose levels can be elevated up to 13.8mmol/L or 250 mg/dL.[9]

Diagnosis of Diabetes Ketoacidosis

Signs and symptoms

An episode of diabetes ketoacidosis develops symptoms over a period of several hours after the inciting event. These symptoms range from nausea, vomiting, polydipsia, polyuria, weakness, mentation changes, and unintentional weight loss. Dehydration and metabolic abnormalities deteriorate progressively with uncontrolled osmolar stress, consequently resulting in lethargy, obtundation, and even grave outcomes such as respiratory failure, coma, and death. DKA patients also commonly report abdominal pain.[6] In severe DKA, the patients present with a breathing pattern that becomes rapid and has a deep, gasping character- Kussmaul breathing. A ketotic odor due to acetone can also be present, which is often described as ‘fruity’ or ‘like pear drops’. [3] On physical examination, there is presentation of dehydration with dry mucous membranes and poor turgor of skin, tachycardia, and hypotension. In addition, Kussmaul respiration and acetone breath can also be observed.[10]

History and presentation

In pediatric patients, DKA is a consequence of insulin deficiency or a surge in insulin requirements. The insulin deficiency can result from undiagnosed T1DM, a gap in insulin therapy, or failure of an insulin pump, along with an increase in the requirement of insulin in conditions with elevated counter-regulatory hormones, such as adrenaline, which can be triggered by sepsis or trauma.[9] Oko et al reported that in 52.7% of observed cases were triggered by infection.[11] Though most patients do not report comorbidities, Alradadi reported that 7.4% of the patients with DKA also had celiac disease. Patients with concurrent T1DM and celiac disease experience inconsistent blood glucose levels, hypoglycemia, and glycemic deterioration.[12]

The incidence rate for DKA for patients under the age of 5 years is reported to be as high as 56.7%.[13] Alradadi et al reported the highest frequency of incidences by female patients, who might be underweight and aged 0-3 years.[12] The factors should be considered for T1DM patients who might be at risk for developing DKA: younger age at diagnosis, ethnic minority populations, low socioeconomic groups, history of psychiatric disorder- eating disorders or drug and alcohol misuse, unstable family circumstances, poor compliance with therapy or poor control of blood glucose, concurrent illness, and peripubertal and adolescent girls.[9] Kostopoulou et al also noted that adolescent patients with T2DM can also present with DKA. These patients can have a genetic predisposition for ketosis-prone T2DM, wherein they have a family history of insulin resistance, and frequently can have obesity. They present

with reduced insulin concentrations and autoimmune markers for T1DM; however, treatment restores their β-cell function and insulin secretion.[14]

Investigation

In a patient with suspected DKA, the initial laboratory evaluation involves blood glucose levels, ketones, blood urea nitrogen, creatinine, electrolytes, calculated anion gap, arterial blood gas, osmolality, complete blood count with differential, blood cultures, and urine studies involving ketones, urinalysis, urine culture, chest radiography, and electrocardiography.[6] Hyperglycemia is typically found in DKA, but a range of plasma glucose levels can be present, with 10% patients exhibiting euglycemic diabetic ketoacidosis.[15] Though ketone bodies are elevated in DKA, a negative report should not exclude the diagnosis of DKA due to the limitation of the laboratory methods being used, especially since beta-hydroxybutyrate which is the chief ketone in DKA, is not detected by the sodium nitroprusside test.[6] Caution should be adhered to as patients being administered antiepileptics like sodium valproate might give false positives with the nitroprusside test.[14] As ketones are unmeasured anions, the anion gap is also elevated. Leukocytosis can also be reported due to an underlying infection from any of the samples- blood, urine, or any other.[6] Glaser reported findings of pyuria in 19% of the pediatric DKA cases observed in their study- suggestive of acute kidney injury.[16]

Due to the osmotic interaction of glucose and sodium ions, relatively low levels of serum sodium can be noted; therefore, elevated sodium levels are indicative of severe volume depletion. Serum potassium may also be elevated due to intracellular compartment shifts necessitating electrolytic correction before initiation of insulin therapy.[6] Electrocardiography can demonstrate findings such as QTc interval prolongation in DKA. It was also observed in children with long-term diabetes, without ketoacidosis. This results from sympathetic and parasympathetic dysfunction, which can result in sudden death of the patient. It is more commonly associated with hypokalemic states in children.[17] The biochemical diagnostic criteria for DKA involve the following in Table 1.[18]

TABLE 1: Diagnostic criteria for DKA [18].

BIOCHEMICAL CRITERIA	
Hyperglycemia	Blood glucose ≥ 11 mmol/L or approx. 200 mg/dL
Venous pH/ serum bicarbonate	Venous pH <7.3 or serum bicarbonate < 18mmol/L
Ketone bodies	Ketonemia (blood beta-hydroxybutyrate ≥ 3mmol/L) or moderate or large ketonuria

After the establishment of ketoacidosis diagnosis, severity assessment should be conducted. Based on the BSPED guidelines, the degree of acidosis aid to provide an indicator for the extent of dehydration, thus guiding fluid replacement therapy.[19]

Table 2: Assessment of severity of DKA. [19]

DEGREE OF ACIDOSIS	**DEGREE OF DEHYDRATION (%)**
Mild: venous pH <7.3 or bicarbonate <15 mmol L−1	5
Moderate: pH <7.2 or bicarbonate <10 mmol L^{-1}	5
Severe: pH <7.1 or bicarbonate <5 mmol L^{-1}	10

Management of Diabetic Ketoacidosis

Diabetic ketoacidosis is a medical emergency that requires the ABC approach with early iv access and placement of a nasogastric tube, in the presence of concerns for loss of consciousness or vomiting. The BSPED guidelines recommend management strategies depending on the severity of dehydration. These guidelines involve the use of crystalloid fluids to manage dehydration and the associated shock,

followed by insulin therapy along with electrolytic correction.[19] Water and salt replacement is needed for the deficits, and on the basis of the hydration status, a 10-20 mL/kg bolus with 0.9% normal saline might be required for 1-2 hours. Kostopoulou emphasized the close monitoring of neurological status and vital signs during fluid administration. Hourly documentation of water balance and glucose levels should be done along with documentation of electrolyte concentration every 2-4h. [14] Wright suggests the following as aims of DKA management: restoration of circulating volume, restoration of glucose for intracellular processes, monitoring for complications- especially cerebral edema, and investigation of underlying causes.[9]

The management of DKA involves the following:

1. Fluid Replacement

Previously, fluid replacement was restricted in DKA, especially in pediatric patients, due to the potential consequence of developing cerebral edema. Hence, the aim of therapy is ensuring rehydration for the child, whilst minimizing risks for cerebral edema. The approach is based on the Pediatric Emergency Care Applied Research Network (PECARN) study, where no significant differences in the outcomes, such as alteration of mental status or diagnosis of cerebral edema, were found between fast or slow infusion rates, or with the use 0.45% saline or 0.9% saline.[20]

Multiple guidelines provide similar approaches for rehydration goals, but varying degrees of fluids being administered to replace the circulating volumes. The 2020 update to NICE NG18 guidelines recommend 20 mL/kg bolus of 0.9% saline over 15 minutes in case of suspected shock. In contrast, the UK Resuscitation Council suggests 10mL/kg boluses that are repeated depending on the requirements of the patient. They also recommend the use of isotonic crystalloids for treatment of shock, only to be substituted by 0.9% saline in case of unavailability. The BSPED guidelines align with the UK Resuscitation Council guidelines.[21] The ISPED and NICE guidelines recommend an initial bolus of 20 ml/kg.[22] For patients not in shock, the initial bolus of 10 mg/kg should be given over 30 mins, instead of the previously recommended 60 minutes.[21]

The BSPED, ISPED, and NICE guidelines recommend that the fluid deficits be replaced within the first 48h of hospital admission. Any volume of fluid already given should be subtracted from the overall fluid being given, except for the volumes given for shock. To avoid overhydration in patients with obesity, the ideal body weight should be avoided. [9] The maximum weight considered for the BSPED guideline is 75 kg, with the maintenance fluids being calculated at 100 ml/kg/day for the first 10 kg body weight, plus 50 ml/kg/day for 10 to 20 kg, and 20 ml/kg/day for each additional kilogram above 20 kg.[21]

Brown et al recommended that overweight and obese children and youth should not receive fluid at lower rates, as it not only increases the risk of hypophosphatemia, but also does not show any mental alteration, elevated risk for cerebral injury.[23] Rewers demonstrated that rapid infusion helped to reduce the anion gap 2-3h earlier than a slow infusion rate.[24] To ensure the complete resolution of ketonemia and acidosis, insulin therapy must be maintained even after plasma glucose concentrations fall below 11 mmol/L (200 mg/dL). To prevent the risk of hypoglycemia, dextrose should be introduced into the fluid replacement regimen, enabling the sustained insulin delivery necessary to correct the underlying metabolic state. [25]

2. Insulin Therapy

Insulin therapy is required to halt ketosis and stimulate the metabolism of existing ketoacids to bicarbonate.[9] Treatment with insulin should be commenced soon after the diagnosis of T1DM is established and within six hours of ketosis to prevent DKA.[12] In most cases, insulin must be dispensed in low dose iv infusion at 0.05 units/kg/h, unless the severity of DKA is grave. The risk of subsequent hypoglycemia also declines, especially in children aged <5 years. At no stage in the treatment should insulin be administered as a bolus dose, and if an insulin pump is being used, IV infusion should not begin before it stops. Long-acting insulin should be continued in prescribed patients alongside iv infusion.[19] DKA should be resolved before the infusion is stopped i.e. pH >7.3; serum bicarbonate >15 mmol L^{-1}; ketones <1 mmol L^{-1}. This elongates the duration of therapy as it takes longer than reducing plasma glucose concentration. Plasma glucose concentration should not be utilized as an indicator for

halting insulin therapy unless it is extremely low.[9] Insulin management in a critical part of T1DM treatment. Doses are required to be adjusted according to the needs to the patient, as obese and pubertal patients require higher doses due to increased insulin resistance. Compared to children without DKA, post-DKA children require higher insulin doses due to lower insulin sensitivity.[12]

3. Electrolytic and Acid- Base Correction

Sodium concentration can be altered by osmotic forces in hyperglycemic conditions, leading to dilutional hyponatremia. Upon treatment of DKA and correction of blood glucose concentration, the sodium concentration should improve. But the failure of sodium correction is indicative of free water in circulation, which can predispose to cerebral edema. There are recommendations for monitoring of corrected sodium concentration, which is defined as (corrected sodium [mmol L^{-1}] = measured Na^{+}+ [[plasma glucose–5.6]/3.5]), an alternative to serum sodium concentration as it is a better indicator of sodium-water deficit in the body.[9]

Metabolic acidosis, in addition to insulin deficiency, can induce extracellular movement of potassium. The serum potassium levels are not indicative of the condition of the patient, as the levels might be normal or elevated in an otherwise depleted patient. Insulin therapy aids in decreasing serum potassium levels by promoting intracellular movement. Replacement of potassium should be initiated when the level is <5.2 mEq/L up to a maintenance level of 4–5 mEq/L. [10] It is recommended that potassium replacement be started in addition to insulin therapy, even if the potassium levels are normal. The maximum rate of potassium replacement should be 0.5 mmol/kg/h. [14]

Administration of large volumes of 0.9% saline during recovery phase can predispose the patient to hyperchloremic metabolic acidosis. Though not a fatal condition, hyperchloremic metabolic acidosis can delay the transition to subcutaneous insulin therapy if the diagnosis of DKA is based on serum bicarbonate concentration.[14] Use of crystalloid fluids with lower chloride content, such as Plasma-Lyte or compound sodium lactate, can help reduce the potential development of hyperchloremic acidosis.[9]

Monitoring of progress

Regular monitoring of the patient's vitals, along with other markers such as capillary glucose, venous pH, bicarbonate, $PaCO_2$, and blood ketone concentrations, should be examined every 2-4h or more frequently, depending on the indication. An urgent review is essential in case of lack of response to treatment. The causes for persistence of ketosis can be due to insufficient insulin, inadequate resuscitation, sepsis, hyperchloremic acidosis, and salicylates or other drugs.[19] The recommendation is to increase the insulin infusion by 0.1units/kg/h if the blood ketone concentration does not reduce within 4-6h. [9] With the exception of poor cardiac function secondary to refractory hyperkalemia or severe acidosis, sodium bicarbonate should not be administered in DKA, and only under the supervision of a pediatric intensivist.[22]

Complication of Diabetes Ketoacidosis

1. Acute Kidney Injury (AKI)

It is a commonly encountered complication of DKA seen in pediatric populations. The incidence rate of AKI is 43%-68% in pediatric cases of DKA.[27] AKI is caused by intrinsic tubular dysfunction, in addition to poor renal perfusion. [28] Early diagnosis and management of AKI is necessary as potassium repletion therapy cannot be initiated in case of renal dysfunction. Potassium replacement should be delayed until urine output is documented.[29] AKI is linked with a substantial risk for the development of microalbuminuria, which can develop into diabetic kidney disease. Therefore, it is imperative to establish timely fluid replenishment to prevent AKI and any associated complications.[30]

2. Cerebral Edema

Cerebral edema is fatal complication of DKA. It is more prevalent amongst pediatric patients than adult patients of DKA. It accounts for nearly 25% mortality rate in children with DKA. 0.3-0.9% cases of DKA in children exhibit severe cerebral edema.[9] The prevailing theory suggests that cerebral edema stems from ischemia-reperfusion injury, with its development further exacerbated by inflammatory responses and impaired cerebrovascular regulation.[31]

The risk factors for cerebral edema include: younger age, severe DKA, elevated serum urea concentration, severe hypocapnia, attenuated increase in serum sodium, new onset diabetes, and treatment with sodium bicarbonate. Cerebral edema presents with sudden onset of headache or progressively worsening or severe headache, hypertension, unexpected fall in heart rate, change in neurological state- including restlessness, irritability, drowsiness and confusion, presence of any neurological deficit- such as cranial nerve palsies, and abnormal respiratory pattern (e.g., Cheyne–Stokes), and recurrence of emesis. The presence of acute and long-term cognitive impairment and memory in children with a history of DKA is indicative of cerebral injury, even in the absence of overt evidence of injury. [9][31]

The management for cerebral edema involves: ABCDE approach, administration of 3% hypertonic saline (3-5 mL/kg) or mannitol (0.5-1g/kg), reduction of fluids to half the maintenance rate, neuroprotective strategies such as: elevation of head of the bed by 30 degrees, avoidance of hypotension, intubation in case of severe respiratory or neurological compromise. Head CT scan to be performed to rule out any other underlying causes.[19]

3. Other complications

Additional complications of DKA in children include hypoglycemia, venous thrombosis, rhabdomyolysis, pulmonary edema, cardiac arrhythmias, and pancreatic enzyme elevation.[14]

Venous thrombosis is observed following the placement of a central venous catheter (CVC) in the femoral line. It is more common in children with DKA than in those with CVC placement for non-DKA causes. Thromboprophylaxis should be considered if CVC placement is necessary, and it should be removed at the earliest possible opportunity.[9] To mitigate the risk of aspiration pneumonia in a child with a decreased level of consciousness (obtunded) who is vomiting, a nasogastric tube should be placed immediately to drain gastric contents.[9] Rhabdomyolysis can occur in patients with DKA. It can increase the risk for acute kidney injury and presents with a triad of symptoms including myalgia, weakness, and dark urine. Creatine kinase should be monitored every 2-3h for early detection.[10]

Differential diagnosis

The differential diagnosis for diabetic ketoacidosis ranges a wide range of condition ranging from gastroenteritis, starvation ketosis, myocardial infarction, hyperosmolar hyperglycemic nonketotic syndrome, pancreatitis, alcoholic ketoacidosis, lactic acidosis, sepsis, Toxicologic exposure (ethylene glycol, methanol, paraldehyde, salicylate), diabetic medication overdose, uremia, respiratory acidosis, and respiratory distress syndrome. Careful examination and timely diagnosis are essential to ensure that there is no fatality or any complications. [29]

Conclusion

Diabetic ketoacidosis is a medical emergency that is involved with mortality and morbidity in pediatric patients. Management of patients with DKA requires expeditious and accurate diagnosis and treatment regimen establishment. It is essential to be up to date with the latest therapy guidelines and treatment modalities to minimize the risk of loss of life and the economic costs associated with prolonged hospital stay for managing complications.

Author contributions

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The authors declare no conflict of interest, financial or otherwise.

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Not Applicable

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