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Chapter 11

Diabetic Ketoacidosis: Clinical Practice Guidelines

Shereen Abdelghaffar

Additional information is available at the end of the chapter

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1. Introduction

Diabetic ketoacidosis (DKA), the most common endocrinal emergency remains a life-threatening condition despite improvements in diabetes care [1]. The mortality and morbidity rates remain high worldwide, especially in developing countries and among non-hospitalized patients [2,3], which highlight the importance of early diagnosis and implementation of effective preventive and management strategies. The adage "The child is not a miniature adult" is most appropriate when considering DKA. The fundamental pathophysiology of DKA is the same in children as in adults; however, the child differs from the adult in a number of characteristics which raise some important considerations in management [2].

The purpose of this chapter is to briefly review the pathophysiology of DKA and discuss recommended treatment protocols and current standards of care pertaining to children, adolescents and adults with type 1 or 2 diabetes presenting with DKA. The information provided is based on evidence from published studies and internationally accepted guidelines whenever possible and, when not, supported by expert opinion or consensus [1-5]. Current concepts of cerebral edema, recommendations and strategies for the prediction and prevention of DKA and hence its complications are finally presented.

The considerations and recommendations included are in agreement with those endorsed by the American Diabetes Association (ADA), Lawson Wilkins Pediatric Endocrine Society (LWPES), European Society for Pediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD) [2-5]. Thus, this book chapter will provide easy and practical information to guide healthcare professional who manage DKA in all age groups.

2. Definition of Diabetic Ketoacidosis (DKA)

The biochemical criteria for DKA include the following triad [4]:

- Hyperglycemia (blood glucose >11 mmol/L [200 mg/dL])
- Venous pH <7.3 and/or bicarbonate <15 mmol/L
- Ketonemia and ketonuria

3. Pathophysiology of DKA

Diabetic ketoacidosis (DKA) results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counterregulatory hormones: catecholamines, glucagon, cortisol and growth hormone [5].

Absolute insulin deficiency occurs in the following conditions:

- undiagnosed type 1 diabetes mellitus (T1DM); DKA is reported be the first presentation in about 25% of cases especially in those less than 5 years old [2].
- patients on treatment who miss their insulin doses, especially the long-acting component of a basal-bolus regimen. It is estimated that 75% of DKA episodes are associated with insulin omission or treatment error [6].
- patients who use insulin pump if insulin delivery fails [7].

Relative insulin deficiency, on the other hand, occurs when the concentrations of counterregulatory hormones increase in response to stress in conditions such as:

- sepsis,
- trauma, or
- gastrointestinal illness with diarrhea and vomiting.

The combination of low serum insulin and high counterregulatory hormone concentrations results in an accelerated catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis), impaired peripheral glucose utilization resulting in hyperglycemia and hyperosmolality, and increased lipolysis and ketogenesis, causing ketonemia and metabolic acidosis [4].

Hyperglycemia and hyperketonemia cause osmotic diuresis, dehydration, and electrolyte loss. This stimulates stress hormone production, which induces insulin resistance and leads to a vicious circle, worsening the hyperglycemia and hyperketonemia. Fatal dehydration and metabolic acidosis will ensue if management is not initiated. Poor tissue perfusion or sepsis may lead to lactic acidosis which can aggravate the ketoacidosis [5].

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At presentation, the magnitude of specific deficits of fluid and electrolytes in an individual patient varies depending upon the extent to which the patient was able to maintain intake of fluid and electrolytes, and the content of food and fluids consumed before coming to medical attention and the duration and severity of illness [8].

4. Epidemiology of DKA

There is wide geographic variation in the frequency of DKA at onset of diabetes; rates inversely correlate with the regional incidence of type 1 diabetes. Frequencies range from 15 to 70% in different regions of the world [9 -14].

4.1. Frequency of DKA

At disease onset

DKA at diagnosis of type 1 diabetes occurs more commonly in [15,16]:

- children younger than four years of age
- children with absent first-degree relative with T1DM and
- families of a lower socioeconomic class

Type 2 diabetes mellitus (T2DM), associated with increased rates and severity of obesity, may account for as much as one half of newly diagnosed diabetes in those aged 10 to 21 years, depending on the socioeconomic and ethnic composition of the population [2]. Acute decompensation with DKA has been recognized to occur at the time of diagnosis in as many as 25% of children with type 2Diabetes Mellitus (T2DM0 [17].

In children with established diabetes (recurrent DKA)[4]

The risk of DKA in established T1DM is 1–10% per patient per year

Risk is increased in the following conditions [18]:

- poor metabolic control or previous episodes of DKA
- peripubertal and adolescent girls
- psychiatric disorders, including those with eating disorders
- difficult or unstable family circumstances
- omission of insulin
- limited access to medical services
- insulin pump therapy

4.2. Diagnosis of DKA

Although DKA is defined by the biochemical triad of ketonemia, hyperglycemia and acidemia, several exceptions do exist which may provide a diagnostic dilemma for the physician in the emergency room. Examples of such are:

- "**Euglycemic ketoacidosis''**: Partially treated children and children who have consumed little or no carbohydrate may present rarely with mildly increased blood glucose concentrations [19].
- **Absent or mild metabolic acidosis, ketonemia and ketonuria**: This may occur in the Hyperglycemic Hyperosmolar State (HHS) or if the patient experiences severe vomiting which may lead to alkalosis which can mask the present acidosis.
- Hyperglycemic hyperosmolar state (HHS), also referred to as hyperosmolar nonketotic coma, may occur in young patients withT2DM, but rarely in T1DM subjects. The criteria for HHS include [20-22]:
  - plasma glucose concentration >33.3 mmol/L (600 mg/dL)
  - arterial pH >7.30
  - serum bicarbonate >15 mmol/L
  - small ketonuria, absent to mild ketonemia
  - effective serum osmolality >320 mOsm/kg
  - stupor or coma

It is important to recognize that overlap between the characteristic features of HHS and DKA may occur. Some patients with HHS, especially when there is very severe dehydration, have mild or moderate acidosis. Conversely, some children with T1DM may have features of HHS (severe hyperglycemia) if high carbohydrate containing beverages have been used to quench thirst and replace urinary losses prior to diagnosis [22].

- Other diagnostic difficulties may be faced in the very young age such as the following [2]:
  - Polyuria, polydipsia and weight loss which are characteristic features of diabetes are difficult to demonstrate in the very young.
  - up to 70% of the young have DKA as a first presentation, hence, at presentation, duration of DKA is usually longer, dehydration and acidosis are more severe, as young children have relatively higher basal metabolic rate, and a relatively large surface area relative to body mass.
- Measurement of blood ß-hydroxybutyrate (ß -OHB) concentration, may not be available in all labs, besides, urine Ketone testing can be misleading due the following reasons [2,4]:
  - The used method does not detect the major ketone body B-hydroxybutyrate. (sodium nitroprusside only measures acetoacetate and acetone). Serum ß-OHB concentrations,

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may be increased to levels consistent with DKA when a urine ketone test is negative or shows only trace or small ketonuria

- The readings are qualitative depending on color comparisons
- High doses of Vitamin C may cause false-negative results, while some drugs may, on the other hand, give false-positive results.

5. Management of DKA

5.1. Goals of therapy

Management of DKA should be mainly directed to correction of acidosis. Immediate aims of management include [1,4]:

- Expansion of the intravascular volume
- Correction of deficit in fluids, electrolyte & acid base status
- Initiation of Insulin therapy
- Assessment and monitoring of therapy

5.2. Place of management

The child with DKA should receive care in a unit that has:

- Experienced nursing staff trained in DKA management
- Written guidelines for DKA management
- Access to laboratories that can provide frequent and timely measurements of biochemical variables
- A specialist/consultant pediatrician experienced in the management of DKA should supervise inpatient management [4].

Children with severe DKA or those at high risk for cerebral edema should be treated in an intensive care unit (pediatric, if available) or in a unit that has equivalent resources and supervision, such as a children's ward specializing in diabetes care [4].

In a child with established diabetes, whose parents have been trained in sick day management, and who presents with mild DKA, can be managed in an outpatient health care facility (e.g., emergency ward), provided an experienced diabetes team supervises the care [15].

Emergency Assessment [23]

- Clinically evaluate the patient to confirm the diagnosis and determine its cause. Carefully look for evidence of infection.
- Assess level of consciousness

- Weigh the patient.
- Assess clinical severity of dehydration. Signs of dehydration include dry mucus membranes, sunken eyes, absent tears, weak pulses, and cool extremities. The three most useful individual signs for assessing dehydration in young children and predicting at least 5% dehydration and acidosis are:
  - prolonged capillary refill time (normal capillary refill is < 1.5-2 seconds)
  - abnormal skin turgor ('tenting' or inelastic skin)
  - hyperpnea
- .≥10% dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension, and oliguria.

Biochemical assessment [1,4]

- Obtain a blood sample for laboratory measurement of serum or plasma glucose, electrolytes, bicarbonate, blood urea nitrogen, creatinine, osmolality, venous (or arterial in critically ill patient) pH, partial pressure of Carbon dioxide(pCO2), calcium, phosphorus, and magnesium concentrations (if possible), Glycosylated Hemoglobin (HbA1c), hemoglobin and hematocrit or complete blood count.
  - Increased serum urea nitrogen and hematocrit may be useful markers of the severity of extracellular fluid (ECF) contraction.
  - It has to be noted that an elevated white blood cell count in response to stress is characteristic of DKA and is not necessarily indicative of infection [24].
  - Metabolic acidosis being an important landmark of DKA is also helpful to grade the severity of the condition and hence the prognosis by assessing its degree as follows [15]:
- Mild DKA: venous pH <7.3 or bicarbonate <15 mmol/L
- Moderate DKA: pH <7.2, bicarbonate <10 mmol/L
- Severe DKA: pH <7.1, bicarbonate <5 mmol/L
- Perform a urinalysis for ketones.
- Measurement of blood ß-OHB concentration, if available, is useful to confirm ketoacidosis and may be used to monitor the response to treatment [25].
- Obtain appropriate specimens for culture (blood, urine, throat), if there is evidence of infection.
- If laboratory measurement of serum potassium is delayed, perform an electrocardiogram (ECG) for baseline evaluation of potassium status.

Supportive measures [1]:

- Secure the airway and empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration, in case there is deterioration in conscious level.

- A peripheral intravenous (IV) catheter should be placed for convenient and painless repetitive blood sampling. An arterial catheter may be necessary in some critically ill patients managed in an intensive care unit.
- Perform continuous electrocardiographic monitoring to assess T-waves for evidence of hyper- or hypokalemia
- Give oxygen to patients with severe circulatory impairment or shock
- Give antibiotics to febrile patients after obtaining appropriate cultures of body fluids
- Catheterize the bladder if the child is unconscious or unable to void on demand (e.g., infants and very ill young children)

6. Further clinical and biochemical monitoring

Meticulous monitoring of the patient's clinical and biochemical response to treatment is mandatory for timely adjustments in treatment as indicated by the patient's clinical or laboratory data. Documentation on a flow chart of hour-by-hour clinical observations, IV and oral medications, fluids, and laboratory results is very helpful.

Monitoring should include the following [4]:

- Hourly (or more frequently as indicated) vital signs (heart rate, respiratory rate, blood pressure)
- Hourly (or more frequently as indicated) neurological observations for warning signs and symptoms of cerebral edema. The latter include:
  - Headache
  - recurrence of vomiting
  - change in neurological status (restlessness, irritability, increased drowsiness, incontinence) or specific neurologic signs (e.g., cranial nerve palsies, abnormal pupillary responses)
  - inappropriate slowing of heart rate
  - rising blood pressure
  - decreased oxygen saturation
- Amount of administered insulin
- Hourly (or more frequently as indicated) accurate fluid input (including all oral fluid) and output.
- Capillary blood glucose should be measured hourly (but must be cross-checked against laboratory venous glucose, as capillary methods may be inaccurate in the presence of poor peripheral circulation and acidosis).

6.1. Laboratory tests

- Serum electrolytes, glucose, blood urea nitrogen, hematocrit and blood gases should be repeated 2-hourly for the first 12 hours, or more frequently, as clinically indicated, in more severe cases.
- Urine ketones until cleared or blood ß-OHB concentrations, if available, every 2 hours
- If the laboratory cannot provide timely results, a portable biochemical analyzer that measures plasma glucose, serum electrolytes and blood ketones on fingerstick blood samples at the bedside is a useful adjunct to laboratory-based determinations [2].
- **Additional calculations that may be informative**:
  - **Anion gap = serum sodium(Na) – {serum chloride (Cl) + serum bicarbonate (HCO3)} : normal is 12 ± 2 (mmol/L).** In DKA, the anion gap is typically 20–30 mmol/L; an anion gap >35 mmol/L suggests concomitant lactic acidosis.
  - **Corrected sodium = measured Na + 2([plasma glucose -5.6]/5.6) (mmol/L)** The measured serum sodium concentration is an unreliable index of the degree of ECF contraction as glucose, largely restricted to the extracellular space, causes osmotic movement of water into the extracellular space thereby causing dilutional hyponatremia.
  - Therefore, it is important to calculate the corrected sodium (using the above formula) and monitor its changes throughout the course of therapy. As the plasma glucose concentration decreases after administering fluid and insulin, the measured serum sodium concentration should increase (positive sodium load), but it is important to appreciate that this does not indicate a worsening of the hypertonic state. A failure of measured serum sodium levels to rise or a further decline in serum sodium levels with therapy is thought to be a potentially ominous sign of impending cerebral edema
  - **Effective osmolality (mOsm/kg)= 2x(Na + K) + glucose (mmol/L)** The effective osmolality (formula above) is frequently in the range of 300–350 mOsm/Kg.

6.2. Fluids and electrolytes

The objectives of fluid and electrolyte replacement therapy are [1]:

- Restoration of circulating volume
- Replacement of sodium and the ECF and intracellular fluid deficit of water
- Improved glomerular filtration with enhanced clearance of glucose and ketones from the blood
- Reduction of risk of cerebral edema

6.3. Fluids

- Establish two I.V. lines: one for fluids and electrolytes and the other for insulin infusion

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- Shock with hemodynamic compromise is rare in pediatric DKA. If the patient is shocked, administer shock therapy: 10 ml/Kg 0.9% normal saline (or Ringer's lactate or acetate) through a large bore cannula, over 0.5 hr. Re-assess the patient and repeat up to a maximum of 30 ml/kg if necessary, with reassessment after each bolus.
- The volume and rate of administration depends on circulatory status and, where it is clinically indicated.
- **Calculate the Fluid Requirements**

1. Deficit Fluid Requirements :

Patients with DKA have a deficit in extracellular fluid (ECF) volume that usually is in the range 5–10%. Clinical estimates of the volume deficit are subjective and inaccurate, therefore, in moderate DKA use 5–7%and in severe DKA 7–10% dehydration [4].

- Assess the degree of dehydration and calculate the deficit (% dehydration x body weight) considering the age of the patient as shown in Table 1.

Degree of Dehydration	Infants & children <8 years		Children "/>8 years	
	Degree	Fluids	Degree	Fluids
Mild	5%	50 ml/kg	3%	30 ml/kg
Moderate	8%	80 ml/kg	5%	50 ml/kg
Severe	10%	100 ml/kg	8%	80 ml/kg

Table 1. Calculation of deficit fluid requirements in children presenting with DKA (1)

2. Maintenance Fluid Requirements:

Age (years)	Amount of fluids
0-2	80 ml/kg/24hr
3-5	70 ml/kg/24hr
6—9	60 ml/kg/24hr
10-14	50 ml/kg/24hr
Adult ("/>15)	35 ml/kg/24hr

Table 2. Calculation of maintenance fluid requirements (1)

3. Total working fluid = deficit + maintenance (calculated for 48 hours)

- Type of fluids

- If blood glucose is over 300 mg/dl, start with isotonic saline, then when blood glucose goes down to 250 mg/dl, add glucose 5% to isotonic saline in a 1:1 ratio if acidosis is corrected. If acidosis is not corrected, add glucose 10% to isotonic saline in 1:1 ratio.

- In case of hyperosmolarity (> 340 mosm/kg), or if corrected Na is 155 mEq/l or more, use half normal saline (0.45%) instead of normal saline (0.9%), to prevent cerebral edema but only after correction of shock and severe dehydration. It is advisable to use it after 6 hours from initiation of fluid therapy.

Principles of Water and Salt Replacement and Reduction of Risk of Cerebral Edema

There is no convincing evidence of an association between the rate of fluid or sodium administration used in the treatment of DKA and the development of cerebral edema [26]. No treatment strategy can be definitively recommended as being superior to based on evidence. The principles described below were endorsed by a panel of expert physicians representing the Lawson Wilkins Pediatric Endocrine Society (LWPES), the European Society for Paediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD) [4,5].

- Water and salt deficits must be replaced
- IV or oral fluids that may have been given in another facility before assessment should be factored into calculation of deficit and repair
- In addition to clinical assessment of dehydration, calculation of effective osmolality may be valuable to guide fluid and electrolyte therapy.
- Urinary losses should not routinely be added to the calculation of replacement fluid, but may be necessary in rare circumstances.
- The use of large amounts of 0.9% saline has been associated with the development of hyperchloremic metabolic acidosis [27].

6.4. Insulin therapy

Regardless of the type of diabetes, the child who presents with severe fasting hyperglycemia, metabolic derangements, and ketonemia will require insulin therapy to reverse the metabolic abnormalities [2]

DKA is caused by a decrease in effective circulating insulin associated with increases in counter-regulatory hormones {glucagon, catecholamines, growth hormone (GH), cortisol}. Although rehydration alone causes some decrease in blood glucose concentration, insulin therapy is essential to normalize blood glucose and suppress lipolysis and ketogenesis [1].

Extensive evidence indicates that '*low dose*' IV insulin administration should be the standard of care [4].

- Start insulin infusion 1–2 hours after starting fluid replacement therapy; i.e. after the patient has received initial volume expansion [28].

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Correction of insulin deficiency

- Dose: 0.1 unit/kg/hour (for example, one method is to dilute 50 units regular [soluble] insulin in 50 mL normal saline, 1 unit = 1 mL)
- Route of administration IV
- An IV bolus is unnecessary, may increase the risk of cerebral edema, and should not be used at the start of therapy

- The dose of insulin should usually remain at 0.1unit/kg/hour at least until resolution of DKA (pH >7.30, bicarbonate >15 mmol/L and/or closure of the anion gap), which invariably takes longer than normalization of blood glucose concentrations.
- If the patient demonstrates marked sensitivity to insulin (e.g., some young children with DKA, patients with HHS, and some older children with established diabetes), the dose may be decreased to 0.05 unit/kg/hour, or less, provided that metabolic acidosis continues to resolve.
- To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia, 5% glucose should be added to the IV fluid (e.g., 5% glucose in 0.45% saline) when the plasma glucose falls to approximately 250–300 mg/dL, or sooner if the rate of fall is precipitous.
  - It may be necessary to use 10% or even 12.5% dextrose to prevent hypoglycemia while continuing to infuse insulin to correct the metabolic acidosis. The fall of blood glucose should not exceed 100 mg per hour. If blood glucose drops more than 100 mg/hr, reduce insulin infusion to 0.05 U/kg/hr. Aim to keep blood glucose at about 11 mmol/L (200 mg/dL) until resolution of DKA
- If biochemical parameters of DKA (pH, anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin; e.g., infection, errors in insulin preparation.
- In circumstances where continuous IV administration is not possible, hourly or 2-hourly subcutaneous (SC) or intramuscular (IM) administration of a short- or rapid-acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as IV regular insulin infusion, but should not be used in subjects whose peripheral circulation is impaired.

6.5. Potassium replacement

Pathophysiology of potassium depletion in DKA [4]

Children with DKA suffer total body potassium deficits of the order of 3 to 6 mmol/kg. The major loss of potassium is from the intracellular pool.

Intracellular potassium is depleted because of the following factors:

- increased plasma osmolality drags water and potassium out of cells

- glycogenolysis and proteolysis secondary to insulin deficiency cause potassium efflux from cells
- Potassium is lost from the body from vomiting and as a consequence of osmotic diuresis.
- Volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion.

- Despite potassium depletion, at presentation, serum potassium levels may be normal, increased or decreased. Renal dysfunction, by enhancing hyperglycemia and reducing potassium excretion, contributes to hyperkalemia. Administration of insulin and the correction of acidosis will drive potassium back into the cells, decreasing serum levels. The serum potassium concentration may decrease abruptly, predisposing the patient to cardiac arrhythmias.

Guidelines of Potassium supplementation [1]

- Replacement therapy is required regardless of the serum potassium concentration
- If the patient is hypokalemic, start potassium replacement at the time of initial volume expansion and before starting insulin therapy. Otherwise, start replacing potassium after initial volume expansion and concurrent with starting insulin therapy.
- If the patient is hyperkalemic, postpone potassium replacement until the patient voids urine
- If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyper- or hypokalemia. Flattening of the T wave, widening of the QT interval, and the appearance of U waves indicate hypokalemia. Tall, peaked, symmetrical, T waves and shortening of the QT interval are signs of hyperkalemia.
- The starting potassium concentration in the infusate should be 40 mmol/L or 20 mmol potassium/L in the patient receiving fluid at a rate >10 mL/kg/h. Subsequent potassium replacement therapy should be based on serum potassium measurements.
- Potassium replacement should continue throughout IV fluid therapy. The maximum recommended rate of intravenous potassium replacement is usually 0.5 mmol/kg/hr
- If hypokalemia persists despite a maximum rate of potassium replacement, reduce the rate of insulin infusion

6.6. Phosphate

Phosphate is lost as a result of osmotic diuresis in DKA. Plasma phosphate levels fall after starting treatment by insulin, which promotes entry of phosphate into cells.

Prospective studies have not shown clinical benefit from phosphate replacement. Severe hypophosphatemia in conjunction with unexplained weakness should be treated. Administration of phosphate may induce hypocalcemia. Potassium phosphate salts may be safely used as an alternative to or combined with potassium chloride or acetate, provided that careful monitoring of serum calcium is performed to avoid hypocalcemia [2]

6.7. Acidosis

Severe metabolic acidosis is hazardous leading to decreased myocardial performance, decreased response of respiratory center, peripheral and cerebral vasodilatation and life threatening hyperkalemia. Nevertheless, it can be reversible by fluid and insulin replacement; insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate. Treatment of hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids[1].

Controlled trials have shown no clinical benefit from bicarbonate administration. Moreover, bicarbonate therapy may be more hazardous than acidosis itself. It can cause paradoxical CNS acidosis and promotes intracellular acidosis and cerebral edema. Moreover, rapid correction of acidosis with bicarbonate causes hypokalemia, while sodium overload can result in increasing osmolality. Late alkalemia can lead to shift of oxygen dissociation curve to the left, with impaired O2 delivery to the tissues & increased anaerobic glycolysis[4].

Nevertheless, there may be selected patients who may benefit from cautious alkali therapy[1]. These include: patients with severe acidemia (arterial pH <6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion, and patients with life-threatening hyperkalemia

- Bicarbonate administration is not recommended unless the acidosis is profound and likely to affect adversely the action of adrenaline/epinephrine during resuscitation.
- If bicarbonate is considered necessary, cautiously give 1–2 mmol/kg over 60 minutes.

6.8. Introduction of oral fluids and transition to SC insulin injections

- Oral fluids should be introduced only when the clinical condition has become stable, however mild acidosis/ketosis may still be present.
- When oral fluid is tolerated, IV fluid should be reduced and change to SC insulin is planned.
- To prevent rebound hyperglycemia the first SC injection should be given 15–30 minutes (with rapid acting insulin) or 1–2 hours (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed. With intermediate- or long-acting insulin, the overlap should be longer and the IV insulin gradually lowered. For example, for patients on a basal-bolus insulin regimen, the first dose of basal insulin may be administered in the evening and the insulin infusion is stopped the next morning.
- After transitioning to SC insulin, frequent blood glucose monitoring is required to avoid marked hyperglycemia and hypoglycemia [2].

7. Morbidity and mortality from DKA

The mortality rate from DKA in children is 0.15% to 0.30% [11,12]. Cerebral edema accounts for 60% to 90% of all DKA deaths [13,14]. Ten % to 25% of survivors of cerebral edema have significant residual morbidity [29]

Other rare causes of morbidity and mortality include:

- Hypokalemia
- Hyperkalemia
- Severe hypophosphatemia
- Hypoglycemia
- Other central nervous system complications (disseminated intravascular coagulation, dural sinus thrombosis, basilar artery thrombosis)
- Peripheral venous thrombosis
- Sepsis
- Rhinocerebral or pulmonary mucormycosis
- Aspiration pneumonia
- Pulmonary edema
- Adult respiratory distress syndrome (ARDS)
- Pneumothorax, pneumomediastinum and subcutaneous emphysema
- Rhabdomyolysis
- Acute renal failure
- Acute pancreatitis [30]

7.1. Cerebral edema

Cerebral edema is responsible for the majority of deaths related to DKA in children, and significant neurologic morbidity persists in many of the survivors. The incidence of cerebral edema in national population studies is 0.5–0.9% and the mortality rate is 21–24%.The pathogenesis of both its initiation and progression is unclear and incompletely understood, although a number of mechanisms have been proposed. These include cerebral ischemia and hypoxia, fluid shifts caused by inequalities in osmolarity between the extravascular and intravascular intracranial compartments, increased cerebral blood flow, and altered membrane ion transport. Demographic factors that have been associated with an increased risk of cerebral edema include [13,14,29]:

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Epidemiological factors

- Newly diagnosed cases
- Young age: < 5 years old
- Longer duration of symptoms
- Prolonged illness
- Extended history of poor metabolic control

Features at presentation

- Severe acidosis (initial pH < 7.1)
- Greater hypocapnia after adjusting for degree of acidosis
- High Blood urea nitrogen
- Severe dehydration
- Abnormal mental status

Therapeutic interventions

- Rapid rehydration (> 50cc/ kg in first 4 hrs)
- Bicarbonate therapy for correction of acidosis
- Insulin administration in the first hour of therapy

Changes in biochemical values during treatment

- Severe Hypernatremia
- Persistent hyponatremia
- An attenuated rise in measured serum sodium concentrations during therapy
- Non closure of the anion gap

Warning signs and symptoms of cerebral edema include:

- Headache & slowing of heart rate
- Change in neurological status (restlessness, irritability, increased drowsiness, incontinence)
- Specific neurological signs (e.g., cranial nerve palsies)
- Rising blood pressure
- Decreased oxygen saturation

Clinically significant cerebral edema usually develops 4–12 hours after treatment has started, but can occur before treatment has begun or, rarely, may develop as late as 24–48 hours

after the start of treatment. Symptoms and signs are variable. A method of clinical diagnosis based on bedside evaluation of neurological state is shown below [23]:

7.2. Diagnostic criteria

- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posture
- Cranial nerve palsy (especially III, IV, and VI)
- Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)

7.2.1. Major criteria

- Altered mentation/fluctuating level of consciousness
- Sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved intravascular volume or sleep state
- Age-inappropriate incontinence

7.2.2. Minor criteria

- Vomiting
- Headache
- Lethargy or not easily arousable
- Diastolic blood pressure >90 mm Hg
- Age <5 years

One diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% and a false positive rate of only 4%.

A chart with the reference ranges for blood pressure and heart rate, which vary depending on height, weight, and gender, should be readily available, either in the patient's chart or at the bedside.

8. Treatment of cerebral edema [1,2,4]

- Start as early as you suspect the condition, do not delay treatment until radiographic evidence
- Transfer to the ICU (if not already there)
- Restrict IV fluids to 2/3 maintenance and replace deficit over 72 hr rather than 24 hr

- Give mannitol 0.5-1 g/kg IV (2.5 ml/kg of 20% solution) over 20 minutes and repeat after 6 hours, if there is no initial response in 30 minutes to 2 hours
- Hypertonic saline (3%), 5-10 mL/kg over 30 minutes, may be an alternative to mannitol or a second line of therapy if there is no initial response to mannitol
- Elevate the head of the bed
- Intubation may be necessary for the patient with impending respiratory failure, but aggressive hyperventilation (to a pCO2 <2.9 kPa [22 mm Hg]) has been associated with poor outcome and is not recommended.
- After treatment for cerebral edema has been started, a cranial CT scan should be obtained to rule out other possible intracerebral causes of neurologic deterioration (10% of cases), especially thrombosis or hemorrhage, which may benefit from specific therapy.

9. Prevention of recurrent DKA

Home measurement of blood ß –OHB concentrations, when compared to urine ketone testing, decreases diabetes-related hospital visits (both emergency department visits and hospitalizations) by the early identification and treatment of ketosis. Blood ß -OHB measurements may be especially valuable to prevent DKA in patients who use a pump because interrupted insulin delivery rapidly leads to ketosis. There may be dissociation between urine ketone (sodium nitroprusside only measures acetoacetate and acetone) and serum ß -OHB concentrations, which may be increased to levels consistent with DKA when a urine ketone test is negative or shows only trace or small ketonuria [4].

A psychiatric social worker or clinical psychologist should be consulted to identify the psychosocial reason(s) contributing to development of DKA. Insulin omission can be prevented by schemes that provide education, psychosocial evaluation and treatment combined with adult supervision of insulin administration. Diabetes education of the child and his/her family is the cornerstone to prevent DKA occurrence and recurrence.

10. Conclusion

10.1. Future thoughts and recommendations

1. DKA is the first presentation of ~25% of young diabetics. Cerebral edema is a major risk causing mortality and morbidity.
2. The child is not a miniature adult. Children and adolescents with DKA should be managed in centers experienced in treatment and monitoring of DKA.

3. Successful management of DKA requires meticulous monitoring of the patient's clinical and biochemical response to treatment so that timely adjustments in treatment can be made when indicated by the patient's clinical or laboratory data

4. Fluid administration should rehydrate evenly over 48 hours at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement.

5. Begin insulin infusion with 0.1 U/kg/h. 1–2 hours after starting fluid replacement therapy. Increase the amount of glucose administered if blood glucose is falling too rapidly or acidosis is not resolving.

6. Even with normal or high levels of serum potassium at presentation, there is always a total body deficit of potassium. Begin with 40 mmol potassium/L in the infusate or 20 mmol potassium/L in the patient receiving fluid at a rate >10 mL/kg/h.

7. There is no evidence that bicarbonate is either necessary or safe in DKA. It is used cautiously in severe acidemia (arterial pH <6.9) and in life-threatening hyperkalemia

8. Despite much effort to identify the cause of cerebral edema, its pathogenesis is incompletely understood. Further research is needed in this area.

9. In case of profound neurological symptoms, Mannitol should be given immediately.

10. All cases of recurrent DKA are preventable

Author details

Shereen Abdelghaffar

Pediatric Endocrinology and Diabetes, Cairo University, Egypt

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