

Diabetic Ketoacidosis in Children: A Systematic Review

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ABSTRACT

Diabetic ketoacidosis (DKA) is an acute life threatening complication of diabetes. It is the most common cause of death in children with type 1 diabetes and unfortunately majority of them present with DKA as an initial presentation. The objective of this article is prevention of DKA through early diagnosis and meticulous management of diabetes in children. Children with T1DM and their parents must be educated regarding DKA, in general and during stressful conditions like infections.

Keywords: Diabetic ketoacidosis, diabetes mellitus, children, prevention

INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute and potentially fatal complication of diabetes characterized by hyperglycemia, acidosis, along with evidence of accumulation of ketoacids in the blood due to insulin deficiency, and increase in counter regulatory hormones. DKA is the most common cause of death in children with Type 1 Diabetes (T1DM).^[1] The mean age of patient with DKA is 9.1 years and girls were more affected than boys.^[4]

DKA is usually seen in patients with absolute insulin deficiency in previously undiagnosed T1DM, and when patients on treatment deliberately or inadvertently do not take insulin, especially the long acting component of a basal bolus regimen. Patients using insulin pump may rapidly develop DKA when insulin delivery fails.

If insulin deficiency is not interrupted with exogenous insulin, fluid and electrolyte therapy, fatal dehydration, and metabolic acidosis will ensue. DKA is precipitated by stressful conditions like gastrointestinal illness like diarrhea and vomiting, sepsis or trauma. Ketoacidosis may be aggravated by lactic acidosis from poor tissue

perfusion or sepsis.

Definition :

The biochemical criteria for the diagnosis of DKA are:

1. Blood glucose: >200 mg/dL
2. Venous pH: <7.3 or Bicarbonate: <15 mmol/L
3. Ketonemia and Ketonuria

Pathogenesis :

The relative or absolute insulin deficiency in combination with increased levels of stress hormones, stimulates lipolysis resulting in the production of acetyl CoA from fatty acid which acts as the substrate for hepatic synthesis of ketone bodies.

The balance between catabolism and anabolism is broken in diabetic ketoacidosis. Due to lack of insulin, there is decreased storage of glucose, increased breakdown of glycogen stores, and increased synthesis of glucose in both the kidney and liver. There is decreased utilization of glucose in peripheral tissues. In this catabolic state there is breakdown of proteins to form new amino acids that in turn are used to build glucose.^[1,2]

In stressed state, there is a relative abundance of epinephrine and cortisol. Epinephrine acts to block the action of insulin and stimulates the release of glucagon. Growth hormone also has a similar role as epinephrine and cortisol. In conditions like infection or stroke there is an increased demand for insulin, but a diminished supply due to stress on the pancreas.^[3,4]

Elevated blood glucose is certainly a major problem, but the cornerstone of DKA lies in ketogenesis. Insulin is normally the most important regulator in production and utilization of ketones. Insulin will inhibit lipolysis, oxidation of free fatty acids, and increases oxidation of ketones in the peripheral tissues. Thus there is both overproduction and underutilization of ketones in an insulin deficient state.^[5] Hormone sensitive lipase stimulated by glucagon, mobilizes adipose stores and

converts triglycerides to free fatty acids. These free fatty acids are then transported across the mitochondrial membrane, and they are eventually used for synthesis of ketones, in the form of acetoacetic acid, which is oxidized to form beta-hydroxybutyrate or decarboxylated to form acetone. With ketone overproduction, peripheral tissues cannot utilize these molecules and ketosis predominates.^[6] The oxidation of free fatty acids facilitates gluconeogenesis and generates acetoacetic and beta hydroxybutyric acids (ketones) that overwhelm buffering capacity, resulting in metabolic acidosis (pH<7.3), which is compounded by lactic acidosis from poor tissue perfusion. Progressive dehydration, hyperosmolarity, acidosis, and electrolyte disturbances exaggerate stress hormone secretion and establish a self-perpetuating cycle of progressive metabolic decompensation (Fig.1).

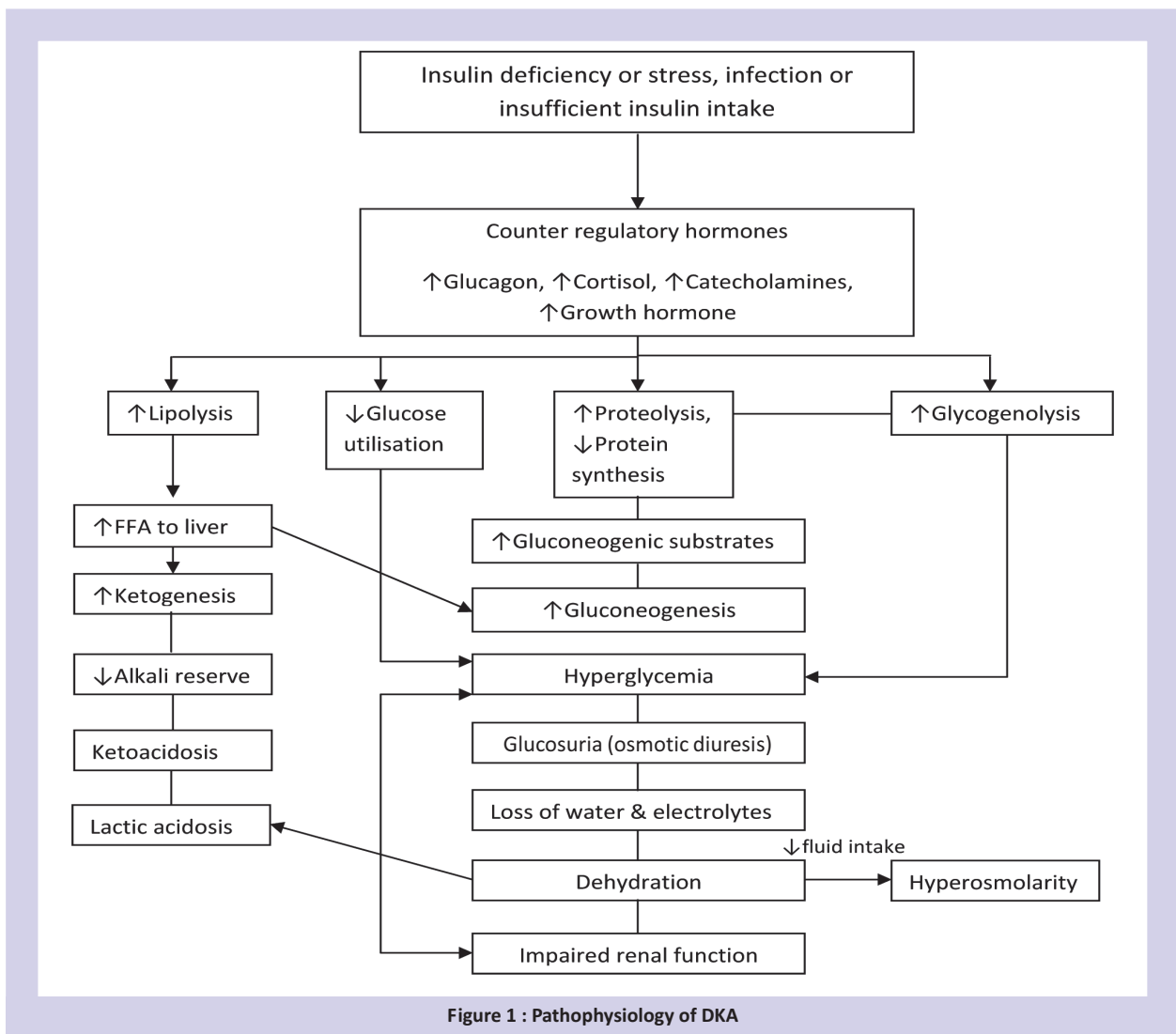


Figure 1 : Pathophysiology of DKA

Acid–Base Balance, Fluids and Electrolytes:

Acidosis in DKA is due to the overproduction of β -Hydroxy butyric acid(β OHB), and acetoacetic acid. At physiological pH, these ketoacids dissociate completely, and the excess hydrogen ions bind the bicarbonate, resulting in decreased serum bicarbonate levels.

Ketone bodies circulate in the anionic form, and this leads to the development of anion gap acidosis that is characteristic of DKA. The normal anion gap is 4-11 mmol/L.

In DKA, bicarbonate is replaced by β hydroxybutyric acid and acetoacetic acid, so the sum of bicarbonate and chloride concentrations is reduced so the anion gap is increased. In spite of losses of ketoacids in the urine, the decrease in serum bicarbonate concentration and the increase in the anion gap observed in DKA are almost equal.^[7]

Normally, β -hydroxybutyric acid levels are 2 to 3 times higher than acetoacetic acid levels. This difference reflects mitochondrial redox state. Increase in redox state, will increase the ratio of β -hydroxybutyric acid to acetoacetic acid.

Hyperventilation is due to metabolic acidosis through stimulation of peripheral chemoreceptors and the respiratory centre in the brainstem, which leads to decrease in the partial pressure of carbon dioxide which partially compensates for the metabolic acidosis.

There is deficit of about 5 to 13 mmol/kg body weight and 3 to 7 mmol/kg body weight of sodium and chloride respectively. Increased glucose concentration initially is restricted to the extracellular space, which forces water from the intracellular to the extracellular compartment, and induces dilutional hyponatremia.

Further hyperglycemia leads to osmotic diuresis, with loss of water and sodium chloride in the urine. The water loss usually is more than that of the sodium chloride.^[7] Eventually, the loss of water from the intracellular and extracellular compartments will become quantitatively similar. Due to the osmotic shift of water, plasma sodium concentrations are usually low or normal in DKA despite extensive water loss.^[7]

The calculation for the corrected sodium concentration accounts for this effect:

$[\text{Na}]_{\text{corrected}} = [\text{Na}]_{\text{measured}} + 1.6 \times ([\text{glucose}] - 100) / 100$
DKA is associated with profound total body potassium depletion, ranging from 3 to 15 mmol/kg of body weight.^[9,11]

Phosphate, magnesium, and calcium are other elements

excreted in excess in urine during the development of DKA due to osmotic diuresis, for a deficit of 1–2 mmol/kg on average.^[7]

Frequency and Risk Factors:

Potential risk factors, at diagnosis or during treatment, have been identified through epidemiologic studies.

- Attenuated rise in serum sodium concentrations during therapy may be associated with increased risk of cerebral edema.^[12] There is little evidence, to show associations between the volume or sodium content of intravenous (IV) fluids or rate of change in serum glucose and risk for cerebral edema.^[12]
- There is some evidence to support an association between severity of acidosis, bicarbonate treatment for correction of acidosis, greater hypocapnia at presentation of DKA, elevated serum urea nitrogen at presentation of DKA after adjusting the degree of acidosis and risk of cerebral edema.^[12]
- Most studies show no association between the degree of hyperglycemia at presentation of DKA with risk of cerebral edema after correcting for other covariates.^[12]
- Poor compliance is most important modifiable precipitating factor in children.^[41]

DKA with New-Onset Diabetes:

The frequency of new-onset diabetes presenting as DKA varies widely by geographic region. DKA at diagnosis is more common in younger children (<5 years of age), and in whose families do not have ready access to medical care for social or economic reasons.

Recurrent DKA:

The risk of DKA in established T1DM is 1 to 10% per patient per years. The risk factors for recurrent DKA were poor metabolic control or previous episodes of DKA, female gender (peripubertal or adolescent), psychiatric disorders including eating disorders, difficult or unstable family circumstances, limited access to medical services, and insulin pump therapy.

Clinical Features:

Clinical manifestations of ketoacidosis include the following^[14]

- Signs of Dehydration: Delayed capillary refill, postural changes of blood pressure and pulse, dry mucous membranes.
- Signs of Acidosis: Deep-sighing respirations

(Kussmaul) in an attempt to blow off carbon dioxide, shortness of breath, chest pain due to accessory muscle exhaustion.

- Results of Vomiting, Dehydration, and Hyperosmolality: Abdominal pain mimicking pancreatitis or an acute surgical abdomen.
- Result of Counter regulatory Hormone release: Elevated leukocyte count to 15,000–20,000/mm³.
- Signs of Hyperosmolality: Progressive obtundation and loss of consciousness related to the degree of evolving hyperosmolality, serum osmolality.
- The degree of sodium loss may be overestimated because of the presence of hyperlipidemia and hyperglycemia. For each increase in glucose of 100 mg/dl (5.5 mmol/L), serum sodium may be decreased by ~2 meq/L.

An increase in corrected serum sodium is a goal of therapy. Serum potassium may be normal, but total-body potassium is commonly depleted. During acidosis, intracellular potassium moves to the extracellular compartment and may be lost in urine or vomitus.

Hyperkalemia in DKA is therefore uncommon unless renal shutdown has occurred. In contrast, hypokalemia may develop rapidly after treatment is initiated because the provision of insulin in the presence of hyperglycemia and the correction of acidosis promote the return of potassium to the intracellular compartment. Hypokalemia may be life-threatening for cardiac arrhythmias; therefore, provision of potassium and monitoring should be done.

- Ketone bodies may cause spurious elevation in creatinine values in some assays. Urine and blood ketone tests measure different metabolites. Urine ketone tests measure acetoacetate, and blood ketone tests measure β OHB. Because β OHB is the predominant ketone body in DKA, urine measurement may give false-negative results.

The concentration of β OHB is 4- to 10-fold higher than that of acetoacetic acid at initial presentation. With correction of acidosis, the β OHB is oxidized back to acetoacetate and is now measured. Hence, physicians should not be misled by the persistence of a strong ketone reaction as long as the patient manifests evidence of clinical and biochemical improvement in acidosis.

- Ketoacidosis takes longer to correct than hyperglycemia. Therefore, insulin therapy should not be discontinued if ketoacidosis has not cleared,

Table 1 : Shows clinical features n the pathophysiology behind them ^[14]

Clinical features	Pathophysiology
Infection	Hyperglycaemia (gluconeogenesis)
Weight loss, muscular weakness	Tissue breakdown (lipolysis, proteolysis)
Polyuria, nocturia, thirst	Osmotic diuresis
Blurred vision	Osmotic changes in the eye
Hyperventilation, abdominal pain, nausea, vomiting	Ketogenesis ketoacidosis

even if glucose concentrations are approaching 300 mg/dL (17 mmol/L).

Laboratory Findings:

Typical laboratory findings are listed in Tables 2 and 3^[8,15,16]. Most patients presenting with DKA have a plasma glucose level of 250 mg/dl or greater. But most patients with Type 1 Diabetes who have such a plasma glucose level do not have ketoacidosis. On the other hand, ketoacidosis may develop in patients with a plasma glucose level below 250 mg/dL.

The increased serum osmolality can be calculated as: (2 × serum Na) + serum glucose, with normal values being 290+/-5 mmol/kg water. Blood urea nitrogen is not included in the calculation of effective osmolality because it is freely permeable in and out of the intracellular compartment.^[16] DKA will have a pH of 7.30 or less.

In DKA, a lower pH will usually be associated with a decrease in bicarbonate to 15 mmol/L or less. In milder forms of DKA bicarbonate level may be between 15 and 18 mmol/L. Less severe DKA is accompanied by moderate to large amounts of ketones in the blood and urine. β OHB levels are measured bed side, using a reagent strip and a reflectance meter.

Other biochemical abnormalities associated with DKA are listed in Table 4.^[16] The majority of patients presenting with DKA will have an elevated leukocyte count, usually in the range of 15,000–20,000/mm³. This may be due to stress and dehydration. Amylase levels are often elevated in patients with DKA, but represent enzyme activity from nonpancreatic tissues such as the parotid gland.

Lipase levels will usually be normal. Additional laboratory tests should include blood culture, urinalysis and urine culture, chest radiography and electro cardiography, as well as measurement of the lactate level if indicated.

Table 2: Typical water and serum electrolyte deficits at presentation of diabetic ketoacidosis (DKA) ^[8,15,16]

Parameter	DKA
Water, mL/kg	100
Sodium, mmol/kg	7–10
Potassium, mmol/kg	3–5
Chloride, mmol/kg	3–5
Phosphate, mmol/kg	1–1.5
Magnesium, mmol/kg	1–2
Calcium, mmol/kg	1–2

Table 3: Laboratory diagnostic criteria for DKA ^[15,16]

Parameter	Normal Range	DKA
Plasma glucose level, mg/dl	70-140	≥ 250
Arterial pH	7.35–7.45	≤ 7.30
Serum bicarbonate level, mmol/L	22–28	≤ 15
Effective serum osmolality, mmol/kg	275–295	≤ 320
Anion gap, mmol/L	< 12	> 12
Serum ketones	Negative	Moderate to high
Urine ketones	Negative	Moderate to high

Table 4: Other biochemical abnormalities associated with DKA ^[16]

Parameter	Normal Range	DKA
Sodium, mmol/L	136–145	134
Potassium, mmol/L	3.5–5.0	4.5
Blood urea nitrogen, mmol/L	2.8–7.9	11.4
Creatinine, µmol/L	38–110	97.2
Free fatty acids, mmol/L	0.4–0.7	1.6
β Hydroxybutyric acid, µmol/L	< 300	9100
Lactate, mmol/L	0.56–2.2	2.4
Insulin, pmol/L	35–145	90
C-peptide, nmol/L	0.26–1.32	0.25
Glucagon, ng/L	50–100	580
Growth hormone, µg/L	< 5	7.9
Cortisol, nmol/L	140–690	1609
Catecholamines, ng/mL	0.150–0.750	1.78

Management:

Goals of therapy:

- Correct dehydration
- Correct acidosis and reverse ketosis
- Restore blood glucose to near normal
- Avoid complications of therapy
- Identify and treat any precipitating event

Children with established diabetes, who do not have vomiting or not severely ill, and whose caregiver is trained in sick day management, can be managed at home or at an outpatient facility, with appropriate supervision and follow-up.

Children who are vomiting and not severely ill may be managed with intravenous (IV) fluids in an emergency department and discharged to home if able to take fluids orally. Children requiring IV rehydration over an extended period need to be admitted and neurological status and vital signs are to be monitored frequently and blood glucose levels measured every hourly.

Emergency Assessment:

Clinical evaluation is done to confirm the diagnosis and cause is determined. More the signs of dehydration more the severity of dehydration. 10% dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension, and oliguria. Assess level of consciousness.

Biochemical Assessment:

Obtain a blood sample for laboratory measurement of serum or plasma glucose, electrolytes (including bicarbonate or total carbon dioxide), blood urea nitrogen, creatinine, osmolality, venous (or arterial in critically ill patient) pH, pCO₂, calcium, phosphorus, and magnesium concentrations, HbA1c, hemoglobin and hematocrit or complete blood count.

Urinalysis for ketones should be done. Measurement of blood β-hydroxybutyrate concentration, is useful to confirm ketoacidosis and may be used to monitor the response to treatment. Obtain appropriate specimens for culture (blood, urine, throat), if there is evidence of infection. Obtain electrocardiogram (ECG) for baseline evaluation of potassium status.

Supportive Measures:

- In the unconscious or severely obtunded patient, secure the airway and empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration.

- A peripheral intravenous catheter should be placed for convenient and painless repetitive blood sampling.
- A cardiac monitor should be used for continuous electrocardiographic monitoring to assess 'T' waves for evidence of hyper or hypokalemia, and to monitor for arrhythmias.
- Oxygen should be given to patients with severe circulatory impairment or shock.
- Give antibiotics to febrile patients after obtaining appropriate cultures of body fluids.
- Catheterization of the bladder is not necessary, unless the child is unconscious or unable to void on demand (e.g., infants and very ill young children).
- Central venous pressure monitoring may be required rarely to guide fluid management in the critically ill, obtunded, or neurologically compromised patient.
- Central lines in children with DKA are frequently associated with thrombosis and should be resorted to only when absolutely necessary.

Fluid and Electrolyte Therapy:

- DKA is characterized by severe depletion of water and electrolytes from both the intracellular fluid and extracellular fluid (ECF) compartments. The range of losses is shown in Table 5.
- The objectives of fluid and electrolyte replacement therapy are restoration of circulating volume, replacement of sodium and the ECF and intracellular fluid deficit of water, restoration of glomerular filtration with enhanced clearance of glucose and ketones from the blood, and avoidance of excessive rates of fluid administration so as not to exacerbate the risk of cerebral edema (Table 6).
- Patients continues to have considerable urine output until there is extreme volume depletion which leads to a critical decrease in renal blood flow and glomerular filtration.
- Children with DKA have a deficit in ECF volume usually in the range of 5 to 10%. Shock is rare in pediatric DKA. 5 to 7% dehydration is used in moderate DKA and 10% dehydration in severe DKA.
- The effective osmolality is in the range of 300mosm/L to 350 mosm/L.
- Markers of the severity of ECF contraction are increased serum urea nitrogen, and hematocrit.
- The serum sodium concentration is an unreliable measure of the degree of ECF contraction as glucose is largely restricted to the extracellular space and causes osmotic movement of water into the extracellular space, thereby inducing dilutional hyponatremia; and the second reason is elevated lipid fraction of the serum in DKA has a low sodium content. So it is important to calculate the corrected sodium and its changes must be monitored throughout the course of therapy.
- As the plasma glucose concentration decreases after administering fluid and insulin, the measured and corrected serum sodium concentration must increase appropriately.
- Volume expansion in order to restore peripheral circulation (resuscitation) should begin immediately with an isotonic solution like 0.9% saline or Ringer's lactate.
- The volume and rate of administration depends on circulatory status, which is 10–20 ml/kg over 1–2 hr and may be repeated if necessary.
- Then the subsequent fluid management, i.e., deficit replacement should be with 0.9% saline or Ringer's lactate or acetate for at least 4–6 hour.
- Then after that, deficit replacement should be with a solution that has a tonicity 0.45% saline with added potassium chloride, phosphate, or acetate.
- The rate should be calculated to rehydrate evenly over at least 48 hours.
- Calculation of effective osmolality may be valuable to guide fluid and electrolyte therapy in addition to clinical assessment of dehydration.
- As the severity of dehydration is either under or overestimated, fluid is infused each day at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement based on age and weight or body surface area.
- Urinary losses should not be added to the calculation of replacement fluid.
- If serum corrected sodium is low and/or the measured serum sodium does not rise appropriately as the plasma glucose concentration falls the sodium content of the fluid may need to be increased.
- The use of large amounts of 0.9% saline may be associated with hyperchloremic metabolic acidosis.

Table 5: Usual losses of fluids and electrolytes in DKA and normal maintenance requirements^[17]

Fluid and Electrolytes	Average losses per kg (range)	Maintenance requirements
Water	70 (30–100) ml	1,500 ml/m ²
Sodium	6 (5–13) mmol	45 mmol/m ²
Potassium	5 (3–6) mmol	35 mmol/m ²
Chloride	4 (3–9) mmol	30 mmol/m ²
Phosphate	0.5–2.5 mmol	0.5–1.5 mmol/kg

Table 6: Fluid and electrolyte losses based on assumed 10% dehydration in a child (weight 30 kg, surface area 1 m²) with DKA

Fluid and electrolyte	Approximate accumulated losses with 10% dehydration	Approximate requirements for maintenance (48 h)	Approximate requirements for maintenance (48 h)
Water (ml)	3,000	3,000	6,000
Sodium (mEq)	180	90	270
Potassium (mEq)	150	70	220
Chloride (mEq)	120	60	180
Phosphate (mmol)	75	20	95

Insulin :

Insulin should be started after initial fluid expansion and it provides a more realistic starting glucose level. Short acting Insulin 0.1 U/kg/hour is given as a continuous infusion, using a infusion pump. Fifty units of regular insulin are diluted in 50 mL normal saline to provide 1 U/mL. A bolus dose of insulin is not indicated as it may increase the risk of cerebral oedema.

Studies in adults show no significant difference in recovery time whether insulin was administered subcutaneously, intramuscularly, or intravenously after the first couple of hours of treatment.

The administration of insulin 0.1 U/kg subcutaneously every hour may be preferable and can be adjusted to maintain blood glucose concentrations at 180-200 mg/dL (10-11 mmol/L). Fluid expansion has a dilutional effect, lowering high blood glucose levels to 180-270 mg/dL (10-15 mmol/L). The rate of glucose decline should be 50-150 mg/dL (2.8-8.3 mmol/L/hour), but not >200 mg/dL (11 mmol/L/hour) with insulin infusion. If serum glucose values are not dropping adequately, the insulin

dose should be increased. If the blood glucose concentration falls below 150 mg/dL, 10% dextrose solution should be given.

The insulin dose should be reduced to 0.05 U/kg/hour if glucose concentration is not sustained by the 10% dextrose solution. Insulin should not be stopped. A continuous supply of insulin is needed to prevent ketosis and permit continued anabolism. If the patient has marked sensitivity to insulin, the dose may be decreased to 0.05 U/kg/hour, or less, provided that metabolic acidosis continues to resolve.

Persistent acidosis, defined as bicarbonate value <10 mmol/L after 8-10 hours of treatment, is usually due to inadequate insulin effect. Insulin dilution and rate of administration should be checked properly, and a fresh preparation must be made. Too dilute solution may enhance insulin adherence to the tubing. If insulin is given by subcutaneous route, inadequate absorption may occur. Rare causes of persistent acidosis are lactic acidosis due to an episode of hypotension or apnea or inadequate renal handling of hydrogen ion due to an episode of renal hypoperfusion.

Potassium :

Children with DKA have total body potassium deficits of about 3–6 mmol/kg. The major loss of potassium is from the intracellular pool. Intracellular potassium is depleted due to transcellular shifts caused by hypertonicity. Increased plasma osmolality results in osmotic water transport from cells to the ECF, thereby concentrating cellular potassium.

Due to increased potassium gradient, potassium is drawn out of cells. Glycogenolysis and proteolysis secondary to insulin deficiency also cause potassium efflux from cells. Acidosis may play a minor role in the distribution of potassium to the ECF.

Potassium is lost from the body as a consequence of vomiting, urinary ketoanion excretion (which requires excretion of cations, particularly sodium and potassium), and osmotic diuresis. Volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion and total body depletion of potassium occurs. But at presentation serum potassium levels may be normal, increased, or decreased.

Renal dysfunction enhances hyperglycemia and reduces potassium excretion and contributes to hyperkalemia. Administration of insulin and the correction of acidosis drives potassium back into the cells, decreasing serum levels. The serum potassium concentration may decrease abruptly, which may cause cardiac arrhythmias. Potassium replacement therapy is required regardless of

the serum potassium concentration. Potassium replacement must be started after initial volume expansion and concurrently with insulin therapy. If the patient is hypokalemic, start potassium replacement immediately after initial volume expansion and before starting insulin therapy. If the patient is hyperkalemic, don't give potassium replacement therapy until urine output is documented.

If immediate serum potassium levels are unavailable, an electrocardiogram may help to determine if 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; subsequent potassium replacement therapy should be based on serum potassium measurements. Potassium administration should continue throughout the period of intravenous fluid therapy. Potassium phosphate can be used together with potassium chloride or acetate. The maximum recommended rate of intravenous potassium replacement is usually 0.5 mmol/kg/hr.

Phosphate :

Depletion of intracellular phosphate occurs in DKA, and it is lost as a result of osmotic diuresis.

Plasma phosphate levels fall after starting treatment. Insulin promotes entry of phosphate into cells which exacerbates low phosphate levels in plasma. If intravenous therapy without food intake is prolonged beyond 24 hrs clinically significant hypophosphatemia may occur.

Severe hypophosphatemia (1 mg/dl), which may manifest as muscle weakness. It should be treated even if there are no symptoms. Phosphate administration may induce hypocalcemia. If hypocalcemia develops, administration of phosphate should be stopped. Potassium phosphate salts may be safely used as an alternative or in combination with potassium chloride or acetate and careful monitoring must be done to avoid hypocalcemia.

Acidosis :

The severity of DKA is defined by the degree of acidosis:

Mild:	pH 7.2–7.3
Moderate:	pH 7.1–7.2
Severe:	pH < 7.1.

Severe acidosis is reversible by fluid and insulin replacement. Insulin stops ketoacid production and

allows ketoacids to be metabolized, which generates bicarbonate. Treatment of hypovolemia improves tissue perfusion and renal function and increases the excretion of organic acids. There is no clinical benefit from bicarbonate administration, and adverse effects of bicarbonate therapy, include paradoxical CNS acidosis and hypokalemia due to rapid correction of acidosis.^[19]

Monitoring:

Vital signs and mental status are monitored at least every hour, and the balance of total fluid intake and fluid output is calculated each hour. The goal of monitoring is to ascertain that the patient shows signs of rehydration and improving mental status over time along with biochemical resolution of the DKA.

Serum glucose, electrolytes, blood urea nitrogen and creatinine, pH and urine ketones should be measured at presentation. Subsequently, serum glucose and pH should be measured hourly, with serum electrolytes and urine ketones assessed every 2 to 3 hours. If phosphate is administered, serum calcium concentrations must be monitored.

The goal for correction of hyperglycemia is to induce a 100 mg/dL (5.6 mmol/L) per hour decrease in the serum glucose value. The persistence of severe hyperglycemia suggests inadequate rehydration (or incorrect mixing of the insulin). Too rapid a decrease may indicate too rapid rate of rehydration. After the first hour, the pH should increase at least 0.03 units per hour. A slower rise suggests a need for a higher insulin dose or for increased hydration.

During treatment of DKA measured and the corrected serum sodium values should increase as the serum glucose concentration decreases. A failure of the corrected sodium value to rise or, even more significantly, a fall in either sodium value suggests overly rapid rehydration.

Transition :

IV fluids can be stopped 1-2 hours after consumption of oral fluids without vomiting. Subcutaneous insulin injection can be started when IV fluids are no longer needed. Presupper or prebreakfast time is most convenient for starting or restarting intermediate- or long-acting insulin.

Before that, rapid-acting or regular insulin 0.25 U/kg subcutaneously can be given every ~6 hours, and the insulin infusion stopped 60-120 minutes after the first subcutaneous dose of regular insulin or 60 minutes after a rapid-acting insulin analog. Established patients with DKA can resume their usual home dose of insulin. The management algorithm of DKA is shown in Figure 2.^[40]

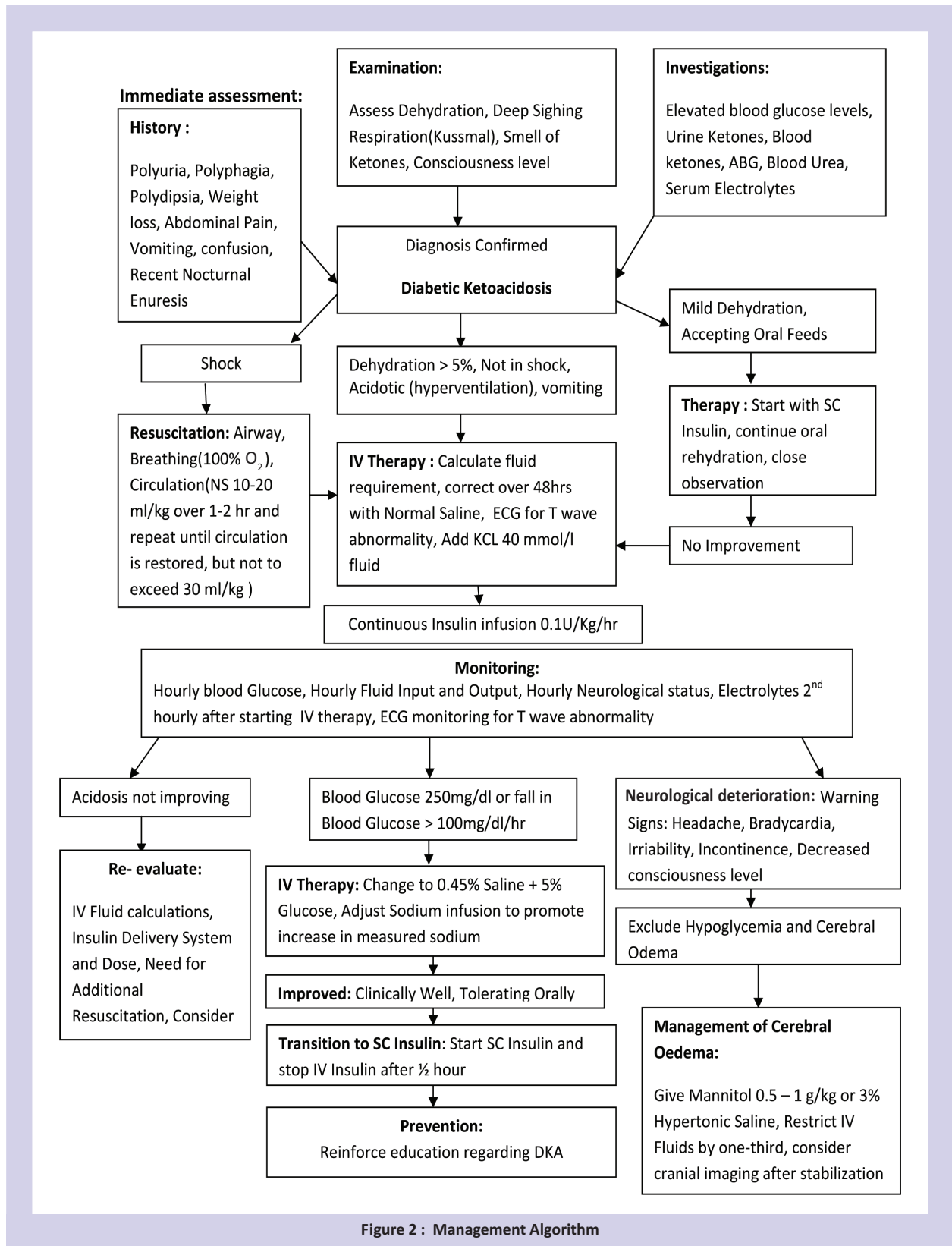


Figure 2 : Management Algorithm

Complications of DKA and Treatment :

Most of the diabetes-related morbidity and mortality in childhood T1DM can be attributed to complications of DKA. Cerebral oedema accounts for 60-100% of mortality.^[20,21] Other causes of death or disability with DKA include hypokalemia, hypophosphatemia, hypoglycemia, other intracerebral complications, peripheral venous thrombosis, mucormycosis, rhabdomyolysis, acute pancreatitis, acute renal failure, sepsis, aspiration pneumonia, and other pulmonary complications.^[18] Hypophosphatemia can cause progressive muscle weakness and death due to cardiorespiratory arrest days after metabolic recovery from DKA.

Peripheral Venous Thrombosis:

DKA is associated with a thrombotic diathesis, which is attributable to dehydration. In the absence of DKA, coagulation factor abnormalities have not been demonstrated in children with diabetes,^[22] but von Willebrand factor activity remains elevated at 120 hours following admission for DKA.^[23]

Thus, DKA and its treatment may promote a prothrombotic state and activation of vascular endothelium, predisposing to thrombosis.^[24] Massive arterial thrombosis resulting in unilateral below-the-knee amputation has been reported in a 12-year-old female patient with a heterozygous factor - V Leiden mutation and a 2-year history of poorly controlled T1DM who was not in DKA.^[25]

Pancreatitis:

Acute pancreatitis must be considered with abdominal pain that does not resolve with correction of acidosis.

Mucormycosis:

Acute, rapidly progressing, and often fatal facultative fungal infection occurs in young patients with diabetes who have chronically poor glycemic control and ketoacidosis. In a series of five patients, the sole survivor had severe neurologic disability; risk factors were African American race and history of poor compliance, poor clinic attendance, risk-taking behaviors, and high rate of hospital admission.^[26]

Cerebral Edema:

The incidence of cerebral edema in population studies is 0.5–0.9% and the mortality rate is 21–24%.^[27-29] The pathogenesis of both its initiation and progression is unclear and incompletely understood. Demographic factors that have been associated with an increased risk of cerebral edema include:

- Younger age^[30]
- New onset diabetes^[30,31]
- Longer duration of symptoms^[32]

These risk associations may reflect the greater likelihood of severe DKA.

Epidemiological studies have identified several potential risk factors at diagnosis or during treatment of DKA. These include:

- Greater hypocapnia at presentation after adjusting for degree of acidosis^[27,33,34]
- Increased serum urea nitrogen at presentation.^[27,34]
- More severe acidosis at presentation^[35,36]
- Bicarbonate treatment for correction of acidosis^[27]
- An attenuated rise in measured serum sodium concentrations during therapy^[27]
- Greater volumes of fluid given in the first 4 hours^[35]
- Administration of insulin in the first hour of fluid treatment^[35]

Disruption of the blood brain barrier may be seen in cases of fatal cerebral edema associated with DKA. In recent studies, the degree of edema formation during DKA in children correlates with the degree of dehydration and hyperventilation at presentation, but not with factors related to initial osmolality or osmotic changes during treatment. These data have been interpreted as supporting the hypothesis that cerebral edema is related to cerebral hypoperfusion during DKA, and that osmotic fluctuations during DKA treatment do not play a primary causal role.^[34]

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 O₂ saturation

Clinically significant cerebral edema usually develops 4–12 hours after treatment, but can occur before treatment has begun^[27,29] or, rarely, may develop as late as 24–48 hours after the start of treatment^[27,30] With early onset individuals tending to be younger.

Mechanisms:

Cerebral oedema refers to an increase of cerebral tissue water causing an increase of tissue volume^[37]. The edema may be vasogenic, due to breakdown of the blood-brain barrier, such as around a tumor or with trauma; cytotoxic,

from poisoning or metabolic derangement; or osmotic, as occurs with hyponatremia. Neither the cause nor the location of the fluid in the swollen brain of children with DKA is known. The mechanism is likely to be complex, and it may not be the same in all affected individuals, as reflected by the time of onset and the brain imaging findings.^[38]

Diagnostic criteria:

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

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

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%.

Treatment of cerebral edema:

Initiate treatment as soon as the condition is suspected. Reduce the rate of fluid administration by one-third. Give mannitol 0.5–1 g/kg IV over 20 minutes and repeat if there is no initial response in 30 minutes to 2 hours.^[39] 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.^[39]

Elevate the head of the bed. Intubation may be necessary for the patient with impending respiratory failure, but aggressive hyperventilation has been associated with poor outcome and is not recommended. A CT brain should be obtained to rule out other possible intracerebral causes of neurologic deterioration, especially thrombosis or hemorrhage, which may benefit from specific therapy. Two third cases presented with cerebral oedema, seizures and sepsis contribute o adverse outcomes.^[41]

Prevention of Recurrent DKA:

- Patients must be educated regarding the adjustment of insulin during illness.
- Children with insulin pump trained to recognise pump failure, symptoms of DKA and to take extra insulin with pen or syringe if necessary.
- Psychosocial reason for insulin omission may be present like an attempt to lose weight in an adolescent girl with an eating disorder, a means of escaping an intolerable or abusive home situation, clinical depression or other reason for inability of the patient to manage the diabetes unassisted.
- A psychiatric social worker or clinical psychologist should be consulted to identify the psychosocial reasons contributing to development of DKA.
- Parents and patients should learn how to recognize and treat impending DKA with additional rapid or short-acting insulin and oral fluids.

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