IAP National Treatment Guidelines

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Diabetic Ketoacidosis in Children

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INTRODUCTION

Diabetic ketoacidosis (DKA) is a life-threatening yet preventable complication of diabetes mellitus. It is also the most common cause of death in children with type 1 diabetes mellitus (T1DM). Worldwide, with an incidence of 3%, TIDM is one of the most common chronic illnesses in children.[1] In the absence of a national registry, the exact prevalence of the disease in India is unknown; however, Diabetes Atlas 2022 reports more than 2.5 lakh children and adolescents with TIDM in India.[2] 15–70% of children with newly diagnosed diabetes mellitus present with DKA compared to 1–10% of children with previously known diabetes mellitus.[3]

DEFINITION

Diabetic ketoacidosis is diagnosed based on the biochemical triad that includes hyperglycemia, metabolic acidosis, and ketosis. All the three criteria are essential for making the diagnosis:[4]

1. *Hyperglycemia:* Blood glucose >200 mg/dL
2. *Acidosis:* Venous pH <7.3 or serum bicarbonate <18 mmol/L
3. Ketonemia (beta-hydroxybutyrate >3 mmol/L) or ketonuria (urine ketones 2+)

Diabetic ketoacidosis without hyperglycemia (euglycemic DKA) can be a rare presentation seen in partially treated cases, those with prolonged fasting, or those with low intake of carbohydrate diet. pH and/or bicarbonate are not only essential for the diagnosis of DKA but also important to monitor improvement and titrate fluid and insulin therapy. Venous pH measurement suffices unless there is a need to assess respiratory function. Three ketone bodies are generated during DKA: Acetone, acetoacetate, and β-hydroxybutyrate (β-OHB). Among these, β-OHB predominately contributes to the metabolic acidosis observed in patients with DKA. During resolution of DKA, β-OHB is converted to acetoacetate which can be detected in urine using a dipstick assay. Consequently, solely relying on urine ketone dipstick assay may incorrectly suggest a lack of improvement. Blood ketone levels using point-of-care meters via capillary finger-prick blood provide a more accurate assessment. This method allows for the direct and precise quantification of β-OHB, facilitating better monitoring and management of children with DKA.[4]

The severity of DKA is categorized based on the degree of acidosis[4] **(Table 1)**:

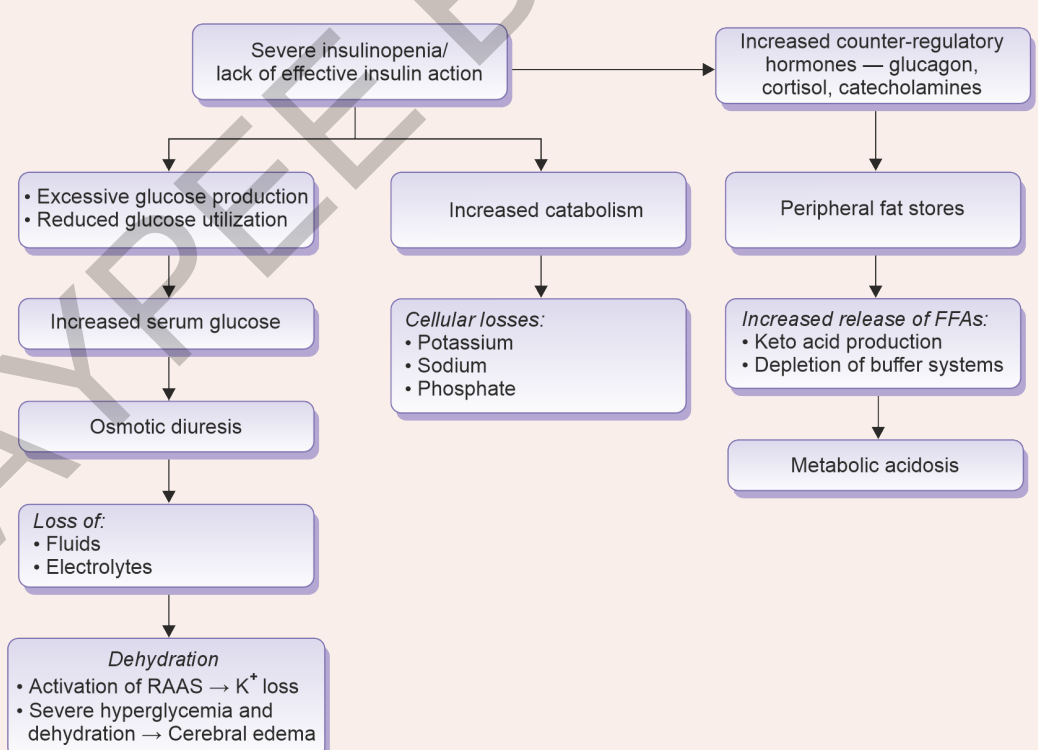
TABLE 1: Classification of severity of diabetic ketoacidosis (DKA).

Severity	*Mild*	*Moderate*	*Severe*
pH	7.2–7.3	7.1–7.2	<7.1
Bicarbonate (mmol/L)	10–18	5–10	<5
Ketones	Positive	Positive	Positive
Sensorium	Alert	Alert/drowsy	Stupor/coma

PATHOPHYSIOLOGY

Diabetic ketoacidosis results from an absolute or relative deficiency of insulin in the presence of heightened counter-regulatory hormone response incited by intercurrent infections **(Flowchart 1)**. In newly diagnosed T1DM, younger age at diagnosis (<2 years of age), delayed diagnosis, and lower socioeconomic status are risk factors for the initial presentation as DKA. In previously diagnosed cases of T1DM, poor compliance to insulin, adolescent and peripubertal age groups, surgery, intercurrent illness, etc., are known triggers for the precipitation of this metabolic crisis.

Flowchart 1: Pathophysiology of diabetic ketoacidosis.



(FFA: free fatty acids; RAAS: renin–angiotensin–aldosterone system)

CLINICAL PRESENTATION

The clinical presentation of DKA may be nonspecific; hence, a high index of suspicion is needed for diagnosis. The common complaints include nausea, vomiting, polyuria, polydipsia, polyphagia, weight loss, and abdominal pain. The mechanism of abdominal pain is not entirely understood and hence is a misleading complaint that can result in missed or delayed diagnosis.

The physical examination findings include signs of dehydration, i.e., tachycardia, loss of skin turgor (tenting of the skin), dry mucosae, prolonged capillary refill time, and cool extremities. Weak peripheral pulses, with or without hypotension, characterize severe dehydration (>10%). Urine output may be preserved due to osmotic diuresis and hence does not serve as a good surrogate of severity of dehydration. Kussmaul breathing, i.e., deep labored and rapid breathing, is an involuntary response to severe acidosis and is a universal finding in a child in DKA. One should not confuse acidotic breathing with tachypnea and breathing patterns associated with airway and/or lung parenchymal diseases. Changes in neurological status are mainly attributed to high serum osmolarity and metabolic acidosis and should progressively improve with therapy. However, suspect cerebral edema if there is deterioration in mental status after initiation of therapy, new-onset neurological symptoms (e.g., cranial nerve palsy), unexplained bradycardia, or other signs of raised intracranial pressure (ICP).

The differential diagnosis of DKA includes hyperglycemic hyperosmolar state, sepsis, acute abdomen, gastroenteritis, asthma/pneumonia, and other causes of high anion gap metabolic acidosis and encephalopathy.

INVESTIGATIONS

- Random blood glucose, blood ketones, and/or urinary ketones
- Serum electrolytes—sodium, potassium, and chloride
- Renal function tests—blood urea nitrogen and creatinine
- Venous blood gas—pH, bicarbonate, lactate, anion gap, serum osmolarity, pCO_2
- HbA1c (glyated hemoglobin)
- Complete blood count
- Calcium, phosphorus, albumin, and magnesium
- Appropriate cultures to rule out infections

MANAGEMENT IN AN EMERGENCY ROOM

- Assessment of airway, breathing, circulation, and level of consciousness
- Oxygen should be started in all children with shock. Intubation is indicated in a comatose/severely obtunded child with absent protective airway reflexes. Drug-assisted intubation should be performed in such cases. The goal of mechanical ventilation in intubated children is to match the baseline CO_2 levels (adaptive physiological ventilation).[5]
- A nasogastric tube should be inserted for gastric decompression and to prevent aspiration.
- Place two peripheral intravenous lines. If the child is in shock, a 20 mL/kg normal saline bolus should be administered over 20–30 minutes. If the child is not in shock but volume depleted, a 10 mL/kg normal saline bolus should be administered over 60 minutes. Reassessment should be done after each bolus. Central line insertion should be avoided due to the high risk of thrombosis.
- Continuous electrocardiogram (ECG) monitoring for tachycardia, arrhythmias, and changes associated with hyperkalemia/hypokalemia
- Measure random blood glucose and blood ketones by a point-of-care bedside glucometer. If ketone strips are unavailable, urinary ketones can be measured to document ketosis. Venous blood gas is used to measure pH, pCO_2, bicarbonate, lactate, anion gap, base deficit, and osmolarity. Baseline serum electrolytes and renal function tests and appropriate cultures (blood, urine, tracheal aspirate, etc.) are done as indicated.

SPECIFIC MANAGEMENT (FLOWCHART 2)

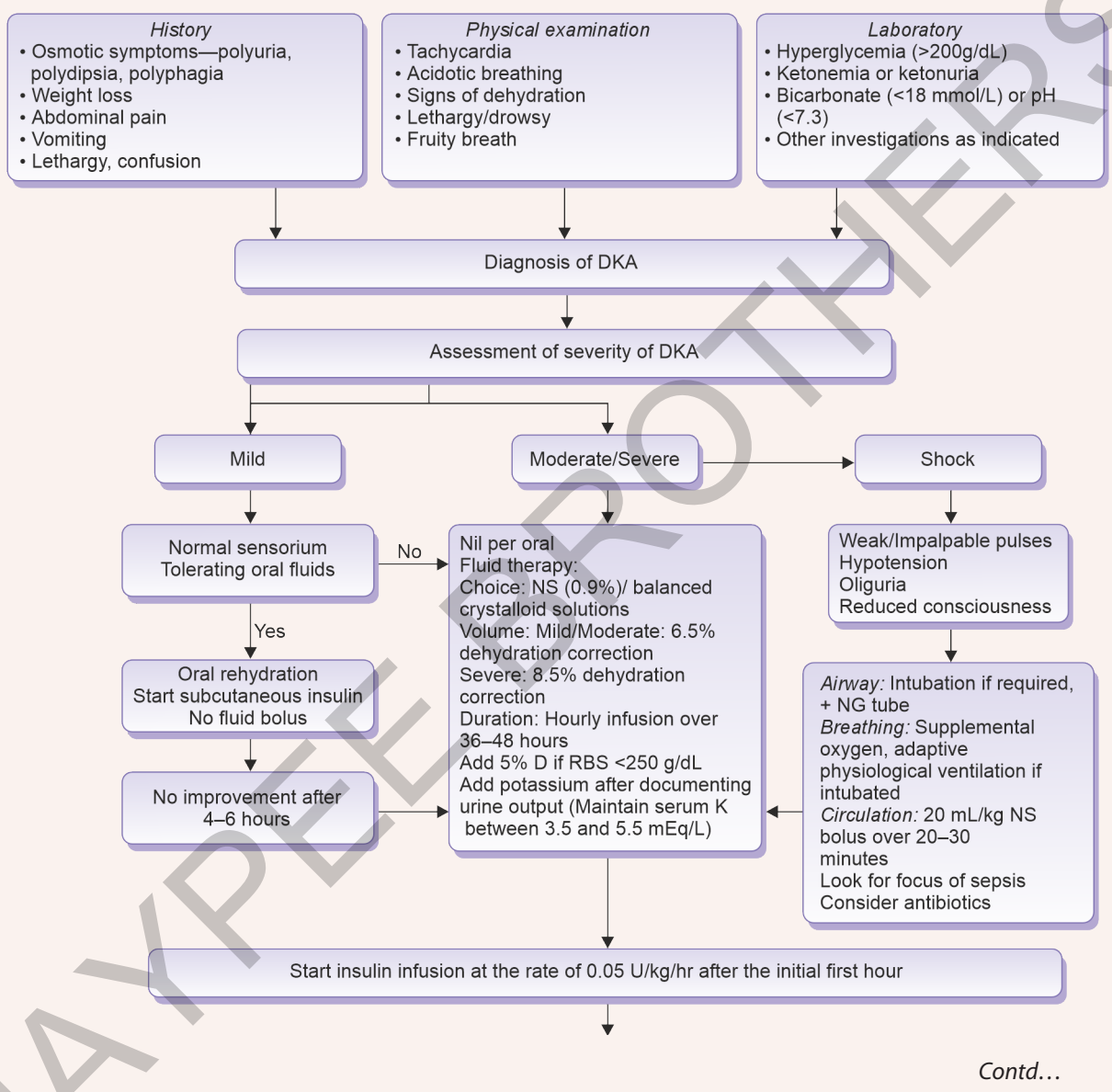
Hydration and insulin therapy, under stringent monitoring of clinical and laboratory parameters, form the basis of the management of DKA. The goals of management include:

- Correction of dehydration and electrolyte imbalances
- Halting ketogenesis and reversing ketoacidosis
- Correction of hyperosmolarity and restoration of blood glucose to near-normal
- Anticipation of treatment-related complications and early intervention
- Identification and treatment of precipitating causes (noncompliance, infections, etc.)

Fluid and Electrolyte Management in Diabetic Ketoacidosis

Fluid therapy aims to restore circulating volume and improve glomerular filtration to enhance renal excretion of ketones and glucose. Fluid resuscitation is the cornerstone of the management of DKA and should always begin before starting insulin therapy.[5]

Flowchart 2: DKA management algorithm.



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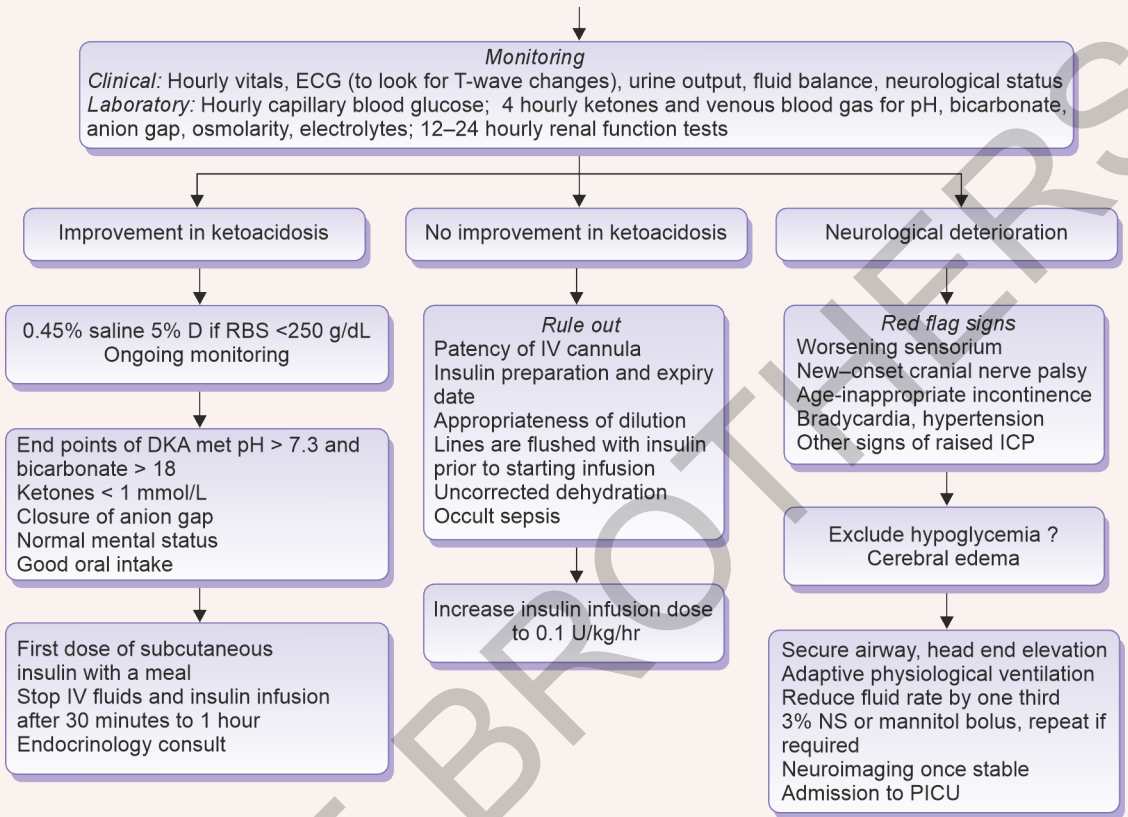

(DKA: diabetic ketoacidosis; ICP: intracranial pressure; NG: nasogastric; NS: nasal saline; PICU: pediatric intensive care unit; RBS: random blood sugar)

Choice of Fluid

- *Resuscitation fluid:* Normal saline (0.9%) is the fluid of choice when a child presents in shock or is volume depleted. There is no evidence to support the use of colloids for immediate resuscitation in DKA.
- *Deficit replacement:* In a hemodynamically stable child, restoring circulating volume by retaining fluid in the intravascular compartment remains the priority. Also, the serum is hypertonic at presentation; hence, initially, isotonic fluids are started to avoid major osmotic shifts. Normal saline (0.9%) or balanced crystalloid solutions (Ringer's lactate, Plasmalyte) are the initial fluids of choice. Using balanced crystalloids over saline has been associated with faster resolution of acidosis and lower postresuscitation chloride levels in adult DKA.[6] Evidence regarding this in pediatric DKA is still evolving. Nevertheless, the latest International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical practice guidelines for pediatric DKA recommend the usage of either normal saline or balanced crystalloids for deficit replacement.[4] After the initial 4–6 hours, while monitoring serum sodium and osmolarity, the tonicity of fluid should be changed to N/2 with addition of 5%D when random blood sugar (RBS) falls to <250 g/dL. In the case of hypoglycemia, 2 mL/kg of 25%D bolus is given, followed by a repeat blood glucose

check after 15 minutes. Potassium is supplemented at 40 mmol/L after ensuring urine output. The indications of phosphate supplementation are cardiogenic shock, respiratory and muscle weakness, or when serum phosphate levels are <1–1.5 mg/dL.

Amount of Fluid

In DKA, clinical estimation of dehydration is not considered accurate. In most cases, fluid deficits range from 5 to 10% and are best correlated with the degree of acidosis and blood urea nitrogen. Hence, a modest correction of 6.5–8.5% is appropriate to avoid over-hydration or under–hydration. Any fluids that were administered before referral should be subtracted. Fluid boluses that are given for resuscitation, however, should not be subtracted.

Duration of Therapy

Rehydration and electrolyte correction should be gradually targeted over 36–48 hours to avoid major osmotic shifts. However, most cases resolve before 24 hours, and oral fluids correct the remaining deficits.

Insulin Therapy

Although fluid therapy alone can partially correct hyperglycemia and ketonemia, insulin therapy is required to normalize blood glucose levels and suppress ketogenesis and lipolysis completely. A low-dose insulin infusion rate (0.05 U/kg/h) is safer and equally effective to the standard dose (0.1 U/kg/h), especially in malnourished children.[6] Insulin infusion is started after 1–2 hours of volume expansion to avoid a precipitous fall in blood glucose. While serum glucose concentrations typically normalize before the complete resolution of ketosis and acidosis, dextrose supplementation in IV fluids are essential to sustain insulin therapy and prevent hypoglycemia. Bolus insulin is not recommended as it increases the risk of cerebral edema. Infusion tubing should be flushed with insulin before connecting to the patient.

Children with mild DKA, i.e., those with normal sensorium and good oral intake, can be managed using oral rehydration protocol and short-acting subcutaneous insulin (lispro, aspart, glulisine) given every 2–4 hours. This lowers the need for infusion pumps, close monitoring, and intensive care unit (ICU) care in such children.[7]

RESOLUTION OF DIABETIC KETOACIDOSIS

The endpoints of DKA resolution include normalization of ketoacidosis (pH >7.3, bicarbonate >18 mmol/L, ketones <1 mmol/L, and closure of anion gap), normal mental status, and good oral intake. After the resolution of DKA, these children are transitioned to a subcutaneous multidose insulin regimen. The insulin infusion is stopped 30 minutes to 1 hour after the first subcutaneous insulin dose.[4]

MONITORING

Monitoring is the most critical part of DKA management. Strict monitoring enables early identification of complications needing early intervention. **Table 2** enlists several variables of clinical and biochemical monitoring in DKA.

TABLE 2: Clinical and biochemical monitoring in DKA.

Monitoring parameter	*Remarks*
Heart rate, respiratory rate, blood pressure, Glasgow Coma Score, pupils	• Hourly • Neurological status improves as dehydration and acidosis improve
Urine output	Hourly
Random blood glucose	• Every hourly until transition to subcutaneous insulin • Desired rate of fall is 50–100 mg/dL/hr
pH, bicarbonate, pCO_2, anion gap, serum osmolarity	• 4 hourly • pH is expected to increase by 0.03/hr
Corrected sodium, potassium, chloride	4 hourly
Blood urea nitrogen and creatinine	• Baseline, 8–12 hourly • Many patients have prerenal AKI at admission, which improves with fluid resuscitation
Serum magnesium and phosphate	Baseline, 8–12 hourly

Complications, broadly, can be prevented if management and monitoring are optimal. The most common complications are hypoglycemia, hypokalemia, hypophosphatemia, hyperchloremic acidosis, acute kidney injury, and infections. Cerebral edema is the most dreaded complication and is seen in 0.5–1% of DKA episodes.[8] The risk factors for developing cerebral edema can be disease-related and treatment-related[9,10] **(Box 1)**. Clinical presentation and management have been discussed in the management algorithm.

BOX 1: Risk factors for developing cerebral edema.

Disease-related	*Treatment-related*
Younger age at presentation	Rapid decline in serum osmolality
Delayed diagnosis of DKA	Use of bicarbonate
Newly diagnosed type 1 diabetes mellitus	Higher volumes of fluids infused within the first 4 hours
Severe acidosis and severe hypocapnia at presentation	Initiation of insulin infusion in the first hour of therapy
	Insulin bolus

(DKA: diabetic ketoacidosis)

Lastly, prevention of DKA is crucial. Improving access to healthcare and day-to-day management of TIDM in individual patients will help in this cause.

KEY LEARNING POINTS

- DKA is a common complication of T1DM in children.
- Clinical features are nonspecific, and a high index of suspicion is required. Clinical symptoms are mainly attributed to dehydration and metabolic acidosis.
- Fluid therapy should always precede insulin therapy.
- Correct dose, rate, technique, and duration of insulin infusion are crucial.
- Stringent monitoring is necessary for favorable outcomes.
- Anticipate and treat complications as and when they occur.
- Equally important is to identify and treat the precipitating trigger.

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ISBN 978-93-6616-365-9