Diabetic Ketoacidosis in Children

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Introduction

Diabetic ketoacidosis (DKA) is a major cause of mortality and morbidity in children with type 1 diabetes mellitus (T1DM). It is caused by a relative or absolute deficiency of insulin along with elevations of counter-regulatory hormones including glucagon, catecholamines, cortisol, and growth hormone. The criteria used for diagnosis is hyperglycemia (blood glucose >200 mg/dL) and acidosis (venous pH <7.3, and/or bicarbonate < 15 mEq/L) associated with glycosuria, ketonuria and ketonemia [1].

The classic clinical presentation is an acutely ill child with dehydration, lethargy, acidotic breathing (Kussmaul respirations) and a fruity smell (acetone) on the breath. The diagnosis is difficult if it is the first presentation of T1DM, as is seen in 15-70% of all newly diagnosed infants and children with DM [2,3].

DKA is categorized by the severity of acidosis, varying from mild (venous pH:<7.30; bicarbonate concentration: <15 mmol/L) to moderate (pH: <7.2; bicarbonate:<10) to severe (pH: <7.1; bicarbonate: <5).

DKA should be considered in the differential diagnosis of a child presenting with dehydration and polyuria, acute abdominal symptoms and signs, respiratory distress or coma.

Pathophysiology

A relative or absolute deficiency of insulin is the initial primary event in the pathogenesis of diabetic ketoacidosis. Delay in diagnosis is the major cause of DKA in a previously undetected diabetic child whereas omission of insulin is the cause of recurrent DKA especially seen in adults.

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Relative deficiency of insulin due to elevations of counter-regulatory hormone as in stress precipitates DKA. The deficiency of insulin results in increased breakdown of glycogen, protein and fat in muscle, liver and adipose tissue leading to a catabolic state. The rise of the counter regulatory hormones like glucagon, cortisol, growth hormone and catecholamines results in glycogenolysis, lipolysis, proteolysis, gluconeogenesis and ketogenesis which are responsible for most of the manifestations of DKA.

Hyperglycemia: Insulin deficiency and counter-regulatory hormone excess leading to decreased peripheral utilization of glucose along with increased glucose production (from glycogenolysis and gluconeogenesis) results in hyperglycemia.

Acidosis: Increased free fatty acids (FFA) are produced in the body due to increased lipolysis. These FFA are shunted towards beta-oxidation resulting in ketonemia and acidosis. This acidosis is compounded by lactic acidosis from poor tissue perfusion secondary to hypovolemia (due to osmotic diuresis). Volume expansion (to improve perfusion) and insulin therapy (which stops ketone production and increased metabolism of ketoacids) hence, are the mainstay of therapy in management of acidosis in DKA. Bicarbonate administration may be counterproductive by producing paradoxical CNS acidosis and hypokalemia due to sudden correction of acidosis [4].

A cautious bicarbonate correction may be given in case of severe acidemia (arterial pH<6.9) and in life-threatening hyperkalemia.

Dehydration: Hyperglycemia leads to osmotic diuresis which results in significant fluid and electrolyte losses. Despite these losses, these patients continue to have polyuria until severe volume deficits lead to impairment in renal blood flow and glomerular filtration. ECF volume deficit in children with DKA is approximately 5-

10% [5].

Hyperosmolality: Osmolality is estimated from the formula: Osmolality = 2[Na(mEq/L)] + [K(mEq/L)] + Glucose (mg/dL)/18 + BUN (mg/dL)/2.8.Hyperosmolality is induced by hyperglycemia and elevated blood urea nitrogen (BUN) in DKA. This hyperosmolar state results in major transcellular shifts of fluid and electrolytes and osmotic diuresis.

Sodium homeostasis: Hyponatremia is usually seen in DKA. Hypertriglyceridemia and hyperglycemia results in artifactually decreased sodium levels. The true serum sodium can be calculated from the formulae:

True[Na]= [measured Na](0.021[T]+ 0:994) and where T is the triglyceride level in g/dL and sodium is expressed in mEq/L[6]. and True[Na]=Na + 2 x [(glucose mg/dl - 100) ÷ 100]

Potassium homeostasis: Hypokalemia is another potentially dangerous element in DKA. Total body potassium deficit of the order of 3-6 mEq /L is usually present [7].

Osmotic diuresis, vomiting and increased renal excretion lead to progressive loss of body potassium stores. On the other hand, there is potassium efflux from intracellular to extracellular compartment due to hypertonicity. Glycogenolysis, proteolysis and acidosis also contribute to this transcellular shift of potassium. Hence serum potassium levels may be falsely normal, decreased or increased despite low body stores [8].

Initiation of insulin therapy results in intracellular shift of potassium leading to hypokalemia. Serum potassium concentrations may drastically fall with start of therapy. Hence, potassium supplementation during the early phase of DKA management after volume expansion but before/along with start of insulin therapy is important. Renal dysfunction may contribute to hyperkalemia [8].

The best way to assess for potassium deficit is through ECG changes [9].

Hypophosphatemia: Intracellular phosphate is depleted in DKA and lost from the body due to osmotic diuresis. Further, plasma phosphate levels fall when insulin administration promotes entry of phosphates into cells. Hypophosphatemia may result in rhabdomyolysis, hemolysis, muscle weakness, and respiratory failure theoretically, but such a case is rarely seen. The role of phosphate supplements in therapy for DKA is controversial. Most of the studies have not shown any benefit from phosphate replacements [10,11].

Hypomagnesemia: Decreased serum total magnesium level has been documented in children with DKA with subsequent self normalization.

Management of DKA

The child with DKA should preferably be managed in a set up with trained medical personnel and nursing staff. Access to laboratory for frequent analysis of biochemical parameters should be present. A thorough history and physical examination along with bedside tests for blood glucose and urine ketones are usually enough for diagnosis and initiate further management. (Figure 1)

Emergency management

· Clinical evaluation for diagnosis and determining cause of DKA (infections, omission of insulin, neglect of sick day rules)

· Assessment of ABCs (airway, breathing, circulation) and level of consciousness

o Heart rate, capillary refill, peripheral pulses, blood pressure, respiratory rate, pulse oximetry

o Glasgow coma score (GCS)

· Assess clinical severity of dehydration

· Weigh the patient

· Intravenous access

· Investigations:

o Blood samples for glucose, electrolytes (sodium, potassium, calcium, magnesium, phosphorus), urea, creatinine, hematocrit, pH, blood gas analysis (pCO2, pO2, bicarbonate), betahydroxybutyrate, HbA1c; calculate osmolality

o Urinalysis; sugar, ketones

o Evidence for infection; counts, appropriate specimens for cultures

o ECG for potassium status

· Grade severity of DKA: venous pH – 7.2-7.3

(mild), 7.1-7.2 (moderate), <7.1 (severe)

Supportive measures

· Secure airway if patient obtunded (GCS <8)

· Insert nasogastric tube and continuous nasogastric aspiration to keep the stomach empty

· Cardiac monitor for continuous ECG monitoring

· Catheterization if unconscious, unable to void on demand for output monitoring

· Central venous pressure monitoring for the critically ill, or neurologically compromised patient

· Management of infection/precipitating factor

Fluid and electrolyte therapy

Clinical estimation of the volume deficit is inaccurate [12] and hence, replacement of 5-7% volume deficit in moderate DKA and 10% in severe DKA is recommended [13]. Volume expansion with 0.9% saline or Ringer's lactate is given as 10-20 ml/kg over 1-2 hours. This may be repeated according to clinical reevaluation. If the child is in shock then the fluids are given as a fast bolus as for management of shock. The remaining deficit (total volume deficit – initial bolus) is replaced evenly over 48 hours [14]. Simultaneously, maintenance fluid therapy is also initiated. Urinary losses are not included in calculations for the fluid therapy. Both the fluids are together given as normal saline or ringer's lactate for the initial 4-6 hours and subsequently as 0.45% saline with added potassium salts. The sodium concentration of the fluid may be increased if the corrected serum sodium does not rise appropriately. Decrease in serum potassium concentrations should be anticipated with volume expansion and insulin therapy due to intracellular shifts. Hence, potassium should be supplemented after administering volume expansion, before/along with start of insulin therapy. The starting potassium concentration should be 40 mEq/L and then adjusted according to biochemical values. A combination of potassium phosphate and potassium acetate or chloride may be used.

Insulin

Insulin is the mainstay of therapy for treating hyperglycemia and acidosis in DKA. After volume expansion, insulin infusion is initiated at 0.1 U/kg/hr. A bolus dose in the beginning should not be used and may in fact, increase the risk of cerebral edema [15].The insulin infusion is continued until venous pH >7.3, bicarbonate >15mEq /L, and/or normalisation of the anion gap. 5% dextrose is added to the ongoing intravenous fluid once blood sugars reach 300mg%. The sugar concentration is increased to allow insulin infusion to continue till correction of the acidosis. If still blood sugar levels fall then insulin infusion may be decreased to 0.05U/kg/hr, provided the acidosis continues to get corrected. If there is inadequate response to insulin therapy, causes like infection or improper insulin preparation and administration should be reviewed. If intravenous insulin is not possible; hourly or 2-hourly subcutaneous or intramuscular short or ultra-short acting analogs may be used [16,17]. With substantial clinical improvement and when the child desires to eat, oral fluids may be introduced. If this is tolerated intravenous fluid may be gradually decreased.

Subcutaneous insulin is introduced when ketoacidosis has revolved (bicarbonate > 18 mEq/L and venous pH >7.3, plasma glucose is <200 mg/dL and oral intake is tolerated. The first dose should be given 1-2 hours before stopping insulin infusion to allow time for the injected insulin to get absorbed. In a known diabetic, the previous dose may be resumed. In new onset diabetes, the insulin dose may be given as per standard dose recommendations according to age.

Monitoring: Clinical and biochemical

Meticulous monitoring forms an essential part of DKA management. It includes documentation of hour-by-hour clinical observations, intravenous and oral medications, fluids, and laboratory results on a flow chart. It includes:

· Vital signs – heart rate, respiratory rate, blood pressure, *hourly or more frequently*

· Neurological monitoring for cerebral edema – headache, vomiting, bradycardia, hypertension, altered sensorium, focal deficits, *hourly or more frequently*

· Fluid input – output, *hourly or more frequently*

· Insulin infusion rate

· Capillary blood glucose, *hourly or more*

frequently

· Serum electrolytes (Sodium, potassium, calcium, magnesium, phosphorus, blood gases) *2-4 hourly or more frequently*

· Blood urea, creatinine, hematocrit, *6-8 hourly*

· Urinary ketones until cleared

Cerebral edema

Symptomatic cerebral edema occurs in 0.5-1 % of pediatric DKA [18,19,20]. It typically occurs 4 to12 hours after treatment initiation but has occasionally been seen before treatment has begun or sometimes may be delayed [21]. It has a high mortality rate (21-24%) and a high incidence of permanent neurological sequelae (15-26%) [22,23].

Cerebral edema manifests with features of raised intracranial pressure like headache, vomiting, altered sensorium, bradycardia, hypertension and sometimes, focal neurological deficits [24]. Osmotically mediated fluid shift into the brain caused by rapid declines in serum osmolality and/or overly vigorous fluid resuscitation has often been cited as a potential cause of cerebral edema [25, 26]. Recent data from animal studies suggest a vasogenic cause due to activation of ion transporters in the blood brain barrier resulting from cerebral hypoperfusion and/or direct effects of ketosis or inflammatory cytokines on blood brain barrier endothelial cells [27]. Children presenting with high BUN, profound acidemia, hypocapnia, and a lesser rise in serum sodium on treatment have been associated with cerebral edema [28,29].

These patients should be aggressively monitored. Prompt treatment with mannitol (0.25-1.0 g/kg) may be beneficial [30]. Supportive measures like airway protection by endotracheal intubation is required. Imaging studies may show focal to diffuse cerebral edema, hemorrhage, or infarction [31].

Prevention of DKA

In previously undetected patients:

· Increased public awareness of signs and symptoms of diabetes for early detection through school and physician awareness campaign

In a known diabetic:

· Diabetes education to patient and attendants

· Adhering to sick day guidelines: parents and patients should be taught to recognize and treat impending DKA with additional insulin and oral fluids

· Psychosocial evaluation and counseling

· Adult supervision of insulin administration

· 24 hour diabetes telephone helpline

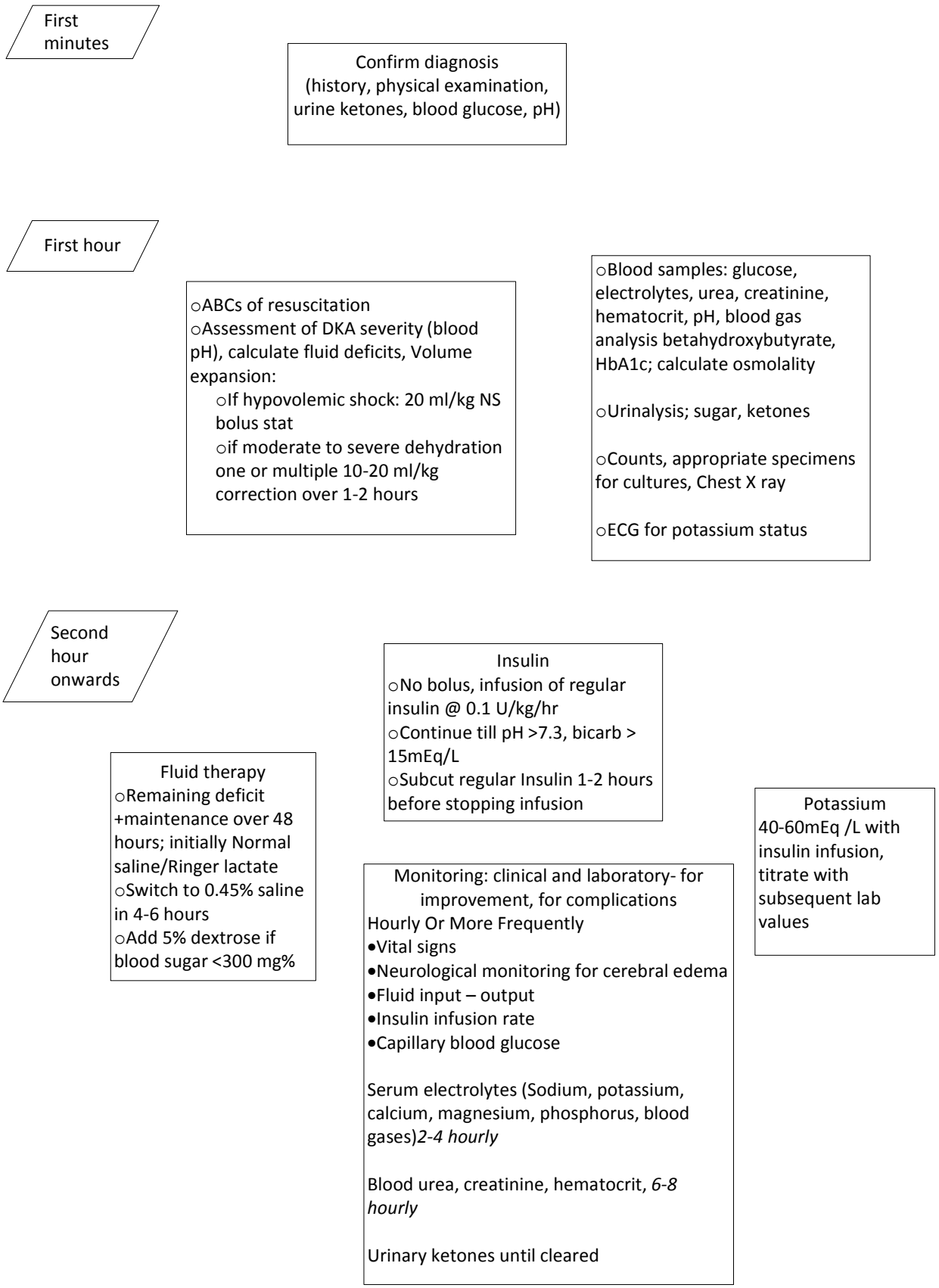

Figure 1: Flowchart for the management of diabetic ketoacidosis in children

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