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Chapter 5

IN-HOSPITAL MANAGEMENT OF PEDIATRIC DIABETIC KETOACIDOSIS (DKA): PRESENTATION, DIAGNOSIS, AND TREATMENT*

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ABSTRACT

Failure to receive appropriate insulin therapy in a patient with type 1 diabetes mellitus (T1DM) results in diabetic ketoacidosis (DKA), a potentially fatal condition. DKA is defined as hyperglycemia, with a serum glucose concentration > 200 mg/dL, acidosis with pH < 7.3 and serum bicarbonate concentration < 15 mmol/L, and the presence of serum ketones.

Currently, no universal standard of care for treating pediatric patients presenting with DKA exists. Additionally, a wide range of subspecialists

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and non-subspecialists are involved in treating pediatric patients with DKA resulting in a variety of treatment options. However, some generally accepted goals for treatment include the slow correction of hyperglycemia thereby slowly correcting serum osmolality, the slow correction of metabolic acidosis, as well as the correction of fluid and electrolyte derangements. Careful and precise management is imperative in an effort to avoid severe complications of DKA and its treatment including hypoglycemia, cerebral edema, permanent neurologic deficits and long-term memory or other neurologic dysfunction. In this chapter, aspects of management of pediatric patients with DKA after admission to the intensive care unit or pediatric acute care unit will be discussed.

BRIEF REVIEW OF PATHOPHYSIOLOGY

Insulin is the hormone responsible for the intracellular transfer of glucose, and is secreted from the β cells of the pancreas [1]. The destruction of the β cells, most commonly from autoantibodies, results in insulin deficiency and T1DM [2]. The lack of insulin results in glucose that remains extracellular and thus is useless for energy production. Counter-regulatory hormones, such as glucagon, attempt to increase glucose production by glucogenolysis and gluconeogenesis [3]. Ongoing hyperglycemia leads to osmotic diuresis, electrolyte loss and dehydration [2]. Additionally, the body's cells are not able to take up the newly available glucose because of the continued lack of insulin, leading to further gluconeogenesis and hyperglycemia. This exacerbates the ongoing osmotic diuresis. As a result, cells ultimately rely on alternate pathways for energy production, such as lipolysis, or the breakdown of fatty acids. Lipolysis leads to ketogenesis [4]. Production of ketones, primarily acetoacetate and β-hydroxybutyrate, result in an overwhelmingly high anion gap metabolic acidosis [2].

Diabetic Ketoacidosis Definition and Severity:

- The diagnosis of DKA requires: hyperglycemia (> 200 mg/dL), elevated ketone body production, and metabolic acidosis (pH < 7.3 and/or serum bicarbonate level < 15 mmol/L) [5].
- The acidotic state must be documented by venous or arterial blood gas analysis plus assessment of serum beta-hydroxybutyrate concentration.

The severity of presentation may be "graded" based on the degree of acidosis:

- Mild DKA: venous pH from 7.2-7.3 or a serum bicarbonate < 15 mmol/L.
- Moderate DKA: venous pH 7.1-7.2 or a serum bicarbonate < 10 mmol/L.
- Severe DKA: venous pH < 7.1 or bicarbonate < 5 mmol/L [6].

As the severity increases, the need for pediatric intensive care management and monitoring, as well as the risk for significant morbidity and mortality of the disease and its treatment increase.

DISPOSITION

Some individuals presenting in mild DKA will not require admission to the hospital. This is especially true if they are a patient with known T1DM rather than a child with a new diagnosis of the disease. In the former group, the expectation is that with 2-3 hours of appropriate fluid management and supplemental insulin administration the patient's nausea and vomiting will be controlled as well as their state of hydration and aberrant glucose excursion.

However, those presenting in moderate DKA would benefit from admission to an intensive care or acute care unit where high-acuity nursing and active physician oversight are provided.

A diagnosis of severe DKA necessitates admission to a facility capable of providing intensive care. Regardless of the location of the Intensive Care Unit (ICU), consultation with Pediatric Endocrinology is imperative.

THERAPY AND CONSEQUENCES FOR SEVERE DKA: THE NEXT 2 TO 48 HOURS

In practice, the patient transported to the ICU will already be diagnosed with DKA and have appropriate fluid and insulin therapy initiated. Additionally, initial laboratory analyses will likely be known and the patient's accurate intravenous intake and urinary output data analysis will be started.

In the emergency department [ED], as discussed in detail in a previous chapter, initial fluid therapy in patients not presenting with frank hypotension or hypovolemic shock should be isotonic Normal Saline or Lactated Ringer's solution at a volume of 10-20 ml/kg. Typically, regular or rapid acting biosynthetic insulin is started by the end of the first hour assuming that the change in glucose concentration has not been abnormally rapid causing a precipitous drop in serum osmolality. Continuous cardio-respiratory monitoring should be ongoing with hourly documentation of vital signs and neurological checks.

Maintenance Fluid: Type, Tonicity and Infusion Rates

As documented in the prior chapters, diabetic ketoacidosis in children is a condition marked by hyperosmolality and dehydration. Cautious and slow correction of both of these deficits is crucial, and requires frequent clinical examinations, laboratory evaluations and ongoing strict analysis of the patient intake and output.

Free water deficits are invariably greater than electrolyte losses, but both are noteworthy and will direct composition of maintenance fluid therapy.

The actual electrolyte losses vary due to duration and severity of disease. However, typical losses are as follows with the ranges noted in parentheses:

Water	30-100 ml/kg
Sodium	6 mmol/kg (5-13)
Potassium	5 mmol/kg (3-6)
Chloride	4 mmol/kg (3-9)
Phosphate	0.5-2.5 mmol/kg

The choice for maintenance fluid composition will reflect the physician's concerns for the slow correction of the patient's state of hyperosmolality. The correction is targeted to allow for lowering of serum osmolality at a rate no greater than 5 mOsm/hr. with a simultaneous reduction in serum glucose of < 100 mg/dl per hour [5.5mmol/L]. Thus, it is important to recognize that the patient in DKA has a relative pathologic hyperosmolality created by severe DKA. As a result, in the acute phase, it is recommended to administer isotonic fluids with potassium and phosphate so as not to give excessive "free water" via the administration of hypotonic fluid solutions.

Normal serum osmolality is generally measured as 278 – 300 mosm/L. Effective serum osmolality is increased by a factor of [Glucose (mg/dl) – 100]/ 18] in a patient with significant hyperglycemia. Best practice guidelines suggest correction of the fluid and electrolyte deficits over 36-48 hours. In practice, major academic centers recommend a broad range of "entire daily rates of fluid infusion":

~ 4000 ml/m^2	University of Texas Southwestern Medical Center, Dallas.
3175 ml/m^2	2006 American Diabetes Association Consensus Statement
2500 ml/m^2	Baylor College of Medicine, Houston, Texas. (personal communication)
1800 ml/m^2	University of Chicago Pritzker Medical School. (personal communication)

Normal fluid requirements are 1200-1500 ml/m^2/day, therefore some centers are quite cautious with regards to deficit replacement. In fact, few centers recommend replacing urine losses [output] during this phase of treatment. All centers advise choosing a replacement fluid rate that minimizes the risk of developing cerebral edema with isotonic fluid administration.

Several studies have been published demonstrating a "two bag system" to expedite bedside titration of intravenous dextrose concentrations [7]. This method involves one bag of intravenous fluids without dextrose (usually normal saline plus potassium and phosphate) and an identical bag of fluids with the addition of 10% dextrose (see Figure 1). A nurse-driven bedside protocol used for titration of a "two bag system" of IV fluids demonstrated an equivalent time to correction with equivalent safety profile. A "two bag system" can manipulate dextrose concentration with only two fluid bags, thereby avoiding a costly third bag of IV fluids (no dextrose, 5% dextrose and 10% dextrose) during acute correction [7].

At present, the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines of 2014 acknowledge that no "rate of rehydration" can be considered superior to another. Having said that, rehydration rates of 1.5 – 2.0 times maintenance [2.25 – 3.0 L/m^2 daily] are commonly employed for the first 24 hours. Beyond the absolute rate of rehydration for many published protocols, individual centers will adjust the 24-48 hour time interval into smaller hourly intervals and alter fluid composition and osmolality in an effort to make slow and steady changes to glucose and osmolar concentrations as described above.

Further, the literature cautions not to exceed an infusion of 40 ml/kg during the first 4 hours of fluid therapy as this will undoubtedly drive a rapid

osmolar shift increasing the pediatric patient's unique risk of cerebral compromise and cerebral edema.

Finally, the patient is to be kept on strict NPO during the duration of this acute treatment process.

INSULIN TREATMENT

Insulin therapy should be started by the end of the first hour of treatment for DKA. The standard of care currently is 0.1 unit/kg per hour. Bolus insulin therapy is definitively not recommended, and can be dangerous to the pediatric patient as the risk of an abrupt osmolar change is detrimental to the pediatric brain. This stands in stark contrast to the treatment of adult patients where the administration of bolus insulin is considered standard protocol in DKA management.

Further, careful attention to insuring "saturation" of the insulin infusion tubing by the drug is mandatory. Insulin is readily adsorbed onto the currently used IV tubing such that, failure to fully saturate the infusion tubing could delay actual delivery of insulin to the patient for hours at the slow infusion rate.

Recent publication suggests that lowering of insulin infusion rates to 0.05 unit/kg per hour will correct the metabolic derangements of DKA potentially as quickly and certainly as safely as the current standard [8, 9]. If a patient develops hypoglycemia during insulin therapy, this should be treated emergently with IV dextrose or oral juice or other oral glucose containing fluid if the patient is mentating appropriately to tolerate oral fluids without the risk of aspiration. Hypoglycemia that persists despite increases in the basal rate of dextrose may require decreasing the administration rate of insulin. However, as discussed in the chapter on the physiology of DKA, uncontrolled lipolysis is central to the biochemical imbalance. Consequently, suppression of lipolysis is paramount. The most sensitive of insulin actions is the suppression of lipolysis. Therefore, low but continuous insulin therapy is needed to emerge from the pathologic state of DKA. Thus, insulin therapy should only be discontinued in symptomatic hypoglycemia such as altered mental status or seizure.

LABORATORY MONITORING

Glucose:

With the onset of dextrose free fluid rehydration, the measured glucose falls quickly. After the first 1-2 hours with the initial fluid "dilutional" decrease, serum glucose decreases should be no more rapid than 100 mg/dl [5.5 mmol/L] per hour.

The usual serum glucose value target during therapy is around 200-250mg/dl. This is a safe zone that should prevent hypoglycemia but is well above the renal threshold. In many centers, the implementation of the "2-bag" system of fluid and glucose delivery has effectively eliminated concern for hypoglycemia when the system is implemented correctly. With appropriate experience, the care team can maintain serum glucose in a more physiologic range, below renal threshold, and allow for more appropriate fluid balance during the resolution of ketoacidosis.

Monitoring of serum glucose should be obtained at the bedside every hour, and as part of a hospital laboratory panel at least every 4 hours. It is relatively common practice to institute dextrose containing fluids when the blood glucose falls below 200mg/dl to ensure that the child's glucose level remains safe, while being able to continue the insulin therapy.

Osmolality:

The need to reduce the patient's hyperosmolality slowly [< 5 mOsm/L hourly] is reported to reduce the risk of developing further cerebral swelling [see Chapter: Complications].

Sodium:

In conditions of marked hyperglycemia, serum sodium is artificially depressed. The degree is on the order of 1.6-2.4 mEq/L for every 100 mg/dl serum glucose above a baseline of 100 mg/dl. This is sometimes referred to as "pseudohyponatremia." The presence of excessive serum glucose exerts an osmotic effect and draws free water out of the cells into the serum. The result is a sodium level that appears artificially low on laboratory evaluation. With proper insulin and fluid administration, the serum sodium corrects in a steady, upward fashion. Failure to steadily improve the "corrected serum sodium" may be observed prior to the clinical development of cerebral edema. The normal control of arginine vasopressin is altered in pathologic states of DKA and can appear to create a state of inappropriate release [SIADH]. If that is the

case, the concern for untoward fluid retention leading to cerebral edema should be appreciated, and fluid infusion rates should be abruptly decreased.

With the use of maintenance fluids that contain generous concentrations of sodium chloride, attention should be paid to the serum chloride concentration. With the resolution of ketoacidosis, the patient may be left with a hyperchloremic metabolic acidosis. However, this is typically of little physiologic significance, and thus should simply be recognized as the instigator for the mild metabolic acidosis that remains after correction of DKA.

Potassium:

Hyperkalemia as a condition is more likely to be evident upon presentation to the ED, but will resolve quickly with the initiation of insulin therapy which drives extracellular potassium to an intracellular position. In fact, the body is typically potassium depleted with the preexisting osmotic diuresis. However, to be safe, supplemental potassium should be withheld from the initial rehydration fluids until renal function is established with appropriate voiding.

By the time the patient reaches the in-patient unit, serum potassium will likely be in the low to normal range, and should be added to the maintenance infusion fluids as ongoing insulin administration will drive the extracellular potassium back into the intracellular spaces. Typically, potassium phosphate and/or potassium chloride are added to the intravenous fluids.

In the intensive care unit, the patient should be on continuous cardio respiratory and pulse oximetry monitoring

Phosphate and Calcium:

Serum phosphate will be driven into the intracellular spaces with insulin, leading to circulating hypophosphatemia. The patient will have total body phosphate depletion due to the preexisting osmotic diuresis in the disease state. Clinically, this electrolyte state is capable of decreasing the dissociation of oxygen off of hemoglobin, and could result in peripheral hypoxia. However, clinical trials have never established this as a credible concern. This is likely due to the prevailing ketoacidosis acting in the exact opposite fashion regarding the binding of oxygen to hemoglobin with increased oxygen delivery to the tissues.

As mentioned above, the use of chloride salts can create a metabolic acidosis following the resolution of ketoacidosis. Potassium phosphate is an excellent substitute for potassium chloride, for just such a reason. However,

the concentration of phosphate supplementation should not exceed 20 mEq/L or a risk of tetany from hypocalcemia may occur with binding of the phosphate to the free calcium.

Beta-hydroxybutyrate and venous blood gas:

In the absence of cardiac compromise or cerebral edema, venous blood gas analysis, rather than arterial sampling, is sufficient. This data should be obtained every 2 hours for the first 12-24 hours, and then every 4 hours through resolution of the acute disease process. Following the initial rehydration in the ED, the measured pH and bicarbonate may be lower than on admission. Thereafter, steady increases in both are expected.

Clinical observation usually will document that the presence of Kussmaul respirations is associated with venous bicarbonate less than10 mEq/L, and that this pattern of breathing will resolve when the bicarbonate rises above 10 mEq/L.

Reagent strip assessment of beta-hydroxybutyrate [B-OHB] concentrations is available. These are more useful in the "at home" maintenance and monitoring of the person with diabetes. These bedside reagent strips are considered "normal" if < 0.6 mmol/L and elevated if > 1.5 mmol/L.

Hospital laboratory analysis of serum B-OHB confirms the existence of DKA if the value is > 7.0 mmol/L. As treatment proceeds, this concentration is expected to decrease steadily until it is absent or nearly absent with full resolution of the pathologic state.

Most children with DKA do not have compromised renal or cardiac function. Therefore the risk of lactic acidosis compounding ketoacidosis is not typical in the pediatric population. In DKA, the anion gap directly resulting from the ketoacidosis is typically 20-30 mmol/L. With a gap > 35 mmol/L, an element of lactic acidosis should definitively be considered.

Anion Gap =	$Na^+ - [Cl^- + HCO3^-]$

Renal function:

At presentation, the obligate dehydration will cause pre-renal azotemia with an increased serum urea nitrogen as compared to the elevation of creatinine. Assessment of renal function is necessary to exclude coexisting primary renal disease at presentation. Significant elevation in serum creatinine will alert the staff to carefully monitor serum potassium.

Accurate fluid Intake and Output:

It is mandatory that the patient be on strict oral fluid restriction, "nothing by mouth." The rapidity with which a thirsty child can drink fluids could severely impact the medical plan to correct fluid deficits slowly and meticulously over 36-48 hours.

With more conservative fluid resuscitation rates, an overall negative fluid balance may occur secondary to an osmotic diuresis from the glucose load during the initial stages of treatment. However, if a patient has evidence of hypovolemic shock, or hypotension, they should receive 10ml/kg of isotonic fluid imminently. Shock states place the patient at risk for decreased peripheral perfusion and untoward consequences of their aberrant hypercoagulation status in the face of critical illness. Further, sudden increased urine output, or the acute onset of diabetes insipidus should alert the physician to posterior pituitary compromise.

As treatment progresses, a positive fluid balance is expected, but if marked, the physician should consider decreasing the fluid infusion rate and more carefully assess neurologic status as this can be problematic as well.

MONITORING OF VITAL SIGNS

Age appropriate normal values for respiratory rate, heart rate and blood pressure

Age	Respiratory Rate (breaths per minute))	Heart Rate (beats per minute)	Blood Pressure (mm Hg)
Neonate	30-60	100-180	50-90
Infant [1 – 12 months]	24-50	100-160	60-100
Toddler [1 – 3 years]	24-40	90-150	80-105
Preschooler [3 – 5 years]	20-30	80-140	95-105
School age [5 – 12 years	10-30	65-120	95-120
Adolescent [> 12 years]	12-20	60-100	100-128

MONITORING OF NEUROLOGICAL SIGNS

The pediatric DKA patient will present with variable levels of alertness related to their critical disease state, level of hydration, level of acidosis, and

potential cerebral compromise. Hourly neurological and Glasgow Coma Scale (GCS) assessments are indicated in the ICU or acute care setting. Presentation with a GCS of < 14 or a decrease of 2 or more from the prior assessment should alert the physician to possible central nervous system compromise. As per the GCS criterion below, the best possible score is 15 while the worst is 3. The score is calculated by the combination of an eye, verbal and motor response. In the nonverbal child or toddler, there is an alternative way of assessing this "verbal" contribution to the overall score seen in the third column.

Glasgow Coma scale:

Best eye response	Best verbal response	Best in nonverbal toddler or child	Best motor response
Opens spontaneously = 4	Age appropriate interactions = 5	Smiles, orients, and follows = 5	Obeys commands = 6
On verbal command = 3	Disoriented and confused = 4	Consolable if crying, but interacts inappropriately = 4	Localizes pain, withdraws to touch = 5
On pain = 2	Verbal but incoherent = 3	Cries to pain, inconsistently consolable = 3	Withdraws to pain = 4
Not at all = 1	Only moans, sounds or groans = 2	Inconsolable, irritable, restless, moans = 2	Flexion to pain [decorticate posture] = 3
	No verbal response = 1	No response = 1	Extension to pain [decerebrate posture] = 2
			No response = 1

Onset of clinically significant cerebral edema [CE] and Neurologic Compromise:

As discussed in the chapter: Clinical Complications, the presence of cerebral brain swelling [edema] and increased intracranial pressure is common in pediatric patients with moderate to severe DKA upon presentation or in the acute states of treatment. In fact, the most serious and deadly complication associated with correction of DKA is cerebral edema. The incidence of clinical cerebral edema is approximated at 1% of total cases of DKA [10]. While the exact cause of the development of cerebral edema is unclear, several risk factors have been identified including: elevated blood urea nitrogen level (BUN), lower age at presentation, and the use of bicarbonate therapy [10].

Other risk factors for the development of cerebral edema also include: younger age, new onset, and a long duration of symptoms. Studies have shown that a substantial number of patients develop some degree of subclinical cerebral edema [10]. However, of those cases of clinically evident cerebral edema, 25% progress to death, 25% suffer severe neurologic disability, and the remainder recover. Cerebral edema may occur at any time during rehydration therapy, but most common develops several hours after the initiation of therapy [10]. If cerebral edema is suspected, it should be immediately treated with hypertonic saline or mannitol to imminently change the osmolar load. As noted above, the deterioration of Glasgow Coma scale scoring must be interpreted as impending cerebral crisis. The greatest majority of such crises are due to cerebral edema; the smaller minority is likely due to cerebral anoxia, ischemia or infarction.

The best bedside evaluation for acute CE is as follows [11]:

1. Any one of the 4 diagnostic criteria!
2. Any two major criteria: likely.
3. Any one major criterion and any two minor criteria: likely.

Diagnostic criterion	1. Decorticate or decerebrate posture 2. Cranial nerve palsy: especially 3,4, & 6 3. Abnormal neurogenic respiratory pattern. 4. Abnormal motor or verbal response to pain
Major criterion	1. Altered or fluctuating level of consciousness 2. Sustained cardiac deceleration > 20 bpm, not otherwise explained 3. Unexpected incontinence.
Minor criterion	1. Vomiting 2. Headache 3. Lethargy or stupor 4. Diastolic hypertension: > 90 mm Hg 5. Age < 5 years old

No patient should be removed from the intensive care unit for radiographic documentation of CE. Data does suggest that the CE is generalized and leads to bilateral, central transtentorial descending herniation with rostrocaudal brainstem compression. Whether suspected or "proven", acute CNS deterioration must be treated immediately. Consequently, the treatment agents are to be pre-ordered and at the bedside of any patient admitted in moderate to severe DKA. Awaiting delivery by pharmacy once the crisis developed is unacceptable. As a clinical caveat: if the patient was treated quickly and CE was not the cause, you likely merely delayed time to recovery; if the patient was treated quickly with CE with resolution of the symptoms,

you likely saved not only his life but also the quality of his life. Another important clinical caveat is that even with careful and meticulous treatment and monitoring, some pediatric patients develop morbid CE that leads to significant compromise. Thus, as mentioned above, the entire pathophysiology of this devastating complication is still not clear.

The current principles of treatment include the following:

Current fluid infusion rate	Immediately reduce by a significant degree.
20% Mannitol [1100 mOsm/L]	0.25 to 1g/kg infused over 20 minutes; may be repeated after 30 minutes if no initial response
3% Sodium Chloride [1030 mOsm/L]	5 – 10 ml/kg over 10-15 minutes; may be repeated after 30 minutes if no initial response
Elevation of the head of the bed	The head should be elevated 30-45 degrees
Intubation and mechanical ventilation	Avoid hyperventilation with goal paCO2 35-40 mmHg. Hyperventilation will potentially cause arteriolar vasoconstriction and cerebral ischemia whereas hypoventilation may cause cerebral arteriolar vasodilation effectively increasing the intracranial pressure with increased arterial blood flow

Failure to recover quickly from the neurological complications of CE should lead to urgent consultation with Neurosurgery to further assess for the presence of increased intracranial pressure and neurologic dysfunction.

TRANSITION OUT OF THE ICU TO THE GENERAL WARD

Pediatric patients with a pre-existing diagnosis of Type 1 diabetes mellitus develop severe DKA due to lack of appropriate treatment. While in the ICU, social work should be contacted to undertake a thorough family assessment to understand the reasons for this event. For the first several days post recovery, insulin resistance is likely significantly elevated such that “current or usual” pattern management profiles maybe insufficient. Patients newly diagnosed with Type 1 diabetes mellitus are usually sufficiently stable and recovered from the physiological aberrations of DKA so as to be moved to the general ward after 36 to 48 hours. Intense, new patient education will be required as part of the discharge process and will require additional inpatient or outpatient education depending on education resources at the institution. In the newly

diagnosed patient, pre-existent hyperglycemia induces significant glucotoxicity and lipotoxicity. These require significantly more exogenous insulin to be administered during the initial 2-14 days of therapy. Control for the person with diabetes is best achieved by focusing on pattern management: the interplay of dietary intake, physical activity levels, and insulin administration.

QUALITY IMPROVEMENT

Aspects of monitoring and management of DKA in the intensive care unit can be improved with a multidisciplinary "plan-do-study-act" quality improvement team approach. This has been accomplished by Merritt et al., in a project organized in a PICU setting [12] and by Koves and colleagues also in children's hospital setting [13]. Merritt's effort resulted in a decrease in patient costs when a comparison with pre-intervention costs was done [12]. The implementation of a DKA order-set utilizing the electronic medical record resulted in:

1. decreases in unanticipated hypokalemic episodes,
2. improvements in insulin infusion management was associated with reduced length of ICU stay,
3. overall improvement in DKA management and education,
4. cerebral edema occurrence and bicarbonate use were both reduced [13].

REFERENCES

[1] Kumar et al. *Robbins and Cotran Pathologic Basis of Disease*. 7th edition (2005):1189-1205.

[2] Behrman et al. Nelson Textbook of Pediatrics. 17th edition (2004):1947-1972.

[3] Wolfsdorf J, Glaser N, Sperling M. Diabetic Ketoacidosis in Infants, Children, and Adolescents: A consensus statement from the American Diabetes Association. *Diabetic Care* 2006 May;29(5):1150-1159.

[4] Champe PC Harvey RA. *Biochemistry.* 2nd edition (1994):291-300.

[5] Kerr J, Moore M, Frank D, Gujral R. Management of Diabetic Ketoacidosis and Other Hyperglycemic Emergencies. *Society of Critical Care Medicine Critical Connections* 2012 6 Dec.

[6] Wolfsdorf JI et al. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium: Diabetic Ketoacidosis and hyperglycemic hyperosmolar state. *Pediatric Diabetes* 2014;15(20):154-179.

[7] Poirier MP, Greer D, Satin-Smith. A prospective study of the "two-bag system" in diabetic ketoacidosis management. *Clin. Pediatr*. 2004;43(9):809-13

[8] Nallasamy K, Jayashree M, Singhi S, Bansai A. Low-Dose vs Standard-Dose Insulin in Pediatric Diabetic Ketoacidosis: A Randomized Clinical Trial. *JAMA Pediatr*. 2014 Nov 1;168(11):999-1005.

[9] Wolfsdorf JI. The International Society of Pediatric and Adolescent Diabetes guidelines for management of diabetic ketoacidosis: Do the guidelines need to be modified? *Pediatric Diabetes* 2014;15:277–286.

[10] Glaser N et al. Risk Factors for Cerebral Edema in Children with Diabetic Ketoacidosis. *N. Engl. J. Med.* 2001;344:264-269.

[11] Muir AB, Quisling RG, Yang MCK, et al Cerebral edema in childhood diabetic ketoacidosis, natural history, radiographic findings, and early identification, *Diabetes Care* 2004;27(7):1541 - 1546.

[12] Merritt BE et al. Protocol for the treatment of Pediatric Diabetic Ketoacidosis. *Poster Society of Critical Care Medicine*, Critical Care Congress 2013.

[13] Koves IH, et al. Improving care for pediatric diabetic ketoacidosis. *Pediatrics* 2014;134:e848-856.