Diabetic Ketoacidosis in Children

Continuing Education Module

By Jacquelyn Peters, PharmD Candidate, 2016

August 2016

Health Sciences North
Horizon Santé-Nord

TABLE OF CONTENTS

PURPOSE AND INTENDED AUDIENCE

This continuing education module will allow pharmacy students and pharmacists alike, to learn about DKA in the child and how to treat it. Using this knowledge, they will be able to better monitor and recommend treatment suggestions to physicians.

LEARNING OBJECTIVES

1. Understand the epidemiology, etiology, risk factors and pathophysiology of DKA in children
2. Recognize the signs and symptoms of DKA in children
3. Understand how to diagnose and classify DKA in children
4. Recommend appropriate treatment of DKA in children
5. Understand the reasoning behind monitoring for DKA in children and know what monitoring to recommend to physicians
6. Recommend appropriate SubQ stepdown of insulin in pediatric patients with resolved DKA
7. Recognize the signs and symptoms of cerebral edema and recommend treatment and monitoring

ABSTRACT

Diabetic ketoacidosis (DKA) is a metabolic process that results in a low blood pH due to the effects of insulin deficiency. Ketone bodies are produced when fatty acids are oxidized for energy because glucose cannot enter the cell in the insulin deficient body. These ketone bodies wreak havoc on the brain and other body systems, causing reduced level of consciousness, hyperventilation, and emesis, as well as the other signs of hyperglycemia. Insulin omission occurs most often in young individuals with undiagnosed type-1 diabetes, and in teenage girls with diagnosed diabetes who are having issues at home or at school and intentionally or accidentally omit their insulin doses. Treatment of DKA consists of fluid replacement, insulin replacement, electrolyte replacement and monitoring for complications of the disease and of therapy. Once the acute phase has passed, it is important to treat the root cause of the problem, and prevent future episodes as individuals who experience recurrent episodes of DKA can end up with permanent neurological sequelae.

1 WHAT IS DIABETIC KETOACIDOSIS?

DKA is a serious condition that occurs when an individual with diabetes does not have enough insulin. The lack of insulin causes cells in the body to use fatty acids instead of glucose for energy, producing ketone bodies, which cause a metabolic acidosis. If left untreated, DKA can cause cerebral edema, dehydration, hypokalemia, diabetic coma, and even death. [1] [2]

2 DEFINITIONS [3] [4]

- **Acidemia:** a state of being where the blood is too acidic (pH < 7.35)
- **Acidosis:** a process occurring in the blood that decreases the pH (causing acidemia)
- **Metabolic Acidosis:** a process that decreases the concentration of HCO_3 in the blood, subsequently decreasing the pH
- **Ketoacidosis:** a form of metabolic acidosis that is the result of production of ketones
- **Ketone Bodies:** also called ketones, in DKA the ketones produced are:
    - Acetone
    - Acetoacetate
    - B-hydroxybutyrate
- **Anion Gap:** an artificial measure of the ion balance in the body, using the ions in the CHEM7, expressed using the following equation:

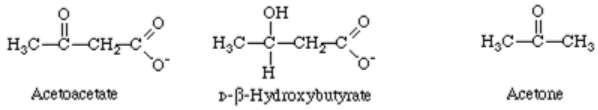


Figure 1: Acetone, acetoacetate, and beta-hydroxybutyrate, the ketone bodies which are produced in DKA.

$$\boldsymbol{Anion\ Gap} = [Na] - ([Cl] + [HCO3]) = 140 - (104 + 24) = 12\ (\pm 2)$$

    - Anion gap is used to diagnose and monitor progression of DKA

3 EPIDEMIOLOGY

In children with un-diagnosed diabetes, there is a 15-67% chance that they will present with DKA when diabetes manifests. [5] The frequency of DKA will increase in areas where type 1 diabetes is not as prevalent, as parents and clinicians will be less likely to recognize and diagnose diabetes prior to presentation with DKA. The prevalence of DKA however, decreases as children age, with younger children (<5 years) being more likely than older children (>14 years) to experience an episode of DKA (36% vs. 16%). [6]

Timely recognition and treatment of DKA is important, as it is the leading cause of morbidity and mortality in children with diabetes. [5] Most often death is due to cerebral edema, a significant complication, but death from DKA only occurs in 1-5% of cases. In a study of 28,770 patients with diabetes under the age of twenty, 94% had no episodes of DKA, 5% had one episode, and 1% had two or more episodes of DKA. [7] These numbers indicate that DKA is not very common in pediatric cases, but that when encountered, it is very important to treat it.

4 ETIOLOGY, PREVENTION AND RISK FACTORS

4.1 ETIOLOGY:

DKA most often transpires due to a failure to take insulin, such as in undiagnosed diabetes (usually in younger children), intentional or accidental insulin omission (usually in older children), or insulin-pump infusion-site problems. As well, DKA can result from poor sick-day management during an illness in a patient with diabetes. [5]

4.2 PREVENTION:

DKA is generally preventable. Most cases are the result of failing to take prescribed insulin or not monitoring urine ketone levels while ill. Proper education on sick-day management is important, and some clinicians may recommend using Ketostix to help monitor ketone levels when patients are sick. [8]

Figure 2: Ketostix, used to measure the concentration of ketones in the urine.

Inadvertent omission of insulin can occur in younger children who have not yet been diagnosed with diabetes. In Canada, public awareness campaigns have helped to increase the number of children whose diabetes was diagnosed early, and therefore improved DKA prevention. [5] For individuals with an insulin pump, infusion site problems (or rarely, pump malfunction) may lead to DKA. Pumps only contain rapid-acting insulin, and therefore it is much more important to make sure they are inserted properly and in working order. [8]

In older children, insulin omission is more likely to be intentional. It has been reported that intentional insulin omission has been associated with eating disorders, depression, insufficient parental supervision, or a poor psychosocial situation. [8] Adolescent girls with diabetes are more likely to meet the DSM-IV criteria for an eating disorder when compared to their peers without diabetes (10% vs. 4%). [5] Involving a social worker, counsellor or psychiatrist may help prevent recurrent DKA in individuals with these risk factors. [8] Studies have shown that psychological interventions can help improve overall well-being, and also indicate that these interventions may improve diabetes treatment adherence and glycemic control. [5]

4.3 Risk Factors for DKA: [6] [9]

In children without previous diagnosis of diabetes, risk of DKA is higher when:

- Younger age: <2 years
- Delayed diagnosis
- Lower socioeconomic status

In children with pre-diagnosed diabetes, risk of DKA is higher when:

- Insulin omission (accidental or intentional)
- Poor metabolic control
- Previous DKA episode(s)
- Clinical depression or other psychiatric disorders (including eating disorders)
- Difficult/unstable family circumstances
- Limited access to medical services
- Lower income/lower education parents
- Insulin pump therapy (see above)
- Female gender
- Age: peri-pubertal/adolescence

5 Pathophysiology [4] [6] [7]

Insulin's actions in the body work to help create and store energy. (See Box 1) Individuals with type 1 diabetes by definition have a lack of insulin. Hyperglycemia can occur quickly in these individuals when exogenous insulin is not administered daily according to the patient's specific regimen.

Box 1: Actions of Insulin

- Promotes glucose entry into cell
- Decreases fatty acid oxidation
- Promotes K+ movement into cells
- Increased glycolysis & glycogen synthesis
- Decreases lipolysis in adipocytes, stimulates fatty acid synthesis, increases uptake of triglycerides into tissues
- Also promotes protein synthesis [15]

In patients with DKA, there is no exogenous insulin administration, resulting in hyperglycemia (>11mmol/L). The increased glucose concentration in the urine promotes diuresis, resulting in dehydration.

The absence of insulin means glucose is not entering the cells (See Figure 3), and therefore the body adapts and begins to acquire its energy from lipolysis and fatty acid oxidation. The breakdown of these fatty acids creates ketones (acetone, acetoacetate, and β-hydroxybutyrate). Ketones can be used by the body as an energy source, but unfortunately they are not very sustainable and accumulate quickly in the body.

The accumulation of these ketones, which are mostly carboxylic acids (See Section 2, Definitions), causes an increase in the concentration of hydrogen ions in the blood (upon disassociation). In order to attempt to keep the pH of the blood within normal range (7.35-7.45), bicarbonate ions (HCO_3^-) are used as a buffer. This results in the production of carbon dioxide according to the following equilibrium equation:

$$[H^+] + [HCO_3^-] \rightleftarrows [H_2CO_3] \rightleftarrows [H_20] + [CO_2]$$

The loss of HCO_3^- is deemed a metabolic acidosis (See Section 2, Definitions), and because it is due to the production of ketones, is termed a ketoacidosis.

Insulin also affects potassium (K^+), and would normally cause an intracellular shift of potassium but in the case of DKA, this mechanism is prohibited, and potassium is moved into the blood as it is exchanged for the hydrogen ions produced by the ketones. The end result of these actions is that there is a total body deficit of potassium, but the serum potassium levels may appear as hyperkalemic, normokalemic or hypokalemic.

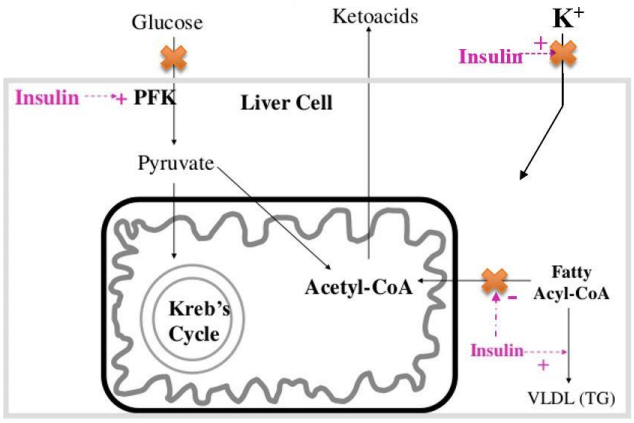


Figure 3: Actions of Insulin in the human body.

In DKA, other hormones are also often affected, and the result is an elevation in plasma catecholamines. This can cause an elevation in the white blood cell count, with a profound left shift, therefore, increased white blood cell counts may be common in DKA. However, if a patient has a fever, investigation into a possible source of infection should be instigated immediately.

6 Clinical Presentation [5] [7] [8] [9]

Listed below are some of the common signs and symptoms of DKA, organized by system:

Older children/Adolescents:

- **Genitourinary**: Polyuria (98%), polydipsia (98%), nocturia, daytime enuresis, vaginal candidiasis
- **Cardiovascular:** Tachycardia, hypovolemia, orthostatic hypotension, poor peripheral perfusion
- **Gastrointestinal:** Polyphagia (23%), nausea/vomiting (46%), abdominal pain (32%), anorexia and weight loss (81%)
- **Respiratory:** Acetone (fruity) smell on breath,
    - Kussmaul Respirations (57%) – These deep, rapid, sighing respirations arise as an involuntary response to metabolic acidosis, due to the compensatory need to release CO_2 – see https://www.youtube.com/watch?v=TG0vpKae3Js for an example.
- **Neurological:** fatigue (62%), lethargy, somnolence, progressive reduction in alertness (obtundation), diminished sensation of pain, cerebral edema, coma

Infants: (harder to diagnose – not toilet trained or able to express thirst)

- Decreased energy/activity, irritability, weight loss, physical signs of dehydration
- Severe Candida diaper rash

The presentation of DKA will vary based on the severity of the DKA and the patient's comorbid conditions. Of note, signs of extracellular dehydration may not be present due to loss of water without loss of sodium, therefore less likely to have decreased skin turgor, decreased urine output and hypotension. They are more likely to have orthostatic hypotension, tachycardia and poor peripheral perfusion. They may also have dry mucous membranes and tear ducts, as well as high SCr and BUN.

7 Diagnosis and Classification

7.1 Assessment: [5] [7] [9] [10]

Upon presentation with the above symptoms, the following initial baseline lab investigations should be performed:

- CBC, blood gases, SCr, BUN, electrolytes, blood glucose, A1c, blood ketones/ β-hydroxybutyrate level (best practice is β-HB level), and blood culture (to rule out infection)
- Urinalysis, specifically urine ketones & glucose (consider urine culture if needed to rule out UTI)
- Vitals, including HR, BP, RR, O_2 sat (%)
- If new-onset diabetes, include TSH, thyroid antibodies and HbA1c [10]
- ECG to monitor for: T-wave flattening/inversion, appearance of U-wave, prolonged PR interval (signs of hypokalemia) [5] [9] [11]
- Calculate Anion Gap based on electrolytes and blood gas [6] [7] [8] [9] [10]

7.2 Diagnosis: [8] [9]

Diagnosis of DKA is defined as the following:

a) Hyperglycemia: blood glucose > 11mmol/L
b) Metabolic acidosis: venous pH <7.3 or plasma HCO3 <15mmol/L

AND

c) Ketosis: presence of ketones in the blood or urine
    i. May also use beta-hydroxybutyrate concentration (> 3mmol/L)

7.3 Differential Diagnosis: [7]

A differential diagnosis must be considered and other possible causes of metabolic acidosis ruled out. Hyperosmolar hyperglycemic state (left column in Table 1) may look very similar, but will not have high ketone levels in the blood or urine. Other causes of high anion gap metabolic acidosis should also be ruled out (right column in Table 1)

Table 1: Differential Diagnosis for DKA. [7]

Gastroenteritis	High anion gap metabolic acidosis:
Hyperosmolar hyperglycemic state	Alcoholic ketoacidosis
Myocardial infarction[14]	Ethylene glycol intoxication
Pancreatitis[18]	Lactic acidosis
Starvation ketosis[14]	Methanol intoxication
	Paraldehyde ingestion
	Rhabdomyolysis
	Salicylate intoxication
	Uremia

7.4 Classification:

Classification of DKA is based on severity of the metabolic acidosis. More severe cases are associated with lower pH or bicarbonate concentrations. (See Table 2)

Table 2: Classification of DKA based on severity.

Severity	Blood pH	Blood [HCO_3] (mmol/L)
Mild	7.2 – 7.3	10 – 15
Moderate	7.1 – 7.2	5 – 10
Severe	< 7.1	< 5

Box 2: Pediatric Changes [6]

Children are not miniature adults. This is evident by the differences seen when treating DKA at the different stages of life:

1) When children are younger, it is much harder to determine accurately the history and signs/symptoms of DKA, such as polyuria, polydipsia and weight loss.
2) Children have a higher basal metabolic rate and body surface area relative to their total body mass, therefore when administering fluids and electrolytes, great care is required.
3) In younger children, auto-regulatory mechanisms are not as well developed. Combined with an increased severity upon presentation, this can lead to cerebral edema
4) In infants and young children, the delay in the diagnosis of diabetes is often the reason behind the episode of DKA, as individuals age, it is more likely that insulin administration was omitted, whether accidentally or intentionally.

8 Goals of Therapy [9]

- Correct any dehydration based on estimation of losses and body weight of child
- Gradually, correct hyper-osmolality and restore blood glucose levels back to normal
- Correct acidosis and reverse ketosis
- Monitor for complications of DKA and its treatment, (eg. cerebral edema)

AND

- Identify and treat any root causes to prevent future DKA events from occurring

9 Treatment

9.1 Fluid Replacement:

In DKA it is very difficult to determine the level of dehydration, because in DKA the patient is in a state of hyperosmolar dehydration, where they have lost water from osmotic diuresis (glucose and ketones in the urine pull out water). As well, these patients are experiencing water losses in diarrhea and emesis. It is estimated that *fluid deficits in children are approximately 5-7% (moderate) or 10-15% (severe)*, therefore fluid replacement of fluids is vital. [6] The following steps can be followed when starting fluid replacement therapy in DKA:

1. Estimate the amount of fluid lost based on the patient's weight and the severity of their DKA (see % losses above).

2. Start fluid replacement slowly, with isotonic fluids*, at **1.5x** usual maintenance rate (or 2500mL/m^2/day). [12]

a) If hypotensive, give one bolus of 10mL/kg of isotonic fluids over 1hr (if necessary, may repeat once). [6]
b) **Usually 0.9% NaCl for the first 4-6 hrs* (with K+ added, see Section 9.3) [6] [9]

3. After first 48 hrs, may increase to **2.0-2.1x** usual maintenance rate (or 3500mL/m^2/day) to complete rehydration. [12]

4. Do **NOT** give excess fluids within the first 24-36h, as this can lead to cerebral edema. [12]

9.2 INSULIN INFUSION:

About 1-2 hours after rehydration therapy has been started, insulin may be introduced as treatment for the DKA. Initiation of insulin within the first 1-2 hours of treatment has been associated with increased risk of cerebral edema. Bolus insulin therapy has also been associated with development of cerebral edema and should not occur in pediatric patients. This is different from the therapy provided in adults and is one of the reasons why we need to be more cautious in pediatric patients with DKA (See Box 2). [6] [7]

Insulin should be started at a *rate of 0.1 units/kg/hr, or 0.05 units/kg/hr* in children with increased insulin sensitivity and this should remain constant until resolution of the acidosis. Acidosis takes longer to resolve than the normalization of blood sugar levels, therefore it is likely that the IV solutions will have to be altered and dextrose will need to be added. Usually D5W is added to the bag OR the "two-bag system" is used.

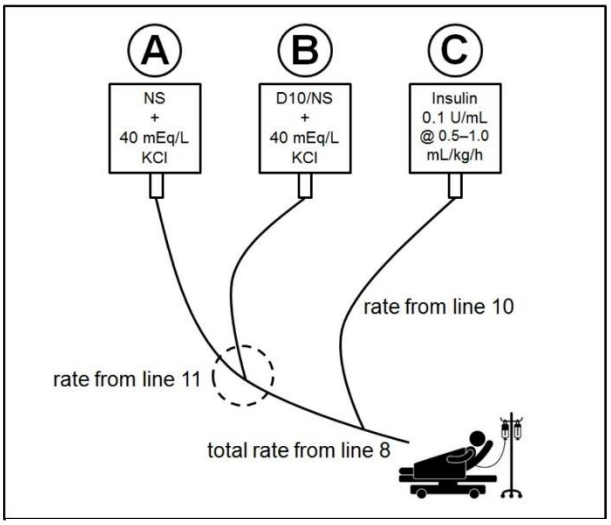


Figure 4: The "two-bag system" as explained by BC Children's Hospital [8]

The "two-bag system" is when two bags are hung with equal electrolyte concentrations, but one has no dextrose, and the second has 10-12.5% dextrose. Both bags are administered together, however the rate of each bag is titrated based on the patient's blood glucose levels and degree of dehydration. More information on the "two-bag system" can be found on the BC Children's Hospital website, http://www.bcchildrens.ca/health-professionals/clinical-resources/endocrinology-diabetes/dka-protocol. [8]

The target blood glucose level is around 10-15mmol/L as that allows for a buffer against hypoglycemia. Usually, if not using the "two-bag system," D5W is required when blood glucose reaches 14-17mmol/L, and D10W is required if blood glucose drops below 8mmol/L. [9] It is recommended that insulin lines be pre-flushed with insulin prior to starting therapy, as insulin will bind to the tubing/syringe and the patient will not receive the full dose of the medication.

Generally, ketoacidosis should resolve within the first 2-4 hours. If this does not occur, first reassess the patient and consider any other diagnoses. Next, attempt to flush a new line as the patient may not have originally received the proper dose of insulin. [9] Finally, it is also possible that the patient simply requires a higher rate of insulin infusion to achieve resolution of ketoacidosis.

If continuous IV administration of insulin is not possible, AND/OR if the patient's DKA is very mild, it is possible to use SubQ insulin injections every hour, or every 2 hours. The insulin analog used should be short- OR rapid-acting, such as insulin aspart. The initial dose should be 0.3 units/kg SubQ, with subsequent hourly administration of SubQ rapid-acting insulin at 0.1 unit/kg OR 0.15-0.2 units/kg Q2h. If blood glucose levels fall below 14mmol/L before DKA has resolved, decrease the dose of rapid-acting insulin to 0.05 units/kg/hr with a target blood glucose level of ~11mmol/L until resolution of DKA. [9]

9.3 Electrolyte Replacement Therapy

Potassium:

In DKA there is a total body deficit of potassium (K^+) (See Section 5, Pathophysiology). However, the serum potassium concentration can be hyperkalemic, normokalemic, or hypokalemic, due to the hyperglycemia present in DKA. The estimated potassium loss in a child is approximately 6-7mol/kg. [6] [13]

Based on the baseline potassium levels, give potassium chloride (KCl) as needed, as per the following: [9]

- **Hyperkalemia** – *hold K^+ replacement* until [K^+] falls and urine production is confirmed
- **Normokalemia** – *give K^+ when starting insulin*, usual starting dose = *40mmol/L*
    - Add to the isotonic fluids once insulin is started, not before
- **Hypokalemia** – *K^+ replacement should start immediately*, and *insulin treatment should be delayed* until [K^+] normalizes
    - Max K^+ IV rate: 0.5mmol/kg/hr – monitor hourly and adjust PRN

There is another helpful algorithm in an article by Westerberg (2013) in American Family Physician that outlines potassium replacement quite clearly. [7]

Sodium:

Sodium levels can vary widely in DKA patients, hence the importance of checking baseline electrolyte levels upon presentation. Usually there is some amount of sodium loss from the diuresis (estimate: approximately 5-13mmol/kg). [6] [13]

After fluid and insulin administration, glucose, and subsequently water, will move into the cells, causing the serum sodium concentration to rise gradually. It is very important to frequently monitor serum sodium levels, because serum sodium levels that decrease, remain the same or rise rapidly, may be indicative of cerebral edema. If no rise occurs, consider increasing the sodium concentration in the fluids, and decreasing the rate of administration.

Phosphate [7] [9]

Patients with DKA may have low phosphate, which can be exacerbated by insulin. Phosphate replacement therapy has not been shown to have a clinical benefit in studies however, and clinically significant hypophosphatemia is only likely if IV insulin occurs for 24h without food intake. If severe hypophosphatemia occurs (level < 0.32mmol/L), or if the patient shows symptoms of low phosphate, treatment should be initiated. Symptoms of low phosphate mostly involve muscle weakness, impaired myocardial contractility, weak diaphragm or rhabdomyolysis in rare cases. Also, the patient can present as irritable, confused or with seizures, or hematological symptoms such as hemolysis and thrombocytopenia.

Phosphate should be administered to correct phosphate levels, but the patient should be monitored for hypocalcemia. If hypocalcemia occurs, phosphate treatment should be stopped, but potassium phosphate may be used (20-30mmol/L) in the IV fluids (with or in place of potassium chloride). Usually, patients do not experience significant hypophosphatemia, and any deficits will be replaced once the patient resumes eating.

Bicarbonate

The use of bicarbonate is controversial. Some argue that individuals with severe acidosis (pH < 6.9) need bicarbonate to avoid cardiac and neurological complications. However, studies have not shown any benefit in clinical outcomes with the use of bicarbonate. [6] [7] [8] Therefore, do **NOT** use sodium bicarbonate to directly replace bicarbonate in DKA.

Bicarbonate also has the potential to be detrimental, due to many side effects, including:

- Paradoxical cerebral acidosis – the rapid rise in pCO2 decreases the stimulus for hyperventilation, and the CO2 crosses the blood-brain-barrier into the CNS, decreasing the pH. [6] [8]
- Hypokalemia – caused by the rapid correction of the acidosis. [6] [8] [9]
- Increased hyper-osmolality – due to the additional sodium load in NaHCO3. [8]
- Slower rate of recovery – studies in animals suggest that bicarbonate may increase hepatic ketogenesis, increasing plasma ketoacid levels and slowing down recovery, prolonging patient's hospital stay. [8]
- Post-treatment metabolic alkalosis – insulin induces metabolism of the ketoacid anions, and promotes renal regeneration of bicarbonate ions. Additional administration of exogenous bicarbonate may cause development of a metabolic alkalosis. [8]
- Has also been associated with development of cerebral edema (CE) – at this time pathophysiology behind the mechanism of CE is unknown - [8] [9] [14]

Although the use of bicarbonate may increase the risk of cerebral edema and many other side effects, in patients with life-threatening hyperkalemia, or who have a pH < 6.9, bicarbonate therapy may be initiated, based on clinician judgement. [6] [7]

9.4 Subcutaneous (SubQ) Stepdown: [8]

Insulin infusion should continue until patient meets the following conditions, after which SubQ insulin may be restarted:

1. Serum anion gap/β-hydroxybutyrate levels normal on 2 successive occasions
2. Venous pH > 7.3 OR serum [HCO_3^-] > 15mmol/L
3. Blood glucose < 11.1mmol/L
4. Tolerating oral intake

The first SubQ injection should be given based on the onset of action of the insulin. Therefore, for rapid-acting insulin, infusion should be discontinued approximately 15 minutes after SubQ insulin administration. For short-acting insulin, the timing should be closer to 30-60 minutes after SubQ administration. Discontinuation of insulin infusion is most convenient when timed just prior to a meal, as it reduces the risk of hypoglycemia.

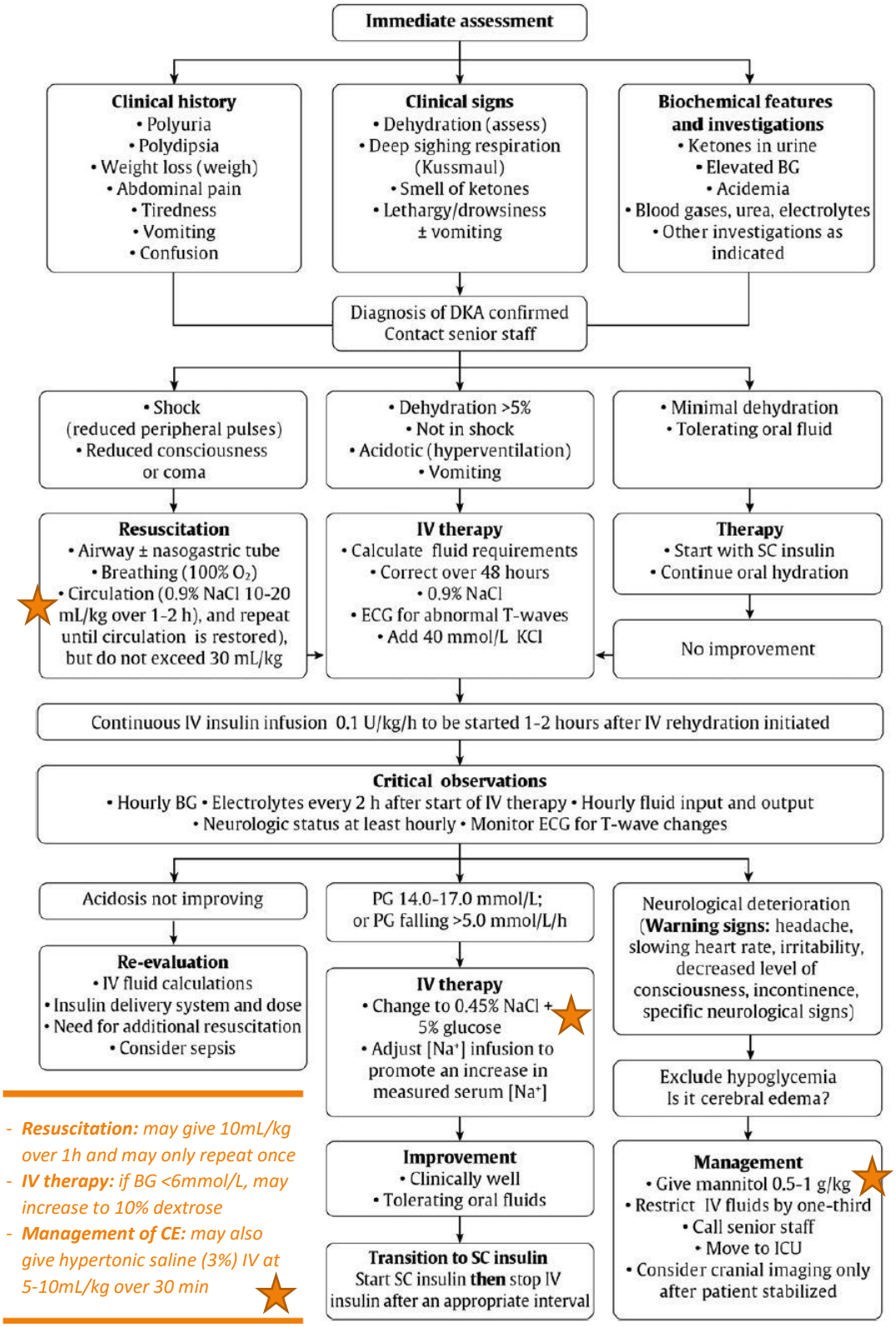


Figure 5: Algorithm for the management of DKA in children. BG=blood glucose; ECG=electrocardiogram; PG=plasma glucose; SC=subcutaneous; ★ = Updated since chart designed. [5] [11]

10 MONITORING

10.1 ANION GAP: [3]

Recall, from Section 2, that the Anion Gap is an artificial measure of the ion balance in the body. The ions in the equation were arbitrarily chosen from the ions in the CHEM7 because its one of the most common lab investigations, but the CHEM7 doesn't include all the ions in the body, such as calcium or phosphate. The theory behind the anion gap is that all the positive and negative charges in the body must balance, so if you subtract the negatives from the positives, what remains represents the excess negative charges that aren't accounted for in the CHEM7. Potassium isn't used in the anion gap calculation because it is a small number by comparison.

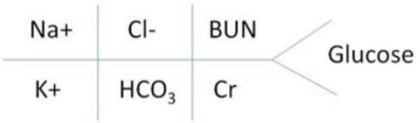


Figure 6: Fishbone diagram of the CHEM7 showing the respective ions.

$$\boldsymbol{Anion\ Gap} = [Na] - ([Cl] + [HCO3]) = 140 - (104 + 24) = 12\ (\pm 2)$$

The 12 negative ions that are extra represent mostly albumin, and normal albumin = 40, therefore:

Normal Anion Gap = albumin x 0.3

The anion gap is only affected by changes in bicarbonate when bicarbonate has been lost to combination with a hydrogen ion (H+). This is because that H+ needed to come off of a conjugate base (CB-), and now there is another negative ion that is not accounted for in the CHEM7. Therefore, if there is a larger anion gap than normal, there are extra CB- somewhere that are causing a decrease in bicarbonate (otherwise known as a metabolic acidosis).

DKA is an example of a metabolic ketoacidosis where the CB- is the ketone bodies (KB's). This is why monitoring the anion gap is important in DKA, as it is helpful in indicating the level of improvement and for monitoring the progression of DKA, especially in hospital, where the CHEM7 results are easily accessible. Throughout treatment, insulin and rehydration work to eliminate KB's from the body. Insulin prevents further production of KB's and promotes metabolism of current KB's and rehydration improves renal perfusion and promotes excretion of current KB's.

Anion Gap: Example

CHEM7 calculated Anion Gap = 20
Measured Albumin = 40 g/L

Predicted anion gap based on albumin = 40x0.3 = 12

Difference = 20-12 = 8 extra CB- units

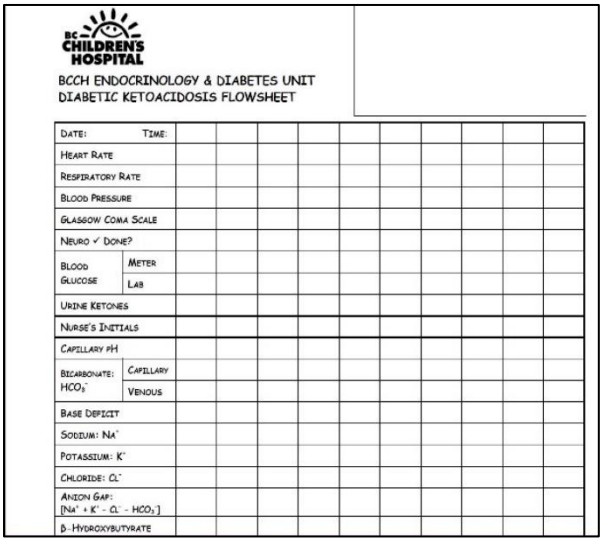
Therefore 8 negative units causing a metabolic acidosis, which is termed an Anion Gap Metabolic Acidosis

The anion gap also correlates better with the improvement in the acidosis in an individual with DKA, whereas the HCO_3^- levels usually respond much more slowly. This is because regeneration of HCO_3^- is usually delayed by high Cl- levels in the IV fluids, and because the kidney takes time to produce more. Some patients may develop a hyperchloremic metabolic acidosis from IV fluids, which allows time for kidney to make more HCO_3^-. Therefore, a patient may still have a lower bicarbonate level, but the acidosis has almost completely resolved, and the patient may be switched back to SubQ insulin.

10.2 Other monitoring [8] [10]

Obtain baseline values of all the following (see section 7.1: Assessment), as well as follow up at the suggested intervals below.

- Vitals hourly - HR, BP, RR, O_2 sat, and ECG (for hyper/hypokalemia)
- Bedside BG levels hourly for initial 4-6hrs, or until dextrose added to IV, then Q2h (and 1h after any changes to insulin dose)
- Blood gas, electrolytes, urea, urine ketones, serum osmolality Q1h for first 3-4hrs, then Q2h – once appropriate, may decrease frequency to Q4-6h
- Neurovitals and presence of headache (HA) hourly – to monitor for cerebral edema (See section 11.1: Cerebral Edema)


BC CHILDREN'S HOSPITAL

BCCH ENDOCRINOLOGY & DIABETES UNIT
DIABETIC KETOACIDOSIS FLOWSHEET

DATE: TIME:											
HEART RATE											
RESPIRATORY RATE											
BLOOD PRESSURE											
GLASGOW COMA SCALE											
NEURO ✓ DONE?											
BLOOD GLUCOSE	METER										
	LAB										
URINE KETONES											
NURSE'S INITIALS											
CAPILLARY pH											
BICARBONATE: HCO_3^-	CAPILLARY										
	VENOUS										
BASE DEFICIT											
SODIUM: Na^+											
POTASSIUM: K^+											
CHLORIDE: Cl^-											
ANION GAP: $[Na^+ + K^+ - Cl^- - HCO_3^-]$											
β-HYDROXYBUTYRATE											

Figure 7: Example monitoring form to recommend to nursing. Helps to quickly identify trends and areas of concern. [8]

- Accurate Ins/Outs Q1hr in ICU, and Q2-4hrs on pediatric floor
- May recommend use of BCCH monitoring form (See Figure 5)

11 Complications

11.1 Cerebral Edema

Cerebral edema (CE) is the most severe complication of DKA in pediatrics as it accounts for 60-90% of all DKA related deaths. [9] Though it is the most severe complication of DKA (approximately one quarter of children who present with CE will die), it only occurs in 0.5-1% of pediatric DKA cases. CE also has a high morbidity rate, with 15-26% of survivors having some form of neurological deficit after CE resolution. [6]

The pathophysiology of CE is poorly understood, with many hypotheses currently attempting to explain the process. [6] [8]

1. Changes in osmolality from too rapid fluid administration causing influx of fluid into brain (osmotic edema)
2. Changes in activity of ion transporters may cause influx of sodium into the CSF, causing water to follow (cytotoxic edema)
3. Blood-brain-barrier may be affected, allowing fluids and proteins into the interstitial and intracellular spaces (vasogenic edema)
4. Newer hypothesis: dehydration and hypoperfusion may cause brain injury that may be worsened during treatment, because degree of edema correlates with degree of dehydration [9]

Signs & Symptoms of CE: (reference [9] provides major and minor criteria for diagnosis of CE) [6] [8] [9]

- Headache
- Recurrence of vomiting
- Inappropriate slowing of heart rate
- Neurological signs:
    - Restlessness, irritability, increased drowsiness, decreased response to pain, incontinence, cranial nerve palsies, papilledema, abnormal pupillary responses, decorticate or decerebrate posturing
- Increase in blood pressure
- Decreased O_2 saturation

Risk Factors for CE: [6] [8] [9]

Table 3: Risk factors for cerebral edema before and after treatment in pediatric DKA patients

Pre-Treatment Risk Factors	Treatment-Associated Risk Factors
Younger age (harder to assess mental state)	Bicarbonate treatment
New-onset diabetes	Marked early decrease in serum osmolality
Longer duration of symptoms	Greater volumes of fluid given within the first 4 hours of therapy
More severe presentation - Greater acidosis (lower pH, lower pCO_2) - More severe dehydration (increased BUN) - Sicker looking	Administration of insulin within first 2 hours of therapy
	Rapid decrease in serum sodium levels
	Attenuated rise in serum sodium levels
	Rapid rise in serum sodium levels

Treatment of CE:

Most episodes of CE start about 4-12 hours after initiation of DKA treatment (fluids, insulin, etc.) therefore monitoring for CE should start immediately. Onset of CE has been reported as late as 28h after initiation of therapy, therefore monitoring should continue for at least 36 hours. [6] [8] [9] According to several guidelines, recommendations are to elevate the head of the bed to 30° and decrease fluid administration rate back down to maintenance levels once signs and symptoms of CE are recognized. [8] [9]

There is no consensus on doses and durations for infusion of hyperosmolar agent treatment:

Table 4: Differences in hyperosmolar agent treatment recommendations for cerebral edema across guidelines

	BCCH (2010)	ADA (2006)	ISPAD (2014)
Mannitol (20%)	0.5-1g/kg Over 20 min	0.25-1.0g/kg	0.5-1g/kg Over 10-15min
Hypertonic saline (3%)	5-10ml/kg IV Over 30min	5-10ml/kg Over 30min	2.5-5ml/kg Over 10-15min

BCCH= British Columbia Children's Hospital; ADA= American Diabetes Association; ISPAD= International Society for Pediatric and Adolescent Diabetes

Patients may also need intubation to ensure proper ventilation (hyperventilation) to keep pCO_2 above 22mmHg. [8] Finally, CT is recommended, once the patient has received treatment with hyperosmolar agents, to rule out other causes of neurological symptoms such as intracranial hemorrhage. [9]

11.2 Other Complications:

Other complications from DKA include: [7] [9]

- Hypokalemia
- Hypoglycemia

} Avoidable with proper monitoring and treatment adjustment

- Acute renal failure
- Shock
- Rare: rhabdomyolysis, thrombosis/stroke, pulmonary edema, memory loss/decreased cognitive function

Summary & Recommendations

Concise summary of this document, helping the HSN pharmacist to monitor pediatric patients with DKA:

1) First confirm diagnosis (BG>11mmol/L, pH<7.3/HCO3<15mmol/L & ketones in blood or urine) and classify based on severity – need baseline labs, especially CBC, blood gas, electrolytes, SCr, BUN, albumin, BG, urinalysis, and blood ketones/β-hydroxybutyrate.
2) Physician will have ordered fluids. Check appropriateness and ensure only running at max 1.5x maintenance rate for first 48h. Appropriate fluids (isotonic fluids) will replace a 5-7% loss in moderate DKA, and 10-15% loss in severe DKA (will need patient's weight to calculate).
    i. Fluids should consist of normal saline (0.9%) for the first 2h, then once insulin is started, add in 40mmol/L of K^+ to prevent hypokalemia (monitored with ECG)
    ii. After hyperglycemia has resolved, ensure dextrose is added, using BG monitoring as a guide for titration and maintain a BG level of 10-15mmol/L to prevent hypoglycemia.
    iii. At 48h may open up fluid rate to 2.0x maintenance to rehydrate fully.
3) Insulin should be started after the first 1-2hours of IV fluids, at 0.1 units/kg/h (unless sensitive, then 0.05 units/kg/h) and ensure K^+ is in the IV fluids to prevent hypokalemia. To avoid cerebral edema, don't use IV bolus insulin or IV bicarbonate, and monitor Na^+ levels for a gradual rise. Once the patient's acidosis has been corrected, and patient is taking food, may stepdown to SubQ insulin with a crossover time that is based on the onset of action of the SubQ insulin.
4) To determine if treatment is working and to monitor progress, use the Anion Gap as it correlates better with the acidosis than bicarbonate levels and will better show resolution of acidosis.
5) Finally, check to see that there is someone following up on the etiology of the DKA event, as prevention of future DKA episodes will reduce the patient's risk of morbidity and mortality from DKA or a related cerebral edema.

Conclusion

DKA in pediatric cases is a very complicated and multifactorial problem that requires delicate yet decisive handling. Once recognized, it is important to treat children with DKA as quickly and efficiently as possible and monitor frequently to avoid possible complications. Once the acute episode has been resolved, investigations into the cause of the incident and education of patients and families on proper sick-day management and insulin administration should be initiated.

REFERENCES

[1] National Health Service England. Diabetic ketoacidosis - Complications. NHS Choices. http://www.nhs.uk/Conditions/diabetic-ketoacidosis/Pages/Complications.aspx. Accessed August 17, 2016.

[2] American Diabetes Association. DKA (Ketoacidosis) & Ketones. Living with Diabetes - Complications. http://www.diabetes.org/living-with-diabetes/complications/ketoacidosis-dka.html. Accessed August 17, 2016.

[3] MEDCRAMvideos. *Medical acid base explained clearly*. YouTube; April 28, 2012.

[4] MEDCRAMvideos. *Diabetic Ketoacidosis (DKA) explained clearly by MedCram.Com*. YouTube; January 9, 2013.

[5] Wherrett D, Huot C, Mitchell B, Pacaud D. Type 1 Diabetes in Children and Adolescents. *Canadian Journal of Diabetes*. 2013;37:S153–S162. http://www.canadianjournalofdiabetes.com/article/S1499-2671(13)00043-9/pdf. Accessed July 10, 2016.

[6] Wolfsdorf J, Glaser N, Sperling MA. Diabetic Ketoacidosis in infants, children, and adolescents: A consensus statement from the American diabetes association. *Diabetes Care*. 2006;29(5):1150–1159. doi:10.2337/dc06-9909. http://care.diabetesjournals.org/content/diacare/29/5/1150.full.pdf. Accessed August 10, 2016.

[7] Westerberg DP. Diabetic Ketoacidosis: Evaluation and treatment. *American Family Physician*. 2013;87(5):337–346. http://www.aafp.org/afp/2013/0301/p337.pdf. Accessed August 14, 2016.

[8] Metzger DL. Diabetic Ketoacidosis in children and adolescents: An update and revised treatment protocol. *BC Medical Journal*. 2010;52(1):24–31. http://www.bcmj.org/sites/default/files/BCMJ_52Vol1_ketoacitosis-core.pdf. Accessed August 10, 2016.

[9] Wolfsdorf JI, Allgrove J, Craig ME, et al. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatric Diabetes*. 2014;15(S20):154–179. doi:10.1111/pedi.12165. http://c.ymcdn.com/sites/www.ispad.org/resource/resmgr/Docs/CPCG_2014_CHAP_11.pdf. Accessed August 10, 2016.

[10] CHEO Diabetes Team. Diabetic Ketoacidosis Guidelines for Champlain LHIN use. Ottawa: CHEO ED Outreach; October 2014. Accessed July 27, 2016.

[11] Julie A Edge. BSPED Recommended Guideline for the Management of Children and Young People under the age of 18 years with Diabetic Ketoacidosis, (2015). http://www.bsped.org.uk/clinical/docs/DKAGuideline.pdf. Accessed August 11, 2016.

[12] Jeha GS, Haymond MW. Treatment and complications of diabetic ketoacidosis in children. UpToDate; July 2016. Accessed July 10, 2016.

[13] Jeha GS, Haymond MW. Clinical features and diagnosis of diabetic ketoacidosis in children. UpToDate; June 2016. Accessed July 10, 2016.

[14] Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic Ketoacidosis. *New England Journal of Medicine*. 2001;344(4):264–269. doi:10.1056/nejm200101253440404.

[15] Dimitriadis G, Mitrou P, Lambadiari V, Maratou E, Raptis SA. Insulin effects in muscle and adipose tissue. *Diabetes Research and Clinical Practice*. 2011;93:S52–S59. doi:10.1016/s0168-8227(11)70014-6.