Owner: Pediatric Department	Protocol Code: PR-PED-002
Title of The Protocol: Diabetic Ketoacidosis (DKA) Management Protocol	

Background:
Diabetes ketoacidosis results from state of insulin deficiency and is the most common cause of diabetes related deaths in childhood. DKA may occur at initial diagnosis, during intercurrent illness, stress or due to insulin omission especially in the adolescent group.

Pathogenesis:
DKA is the result of a critical relative or absolute deficiency of insulin, resulting in intracellular starvation of insulin-dependent tissues (muscle, liver, adipose), stimulating the release of the counter-regulatory hormones glucagon, catecholamines, cortisol, and growth hormone. The counter-regulatory hormonal stimulates lipolysis and proteolysis, hepatic and renal glucose production, and hepatic oxidation of fatty acid to ketone bodies.
The evolution of DKA is characterized by hyperglycemia and hyperketonemia. Hyperglycemia is caused by a combination of increased hepatic glucose output due to enhanced glycogenolysis and gluconeogenesis, together with decrease peripheral glucose utilization rate. The hyperketonemia is the product of increased peripheral lipolysis, the increased conversion of these free fatty acids to ketoacids (acetoacetic and β -hydroxybutyric acids) by the liver and decreased peripheral utilization of ketoacids as energy substrates.

Criteria of Diagnosis:

Diabetic ketoacidosis (DKA) is biochemically defined as: Hyperglycemia (blood glucose >11 mmol/L (≈200 mg/dl), venous pH < 7.3 or serum bicarbonate <15 mmol/l, Ketonemia (blood ß-hydroxybutyrate ≥3 mmol/l) or moderate or large ketonuria. Rarely, DKA may occur with normal circulating glucose concentrations if there has been partial treatment. The severity of DKA is determined by the degree of acidosis as follows:

- **Mild:** venous pH >7.2 and <7.3, bicarbonate <15 mmol/l.
- **Moderate:** venous pH > 7.1 and <7.2, bicarbonate <10 mmol/l.
- **Severe:** venous pH <7.1, bicarbonate <5 mmol/l.

Clinical signs of DKA include: Dehydration, tachycardia, tachypnea, deep sighing respiration "Kussmaul", breath smells of acetone, nausea and/or vomiting, abdominal pain, blurry vision, confusion, drowsiness, progressive decrease in level of consciousness and, eventually, loss of consciousness (coma).

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Baseline investigations:

- Serum glucose.
- Serum electrolytes.
- Serum urea & creatinine.
- Venous pH & bicarbonate.
- Serum osmolarity.
- Full blood count & septic screen only if infection is the precipitating factor. *(Remember, not all infections are bacterial, so antibiotics are not always indicated in DKA management).*

Important calculations:

Anion gap = Na − (Cl + HCO3): normal is 12 ±2 mmol/L (In DKA the anion gap is typically 20 - 30 mmol/L; an anion gap >35 mmol/L suggests concomitant lactic acidosis)

Corrected sodium = measured Na + 2([plasma glucose − 5.6]/5.6) mmol/L.

Osmolality (mOsm/kg) = 2 × (plasma Na) + plasma glucose mmol/L (normal range is 275 to 295 mOsm/kg).

Observations:

- Body weight should be determined for calculation purposes.
- Dehydration can be estimated as mild, moderate or severe.
- Hourly vital signs measurements.
- Hourly neurological observations (Glasgow coma scale).
- Hourly monitoring of blood glucose is needed with the initiation of insulin to avoid hypoglycemia or rapid drop of glucose > 100 mg/hr.
- Accurate fluid balance chart (an indwelling urinary catheter might be needed).
- Testing urine for ketones every nursing shift.

Criteria for PICU admission:

- Age < 2 years.
- Arterial pH < 7.
- Altered mental status.
- Severe dehydration (shock).

**Patients not meeting any of these criteria may be candidates for intravenous insulin on the in-patient.*

DKA management include the following:

- Correction of shock (rarely is present).
- Correction of dehydration.
- Correction of hyperglycemia.
- Correction of electrolyte deficits.
- Correction of acidosis.
- Correction of the underlying cause (infection, stress, omission of insulin…. etc.).

Correction of dehydration:

- The patient initially should be "Nil by mouth" except for ice to suck.
- Hypovolemic shock is a rare occurrence in DKA.
- Initial volume expansion should be with isotonic solution e.g. Ringer's lactate or 0.9 saline.
- Fluid repletion in moderate to severe DKA is usually begun with *infusion of 10 ml/kg over 60 minutes.*
- If the circulating volume is still compromised, additional infusion of *10 ml/kg to be given over the next hour.*
- Once the child is hemodynamically stable, subsequent fluid replacement should be started.

Maintenance fluid:

Maintenance can be calculated as 1000 ml for the first 10 kg body weight + 500 mL for the next 10 kg + 20 mL/kg over 20 kg or 1500 mL/m^2 body surface area. The calculated maintenance fluid should be divided equally on 24 hours.

Deficit fluid:

- Calculations depends on percentage of dehydration to be given slowly over 48 hours to minimize risk of cerebral edema (usually dehydration is between mild to moderate).
- In order to calculate deficit is by multiply degree of dehydration multiply by body weigh multiply by10. Example: (weight of the child is 20 kg with 7 % dehydration, so the calculated deficit would be (20x7x 10=1400 ml) will be infused on 48 hours as deficit in addition to maintenance rate as mentioned previously.
- *Remember to subtract any initial resuscitation fluid boluses given from the total calculated deficit.*
- *In moderate DKA assume 5% - 7% and in severe DKA 7% - 10% dehydration.*

- Type of fluid initially by administration of isotonic 0.9 saline till serum glucose is < 250 mg/dl then fluid will be changed to D5% in 0.45 NS.
- Urinary losses should not be added to the calculated total volume of fluids.
- If the corrected serum sodium value is in the hypernatremia range even slower rehydration over 72 hours may be considered.

Intravenous continuous insulin infusion:

- Start insulin infusion at least 1 hour after starting fluid replacement therapy; that is, after the patient has received initial volume expansion.
- If initial potassium is low, delay insulin infusion and continue with hydration with KCL added to the fluid till serum potassium is corrected then start insulin infusion.
- Insulin therapy is essential to restore normal cellular metabolism, to suppress lipolysis and ketogenesis, and to normalize blood glucose concentrations.
- In general, the insulin infusion dose of 0.1 units/kg/hr.
- It is contraindicated to give bolus of insulin.
- *The aim is to produce a gradual fall in serum glucose of 5 mmol/l per hour (No hurry).*
- When the serum glucose falls below 14 mmol/l, the IV solution changed to 5% Dextrose 0.45% saline.
- It may be necessary to use 10% or even 12.5% dextrose to prevent hypoglycemia while continuing to infuse insulin to correct the metabolic acidosis.
- The insulin infusion rate and/or the dextrose infusion rate should then be adjusted to keep the serum glucose level between 8-12 mmol/l.
- Insulin is needed to clear the ketonemia.
- Insulin IV infusion must be continued until acidosis has cleared.

Criteria to switch from intravenous to subcutaneous route:

- Venous pH is > 7.30 & HCO3 is > 15 mmol/l.
- Child is well hydrated.
- No vomiting or abdominal pain.
- Child is conscious, alert & willing to have oral intake.

Correction of electrolyte disturbances:

Sodium:

- Hyperglycemia results in osmotic water movement out of the cells, thereby lowering serum sodium concentration by dilution. This laboratory artifact is called "Pseudohyponatremia".
- Reversing the hyperglycemia with insulin, will sequentially lower the plasma osmolality, cause water to move from the extracellular fluid into the cells, and raise the serum sodium concentration.
- Initially infusing 0.9% saline solution then dextrose 5% in 0.45 % saline will be enough to correct deficient sodium and chloride.
- *Failure of serum sodium to rise appropriately may be an early sign that the patient is at risk for cerebral edema.*
- Sodium replacement is individualized based on biochemical monitoring.
- If corrected sodium is greater than 150 mmol/l, then correction of the dehydration and electrolyte imbalance should be slower over 48-72 hours is advocated to minimize the risk of cerebral edema.

Hypernatremia in DKA:

- In 30 % of DKA cases, hypernatremia could happen.
- If happened the following is needed:
- Correct sodium slowly drop rate of 2-3 mmol/L/h (for 2-3 h) (maximum total, 12 mmol/L/day).
- Re-calculate deficit fluid to be slower over 60 hours rather than 48 hours.
- Free water to be given (D5% water in separate iv cannula or through NG tube).
- **Use Adrogué–Madias formula, are preferred equation for water deficit:**
    - Total water deficit = total body water X 1 – desired sodium /actual sodium) or visit website http://www.medcalc.com/sodium.html (for easy and rapid calculation of free water rate of infusion).

Potassium:

- Serum potassium at the time of presentation can be false normal or false increased or decreased. (false normal or false high due to presence of metabolic acidosis).
- Actual serum potassium is usually low because of polyuria. A renal loss leads to marked degree of potassium depletion in DKA.
- Combination of insulin deficiency & acidosis impairs potassium entry into the cells & pulls potassium out of cells, tend to raise falsely serum potassium.
- Insulin therapy drives potassium into cells, resulting in fall in serum potassium concentration.

- *Please don't start insulin infusion without adding KCL in the fluid*.
- If there is no urine out or initial serum potassium is > 5.5 mmol/1, delay potassium administration.
- If initial serum potassium is low, then delay insulin infusion and KCL added to the fluid.
- Absence of bowel sounds (paralytic ileus) indicate extreme potassium deficiency.
- Serum potassium should be carefully monitored during DKA management.
- Electrocardiography monitoring is recommended in patients with either hypokalemia or hyperkalemia.
- If initial serum potassium is normal (3.5 - 5.0 mmol/l), add 40 mmol to each liter of IV fluid.
- *If initial serum potassium is low (< 3.5 mmol/l), add 40 mmol to each liter of fluid and delay starting insulin infusion until getting serum potassium above 3.5 mmol/l.*
- Goal of replacement to maintain plasma potassium level between 3.5 - 5 mmol/l.
- Potassium is discontinued once intravenous insulin discontinued, patient resumes eating or drinking and serum potassium above 3.5 mmol/l**.**

Phosphate:

- Serum phosphate concentration may initially be normal or elevated due to movement of phosphate out of the cells.
- Phosphate depletion is rapidly unmasked following the institution of insulin therapy, frequently leading to hypophosphatemia.
- There have been concerns that low plasma phosphate levels could result in low level of erythrocyte 2, 3 diphosphoglycerate concentrations and its effect on tissue oxygenation.
- However, hypophosphatemia has not been shown to affect tissue oxygenation in patients with DKA.
- Prospective studies of phosphate replacement have failed to show clinical benefit.
- In addition to lack of efficacy, phosphate administration may induce hypocalcemia.
- Despite the lack of evidence that phosphate therapy is beneficial, potassium phosphate has been used in some centers for concurrent potassium replacement in children with DKA.
- Careful monitoring of the serum calcium is required.
- *Routine phosphate replacements are unnecessary in DKA.*

Correction of metabolic acidosis:

- In DKA, β-hydroxybutyrate makes up 75 % of the circulating ketones.

- Insulin & fluid repletion leads to correction of acidosis seen in DKA.
- Insulin promotes metabolism of ketoacid anions, resulting in the generation of bicarbonate & stops ongoing production of new ketoacids.
- Improved tissue perfusion corrects any lactic acidosis
- ***Bicarbonate administration is not recommended except for treatment of life-threatening hyperkalemia or unusually severe acidosis (pH <6.9) with evidence of compromised cardiac contractility.***
- Ketonuria may persist for > 36 hours due to slow removal of acetone.
- Controlled trials both in children have been unable to demonstrate any clinical benefit from the routine administration of sodium bicarbonate.
- In addition to lack of benefit, there are potential risks from bicarbonate therapy:
  - Can lead to rise in PCO2 resulting in paradoxical fall in cerebral PH as lipid- soluble CO2 rapidly crosses the blood-brain barrier.
  - May slow the rate of recovery of ketosis.
  - Can lead to over correction of metabolic alkalosis.
  - May be a risk factor for cerebral edema.
  - May result in hypokalemia.
  - Can further increase degree of hypernatremia & hyperosmolality.
- If needed, bicarbonate should be given as slow intravenous infusion over 30-60 minutes.
  - Bicarbonate dose of 1-2 mmol/kg/infusion, to be given very slowly unless thermodynamically compromised.

Management of the ketoacidosis recovery phase:

Use of insulin infusion to cover meals and snacks:

It is useful to maintain the insulin infusion until the child has had at least one meal. For snacks the basal infusion rate is doubled at the start of the snack and continued for 30 minutes afterwards, before returning to the basal rate. For main meals the basal infusion rate should be doubled at the start of the meal and continued for 60 minutes after the meal, before returning to the basal rate.

When to stop the infusion?

Most convenient to change to subcutaneous insulin just before mealtime.

Subcutaneous insulin is given 30 minutes before the meal (if short acting insulin is used or 15 minutes before the meal if rapid acting insulin is used, and insulin infusion continued throughout the meal for a total of 90 minutes after the subcutaneous insulin injection, then cease both insulin infusion and intravenous fluid.

The half-life of intravenous insulin is only 4.5 minutes; therefore, it is important that the subcutaneous insulin is given before stopping the infusion.

Treatment of complications:

Cerebral edema

- Cerebral edema is a complication of therapy that is reported to occur in 0.4 -1% of patients with DKA.
- Subclinical brain swelling, as detected by CT scan, has been much more common in most but not all studies.
- *Warning signs and symptoms of cerebral edema include:* Onset of headache after beginning treatment or progressively worsening or severe headache, slowing of heart rate not related to sleep or improved intravascular volume, change in neurological status (restlessness, irritability, increased drowsiness, confusion, incontinence), specific neurological signs (e.g., cranial nerve palsies), rising blood pressure, and decreased oxygen saturation.

Pathophysiology:

It is generally believed that cerebral edema is related to management of DKA. Numerous factors have been implicated, but none has been proven. In addition, cerebral edema may be present before treatment has begun but more commonly occurs 4 -12 hours after the initiation of therapy. Therapy may exacerbate but not initiate the pathologic processes that lead to cerebral edema.

Risk factors:

- Children with newly diagnosed diabetes.
- Failure of the serum sodium to rise as predicted following insulin therapy and fluid repletion, indicating a greater fall in plasma osmolality.
- Severity of acidosis at presentation.
- The use of bicarbonate therapy for correction of the acidosis in DKA.
- The rate of decrease in plasma glucose concentration.
- The rate of fluid delivery.
- The rate of insulin delivery.
- The initial glucose and sodium concentrations.

Cerebral edema management:

- Elevate the head of the bed to 30 degree and keep the head in the midline position.
- Rate of fluid administration should be reduced to maintenance or even lesser depending on the general condition of the child.

- *Give mannitol, 0.5 - 1 g/kg IV over 10 to 15 minutes. The effect of mannitol should be apparent after ~15 minutes and is expected to last about 120 minutes. If necessary, the dose can be repeated after 30 minutes.*
- *Hypertonic saline (3%), suggested dose 2.5 to 5 mL/kg over 10 to 15 minutes, may be used as an alternative to mannitol, or in addition to mannitol if there has been no response to mannitol within 15 - 30 minutes. (Hypertonic saline (3%) 2.5 mL/kg is equimolar to mannitol 0.5 g/kg).*
- Intubation & hyperventilation. Please note, aggressive hyperventilation (PCO2 below 22 mmHg) should be avoided, as it might be more harmful than beneficial as it may decrease cerebral blood flow enough to cause cerebral ischemia& increase extent of brain injury in any form of cerebral edema.
- After treatment for cerebral edema has been started, cranial imaging may be considered However, treatment of the clinically symptomatic patient should not be delayed in order to obtain imaging.
- The primary concern that would warrant neuroimaging is whether the patient has a lesion requiring emergency neurosurgery (e.g., intracranial hemorrhage) or a lesion that may necessitate anticoagulation (e.g., cerebrovascular thrombosis), as suggested by clinical findings of focal or severe, progressive headache, or focal neurologic deficit

Other DKA complications:

- **Venous thrombosis:** Children with DKA appear to be at increased risk, particularly in association with femoral central venous catheter placement.
- **Aspiration pneumonia:** Children with DKA who present with an altered state of consciousness and vomiting are at increased risk for aspiration.
- **Cardiac arrhythmia:** Cardiac arrhythmias may be seen with either hypokalemia.

Reference:

ISPAD gaudines, Pediatric Diabetes. Oktober 2018; 19 (Suppl. 27): 155–177

PROTOCOL APPROVALS:

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