Season 1, Episode #02

MANAGEMENT OF THE PEDIATRIC PATIENT WITH DIABETIC KETOACIDOSIS

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Key Electronic Resources:

- LearnPICU: DKA
- OPENPediatrics: Management of Diabetic Ketoacidosis
- Pediatric DKA Protocol App

A. Pathophysiology of DKA:

1. Absolute or relative insulin deficiency results in increased lipolysis, gluconeogenesis, glycogenolysis, hyperglycemia, and ketogenesis due to impaired glucose utilization.
2. Hyperglycemia > 180 – 200 mg/dL results in an osmotic diuresis with worsening dehydration.
3. Unopposed ketogenesis results in formation of an anion gap metabolic acidosis.
4. Metabolic acidosis results in respiratory compensation with deep, rapid breathing known as Kussmaul respirations.
5. Insulin deficiency also results in depletion of intracellular potassium and phosphate that are eventually lost in the urine.

B. Definition of DKA:

1. Hyperglycemia > 200 mg/dL
2. Acidosis: venous pH < 7.3 or bicarbonate < 15 mEq/L
3. Ketosis: serum beta-hydroxybutyrate ≥ 3 mmol/L or moderate to large ketonuria on urinalysis

C. Grading the Severity of DKA:

1. Mild: venous pH 7.2 - 7.3 or serum bicarbonate < 15 mEq/L
2. Moderate: venous pH 7.1 - 7.2 or serum bicarbonate < 10 mEq/L
3. Severe: venous pH < 7.1 or serum bicarbonate < 5 mEq/L

D. Common Laboratory Abnormalities:

1. Obtain baseline labs to include a renal panel, VBG, blood glucose, and urinalysis.
2. Anion gap (AG) metabolic acidosis
    a. Anion gap can be calculated as:

$$AG = [Na^+ - (Cl^- + HCO3^-)]$$

    a. DKA is the "D" part of our 'MUD PILES' anion gap mnemonic
    b. Normal anion gap with modern chemistry analyzers is ~6 – 10 mEq/L.
    c. The anion gap in DKA is typically ~20 – 30 mEq/L.
    d. An anion gap of > 35 mEq/L may suggest a concomitant lactic acidosis
3. Hyponatremia ('pseudohyponatremia')

a. Corrected serum Na^+ can be calculated as:

$$\text{Corrected serum } Na^+ = \text{Measured } Na^+ + [1.6 * \frac{\left(\text{Serum glucose } \left(\frac{\text{mg}}{\text{dL}}\right) - 100\right)}{100}]$$

Or, equivalently:

$$\text{Corrected serum } Na^+ = \text{Measured } Na^+ + [0.016 * \left(\text{Serum glucose } \left(\frac{\text{mg}}{\text{dL}}\right) - 100\right)]$$

b. Hyperglycemia causes osmotic movement of water out of the cell into the extracellular space causing a dilutional hyponatremia.
c. Serum sodium should slowly normalize as hyperglycemia is corrected; failure of sodium to rise appropriately may be an ominous sign of impending cerebral edema.

4. Potassium derangements
   a. Hypertonicity, acidosis, and insulin deficiency result in intracellular potassium efflux from cells into the extracellular space causing hyperkalemia.
   b. Over time, vomiting, osmotic diuresis, and volume depletion induced hyperaldosteronism lead to a total body potassium deficit.
5. Hypophosphatemia, secondary to insulin deficiency and osmotic diuresis.
6. Hyperosmolality, secondary to ketone production (beta-hydroxybutyrate >>> acetoacetate).
7. Elevations in serum BUN, creatinine, hematocrit, and albumin are useful markers of extracellular free water loss and may be used to guide fluid deficit replacement.

E. Initial Resuscitation:

1. The initial resuscitation goal is to improve perfusion and treat any inciting (infectious) events.
2. Establishing 2 peripheral IVs is ideal, to allow for both resuscitation and the frequent lab checks needed during treatment of DKA.
3. For patients who are dehydrated, but NOT in shock, begin with a 10 mL/kg (max 1L) isotonic fluid bolus over 30 to 60 minutes.
4. In the rare case of a DKA patient in shock, repeated 20 mL/kg boluses over 15 to 30 minutes to restore adequate perfusion may be necessary, as per PALS guidelines.
5. The ISPAD 2018 guidelines recommend using crystalloid, not colloid for the initial resuscitation. Isotonic crystalloids are preferred. Resuscitation fluids should first be infused before starting insulin therapy.
6. NS is isotonic to plasma, but leads to a normal anion gap hyperchloremic metabolic acidosis over time. LR is considered a “balanced” solution, but is relatively hypotonic due to a lower sodium content. LR also contains lactate that is metabolized to bicarbonate and may have additional implications in DKA (see “Bicarbonate Therapy” below for further discussion).
7. High chloride loads from NS have been associated with acute kidney injury, need for dialysis, and increased mortality among critically ill adults.

F. Resuscitation with LR Compared with NS:

1. Bergmann et al conducted a retrospective study of over 49,000 children with DKA describing the use of Ringer’s lactate (LR) or normal saline (NS) for resuscitation and comparing cost, length of stay, and rates of cerebral edema.
2. The majority of patients (88%) were treated with NS compared with only 4% that were exclusively treated with LR.
3. Total adjusted cost was $1160 less for the LR group. Cerebral edema was also less common with LR than NS (12.7/1000 vs. 34.6/1000). Length of stay was not significantly changed.

4. Study limitations include the relatively low number of patients receiving LR and the potential confounder that more critically ill patients preferentially received NS than LR.

G. Fluid Deficit Replacement:

1. The goal with fluid management in the child with DKA is to provide the usual ongoing maintenance needs plus replacing the fluid deficit at an even rate over 24 to 48 hours.
2. The ISPAD 2018 guidelines suggest the deficit fluid choice itself should be something with tonicity in the range of 0.45% to 0.9% saline or a balanced salt solution (i.e. Ringer's lactate, Plasmalyte, Hartmann's solution).
3. There is often great inter-provider variability and inaccuracy in estimating the degree of dehydration clinically. Fluid replacement based on this alone may be inaccurate.
4. Multiple approaches to fluid replacement exist, however, one simplified approach use 0.675% saline (3/4 normal saline) at 2 to 2.5x maintenance (~ 3L/m^2/day) and then decreased IV fluids to 1 to1.5x maintenance at 24 hours or once the acidosis has resolved.
5. Fluids given IV or orally in another facility prior to the initial assessment should also be counted toward the fluid replacement.
6. Urinary losses generally do not need to be added to the calculation of replacement.
7. In most patients, the acidosis will resolve when treated by 24 hours, so the completion of fluid deficit replacement may be done orally once transitioned to SQ insulin.

H. PECARN DKA FLUID Study:

1. Kuppermann et al conducted a 13-center randomized, controlled clinical trial that examined the effects of the rate of administration and the sodium chloride content of IV fluids on neurologic outcomes in children with DKA.
2. Children were randomly assigned to one of four treatment groups in a 2-by-2 factorial design (0.9% or 0.45% sodium chloride content and fast or slow rate of administration).
3. The primary outcome was a decline in mental status (GCS < 14) during treatment of DKA as a marker of possible cerebral edema. Secondary outcomes included clinically apparent brain injury and short-term memory during treatment and IQ testing at 2 and 6 months after recovery from DKA.
4. Researchers found that neither the rate of administration nor the sodium chloride content of IV fluids significantly influenced these neurologic outcomes in children with DKA.

I. Insulin Therapy:

1. Insulin is the key to treating DKA. Insulin corrects the underlying acidosis by restoring normal glucose utilization and halting unopposed lipolysis and ketone production.
2. Typically insulin is withheld for at least 1 hour after starting fluid replacement therapy then started at 0.05-0.1 units/kg/hr.
3. During insulin treatment, point-of-care glucoses should be monitored hourly. Electrolytes should be checked frequently as well, such as with a renal panel every four hours.
4. Unlike in the adult DKA population, a bolus of insulin is not generally recommended for pediatric DKA. An insulin bolus should not be used in the beginning of therapy due to a concern of exacerbating hypokalemia, and it may increase the risk of developing cerebral edema.
5. As the serum glucose falls below ~250-300 mg/dL after initiation of insulin therapy, glucose will have to be added to the IV fluids to prevent hypoglycemia before the complete correction of the underlying acidosis.

6. One common technique to do this is the "two-bag" system which uses two bags with identical content except one is D10% (alternatively, D12.5%) and the other contains no dextrose. By Y-ing them in together and changing the rates relative to each other, D0%, D5%, and D10% can all be rapidly selected.
7. We typically prefer that the glucose not drop any faster than 100 mg/dL/h. As the glucose declines, we first increase the glucose infusion rate (GIR). If necessary, the insulin infusion may also need to be titrated down.
8. Insulin therapy continues until there is resolution of acidosis, indicated by pH >7.3, bicarbonate > 15, BOHB < 1 mmol/L and/or closure of the anion gap.

J. Potassium Replacement:

1. DKA patients have total body potassium depletion regardless of serum values on arrival.
2. Serum potassium will drop as insulin therapy is initiated, driving available potassium intracellularly. Thus, potassium replacement is required regardless of serum potassium concentration on arrival, except if renal failure is present.
3. If the patient is hyperkalemic (K > 6 – 6.5), it is recommended to defer potassium replacement until urine output is documented. Otherwise potassium replacement may be started after initial volume expansion is complete and concurrently with insulin therapy.
4. Replacement typically requires 40 mEq/L in the form of potassium chloride, potassium phosphate, and/or potassium acetate.

K. Bicarbonate Therapy:

1. Controlled trials show *no* clinical benefit from bicarbonate administration.
2. Bicarbonate therapy may cause a paradoxical intracellular and CNS acidosis possibly worsening the patient's clinical condition, cerebral edema, and hypokalemia.
3. The role of bicarbonate should be limited to the rare patient with life-threatening hyperkalemia or unusually severe acidosis (pH < 6.9) with compromised cardiac contractility (i.e. severe shock).

L. Cerebral Edema:

1. The pathogenesis of cerebral edema is not known. Previously, rapid fluid administration and abrupt changes in serum osmolality were suspected. More recent evidence suggests that the degree of dehydration and cerebral hypoperfusion are associated with DKA-related brain injury.
2. Though clinically overt cerebral edema is extremely rare in DKA (0.5 – 0.9%), the mortality is high (21%). So having a high index of suspicion is critical.
3. Symptoms may first start as non-specific complaints such as headache then progress to irritability, confusion, and an overall decline in neurological status (i.e. Glasgow Coma Scale <14). Papilledema and cranial nerve palsies are very concerning. Cushing's triad of HTN, bradycardia, and irregular breathing is very late finding of impending herniation.
4. Neuroimaging is *NOT* required to make the diagnosis of cerebral edema; this is a clinical diagnosis.
5. From an epidemiologic perspective, cerebral edema is more common in younger patients, especially with new onset diabetes or with longer duration of symptoms. Cerebral edema is exceedingly rare after adolescence.
6. Other risk factors include greater hypocapnia, increased BUN, and more severe acidosis at presentation.

M. Cerebral Edema Treatment:

1. Treatment should be initiated as soon as the condition is suspected.
2. Focus should be on maintaining a normal blood pressure while avoiding excessive fluid administration.
3. Hypotension should not be tolerated because it might compromise cerebral perfusion pressure.

4. Quick and easy interventions include elevating the head of bed to 30 degrees, keeping the head in the midline position, and applying oxygen to treat any hypoxemia.
5. Neuroprotective intubation may be necessary if the patient is having progressive neurologic compromise and is as risk of respiratory failure.
6. Hyperosmolar agents are the main line of therapy.
    a. Mannitol: Usual range: 0.5 to 1 g/kg/dose infused over 10 to 15 minutes.
    b. Hypertonic saline (3%): 2.5 to 5 mL/kg over 10 to 15 minutes, may be used as an alternative, or in addition to mannitol.
7. After initiating therapy, neuroimaging may then be considered to evaluate for other intracranial cause that may require intervention (i.e. hemorrhage or thrombosis).

Summary:

- Be on the lookout for possible new cases of diabetes. Many cases of pediatric DKA are made at the time of initial diagnosis of DM.
- A bolus of 10 mL/kg of either NS or LR is a reasonable start in most pediatric DKA patients.
- Potassium levels are critical to be aware of in DKA, as total body potassium is almost always low. Begin replacing potassium when starting insulin, unless severely hyperkalemic (K > 6 – 6.5).
- An insulin bolus is not needed in pediatric DKA and may exacerbated cerebral edema.
- Look for subtle signs of change in mental status, headache, or changes in vital signs that suggest cerebral edema. Rapid identification and intervention are key.

References:

1. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes. 2018 Oct;19 Suppl 27:155-177. doi: 10.1111/pedi.12701.
2. Bergmann KR, Abuzzahab MJ, Nowak J, et al. Resuscitation With Ringer's Lactate Compared With Normal Saline for Pediatric Diabetic Ketoacidosis. Pediatr Emerg Care. 2018 Jul 16. doi: 10.1097/PEC.0000000000001550.
3. Kuppermann N, Ghetti S, Schunk JE, et al. Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis. N Engl J Med. 2018 Jun 14;378(24):2275-2287. doi: 10.1056/NEJMoa1716816.