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Pharmacologic Considerations for Diabetic Ketoacidosis

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Diabetic ketoacidosis (DKA) is responsible for over 160,000 hospital admissions per year.[1] Additionally, 35% to 40% of pediatric patients present in DKA correlating with their initial diagnosis of type 1 diabetes mellitus.[1] As with many other disease states, some of the complications of DKA are unique to pediatric patients, most notably cerebral edema. Understanding the pathophysiology and proper management can prevent many of the complications associated with DKA. In general, managing diabetes is key to prevention of DKA.

Pathophysiology

Diabetes occurs when the body is unable to utilize glucose. DKA results from insulin deficiency and is characterized by hyperglycemia, water and electrolyte depletion, and acidosis. The lack of insulin, either from noncompliance, lack of diagnosis, inadvertently missing doses, or failure to give adequate insulin to meet the body's needs during intercurrent illnesses, causes glucose levels to rise. This lack of utilization then sets the counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) in motion as the body reacts as if it does not have enough glucose for energy. Glucose levels begin to rise and create an osmotic gradient due to the hypertonicity of the extracellular fluid. This fluid shift affects many of the electrolyte imbalances seen in DKA. Additionally, the increase in extracellular glucose tends to exceed the renal threshold, resulting in an osmotic diuresis leading to dehydration and the symptoms of polyuria and polydipsia. Polyphagia is another symptom of DKA as the body act as though it lacks glucose needed for normal function.

In addition to glucose and insulin abnormalities, lipolysis occurs, increasing the free fatty acids. The oxidation of these fatty acids results in the production of ketones, which then lead to a metabolic acidosis. Kussmaul respirations are a subsequent symptom of DKA as the body tries to compensate for the increase in partial pressure of carbon dioxide.[1,2] Individual institutions may define when DKA exists based on a patient's level of hyperglycemia, ketonemia, and acidosis (eg, pH <7.3 and serum bicarbonate <15 mEq/L).

Table 1 Goals of Fluid and Electrolyte Therapy in DKA[2]

Volume restoration
Replace electrolytes and fluid deficit
Enhance glucose and ketone clearance with increased glomerular filtration
Avoidance of fluid overload to prevent exacerbation of cerebral edema

Management

Fluid and Electrolytes

Once the necessary arterial blood gasses have been established, fluid and electrolytes are managed because dehydration is usually present in these children. An initial rapid infusion of 10 to 20 mL/kg with isotonic saline or lactated Ringer's solution is appropriate when necessary to help with volume expansion and potentially poor perfusion and hypotension, if present. Unless the latter two symptoms are present, additional boluses are usually not required, and a maintenance fluid can be started. Goals of this maintenance fluid are listed in Table 1. Due to the osmotic diuresis and extracellular fluid shifts, a sodium deficit of 5 to 25 mEq/kg can be present.[1] Additionally, this fluid shift can cause a dilutional hyponatremia, which dictates the use of isotonic saline (0.9%) as maintenance fluid in these patients.

Potassium is also depleted in DKA, usually along the order of 4 to 10 mEq/kg.[1] Unless there is no urine output or hyperkalemia exists, potassium is added to the fluids in the salt forms of chloride, phosphate, or acetate or a combination of these. Institutions vary as to which salt forms are used. Phosphate helps with restoration of oxygen delivery to tissues.[1] Other electrolytes to monitor in patients with DKA are calcium and magnesium, to prevent them from falling too low.

Insulin

Insulin is one of the mainstays of

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Understand the pathophysiology of diabetic ketoacidosis (DKA) in the pediatric patient
- Describe effective management strategies for DKA in the pediatric patient
- Discuss complications associated with DKA

TARGET AUDIENCE

Pediatric nurses, physician assistants, and other interested healthcare professionals, especially those caring for pediatric patients with diabetes.

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treatment for DKA in conjunction with fluid management. Endogenous insulin is deficient or ineffective in patients with DKA, and therefore supplementation is necessary. Insulin works to utilize glucose and suppress gluconeogenesis as well as to suppress lipolysis, thereby stopping ketone production and acidosis.[1] Insulin boluses are not recommended for use in DKA by the American Diabetes Association (ADA).[2] Instead, a continuous infusion of insulin is recommended at an initial rate of 0.05 to 0.1 unit/kg/hr. Only regular insulin is permitted in an insulin infusion, never an insulin analog (such as insulin aspart or insulin lispro) or intermediate-acting insulin (such as NPH). Insulin is used to treat acidosis, not hyperglycemia. The insulin infusion should not be stopped if acidosis persists. Therefore, to avoid decreasing the insulin rate to treat falling serum glucoses, dextrose is added to the maintenance fluids (see next section). The insulin infusion is continued until resolution of DKA based on closure of the anion gap, bicarbonate levels, and increasing pH. Transition to subcutaneous insulin occurs once the acidosis has resolved and the patient can tolerate oral intake. Usually the blood glucose has fallen to <200 mg/dL as well.

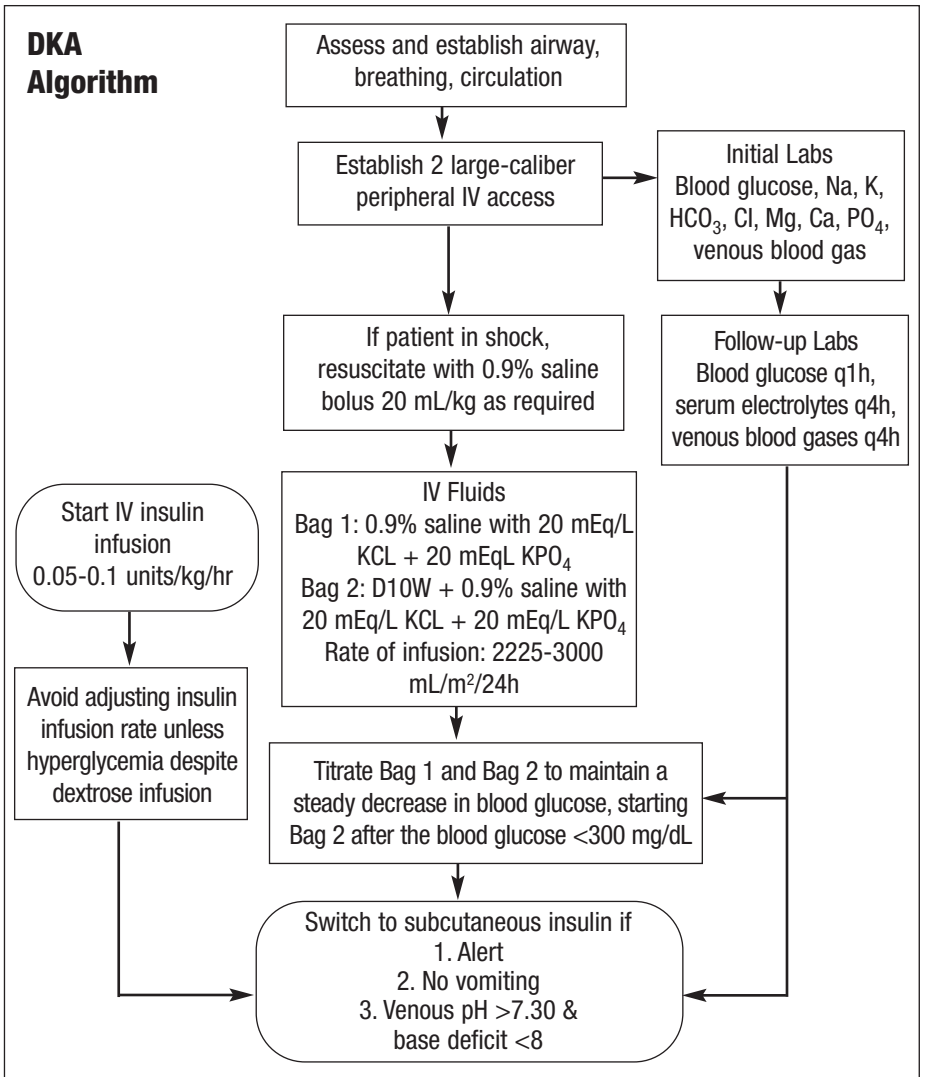
Interestingly, a retrospective cohort study at Monroe Carell Jr. Children's Hospital at Vanderbilt by Shankar and colleagues found that the addition of subcutaneous insulin glargine (Lantus) within the first 6 hours of treatment actually decreased the length of infusion time for regular insulin and shortened the time to acidosis correction. Additionally, no adverse effects were seen with the addition of insulin glargine to the DKA treatment plan.[3]

Glucose

Because of the addition of insulin to the treatment regimen, blood glucose levels will slowly fall, necessitating the use of additional dextrose to prevent hypoglycemia and to allow for the continuation of an insulin infusion until resolution of the acidosis. This is achieved by adding dextrose to the maintenance fluids in a range from 0% to 10%. To accommodate changes in blood sugars, a "two-bag system" may be used for fluid management. In a prospective study, Poirier and colleagues found this system to be most efficient for making changes to the IV fluid rates in DKA patients presenting to the emergency department.[4] An example to illustrate this system is the use of one bag containing 0.9% saline and potassium but no dextrose, and a second bag containing 0.9% saline and potassium plus 10% dextrose. Adjustment of the rates for each bag allows the amount of glucose being infused to be changed easily instead of mixing a new bag of fluid for each change.

Table 2 Signs and Symptoms of Cerebral Edema[6]

Decreased or altered mental status
Headache
Abnormal pupil findings
Sudden hypertension or hypotension
Seizures
Incontinence
Bradycardia
Respiratory arrest



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Bicarbonate

Supplemental bicarbonate is never recommended for correction of the acidosis in patients with DKA as there is no clinical benefit associated with its addition to the treatment. In fact, the adverse effects of bicarbonate therapy, including hypokalemia and paradoxical central nervous system acidosis, preclude its use even more. Rather, the acidosis is corrected using a combination of the aforementioned measures.[2]

Complications of DKA

Cerebral edema, venous thrombosis, hypoglycemia, aspiration, and fluid overload leading to congestive heart failure are all complications of DKA. However, with the exception of cerebral edema, complications can be avoided with proper management of the patient. Cerebral edema is a complication seen only in children, occurring at a rate of 1% to 2%.[1] Though this rate may appear low, the associated mortality rate ranges from 21% to 90%.[5] While there are several proposed mechanisms for this complication, including fluid overload and improper clinical management, it appears that cerebral edema may occur prior to treatment of DKA, thereby lessening these arguments.[6] Signs and symptoms of cerebral edema are shown in Table 2. Marcin and colleagues performed a retrospective review of pediatric patients with DKA and cerebral edema and found that elevated BUN levels, intubation with hyperventilation and hypocapnia, and more profound neurological depression at onset are correlated with poorer outcomes.[5] Cerebral edema is usually treated with mannitol, though hypertonic saline may have a role as well.[2]

DKA in Children vs Adults

In its consensus statement on DKA in the pediatric population, the ADA listed four differences of DKA in children vs adults[2]:

- A standard history of polyuria, polydipsia, and polyphagia symptoms as well as weight loss are less likely to be obtained in younger children, resulting in missed or delayed diagnosis
- Replacement of fluid and electrolytes requires greater precision in the pediatric population due to differences in body mass
- Pediatric patients have a higher risk of cerebral edema due to greater severity at presentation, together with less mature autoregulatory systems
- Recurrent DKA is greatest among adolescents due to lack of compliance with their insulin regimen

Prevention Is Key

For pediatric patients, prevention of DKA is imperative and should be the main goal of diabetic management. With DKA being "10 times as likely to be the cause of death as hypoglycemia," and cerebral edema from DKA as "the most common cause of death and neurologic sequelae in children younger than 12 years of age," education of diabetes and its management in this patient population is of the utmost importance.[7] In the future, identification of individuals at high risk for developing type 1 diabetes by screening for diabetes-related antibodies in the blood may help reduce the frequency with which diabetes presents as DKA.[8]

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