

PEDIATRIC EMERGENCY MEDICINE PRACTICE

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Pediatric Diabetic Ketoacidosis: An Outpatient Perspective On Evaluation and Management

Abstract

Diabetic ketoacidosis is a common, serious acute complication in children with diabetes mellitus. Diabetic ketoacidosis can accompany new-onset type 1 diabetes mellitus or it can occur with established type 1 diabetes mellitus during the increased demands of an acute illness or with decreased insulin delivery due to omitted doses or insulin pump failure. Additionally, diabetic ketoacidosis episodes in children with type 2 diabetes mellitus are being reported with greater frequency. Although the diagnosis is usually straightforward in a known diabetes patient with expected findings, a fair proportion of patients with new-onset diabetes present in diabetic ketoacidosis. The initial management of children with diabetic ketoacidosis frequently occurs in an emergency department. Physicians must be aware that diabetic ketoacidosis is an important consideration in the differential diagnosis of pediatric metabolic acidosis. This review will acquaint emergency medicine clinicians with the pathophysiology, treatment, and potential complications of this disorder.

Author

William Bonadio, MD

Attending Physician, Pediatric Emergency Medicine, Maimonides Medical Center, Brooklyn, NY

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Associate Professor of Pediatrics, University of Colorado, Denver, School of Medicine, Aurora, CO

Joseph I. Wolfsdorf, MD

Clinical Director, Division of Endocrinology, Boston Children's Hospital, Professor of Pediatrics, Harvard Medical School, Boston, MA

CME Objectives

Upon completion of this article, you should be able to:

1. Describe the pathophysiology of DKA and the associated clinical signs and symptoms of this disorder.
2. Discuss management of DKA to restore metabolic homeostasis.
3. Describe the potential complications of DKA therapy.
4. Recognize the importance of monitoring and therapeutics in managing DKA.

Prior to beginning this activity, see "Physician CME Information" on the back page.

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Assistant Professor, Director, Undergraduate and Emergency Simulation, Mount Sinai School of Medicine, New York, NY

Case Presentation

A 7-year-old girl presents to the ED with low-grade fever, vomiting, and abdominal pain. A review of systems reveals a 2-week history of increasing polyuria and polydipsia with a 2-pound weight loss. Vomitus is not bloody or bilious, and she has no headache. The family history is pertinent for a first cousin with type 1 diabetes. On physical exam, she is somewhat lethargic, but alerts fully and is oriented. Her GCS score is 14. There is no evidence of trauma. Vital signs include a heart rate of 122 beats/min, a respiratory rate of 32 breaths/min, and a blood pressure of 113/63 mm Hg. The oral mucosa is dry, and capillary refill time is 3 seconds. Pulses are equal and full. Lungs are clear to auscultation, and the cardiac exam is unremarkable. Her abdomen is soft and slightly tender in the epigastric area, and there is no guarding or rebound tenderness. There is no focal neurologic deficit. IV access is obtained; a point-of-care (bedside) glucose measurement is 625 mg/dL. Subsequent lab results obtained on presentation show the serum HCO_3^- is 12 mg/dL and venous pH is 7.22. Urinalysis shows large glucose and ketones. As you begin considering the differential diagnosis for this child, you ask yourself: What questions are most pertinent to ask the parents in determining the etiology? What lab tests should be initially obtained? What is the top initial priority in management? What parameters are most important to follow in this patient's clinical course? What complications can occur during management?

Introduction

Diabetic ketoacidosis (DKA) is the most common acute complication requiring hospitalization of children with type 1 diabetes mellitus.¹⁻³ DKA is potentially fatal, accounting for 70% of diabetes-related deaths in children < 10 years of age.^{3,4} Most DKA fatalities are caused by cerebral edema.³⁻⁵

Successful emergency department (ED) management of DKA requires timely intervention, meticulous monitoring, and protocol-based hour-by-hour therapy adjustment aimed at ensuring tissue perfusion, correcting fluid and electrolyte depletion, arresting ketogenesis, and restoring normal cellular utilization and metabolism of glucose. To successfully manage the crucial initial phase of DKA, emergency clinicians must thoroughly understand the pathophysiology of DKA and the appropriate therapeutics and monitoring requirements of this complex disorder as well as maintain a keen awareness of potential complications as therapy proceeds. The purpose of this review is to discuss the pathogenesis, evaluation, and management of pediatric DKA in the outpatient setting.

Definition Of Diabetic Ketoacidosis

DKA is defined as hyperglycemia (serum glucose concentration > 200 mg/dL), with metabolic acidosis (venous pH < 7.3 or serum bicarbonate [HCO_3^-] concentration < 15 mEq/L), and ketonemia or ketonuria.³ The severity of DKA is determined by the degree of acidosis.⁴ (See Table 1.)

Critical Appraisal Of The Literature

A 12-year review of PubMed entries using the key word *pediatric diabetic ketoacidosis* revealed scant medical literature comparing the efficacy of various protocols for managing DKA. Most protocols are time honored and are intuitively based on well-defined pathophysiologic considerations. They share the aims of carefully restoring metabolic homeostasis through rehydration, replacing electrolyte and mineral deficits, insulin replacement to reverse ketogenesis, and diligent clinical monitoring.⁴

Since the most serious complication of DKA—cerebral edema—is uncommon, studies describing risk factors have been retrospective multicenter case series⁶ and case reports.^{7,8}

Epidemiology, Etiology, And Pathogenesis

Diabetes mellitus is the most common metabolic/endocrine disorder of childhood.⁴ The mechanism of acquired insulinopenia is incompletely understood, although evidence points to an autoimmune destruction of pancreatic islet beta cells in genetically predisposed individuals.⁹

The prevalence of pediatric type 1 diabetes mellitus (insulin-dependent diabetes mellitus) is estimated at 2 in 1000 school-aged children.⁵ New cases most commonly occur in autumn and winter. It is thought that symptoms of newly recognized type 1 diabetes mellitus manifest when the insulin-secreting reserve diminishes to < 20% of normal. Symptoms include polyuria, polydipsia, weight loss, and fatigue.⁴ The duration of prediagnosis symptoms varies but is usually 1 to 2 weeks.⁴

Typically, DKA manifests when > 90% of pancreatic islet beta cells have been destroyed. The overall risk of DKA in children with established type 1 diabetes mellitus is estimated to range between 1 and 10 per 100 person-years.^{2,5}

Table 1. Definition Of Diabetic Ketoacidosis Severity

Severity	pH	HCO_3^-
Mild	≥ 7.2 to < 7.3	> 10 mEq/L to ≤ 15 mEq/L
Moderate	≥ 7.1 to < 7.2	> 5 mEq/L to ≤ 10 mEq/L
Severe	< 7.1	≤ 5 mEq/L

Newly Diagnosed Insulin-Dependent Diabetes Mellitus

In the United States, approximately one-quarter of children with newly diagnosed insulin-dependent diabetes mellitus present with DKA.^{10,11} This is more common in younger children and is frequently the result of a delay in diagnosis.¹²⁻¹⁴ In a study of children with new-onset diabetes mellitus, 23% presented with DKA; specifically, 36% of children < 5 years of age presented with DKA at the initial diagnosis, compared with only 16% of adolescents.¹² The rates of DKA at presentation are even higher in developing countries.

The symptoms of ill infants and toddlers with undiagnosed DKA are commonly misinterpreted as respiratory disorders, and they are often treated with beta agonist bronchodilators and steroids, which can exacerbate diabetes mellitus metabolic derangements. As a result, symptom duration may be prolonged, leading to more severe dehydration and acidosis and increasing the risk of neurologic compromise. A Canadian study documented that DKA at the time of diabetes mellitus presentation was significantly more common in children < 3 years of age, and 39% had had at least 1 prior healthcare visit (ie, missed diagnosis) during the week prior to the diabetes mellitus diagnosis.¹⁴

Established Insulin-Dependent Diabetes Mellitus

In children with established type 1 diabetes mellitus, the risk of recurrent DKA is 1% to 10% per patient per year.⁴ Increased risk of DKA is associated with the following conditions:¹⁵⁻¹⁷

- Poor metabolic control (reflected in higher HgbA1c levels)
- Prior DKA
- Factors of age and gender (adolescent females have the highest risk)
- Psychiatric disorders, including eating disorders
- Unstable family circumstances
- Poor compliance with insulin regimen
- Limited access to medical services and/or lack of healthcare insurance
- Insulin pump utilization¹⁸

Insulin-Resistant Diabetes Mellitus

The pediatric incidence of insulin-resistant (type 2) diabetes mellitus is rising, as it is associated with epidemic rates of obesity. Some centers report that type 2 diabetes mellitus accounts for 50% of all newly diagnosed diabetes mellitus cases in patients aged 10 to 21 years.¹⁹ This disorder typically presents in obese pubertal children of minority ethnic background. In contrast to type 1 diabetes mellitus, type 2 disease is primarily due to insulin resistance. Normally, insulin suppresses glycogenolysis and gluconeogenesis in the liver; however, in the set-

ting of insulin resistance, the liver inappropriately releases glucose into the blood.

Acute hyperglycemic emergencies in children with type 2 diabetes mellitus include DKA and the hyperglycemic hyperosmolar state. DKA is reportedly present at the time of diagnosis of type 2 diabetes mellitus in as many as 10% to 25% of children¹⁹ and has been labeled "ketosis-prone type 2 diabetes mellitus."²⁰ It is usually due to relative insulin deficiency in a patient with severe insulin resistance and longstanding hyperglycemia that is exacerbated by a sudden increased demand for insulin during an intercurrent illness. The hyperglycemic hyperosmolar state is characterized by severe dehydration and hyperosmolarity, and it has a high risk of serious complications, including coma and death. In contrast to DKA, in the hyperglycemic hyperosmolar state, there is often sufficient insulin effect to prevent marked lipolysis and inhibit ketogenesis.

Pathophysiology

Type 1 diabetes mellitus is a disease caused by destruction of beta cells, leading to insulin deficiency that results in abnormalities of carbohydrate, fat, and protein metabolism. DKA is a complication caused by either a relative or absolute deficiency of insulin. With progressive beta cell failure, lack of insulin and increased levels of counterregulatory hormones (especially glucagon) result in unregulated hepatic glucose production and decreased glucose utilization in insulin-dependent tissues (muscle and adipose tissue). DKA is characterized by increased secretion of the counterregulatory hormones glucagon, epinephrine, norepinephrine, cortisol, and growth hormone. This hormonal milieu causes a catabolic state, with increased mobilization of long-chain fatty acids from adipose stores, augmented hepatic gluconeogenesis, and increased oxidation of fatty acids, producing large quantities of acetoacetic and beta-hydroxybutyric acids. As shown in **Figure 1 (page 4)**, this cascade results in hyperglycemia and ketoacidosis.

Whereas the most common cause of DKA in patients with newly diagnosed diabetes is a delayed diagnosis, the most common cause of DKA in patients with known diabetes mellitus is a lack of insulin due to missed injections or (in patients who use an insulin pump) failure of insulin delivery, often due to causes such as insulin pump failure, prolonged pump disconnection without appropriate monitoring, and inappropriate reduction of insulin dosing or discontinuation of insulin administration during an illness with reduced oral intake. In older children and adolescents who self-manage their diabetes regimen and do not receive adequate adult supervision, DKA commonly results from missed insulin doses. With patient education and careful supervision by parents or other responsible adults and

24-hour access to professional telephone guidance, recurrent DKA should be preventable.

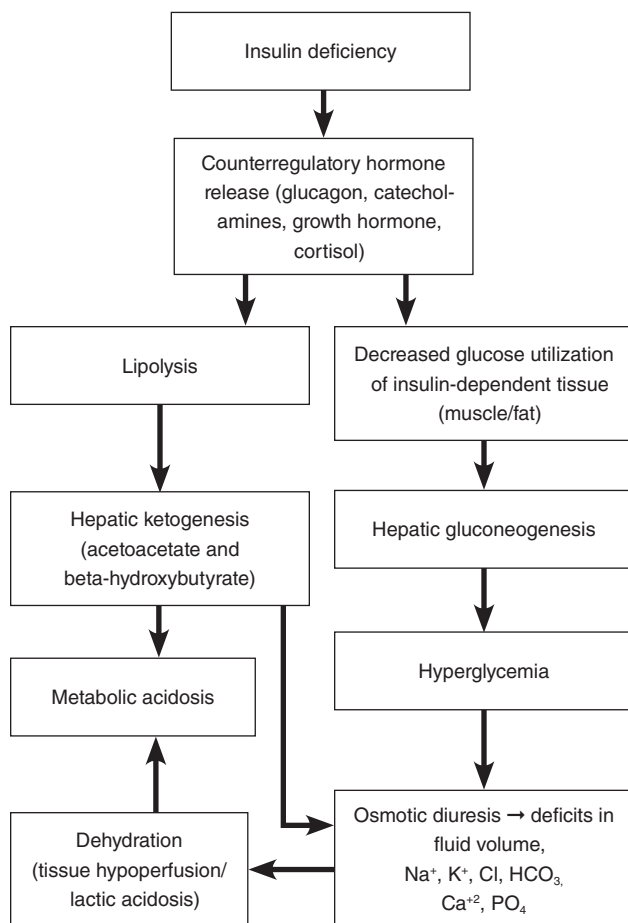
DKA is commonly precipitated by the stress of an intercurrent febrile or vomiting illness that results in relative insulin insufficiency.²¹ Intercurrent failure to provide additional insulin in a timely fashion can lead to the development of ketoacidosis.

Hyperglycemia and hyperketonemia induce an osmotic diuresis, resulting in total body fluid depletion typically of the order of 7% to 10% of body weight. Ketogenesis and poor tissue perfusion (resulting in lactic acidosis) from dehydration combine to produce metabolic acidosis, which may be severe.²¹ If the metabolic derangements are not arrested and reversed with rehydration and replacement of insulin and electrolytes, fatal dehydration and metabolic acidosis will ensue.

Differential Diagnosis

DKA must be differentiated from other causes of metabolic acidosis with an increased anion gap, all of which can present with similar symptoms. Con-

Figure 1. Pathophysiology Of Diabetic Ketoacidosis



ditions to consider in the differential diagnosis of diabetic ketoacidosis include the following:

- Metabolic acidosis (using the MUDPILES mnemonic: **m**ethanol intoxication, **u**remia, **D**KA, **p**araldehyde intoxication, **i**soniazid toxicity, **i**ron intoxication, **l**actic acidosis, **e**thylene glycol intoxication, **s**alicylate intoxication)
- Asthma/respiratory insufficiency with respiratory acidosis
- Meningitis or pneumonia with sepsis
- Acute abdomen/appendicitis
- Gastroenteritis with dehydration
- Hyperglycemic hyperosmolar state

The diagnosis is usually straightforward in a patient with known diabetes who presents with dehydration, metabolic acidosis, and ketonuria.

Prehospital Care

Prehospital care of suspected pediatric DKA is limited to thorough assessment of airway, breathing, and circulation, obtaining intravenous (IV) access, performing a bedside glucose measurement, and administering a conservative fluid bolus of normal saline (NS) at a volume of 10 mL/kg. Insulin should not be administered. Expedited transport to a hospital ED with frequent assessment of vital signs and neurologic status is essential. In the patient with signs of respiratory insufficiency, securing the airway and providing adequate ventilation should take precedence.

Emergency Department Assessment

Patients with DKA often present with nausea and vomiting. As DKA intensifies, patients become lethargic from dehydration, acidosis, and hyperosmolality, and they can progress to coma. Other physical findings typically include tachycardia, tachypnea, Kussmaul respirations, and abdominal pain. Acidosis (along with poor splanchnic perfusion) can cause an intestinal ileus, and patients frequently complain of abdominal pain that may mimic an acute abdomen. A fruity odor to the breath suggests the presence of acetone (formed by the spontaneous decarboxylation of acetoacetate) that is excreted by the lungs. This mechanism removes about one-fourth of the exogenous hydrogen ions generated by hepatic ketogenesis.²¹

Laboratory Abnormalities In Diabetic Ketoacidosis

Although significant depletion of minerals and electrolytes occurs with DKA, serum levels of many of these components often appear only minimally altered.

Despite profound total body sodium depletion (8-10 mEq/kg) due to osmotic diuresis and renal

excretion of sodium-buffered anions, mild hyponatremia usually accompanies DKA.²² A factitious hyponatremia is due to hyperglycemia, where the serum sodium measured is artificially lowered by approximately 1.6 mEq/L for every 100 mg/dL increase in serum glucose.²³ Factitious hyponatremia is also due to hypertriglyceridemia, as lipids have low sodium content and thus dilute the measured serum sodium level.

Children with DKA experience a total body potassium deficit averaging approximately 5 mEq/kg. Most of the potassium is lost from the intracellular pool, and it is then excreted by the kidney due to the osmotic diuresis of potassium-buffered anions. Volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion. Despite total body potassium depletion, the serum potassium level at presentation may be normal, increased, or decreased, depending largely on the severity of total body potassium depletion and the degree of acidosis. Additionally, both insulin administration and correction of acidosis drive potassium back into cells, decreasing serum levels as therapy progresses. Emergency clinicians must anticipate an early decline in serum potassium concentration with ongoing therapy. An electrocardiogram (ECG) (which reflects the effect of intracellular potassium concentration) can assess for U-waves and flattened T-waves indicative of intracellular potassium deficit.²⁴

Although the serum phosphate level may, initially, be normal, total body depletion of this mineral is common (4 mEq/kg) due to the osmotic diuresis. Hypophosphatemia can be exacerbated by insulin therapy, which promotes entry of phosphate into cells.²⁵ Additionally, there are deficits of chloride (5-7 mEq/kg), calcium, and magnesium.

Dehydration with decreased glomerular filtration causes elevated blood urea nitrogen (BUN) and creatinine concentrations. Leukocytosis (suggesting infection) typically occurs from increased stress hormones, epinephrine, and cortisol. Pediatric DKA is infrequently associated with infection; in 1 series, only 18% of patients had a viral infection and only 13% had a bacterial infection.²⁶

The goals of DKA therapy are to correct dehydration and acidosis, reverse ketogenesis, normalize serum glucose levels, and prevent complications. After expedited triage, the ED assessment of DKA includes a thorough clinical evaluation to confirm the diagnosis and determine its cause (including a careful search for underlying infection). A detailed history of outpatient management is important in recurrent DKA, since factors such as insulin omission, failure to follow sick-day regimens, or pump failure account for most episodes. Compliance issues may be improved with appropriate psychoeducational intervention.

Airway, breathing, and circulation take precedence. Vital signs should be measured and regularly reassessed. The level of consciousness can be serially quantified using the Glasgow Coma Scale (GCS) score. The degree of dehydration can be estimated by assessing vital signs, capillary refill time, quality of skin turgor, respiratory pattern, adequacy of oral mucosa hydration, pulse strength, and extremity perfusion. Severe dehydration is usually associated with greater degrees of hyperglycemia. Dehydration > 10% is suggested by the presence of marked hyperglycemia, weak peripheral pulses, widened pulse pressure, and oliguria.

Ideally, vascular access is obtained via 2 IVs, with 1 being used for serial blood sampling. Blood should be sampled to measure serum glucose; electrolytes; BUN; creatinine; osmolality; venous blood gas (pH/partial pressure of carbon dioxide [pCO₂]); complete blood count; HgbA1c; and calcium, phosphorus, and magnesium concentrations. Appropriate specimens for culture (blood, urine, throat) should be obtained, as indicated. Some centers have reported that point-of-care measurement of blood beta-hydroxybutyrate concentrations are useful for confirming the diagnosis of DKA and monitoring effectiveness of therapy. Urine should be serially assessed for ketonuria, and a pregnancy test should be performed in the adolescent female. Continuous cardiorespiratory monitoring can be employed when clinically indicated. Oxygen should be administered to patients with hypoxia, severe circulatory impairment, or shock.

Diagnostic Studies

Besides the blood and urine samples, there are no other routine diagnostic studies indicated unless the patient has altered mental status, which would mandate emergent cranial computed tomography (CT) scan performance after instituting effective therapy to reverse cerebral edema. Management decisions, prognosis, and disposition are based on the clinical response and laboratory profile as therapy proceeds.

Treatment

Fluid And Electrolyte Therapy

The objectives of fluid and electrolyte therapy are to restore intravascular volume, to improve glomerular filtration (with enhanced serum clearance of glucose and ketones), and to replenish depleted electrolytes and minerals.

Fluid repletion is the single most important initial intervention in managing DKA. Due to osmotic diuresis, DKA patients have a total body fluid deficit of 7% to 10% of body weight. IV fluid corrects dehydration and restores adequate renal perfusion and glomerular filtration, which enhances glucose

excretion, ameliorates lactic acidosis, and decreases the serum level of counter-regulatory hormones.

The first step in rehydration is a bolus infusion of NS. Shock is rare in pediatric DKA. Assuming patients with DKA are hyperosmolar due to hyperglycemia and ketonemia, a gradual decline in serum glucose and osmolality is desirable. Patients with an adequate blood pressure should receive a bolus infusion of 10 mL/kg of IV NS during the initial hour. The NS bolus infusion may decrease the blood glucose by 20% solely by dilution and improving renal perfusion, leading to enhanced urinary glucose excretion.²⁷

Subsequent fluid administered should be with a fluid whose sodium content ranges from at least 0.45% to 0.9%. Some protocols recommend exclusive use of 0.9% during the first 6 hours of therapy, converting to 0.45% thereafter. The total volume administered over the next 47 hours should equal the sum of maintenance fluid volume (1500 mL/m² body surface area/day) added to a replacement volume to replace the fluid deficit based on degree of dehydration.⁴ The total fluid volume administered rarely exceeds 1.5 to 2 times the usual daily fluid requirement. Urine losses are not replaced to avoid excessive fluid volumes.

Once the serum potassium concentration is determined and urine output is established, potassium supplementation should commence. Further adjustment is based on serum potassium levels, which should be measured hourly. Potassium administration (concentration of 40 mEq/L; approximately double the usual maintenance requirement) can be given as ½ potassium chloride and ½ potassium phosphate (or K-acetate) formulations to avoid chloride overload, which can exacerbate acidosis.⁴

Prospective studies have not shown clinical benefit from phosphate replacement;²⁸⁻³⁰ this aspect of therapy is controversial. One theoretical concern against routine replacement is that it may lead to symptomatic hypocalcemia. By contrast, uncorrected hypophosphatemia may detrimentally lower levels of 2,3-DPG (diphosphoglycerate) in red blood cells and reduce tissue oxygen delivery.²⁸ Rhabdomyolysis and hemolytic anemia have been rarely reported in cases of severe hypophosphatemia during DKA. Regardless of whether phosphate is replaced, serum calcium concentration should be monitored.

Insulin Therapy

Insulin must be administered to resolve DKA. Insulin therapy counteracts the effects of glucagon in the liver (suppressing gluconeogenesis and ketogenesis), inhibits lipolysis and proteolysis, and enhances glucose utilization in muscle and adipose tissue. Only regular insulin is used to treat DKA. Following the initial bolus infusion of NS, insulin should be administered as a continuous infusion of 0.1 units/

kg/h,³¹ because, at that point, fluid repletion will have improved peripheral perfusion and partially corrected the metabolic acidosis, both of which will enhance insulin efficacy. Ideally, this titration will slowly decrease the serum glucose level approximately 50 to 100 mg/dL/h (with associated gradual decline in serum osmolality). The insulin infusion should not be discontinued (eg, during transport to CT or inpatient ward) until the acidosis is resolved, since the half-life of IV insulin is only 6 minutes in blood and 30 minutes in tissue. A bolus infusion of insulin does not hasten resolution of DKA and is not recommended at any point in management.³²

Typically, the serum glucose concentration decreases to the normal range before ketosis and acidosis have resolved.⁴ To prevent hypoglycemia, 5% dextrose should be added to IV fluids when the serum glucose level declines to 250 to 300 mg/dL. In the uncommon event that the serum glucose concentration continues to decline below 150 to 200 mg/dL despite the addition of 5% dextrose without a concomitant increase in serum pH/HCO₃, the appropriate maneuver is to administer a higher rate of glucose infusion (in the form of a 10% dextrose solution) instead of decreasing the rate of insulin infusion. Continued insulin infusion is essential to inhibit gluconeogenesis and ketogenesis, promote peripheral glucose utilization, and correct metabolic acidosis.

Sodium Bicarbonate Therapy

Despite sometimes profound metabolic acidosis, sodium bicarbonate (NaHCO₃) supplementation is not recommended for patients with DKA.³³⁻³⁶ Controlled trials have shown no clinical benefit from NaHCO₃ administration.^{37,38} Paradoxical cerebral acidosis can occur with NaHCO₃ administration due to formation and diffusion of CO₂ from the systemic circulation into the central nervous system.³⁹ Rapid administration of NaHCO₃ can cause intracellular influx of potassium and induce acute hypokalemia.³⁸⁻⁴⁰ NaHCO₃ therapy has been associated with cerebral edema, the most common cause of mortality for children with DKA.⁴¹ NaHCO₃ supplementation should only be considered in the critical instance of severe acidosis (serum pH < 7.0) associated with myocardial depression and circulatory insufficiency.⁴

As with treating hyperglycemia and hyperosmolarity, the metabolic acidosis of DKA should be gradually resolved with measured repletion of fluid and insulin supplementation. Although HCO₃ losses are large in DKA, the body will replenish a substantial amount during DKA treatment, as insulin stimulates HCO₃ generation from ketone metabolism.

Monitoring

Meticulous clinical monitoring is the cornerstone of successful DKA management. It is essential to

frequently assess vital signs, neurologic status, and progression of abnormal clinical findings as DKA resolves. A bedside data flow sheet should be utilized to enter hour-by-hour clinical information and should include:

- Vital signs
- GCS score
- Laboratory values, including:
 - Serum glucose
 - pH/pCO₂
 - Electrolytes measured hourly during the initial 4 hours of therapy
 - Serum calcium and phosphorus measured every 2 to 4 hours (or more frequently, as clinically indicated in more severe cases)
 - Qualitative urine ketone analysis every 2 hours until cleared
- Medications received
- Amount of insulin administered
- Fluid input and output

Complications Of Diabetic Ketoacidosis

Potential complications of DKA and their management are listed in **Table 2**. The most frequent complications are hypoglycemia and hypokalemia, the risks of which can be minimized with frequent monitoring of serum levels and adequate and timely replacement of glucose and potassium, respectively. Cerebral edema is the most serious complication of DKA.

Cerebral Edema

Clinically overt cerebral edema, although rare (< 1% of DKA cases), is a potentially devastating consequence of DKA therapy, accounting for 60% to 90% of all DKA deaths.⁴¹ The associated mortality rate of cerebral edema is 20% to 25%, and approximately one-quarter of survivors suffer lasting neurologic complications.⁴¹

Risk factors for DKA-associated cerebral edema include:⁴²⁻⁴⁴

- Younger patient age
- New-onset diabetes mellitus
- Prolonged duration of symptoms
- Hypocapnia
- Relatively greater degree of hyperglycemia or acidosis or elevated BUN (on presentation)
- NaHCO₃ therapy
- Attenuated rise in serum sodium concentrations during therapy
- Relatively greater fluid volumes administered in the initial 4 hours
- Insulin administration in the initial hour of therapy

Cerebral edema usually occurs during the initial 4 to 12 hours of therapy, although onset can be earlier or later. The mechanisms underlying the

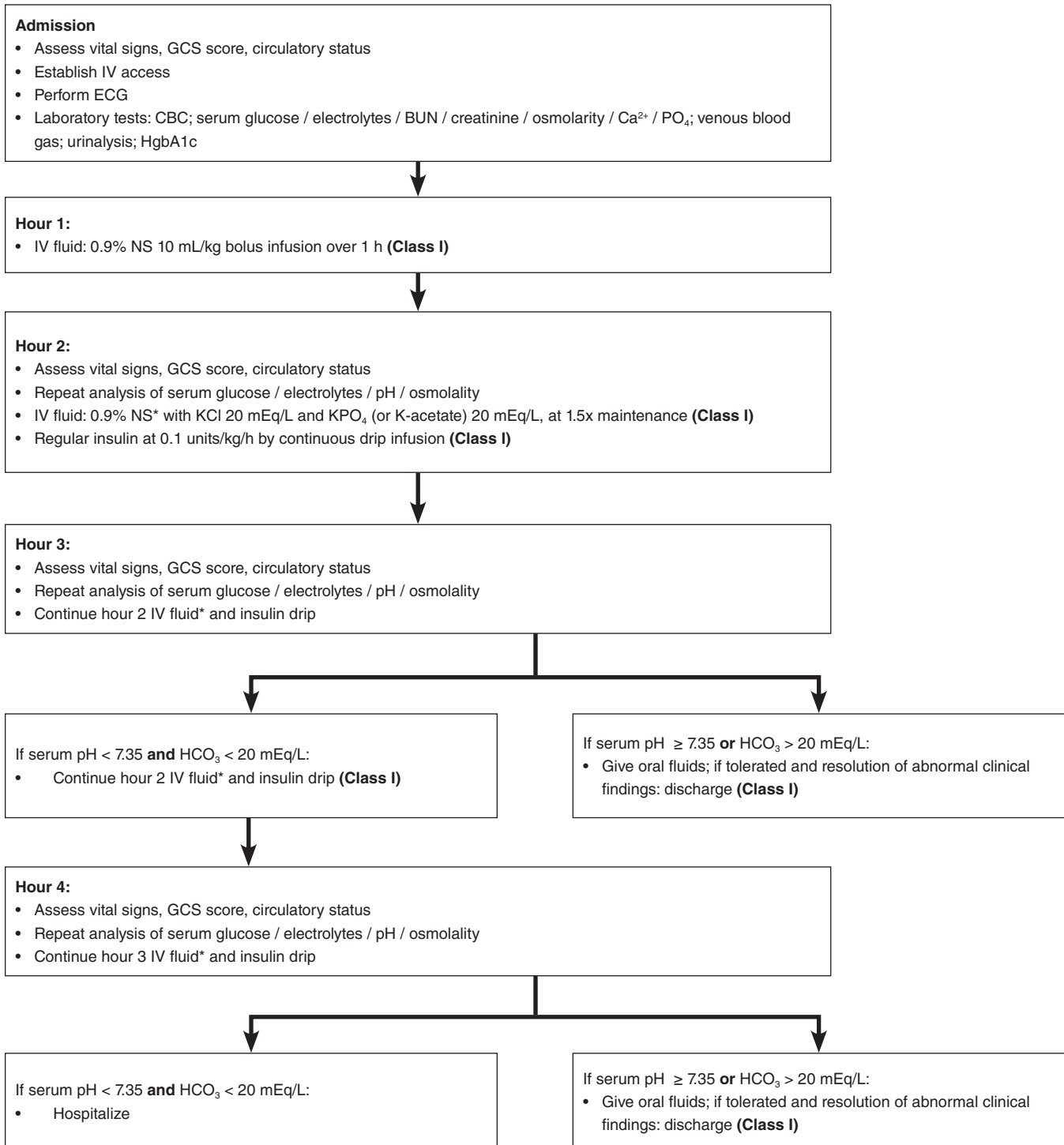
development of this disorder are poorly understood. There is evidence to suggest that various aspects of DKA therapy may contribute to its development. Magnetic resonance imaging (MRI) findings suggest that DKA-related cerebral edema is vasogenic (disrupted blood-brain barrier), not cytotoxic.⁴⁵ A long-standing theory involves the interplay between central nervous system hyperosmolarity and therapeutic fluid resuscitation in the susceptible patient. During treatment, serum hyperosmolarity may decrease more rapidly than in the central

Table 2. Potential Complications Of Diabetic Ketoacidosis

- Cerebral edema
 - < 1% of cases
 - Risk factors: younger age (< 5 years), severe acidosis, hypocapnia, greater degree of elevated serum BUN
 - Associated with rapid rehydration or with overly aggressive rehydration or correction of acidosis/hyperglycemia
 - Treatment: mannitol, 0.25-1 g/kg IV; 3% hypertonic saline, 5-10 mL/kg IV; consider intubation with hyperventilation, if respiratory insufficiency
- Hypoglycemia
 - Due to insufficient serum glucose for insulin administered
 - Treatment: add 5%-10% dextrose to IV fluids when serum glucose level is 250-300 mg/dL
- Hypokalemia
 - Due to renal losses
 - Exacerbated with resolution of dehydration and acidosis
 - Treatment: add potassium to IV fluids when urine output is established
- Cardiac dysrhythmia
 - Due to hyperkalemia, hypokalemia, or hypocalcemia
 - Treatment: correct specific imbalance
- Pulmonary edema / acute respiratory distress syndrome
 - Due to increased pulmonary capillary permeability
 - Treatment: administer oxygen and a diuretic
- Pancreatitis
 - Typically subclinical (may be due to hypertonicity or hypoperfusion)
 - Consider measuring amylase/lipase
- Rhabdomyolysis
 - Due to muscle proteolysis
 - Measure serum creatine phosphokinase
 - Treatment: hydration and alkalization of the urine
- Thromboembolism
 - Enhanced by subclinical endothelial injury, hypofibrinolysis, and platelet aggregation as well as elevated levels of procoagulant factors
- Acute renal failure

Abbreviations: BUN, blood urea nitrogen; IV, intravenous.

Clinical Pathway For The Outpatient Management Of Pediatric Diabetic Ketoacidosis



*Add D5 if serum glucose concentration declines to 250-300 mg/dL **(Class I)**.

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; D5, 5% dextrose; ECG, electrocardiogram; GCS, Glasgow Coma Scale; HCO₃, bicarbonate; IV, intravenous; KCl, potassium chloride; KPO₄, potassium phosphate; NS, normal saline.

For class of evidence definitions, see page 9.

nervous system, resulting in intracranial fluid shifts and cerebral edema. Evidence from clinical studies, however, suggests that this mechanism may not play a central role; various case reports have documented DKA-induced symptomatic (and even fatal) cerebral edema in patients prior to receiving therapy.⁴⁶⁻⁴⁹

Another postulated mechanism for DKA-related cerebral edema involves acidosis-activated cell membrane sodium-hydrogen (Na^+/H^+). The high H^+ concentration promotes intracellular Na^+ and water influx, with consequent edema.^{50,51} Additionally, the ketone bodies beta-hydroxybutyrate and acetoacetate may affect vascular permeability and contribute to edema formation.⁵²

Up to 40% of initial brain imaging studies in children with DKA and cerebral edema are normal.⁵³ Therefore, cerebral edema complicating DKA is a clinical diagnosis, and its presumptive diagnosis should be based on clinical assessment. Signs and symptoms of DKA-related cerebral edema include:

- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posturing
- Cranial nerve palsy (especially cranial nerves III, IV, and VI)
- Abnormal neurogenic respiratory pattern (eg, grunting, tachypnea, Cheyne-Stokes respiration, apneusis)
- Altered mentation/fluctuating level of consciousness
- Bradycardia
- Vomiting
- Headache
- Hypertension

If clinically indicated, therapy to decrease intracranial pressure should commence prior to confirmatory imaging. Decrease the IV fluid infusion rate by 30% and immediately infuse mannitol 0.25 to 1 g/kg IV over 20 minutes; give a repeat dose if there is an inadequate response. If 2 doses of manni-

tol are ineffective, consider 3% hypertonic saline 5 to 10 mL/kg IV infused over 30 minutes. With respiratory insufficiency requiring intubation, aggressive hyperventilation should be avoided, as it has been associated with worse outcomes. Cranial CT imaging for suspected cerebral edema is recommended to confirm the diagnosis and to rule out other etiologies of DKA-induced altered mental status (such as central nervous system thromboses or hemorrhage).

Monitoring Progress

Efficacy of DKA therapy is monitored by following hourly trends in vital signs, fluid balance, neurologic status (via GCS scores), and serum glucose/acid-base/electrolyte balances. Inhibition of ketogenesis, essential to resolving DKA, is reflected by decreasing serum glucose and increasing serum pH/ HCO_3^- levels and a narrowing of the anion gap. It is important to note that resolving hyperglycemia alone does not denote resolution of DKA; there must be a concomitant resolution of metabolic acidosis to signify cessation of ketogenesis. For this to occur, adequate insulin and glucose must be administered to arrest lipolysis and ketogenesis and decrease levels of counterregulatory (stress) hormones.

Controversies And Cutting Edge

Rate Of Insulin Administration

A recent study compared lower-dose (0.05 units/kg/h) IV insulin infusion with standard-dose (0.1 units/kg/h) IV insulin infusion for the initial treatment of diabetic ketoacidosis in children with insulin-dependent diabetes mellitus and noted equivalent efficacy.⁵⁴ A possible advantage to lower-dose infusion is a more gradual decline in hyperglycemia and, therefore, of serum osmolarity, which could potentially lower the risk for cerebral edema. Further study of this issue is necessary before any

Class Of Evidence Definitions

Each action in the clinical pathways section of *Pediatric Emergency Medicine Practice* receives a score based on the following definitions.

Class I

- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:

- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II

- Safe, acceptable
- Probably useful

Level of Evidence:

- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III

- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:

- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate

- Continuing area of research
- No recommendations until further research

Level of Evidence:

- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and represen-

tatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA*. 1992;268(16):2289-2295.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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Risk Management Pitfalls For Pediatric Diabetic Ketoacidosis

- 1. “The patient didn’t appear to be severely dehydrated, so I waited to see if she could tolerate oral liquids.”**
Patients in moderate or severe DKA should be assumed to be 7% to 10% dehydrated, and although rehydration should proceed at a carefully calibrated, gradual pace, there should be no delay in administering IV fluid therapy.
- 2. “The patient was tachycardic, so I gave several boluses of NS.”**
The risk for cerebral edema increases with overly aggressive fluid supplementation (ie, volume and rate of administration). If the blood pressure is normal and peripheral perfusion is adequate, conservative rehydration is preferred.
- 3. “I wasn’t sure if the patient’s lethargy, tachypnea, and vomiting were due to increased intracranial pressure, so I delayed giving mannitol until performing a head CT.”**
DKA-related cerebral edema is a clinical diagnosis, and therapy to reduce intracranial pressure should commence prior to confirmatory imaging.
- 4. “The serum potassium concentration was 4.2 mEq/L on admission, so I withheld potassium supplement during hour 2.”**
Total body stores of potassium are depleted with DKA. Hypokalemia should be anticipated with initiation of insulin replacement and correction of acidosis; therefore, potassium should be added to the IV fluids after the initial hour of rehydration.
- 5. “The patient had severe hyperglycemia, so I gave him a bolus of regular insulin during the initial hour of therapy.”**
A bolus of regular insulin during the first hour of therapy has been associated with increased risk for developing cerebral edema. Insulin should never be bolused and should not be administered prior to the second hour after NS rehydration. Hydration alone will cause the plasma glucose concentration to decrease rapidly.
- 6. “Why should I do an ECG if I’m measuring the serum potassium on admission?”**
The ECG is a reflection of the intracellular potassium level (which is distinct from the extracellular serum concentration [measured]) and can show signs of intracellular potassium deficiency when the measured serum potassium concentration is normal.
- 7. “The blood glucose was dropping below 200 mg/dL, so I decreased the insulin infusion.”**
The insulin infusion should never be decreased for falling glucose levels; rather, the amount of glucose infused should be increased by providing 10% dextrose solution so as to continue inhibition of ketogenesis and prevent hypoglycemia.
- 8. “During transport to CT, I turned off the insulin infusion until we returned to the ED.”**
The insulin infusion should never be discontinued; the half-life of insulin in the serum is only 6 minutes.
- 9. “The admission serum glucose was 828 mg/dL and the serum pH was 7.34, so I started the DKA protocol.”**
DKA is present only if there is metabolic acidosis.
- 10. “The patient has type 2 insulin-resistant diabetes and therefore cannot have DKA.”**
DKA is not uncommon with type 2 diabetes; up to 25% of patients with new-onset type 2 diabetes can present in DKA.

recommendations deviating from standard insulin therapy are entertained.

Rate Of Rehydration

A recent study compared 2 different rehydration protocols in children with DKA in order to assess the risk for associated MRI-documented subclinical cerebral edema.⁵⁵ Of a total of 18 patients, 8 received more-rapid IV hydration (assumed 10% dehydration; 20 mL/kg initial 0.9% NS IV bolus infusion, 2/3 of fluid deficit replaced over initial 24 h, and urine output volume replacement) versus 10 who received slower IV hydration (assumed 7% dehydration; 10 mL/kg initial 0.9% NS IV bolus infusion, fluid deficit evenly replaced over initial 48 h, and no urine output replacement). There was no significant difference in rates of MRI changes consistent with subclinical cerebral edema between the groups.

Special Circumstances

Patient demographics that identify greater risk for DKA-related cerebral edema include younger patient age; prolonged symptoms; and presenting laboratory profile with: (1) a greater degree of acidosis; (2) a greater elevation in BUN; (3) a greater degree of hypocapnia; and (4) a blunted rise in serum sodium concentration with ongoing therapy. If any of these factors is present, special attention to monitoring and gradual therapy to correct DKA is especially important.

Hospital Management And Disposition

The hospitalized child with DKA requiring an insulin drip infusion should receive initial care in an intensive care unit setting with experienced nursing staff trained in DKA monitoring and management. Written guidelines for DKA management should be followed to safeguard against error. Frequent and timely evaluation of biochemical trends is essential. A pediatric endocrinologist should be consulted to help guide management and monitor for complications.

Outpatient Management

The outpatient management of mild DKA⁵⁶ outlined in the **Clinical Pathway (page 8)** employs all of the previously mentioned therapeutic measures for restoring glucose homeostasis and intermediary metabolism to a normal state. With this approach, patients receive standard therapeutic measures and close monitoring for up to 3 hours in an outpatient setting. Based on the average deficits accrued by patients with DKA, approximately one-third of the fluid deficit and one-half of the sodium deficit are replenished during this therapeutic interval. With this method of "abbreviated" DKA treatment, more than 90% of selected

patients will experience resolution of metabolic acidosis and hyperglycemia.

Metabolic parameters on admission accurately predict the outcome of patients with DKA during the initial 3 hours of therapy. A study of 63 consecutive children presenting to an ED with DKA found the following results⁵⁶:

1. Of the patients with admission serum pH > 7.2 or HCO₃ > 10 mEq/L, 94% experienced resolution of metabolic acidosis and hyperglycemia within 3 hours of initiating therapy, tolerated oral feeding, and were discharged from the outpatient setting. The rate of DKA relapse or other complication within 48 hours of discharge was only 3%.
2. By contrast, of the patients with admission serum pH < 7.2 and HCO₃ < 10 mEq/L, 92% had persistence of metabolic acidosis after 3 hours of therapy, necessitating hospitalization for further treatment. The rate of DKA relapse or other complication within 48 hours of discharge from the hospital was 4%, similar to those treated as outpatients.
3. Of those patients with initial serum pH > 7.2 or HCO₃ > 10 mEq/L who were successfully treated as outpatients, the admission serum glucose concentration was predictive of the duration of therapy necessary to resolve metabolic acidosis; 83% with serum glucose < 500 mg/dL required 2 hours of therapy, whereas 78% of patients with a serum glucose > 500 mg/dL required 3 hours of therapy. The longer duration of therapy associated with more marked hyperglycemia may reflect a greater degree of dehydration, thus necessitating more prolonged fluid repletion to restore glomerular filtration.

Summary

The goals of treating children with DKA are to: (1) provide rehydration to restore perfusion and increase glomerular filtration; (2) replace mineral and electrolyte deficiencies and provide insulin to arrest ketogenesis and gluconeogenesis; and (3) increase cellular glucose metabolism in insulin-dependent peripheral tissues. The key to effective management of pediatric DKA includes accurate diagnosis, timely therapy, and gradual correction guided by meticulous monitoring. Children with mild DKA can be safely and effectively managed with 2 to 3 hours of therapy administered in an outpatient setting, resulting in discharge with little risk of relapse or other complication provided they have parental support and stable home situations. The metabolic parameters of acid-base status on admission are accurate in distinguishing those children with DKA who are candidates for outpatient management.

Case Conclusion

The patient presented with classic signs of diabetes mellitus with DKA. The history of polyuria and polydipsia with weight loss was consistent with chronic hyperglycemia and glucosuria. Assessment of hydration status showed 5% to 7% dehydration with tachycardia, delayed capillary refill time, and dry oral mucosa. Metabolic acidosis was indicated by tachypnea. Although clinically consistent, lab confirmation was necessary to confirm the diagnosis of DKA (as distinct from a nonketotic hyperglycemia). In this case, all 3 criteria (hyperglycemia and metabolic acidosis with ketonuria) were present. You gave the child an infusion of NS 10 mL/kg IV during the first hour of therapy, and her hydration improved. The patient voided, and her serum potassium level was measured at 5.2 mEq/L. In the second hour of therapy, you added potassium to the IV fluids and initiated a continuous IV insulin infusion. After 4 hours of therapy, the venous pH was 7.32, the serum HCO₃ was 19 mEq/L, and the serum glucose concentration had declined to 275 mg/dL. Subsequent IV fluids included 5% dextrose, and her GCS score was 15. The patient made an unremarkable recovery, eventually tolerated oral feedings, and was discharged home after she and her family received appropriate diabetes management instructions.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study will be included in bold type following the references, where available. The most informative references cited in this paper, as determined by the author, will be noted by an asterisk (*) next to the number of the reference.

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CME Questions



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- The definition of DKA includes all of the following EXCEPT:**
 - Hyperglycemia
 - Serum pH < 7.30
 - Anemia
 - Ketonuria
- Patients with moderate or severe DKA can be assumed to be:**
 - In renal failure
 - At high risk for sepsis
 - At risk for retinal detachment
 - 7% to 10% dehydrated
- With DKA, total body concentration of all of the following are depleted EXCEPT:**
 - Sodium
 - Potassium
 - Albumin
 - Phosphate
- Efficacy of DKA therapy is measured by hourly assessment of:**
 - Serum pH
 - Serum HCO₃ concentration
 - Serum glucose level
 - All of the above
- During the first hour of DKA therapy, patients should receive:**
 - Insulin replacement
 - NS infusion
 - Potassium supplementation
 - HCO₃ supplementation
- Cerebral edema can occur during therapy for DKA:**
 - With a mortality rate up to 25%
 - Only after 12 hours of IV fluid administration
 - After antibiotic administration
 - More commonly when the patient has a fever
- Cerebral edema during DKA therapy is associated with all of the following EXCEPT:**
 - NaHCO₃ administration
 - Hypocapnia
 - Elevated serum BUN
 - Obesity
- Criteria for ED discharge of a patient with DKA includes all of the following EXCEPT:**
 - Normal ECG
 - Serum HCO₃ > 20 mEq/L
 - Tolerating oral intake
 - Serum pH > 7.30
- All of the following statements are true regarding the initial presentation of children with type 1 diabetes EXCEPT:**
 - In the United States, approximately 25% are in DKA
 - DKA presentation is most common in younger-aged children
 - 30% to 40% had a healthcare visit within a week of insulin-dependent diabetes mellitus presentation with DKA
 - 15% experience cerebral herniation
- Which of these hormones is increased in DKA?**
 - Histamine
 - Insulin
 - Thyroxine
 - Glucagon

Coming Soon In

Pediatric Emergency Medicine Practice

Acute Otitis Media: An Evidence-Based Update

AUTHORS:

MARGARET POWERS, MD

Allegheny General Hospital; Temple School of Medicine, Pittsburgh, PA

CHADD E. NESBIT, MD, PHD, FACEP

Allegheny General Hospital; Temple School of Medicine, Pittsburgh, PA

Acute otitis media is one of the most common pediatric illnesses. However, there has been considerable controversy in its management. While most cases are treated with antibiotics, there is a growing concern regarding antibiotic overuse and subsequent drug resistance. Researchers in the Netherlands have developed a “wait and see” approach that has been successful in treating acute otitis media, although it has not gained much popularity in the United States. This issue of *Pediatric Emergency Medicine Practice* will summarize the latest research on the diagnosis of acute otitis media and on the different treatment regimens, including the efficacy of a “wait and see” approach.

Management Of Acute Asthma In The Pediatric Patient: An Evidence- Based Review

AUTHORS:

BRITTANY P. JONES, MD

Clinical Fellow, Pediatric Emergency Medicine, Mount Sinai School of Medicine, New York, NY

AUDREY PAUL, MD, PhD

Assistant Professor of Emergency Medicine, Mount Sinai School of Medicine, New York, NY

According to data from the Centers for Disease Control and Prevention, 1 of 11 children in the United States has asthma and 1 of 5 children with asthma presented to the emergency department for asthma-related care in 2009. It is the most frequent cause of hospitalization in children, and it costs the nation billions of dollars annually. The symptoms of asthma can vary widely from mild shortness of breath to fatal status asthmaticus. Timely and targeted intervention during an acute exacerbation can significantly improve morbidity and mortality. Given the high prevalence of asthma and its potential to progress from mild to moderate to life-threatening, it is vital for emergency clinicians to have an understanding of the management of acute asthma exacerbations. This issue of *Pediatric Emergency Medicine Practice* reviews the timely and aggressive use of inhaled beta agonists and systemic corticosteroids (the foundation of acute asthma treatment for most children) as well as several adjunct therapies including magnesium, terbutaline, epinephrine, and heliox. In addition, emergency department treatments for more severe exacerbations and airway management are examined.



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AOA Accreditation: *Pediatric Emergency Medicine Practice* is eligible for up to 48 American Osteopathic Association Category 2A or 2B credit hours per year.

Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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Direct all questions to:

EB Medicine

Phone: 1-800-249-5770 or 678-366-7933

Fax: 1-770-500-1316

5550 Triangle Parkway, Suite 150
Norcross, GA 30092

E-mail: ebm@ebmedicine.net
Website: EBMedicine.net

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