

Diabetic Ketoacidosis

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AN 18-YEAR-OLD PATIENT presented with complaints of shortness of breath, chest and upper abdominal pain, and nausea. The patient first experienced nausea and emesis the previous evening, then had shortness of breath and chest pain in the morning.

The patient noted no polydipsia or polyuria. The youth, who recently moved to the area, had no health care practitioner and had a history of asthma and type 1 diabetes. He takes ultralente insulin mixed with sliding scale regular insulin before dinner and lunch. His past medical history was otherwise unremarkable.

According to the patient and his father, the patient checks his blood glucose level at least once daily. They report blood glucose in the 180 to 200 mg/dL range, which they believe indicates good control. The patient had not taken his insulin that morning.

Physical examination demonstrated a thin, pale, anxious young man. Respiratory rate was 28; blood pressure was 130/64 mm Hg; heart rate, 100 beats per minute; temperature, 98.8°F; and pulse oximetry, 97%. Head, eye, ear, nose, and throat examination demonstrated mild erythema of the tympanic membranes and oropharynx, with dryness of the nasal mucosa and oropharynx.

The patient's neck was supple without adenopathy and his chest was clear to auscultation. Chest and abdomen appeared unremarkable, but tenderness was noted diffusely over the chest. Abdomen was soft and nontender; bowel sounds were present in 2 of 4 quadrants.

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Laboratory findings showed a blood glucose level of 333 mg/dL. A complete blood count with differential showed an elevated white blood cell (WBC) count of 15,300 mm³/μL. (normal range, 4,000 to 10,600 mm³/μL.) Electrocardiogram (ECG) showed sinus tachycardia at 116 beats per minute and rightward axis with pulmonary disease pattern. Electrolytes were 333 mmol/L indicating hyponatremia (normal range, 136 to 146 mmol/L). CO₂ was decreased (less than 5 mmol/L; (normal range, 25 to 35 mmol/L). The anion gap was 28. Alkaline phosphatase, amylase, and serum glutamic-oxaloacetic transaminase (SGOT) were within normal limits.

Arterial blood gases showed pH at 6.90, indicating acidemia (normal range, 7.35 to 7.45), Pco₂ at 6 (normal, 35 to 45 mm Hg), Po₂ at 145 (normal, 70 to 90 mm Hg), bicarbonate at 1 mEq/L (normal, 22 to 28 mEq/L), and serum acetone was small (1+).

DISCUSSION

Diabetic ketoacidosis (DKA) is a life-threatening condition that can occur when there is a complete lack of insulin, as in type 1 (insulin-dependent) diabetes, or inadequate insulin levels associated with stress or severe illness in either type 1 or type 2 (non-insulin-dependent) diabetes.¹⁻⁴ DKA was originally described by Dreschfeld in 1886; until insulin was discovered in 1922, the mortality rate of this illness was almost 100%. Diabetes mortality for both types remains at 1% to 2%.⁵ Between 20% and 30% of cases occur in patients with newly diagnosed diabetes.¹

Most deaths occur from intercerebral complications relating to cerebral edema. This sequelae of DKA can-

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not be predicted with certainty for any given patient.⁵⁻⁶ Other complications associated with DKA are adult respiratory distress syndrome (ARDS) and hyperchloremic acidosis.

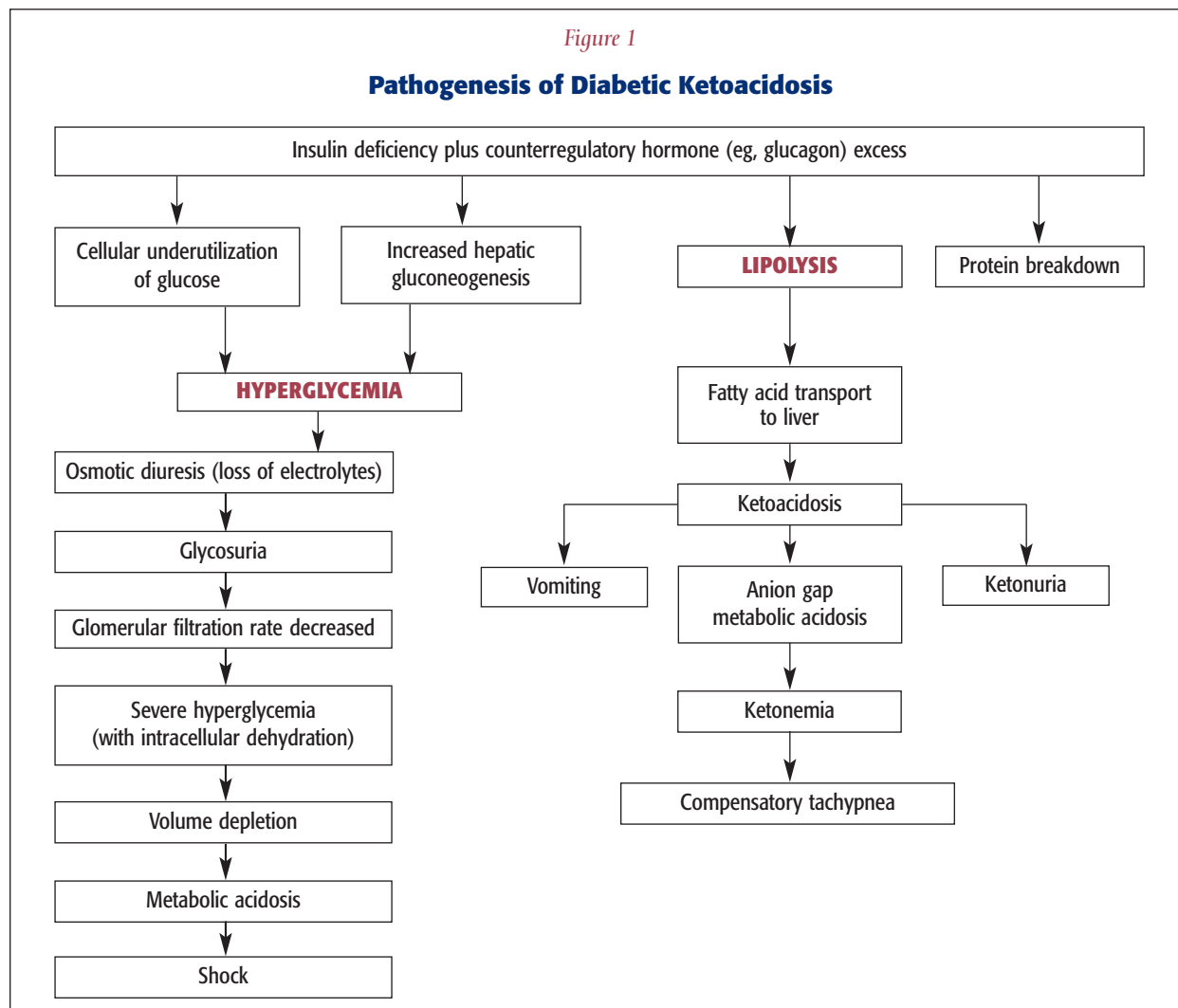
The incidence of DKA is 0.2 per patient year with type 1 diabetes. Diabetic ketoacidosis tends to be more common in younger patients⁷ and is still the major cause of death in children with diabetes.

ETIOLOGY AND DIAGNOSIS

DKA results from severe alterations in the metabolism of carbohydrates, protein, and lipids. It is the result of

two processes: hyperglycemia and lipolysis^{1,2,6} (see Figure 1). With inadequate insulin levels, hyperglycemia results in part because of decreased glucose uptake by muscle, fat, and the liver. Excess counterregulatory hormones (glucagon, catecholamines, growth hormone, glucocorticoids) also play a role. The liver specifically initiates gluconeogenesis (the creation of glucose from protein precursors) because increased glucagon and decreased insulin levels are present. Glycogen stores are also broken down by the liver via glycogenolysis, thereby producing glucose.

Lipolysis, the breakdown of triglycerides into gly-



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erol and free fatty acids, is promoted by counterregulatory hormones, including catecholamines and inadequate or absent insulin levels.² Thus, free fatty acids in glycerol cannot be shunted into the tricarboxylic acid (Krebs cycle) through insulin. Instead, free fatty acids are shunted by mitochondria to form ketone bodies. This shunting, potentiated by high glucagon levels, occurs because malonyl coenzyme A levels decrease and carnitine O-palmitoyltransferase levels increase in the absence of insulin,⁶ resulting in ketonemia.

Low insulin levels decrease the ability of the brain and the skeletal and cardiac muscles to use ketones as energy, further increasing ketonemia. Because these ketones cannot be used, the endogenous bicarbonate needed to prevent acidosis is not generated.

In such cases, the patient has both hyperglycemia and a level of ketonemia. The hyperglycemia primarily results from increased gluconeogenesis, and ketonemia primarily results from excessive catecholamines. Both processes make insulin-sensitive tissues (muscle, fat, and liver) convert from carbohydrate to fat metabolizing.⁶

This process promotes polyuria, polydipsia, and polyphagia with progressive loss of fluid and electrolytes leading to dehydration. The excessive fluid loss causing dehydration occurs via osmotic diuresis from excessive glucosuria. This fluid loss causes sodium and potassium to be excreted in large amounts, accompanied by severe water loss.^{2,6} Although generated ketoacids are buffered by cellular and extracellular buffers, metabolic acidosis results. Glucagon excess and insulin deficit bring about increased proteolysis, with the free amino acid serving as a substrate for gluconeogenesis.^{2,6}

Many things cause DKA, including gastroenteritis, stress, infections, and missed insulin injections. The factors that precipitate DKA in adults differ from those in children and adolescents.⁷ The common precipitating factors in children and adolescents are emotional stress, infections, and, to a lesser extent, missed injections. In adolescents, underdosing insulin, overeating, and drinking too much alcohol are also common causes for DKA.^{5,7}

Interestingly, a specific phenomenon can be seen with diabetic patients who are in families having a

medically trained family member where ongoing DKA is denied and a marked delay in diagnosis occurs.⁵ Mecklenburg and associates reported an increased incidence of DKA in individuals who changed from conventional insulin therapy to an insulin pump.⁸ These authors found that patients who remained on insulin pumps had a higher rate of DKA than those who remained on conventional insulin therapy.

These findings were similar to those of the Diabetes Control and Complications Trial Research Group.⁹ Patient education is essential in preventing DKA, and both studies found that the level of patient education relates to DKA occurrences.^{8,9}

DIABETIC KETOACIDOSIS IN PREGNANCY

Pregnant patients with diabetes are at special risk for DKA due to their increased insulin resistance and accelerated ketosis.¹⁰ Infection also plays a major role.

Factors in nonpregnant individuals include emesis, insulin deficiency, stress, and dehydration. Drugs, such as beta sympathomimetic agents and steroids, can also precipitate DKA.⁵

DKA does not occur as often in women who develop gestational diabetes mellitus as in women who were already diabetic when they became pregnant.¹⁰ Kilver and Nagy reported an overall incidence of 0.7% in 27 of 150 women with gestational diabetes complicated by DKA.¹⁰ This is in contrast with the 1993 study by Kilver and colleagues that reported an incidence of DKA in 1.73% of 635 women previously diagnosed with type 1 diabetes.¹⁰ The second study disclosed an overall fetal loss rate, including spontaneous abortion, of 22%.¹⁰ Although DKA incidence is low in both women with preexisting diabetes and those who develop gestational diabetes, clinicians should follow these patients closely.

Treatment of DKA during pregnancy is the same as DKA in nonpregnant patients. Slow but decisive blood glucose lowering is essential. Fetal heart rate monitoring in the pregnant patient with DKA can show late decelerations, indications of uteroplacental insufficiency. Decreased beat to beat variability is also noted, due in large part to maternal acidosis.

Effectively diagnosing DKA includes noting symptoms and laboratory values as well as a thorough history. Patients with DKA usually have a 12- to 24-hour history of polyuria, polydipsia, abdominal pain, nau-

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sea, and vomiting.^{1,3,4,6} Additionally, retrosternal or neck pain with dysphonia, dyspnea, or subcutaneous emphysema can occur.

Pneumomediastinum can occur due to alveolar rupture from hyperventilation or vomiting.⁵ Patients may experience “fruity” ketotic breath odor. Tachycardia and hypotension frequently result from dehydration, and patients may show deep Kussmaul’s respirations. Respiratory signs from ketoacidosis result from the respiratory system compensation for metabolic acidosis.^{1,5} Urinalysis will show glucosuria and ketonuria.

Interestingly, patients may not demonstrate marked hyperglycemia: Approximately 15% of patients with DKA present with serum glucose levels less than 350 mg/dL.⁸ Blood glucose levels of 250 mg/dL or higher, ketones in urine or serum, and metabolic acidosis with a calculated serum bicarbonate level of less than 15 mEq/L and pH below 7.3 confirm the diagnosis.^{1,3,6,11} Additionally, clinicians may find leukocytosis as high as 25,000 WBC/ μ L without a left shift when no associated infection is present.^{3,5,6}

DIFFERENTIAL DIAGNOSIS

In this case, the differential diagnosis included nonketotic hyperosmolar coma, lactic acidosis, acute pancreatitis, and hyperchloremic metabolic acidosis (see Table). Nonketotic hyperosmolar coma was also ruled

out in this case because, although similar to ketoacidosis, it occurs primarily in middle-aged to elderly patients.^{3,11} It is characterized by severe (greater than 600 mg/dL) hyperglycemia without significant ketosis, a blood pH above 7.3, a serum bicarbonate greater than 15 mEq/L, and a normal anion gap.^{3,11} Nonketotic hyperosmolar coma also causes dehydration because of hyperglycemia and this water loss contributes to any preexisting water loss from illness.

Lactic acidosis is similar to DKA because it also causes acidosis with dehydration. These patients show a decreased bicarbonate level and an increased anion gap. Lactic acidosis is distinguished from DKA by patient history, the absence of serum ketones, and presence of serum lactate (greater than 5 mmol/L).^{3,4,11} Clinicians can rule out lactic acidosis by obtaining a plasma lactic acid level. Lactic acidosis may occur in patients with cardiac decompensation, septicemia, respiratory or hepatic failure, and bowel or extremity infarction.^{3,11} Lactic acidosis became uncommon in patients with diabetes mellitus after phenformin use was decreased.

Hyperchloremic metabolic acidosis is distinguished from DKA by hyperchloremia and a normal anion gap.^{3,11} It is associated with bicarbonate loss secondary to diarrhea, pancreatic drainage, or defects in renal acidification.

Table

LABORATORY FINDINGS IN THE DIFFERENTIAL DIAGNOSIS OF DKA					
Laboratory Findings	Diabetic Ketoacidosis	Nonketotic Hyperosmolar Coma	Hyperchloremic Metabolic Acidosis	Lactic Acidosis	Acute Pancreatitis
Blood glucose	Elevated (mild to severe) >250 mg/dL	Severe elevation >600 mg/dL	Normal	Normal	Normal
Blood gases (pH, bicarbonate)	Decreased bicarbonate, pH decreased	Mildly decreased bicarbonate, pH >7.3	Decreased bicarbonate	Decreased bicarbonate, pH decreased	Normal
CBC	Elevated without left shift unless infection	Normal	Normal	Normal	Elevated
Electrolytes (Na ⁺ , K ⁺ , Cl ⁻ , phosphate)	Increased anion gap	Normal anion gap	Hyperchloremia, normal anion gap	Increased anion gap	Normal
Urine/serum ketones (acetone)	Frequently present	Absent	Absent	Absent	Absent
Chemistry (lactate, amylase, BUN, creatinine)	Increased BUN	Marked increased BUN and creatinine	Normal	Lactate present	Elevated amylase

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Acute pancreatitis was included in the differential diagnosis because of this patient's upper abdominal discomfort, nausea, vomiting, and elevated WBC count.^{4,11} Most patients with DKA present with a high WBC count without a shift to the left; however, the WBC count in DKA is seldom greater than 25,000/mm³ in the absence of bacterial infection. Bacterial infection causes the WBC count to rise to more than 25,000/mm³ with a left shift.⁶

TREATMENT

Despite a wealth of literature discussing recommended management, the optimal strategy for DKA is still controversial.¹² A study of pediatric patients with diabetes conducted by Glaser and colleagues reveals considerable variation in management strategies, which are determined largely by specialty training.¹² Areas of disagreement include the rate of replacement fluid deficits, content of intravenous fluids, the use of insulin bolus, and appropriate responses to glucose levels below the desired range. Despite this disagreement, clinicians can follow several basic principles when treating DKA (see Figure 2).

Resuscitation

As in any life-threatening illness, maintaining the patient's airway is primary. Clinicians should insert a nasogastric tube in patients with impaired consciousness. These patients may also need an oral airway. Although some patients may need intubation and ventilation, most are adequately managed with oxygen by facemask.

If a patient experiences shock, it is usually hypovolemic and must be corrected rapidly. Some authorities suggest colloid solutions because they stay within the intravascular space longer than crystalloid.⁶

Patients in shock should be given an infusion of 10 mL/kg to 25 mL/kg colloid solution, such as 4.5% albumin in a bolus, with the dose repeated until shock is corrected.^{5,7} Clinicians can titrate the total quantity needed against changes in tissue perfusion.

Fluid Replacement

Once shock is corrected, clinicians need to replace fluid rapidly to correct volume and electrolyte deficits and to suppress counterregulatory hormones.

Figure 2

Guidelines for the Treatment of DKA

Oxygen, nasogastric tube if consciousness impaired

- Intubation if necessary

Fluid hydration

- Crystalloid or colloid solutions of isotonic saline
- 20 mL/kg bolus in first 1 to 2 hours
- Calculated maintenance fluids plus any remaining fluid deficit plus ongoing losses

Insulin replacement

- 0.1 U/kg continuous infusion preferred; IM, IV bolus, or SQ
- 50-100 mg/dL per hour reduction in glucose
- Switch to D5 normal saline after glucose drops to 250-200 mg/dL

Potassium and bicarbonate

- Not usually needed
- May use if needed bicarbonate in bolus of 50-100 mEq in normal saline with 15 mEq potassium chloride added

Authorities disagree about the optimal initial fluid therapy, but most experts give 20 mL/kg of isotonic saline in the first 1 to 2 hours to restore extracellular fluid volume.⁶

The degree of dehydration can be assessed by calculating plasma osmolality using the formula: $mOsm/kg = 2(Na+K) + BUN/2.8 + glucose/18$ or plasma sodium concentration. Calculated plasma osmolality greater than 340 mOsm/kg and a plasma sodium level greater than 140 mEq/L are associated with the greatest fluid deficits.

Although dehydration can be calculated, one can generally assume 10% dehydration (100 mL/kg up to 15% in infants). Clinicians can use a variety of calculations to determine how much fluid will replenish ongoing fluid losses, but the usual method is 100 mL/kg for the first 10 kilograms of bodyweight, 50 mL/kg for the next 10 kilograms, and 20 mL/kg for any weight beyond 20 kilograms.

During the first hour of therapy, 20 mL/kg (in an adult, 1 to 2 liters of isotonic saline) is usually given rapidly to restore peripheral perfusion. The rate is then decreased, primarily to reduce the incidence of cere-

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bral edema and risk of respiratory distress syndrome.⁵ Replacing fluids in both intracellular and extracellular compartments in this manner effectively lowers blood glucose levels, BUN level, and potassium concentrations.⁶

Most clinicians agree that the calculated maintenance fluids plus the balance of fluid deficit can be replaced over 24 to 36 hours.^{5,7} Once patients receive this initial fluid, they can be switched to more hypotonic fluids, such as 0.45% sodium chloride, to avoid hypernatremia as fluid shifts in the intracellular and extracellular spaces. When serum glucose approaches 250 to 300 mg/dL, fluids should be changed to contain 5% dextrose, with the goal of maintaining glucose in this range and permitting gradual equilibrium of osmotically active substances across cell membranes.^{3,4}

Potassium Replacement

Because electrolytes shift in DKA, plasma potassium is usually falsely elevated. This occurs because insulin mediates potassium entrance into the intracellular compartment; if the insulin level is not adequate, potassium remains in the plasma. Clinicians may see hypokalemia when they subsequently assess potassium levels.

Volume expansion and osmotic diuresis also play roles. Some potassium replacement is necessary because significant hypokalemia development is potentially the most life-threatening electrolyte imbalance, predisposing patients to cardiac arrhythmias. Potassium administration is a debated topic, but most experts suggest adding 20 to 30 mEq/L potassium to the second liter of replacement fluids.⁵ Before initiating potassium replacement, clinicians should check that a potassium level is available and verify urine output to confirm renal function.

Researchers continue to debate whether to use potassium chloride alone or with potassium phosphate or potassium acetate.¹² This debate arises from the fear that hyperchloremia or hyperphosphatemia will develop. One strategy is using two thirds of potassium replacement in the potassium chloride form and one third as potassium phosphate.^{4,12}

The clinical goal is maintaining serum plasma levels within the normal range of 4 to 5 mEq/L, with an

infusion rate of 10 to 40 mEq/hour.^{3,4,10} Clinicians must assess serum potassium every 2 to 4 hours, followed by an ECG.

Glucose and Insulin Replacement

Insulin is critical in treating DKA. Clinicians can give regular insulin immediately or hold it until the replaced fluids and glucose levels are within normal range. The most widely used approach is 0.1 U/kg hourly as a continuous infusion with an insulin pump.⁵ Alternatively, give intravenous (IV), intramuscular, or subcutaneous (SC) injections of 0.1 U/kg after the initial dose.²⁻⁴

Frequent monitoring of glucose levels is a must. The insulin determination should be adjusted so that glucose measurements from bedside monitoring drop by 50 to 100 mg/dL an hour.¹ Even after blood glucose levels drop below 250 to 200 mg/dL, insulin may be maintained. Insulin is used preferably as infusion, but to avoid hypoglycemia, the IV fluid should be switched to 5% dextrose in normal saline. Evidence indicates that cerebral edema may occur if blood glucose is reduced too quickly.¹⁰

Once the patient is feeling better and is ready to eat, SC insulin is given 1 hour prior to discontinuance of IV insulin.

Bicarbonate Therapy

Most authorities do not recommend routine bicarbonate because no data support its benefits in DKA.^{4,6} Usually, the expansion of extracellular fluid volume from fluid replacement increases blood flow. Venous P_{CO_2} and tissue P_{CO_2} declines and hydrogen ion concentration in the cells falls. Hydrogen is released from intracellular proteins, and a normal net charge is frequently established.

In this patient's case, bicarbonate was used, although use of bicarbonate is optional.¹⁵ Bicarbonate use is generally limited to patients with severe acidemia and pH values less than 7.0 to 7.1.^{1,10} When needed, bicarbonate should be infused in small boluses (50 to 100 mEq) in isotonic solution with 15 mEq of potassium to maintain the pH at 7.0 or above.⁴ Clinicians must balance the risk of cardiac effects from a pH below 7.0 with the risk of a paradoxical drop of central nervous system pH and hypokalemia that may

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occur with excessive bicarbonate use.¹ Clinicians should consider consulting with a diabetologist or endocrinologist.

Other Therapeutic Concerns

Hypomagnesemia and hypocalcemia also occur in DKA. Magnesium and calcium usually return to normal levels once the patient is hydrated and resumes eating. Serum acetone tests, while helpful, can show false increases during recovery and give the false impression that ketosis is worsening. The nitroprusside reaction shows ketone bodies in serum and urine; however, this reaction does not demonstrate beta hydroxybutyrate, but does show acetone weakly and acetoacetate strongly.

During clinical improvement of DKA, clinicians may see a shift from the more acidic beta hydroxybutyrate to the less acidic acetoacetate or acetone bodies. Thus, measured ketone levels can increase although the patient is recovering.

Clinicians need to know the potential complications of DKA. Deep vein thrombosis and pulmonary embolism are infrequent but do occur in patients with prolonged immobility or increased hemoconcentration. Congestive heart failure can develop if too much fluid is administered. Cerebral edema is an extremely serious, although relatively unusual, complication that occurs more in children than in adults.^{1,7} The clinician should assess the patient frequently and look for signs of increased intracranial pressure. Judicious isotonic fluids and decreasing blood glucose levels gradually will reduce the risk of this complication. A combination of acidotic state, hyperventilation, and possibly large volumes of hypotonic fluid can cause adult respiratory distress syndrome.¹

In pregnant patients with DKA, clinicians should monitor the fetus during the mother's treatment.

Administering maternal oxygen, placing the mother in the recumbent position, and slowly reducing blood glucose all improve the condition of the fetus.

CONCLUSION

In this case, the patient was admitted to the intensive care unit and administered IV regular insulin, 8 units/hour. Given fluids and bicarbonate concurrently with the insulin, he was alert, comfortable, and eating within 24 hours. Hemoglobin A_{1c} performed at admission showed an elevated value of 16.7% (normal range, 4.8% to 7.8%). Because this patient had issues with long-term glycemic control, a follow-up was scheduled with an endocrinologist on discharge. The patient also received diabetic education while in the unit. ●

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