### Objectives

1. Describe the epidemiology, clinical features, and emergency management of diabetes mellitus (DM), adrenal insufficiency, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), water intoxication, and diabetes insipidus (DI).

2. Describe the fluid and electrolyte problems associated with these conditions.

3. Discuss the clinical features and emergency management of metabolic diseases of the newborn and young child.

### Chapter Outline

- Introduction
- Diabetic Ketoacidosis
- Hypoglycemia in Children With Diabetes
- Hypoglycemia in Nondiabetic Children
- Adrenal Insufficiency/Congenital Adrenal Hyperplasia
- Diabetes Insipidus
- Syndrome of Inappropriate Secretion of Antidiuretic Hormone
- Water Intoxication
- Metabolic Disease of the Newborn and Young Child: Inborn Errors of Metabolism
CASE SCENARIO

A 10-year-old boy presents to the emergency department (ED) with altered mental status and a 2-week history of polyuria and weight loss. He is experiencing abdominal pain. On examination, he has a respiratory rate of 36/min, a heart rate of 150/min, a systolic blood pressure of 80 mm Hg, and a temperature of 37.9°C (100.2°F). Pulse oximetry oxygen saturation is 97% on room air. On examination, he appears lethargic, has dry mucous membranes, has normal abdominal examination results, and has a nonfocal neurologic examination results. Bedside rapid glucose measurement is above the upper limit of the glucose meter (>500 mg/dL).

1. What therapeutic actions must be taken immediately?
2. What laboratory tests would you order?
3. What is the most important potential complication?

Introduction

The emergency management of endocrine and metabolic disorders presents diagnostic and therapeutic challenges. Many of these disorders, such as congenital adrenal hyperplasia (CAH) and inborn errors of metabolism, occur relatively infrequently. Nonetheless, rapid and appropriate intervention is necessary to prevent complications. Awareness of key clinical and laboratory findings that differentiate endocrine and metabolic disorders from other entities with similar presenting features is essential.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is the most important complication of type 1 DM (Figure 16.1). Diabetic ketoacidosis occurs when insulin concentrations are low relative to the concentrations of counterregulatory hormones, particularly glucagon. This imbalance results in hyperglycemia along with the breakdown of fat to form ketone bodies, eventually resulting in acidosis. Diabetic ketoacidosis occurs in 25% to 40% of children with new onset of type 1 diabetes mellitus (DM).1–3 Repeat episodes of DKA in children...
Clinical Features

Diabetic ketoacidosis is characterized by hyperglycemia and elevated serum ketone concentrations, resulting in acidosis. Inadequate insulin concentrations allow the partial oxidation of fatty acids to form ketone bodies. This process then results in acidosis with an increased anion gap. Hyperglycemia results in osmotic diuresis with polyuria, polydipsia, and eventual dehydration. Presenting features of DKA include a history of polyuria, polydipsia, nausea, and vomiting. Abdominal pain and intestinal ileus are common features and can mimic an acute abdomen. In a patient with clinical signs of dehydration, the presence of polyuria helps differentiate DKA from gastroenteritis and other causes of dehydration. Acidosis results in compensatory tachypnea, and a characteristic fruity (acetone) breath odor can often be detected. Because the hyperosmolar state allows for the relative preservation of intravascular volume, some signs of dehydration can be less obvious than in dehydrated patients with more normal serum osmolality. Alterations in mental status can range from disorientation to depressed consciousness. This alteration of mental status can

![Figure 16.1 Diabetic ketoacidosis.](image)

be due to acidosis and dehydration but can also reflect more serious underlying intracranial disease. Rarely, children with DKA present to the ED with clinically apparent cerebral edema, as well as cerebral infarctions or thromboses.

**Complications**

The most frequent complications of DKA treatment include hypokalemia and hypoglycemia. Hypocalcemia, hypophosphatemia, and hypomagnesemia can also occur but are much less common. Of the more serious complications of DKA, clinically apparent cerebral edema is the most frequent, occurring in approximately 1% of DKA episodes. Cerebral edema is the most important diabetes-related cause of mortality in children with type 1 DM.

Although cerebral edema can occur before hospital treatment of DKA, this complication more typically occurs several hours after initiation of therapy. The clinical presentation of cerebral edema can take different forms. Typically, patients with cerebral edema experience headache and exhibit alterations in mental status. Obitudnation, papilledema, pupillary dilation or anisocoria, blood pressure variability, bradycardia, and apnea can also occur in severe cases.

Deep venous thromboses can occur in children with DKA, particularly when central venous catheters are used. Other complications of DKA are rare but include cerebral infarctions or thrombosis, acute renal tubular necrosis leading to renal failure, pulmonary edema, pulmonary embolus, arrhythmia, pancreatitis, and intestinal necrosis.

**Diagnostic Studies**

Diabetic ketoacidosis is defined as hyperglycemia (serum glucose concentration >200 mg/dL), acidosis (venous pH <7.25 or serum bicarbonate concentration <15 mEq/L), and the presence of ketones in the serum or urine. Electrolyte abnormalities also occur as a result of urinary losses and shifts due to acidosis. High serum concentrations of potassium are often found at the time of presentation of DKA, but normal or low concentrations can occur if the ketoacidotic state is prolonged. Intracellular potassium concentrations are characteristically depleted, as are total body concentrations of sodium, phosphate, calcium, and magnesium. Although total body sodium is depleted, the degree of depletion is less than that suggested by the measured serum sodium concentration, which is artificially depressed due to hyperglycemia. Blood urea nitrogen (BUN) concentrations are usually elevated due to prerenal azotemia. The white blood cell count is often elevated and frequently left-shifted as a result of the ketoacidotic state alone. It is generally unnecessary to search for a source of infection beyond performing a careful physical examination unless fever or other specific signs of infection are present.

**Differential Diagnosis**

The presenting symptoms and signs of DKA can initially be confused with gastroenteritis or other gastrointestinal disorders that present with vomiting and abdominal pain. Infections such as pneumonia, meningitis, and urinary tract infections also can present with metabolic acidosis, tachypnea, and altered mental status or can be a cause of the development of DKA. The history of polyuria despite clinical dehydration, absence of diarrhea, and presence of tachypnea with fruity breath odor should differentiate DKA from these other entities even before laboratory tests are ordered. Diabetic ketoacidosis must also be differentiated from hyperglycemic hyperosmolar state (HHS) (formerly known as hyperglycemic hyperosmolar nonketotic coma), which presents with severe hyperglycemia (serum glucose concentration >600 mg/dL and often >1,000 mg/dL) and hyperosmolality (serum osmolality >330 mOsm), profound dehydration, and a depressed level of consciousness, but mild or no ketosis. Hyperglycemic hyperosmolar state can in fact represent
one extreme in a continuum of presentations of DKA and a mixed presentation with features of DKA and HHS can also occur. Although HHS is uncommon in children, recent reports suggest that the frequency might be rising. 13 Hyperglycemic hyperosmolar state occurs more frequently in patients with type 2 rather than type 1 diabetes and in children with neurologic abnormalities that lead to abnormal thirst mechanisms or limited access to liquids. The treatment approach for HHS differs from DKA. Discussion of HHS treatment is beyond the scope of this chapter but has been reviewed elsewhere. 10

Management
The fundamental treatment measures for DKA include replacement of fluid deficits, correction of acidosis and hyperglycemia via insulin administration, replacement of depleted electrolytes, and monitoring for complications.

Fluid Replacement
Optimal fluid management of DKA has been a subject of great controversy, mainly due to theoretical concerns about the role of fluid administration in contributing to cerebral edema. Available evidence, however, does not confirm a primary role for fluid administration in causing this complication. 9,11 The most compelling evidence suggests that children who present with low PaCO2 and high BUN concentration and those treated with bicarbonate are at higher risk for cerebral edema. 1 Appropriate restoration of perfusion and hemodynamic stability, therefore, should not be compromised by theoretical concerns associated with fluid administration.

The average degree of dehydration in children with DKA is approximately 7%. 12 The typical child with DKA should receive an initial fluid bolus of 10 mL/kg of isotonic fluid (ie, isonatremic fluids such as 0.9% saline [normal saline] or lactated Ringer’s solution) for 30 to 60 minutes. If there is evidence of poor perfusion or significant hypovolemia, 20 mL/kg can be used as the initial bolus. Greater administration of fluids is indicated if signs of shock are present. Isotonic fluid boluses can be repeated if necessary to restore perfusion. Once perfusion has been restored, the remaining fluid deficit plus maintenance fluids can be replaced during the next 36 to 48 hours using half normal (0.45% sodium chloride solution) to normal saline (0.9% sodium chloride solution). 6,7

Hyperglycemia
After the initial fluid bolus(es), insulin should be administered via continuous intravenous (IV) infusion at a dosage of 0.1 U/kg per hour. Maximal suppression of ketogenesis occurs rapidly using a continuous insulin infusion at this dosage and an initial IV bolus or “loading dose” of insulin is unnecessary. When serum glucose concentrations fall below 250 to 300 mg/dL during treatment, glucose should be added to the IV fluids to ensure that hypoglycemia does not occur. The insulin infusion rate generally should not be decreased until ketoacidosis resolves (pH >7.30 and bicarbonate >15). This will likely take roughly 10 to 24 hours to achieve, so the insulin infusion must often continue on the inpatient service.

Acidosis
The acidosis in DKA is due primarily to two factors: the production of ketone bodies due to relative insulin deficiency and the accumulation of lactate due to dehydration and poor tissue perfusion. Insulin treatment promotes the metabolism of ketone bodies and halts further ketone production, whereas the administration of IV fluids treats the dehydration. This therapeutic combination is generally sufficient for the correction of acidosis. Bicarbonate administration generally should be avoided because associations between bicarbonate therapy and
KEY POINTS

DKA Management Guidelines

IV fluids:
- Administer initial 10- to 20-mL/kg bolus of normal saline. Fluid bolus can be repeated if necessary to restore perfusion.
- Subsequent fluid administration should replace the remaining fluid deficit (typically approximately 70 mL/kg) plus maintenance fluids during 36 to 48 hours using half normal to normal saline. Normal saline can be used initially with a transition to half normal saline after several hours.

Insulin:
- Insulin should be administered after initial fluid bolus(es).
- Insulin should be administered as a continuous infusion of 0.1 U/kg per hour.
- An initial insulin bolus dose is not necessary.
- Insulin should be administered at the above rate until ketoacidosis resolves (pH >7.30 and bicarbonate >15 mEq/L). To prevent hypoglycemia, glucose-containing IV fluids should be used after the plasma glucose concentration declines below approximately 250 to 300 mg/dL (13.9 to 16.7 mmol/L).

Electrolyte replacement:
- For DKA patients presenting initially with hypokalemia, potassium replacement should begin immediately. If potassium levels are normal, potassium replacement should begin concurrent with insulin administration, provided that renal function is adequate. For patients with hyperkalemia, potassium replacement should begin when serum potassium levels decline to the normal range.
- Potassium replacement should be given as potassium chloride (KCl) or a 50:50 mixture of potassium chloride (KCl) and potassium phosphate or potassium acetate to sum to 40 mEq of potassium per liter of IV fluids. Serum potassium concentrations should be monitored frequently and rates of administration adjusted according to measured concentrations.
- Calcium, magnesium, and phosphate concentrations should be monitored. Phosphate concentrations typically decrease during treatment, and replacement of phosphate (see above) can be considered. Replacement of calcium and magnesium is rarely required.

Bicarbonate treatment:
- Bicarbonate treatment should be avoided except in rare circumstances of symptomatic hyperkalemia and/or cardiovascular instability caused by severe acidosis and not responding to fluid and insulin therapy.

Monitoring:
- Vital signs should be measured hourly.
- Continuous cardiac monitoring is recommended.
- Accurate recording of fluid intake and output should be performed.
- Blood glucose concentrations should be measured hourly. Electrolytes, serum urea nitrogen, creatinine, venous pH, and Pco₂, should be measured every 2 to 4 hours. Calcium, magnesium, and phosphate should be monitored approximately every 6 hours. More frequent measurements might be needed in patients with abnormal or rapidly changing electrolyte concentrations.
- Mental status should be assessed hourly or more frequently in patients with headache or other symptoms or signs of cerebral edema (see text).

Admission to the pediatric intensive care unit vs pediatric ward:
- Admission to the pediatric intensive care unit is recommended for children requiring more intensive monitoring or those at risk for complications. These patients include:
  - Children younger than 5 years
  - Children with altered mental status
  - Children with very high initial BUN concentration and/or very low initial Pco₂ levels or severe acidosis
  - Children with mixed presentation of DKA and hyperglycemic hyperosmolar state
Electrolyte Imbalances

Regardless of the serum potassium concentration at presentation, total body potassium is depleted in patients with DKA. With the treatment of DKA, serum potassium concentrations can decrease rapidly as insulin and fluid therapy improve the state of acidosis and potassium shifts to the intracellular space. Potassium should typically be added to the IV fluids at the time of initiation of insulin treatment, provided that adequate renal function is verified. For patients presenting with hypokalemia, potassium replacement should begin sooner. For patients with initial hypokalemia, potassium replacement should begin after potassium levels decrease to the normal range. Potassium replacement should be given as a mixture of potassium chloride and potassium phosphate or potassium acetate at a concentration of 30 to 40 mEq/L. Although severe hypophosphatemia occurs rarely in children with DKA, the consequences (eg, rhabdomyolysis and hemolytic anemia) can be devastating. Therefore, it seems prudent to administer a portion of the potassium replacement as the phosphate salt, although a thorough study of this issue is lacking.

Monitoring and Treating Complications

Glucose concentrations should be measured hourly using a bedside glucose meter throughout the period of IV insulin treatment. A reasonable rate of decline in the serum glucose concentration is approximately 50 to 100 mg/dL per hour. With the initial infusion of IV fluids and restoration of renal perfusion, however, glucose concentrations might decrease more rapidly. Electrolyte concentrations should be measured every 3 to 4 hours or more frequently if severe abnormalities are present.

Careful monitoring is essential for early detection of complications of DKA, particularly cerebral edema. Therefore, neurologic and mental status should be checked hourly. Although the effectiveness of cerebral edema treatment interventions is unclear, patients who have deterioration in mental status generally should be treated for presumed cerebral edema and subsequently evaluated using computed tomography or magnetic resonance imaging (MRI). It is commonly believed that early treatment with hyperosmolar agents, such as mannitol or 3% saline (hypertonic saline), in patients with DKA and cerebral edema can be beneficial, although clinical data are lacking. The potential adverse effects of hyperosmolar agents in this setting, however, are relatively minor in relation to the potential for cerebral injury caused by cerebral edema, and therefore hyperosmolar treatment should be strongly considered if cerebral edema is suspected. Aggressive hyperventilation has been shown to be associated with a greater likelihood of an adverse outcome in DKA-related cerebral edema; therefore, this should probably be avoided unless necessary to avoid cerebral herniation.

Hypoglycemia in Children With Diabetes

Hypoglycemia, the most common complication of type 1 diabetes in childhood, can occur in any child in whom the dose of administered insulin exceeds insulin requirements. Albeit less frequently, hypoglycemia can also occur in patients with type 2 diabetes on oral hypoglycemic or insulin regimens. Responses to hypoglycemia include release of counterregulatory hormones, such as glucagon, epinephrine (adrenaline), cortisol, and growth hormone. However, over time both the glucagon and epinephrine (adrenaline) responses might be impaired, increasing the risk of persistent hypoglycemia due to lack of adrenergic symptoms.

The American Diabetes Association criteria for the clinical classification of hypoglycemia in patients with DM include all episodes of an abnormally low plasma glucose concentration (<70 mg/dL or <3.9 mmol/L) with or without symptoms that expose the individual to harm. A glucose concentration of 70 mg/dL is higher than the value used to diagnose hypoglycemia in people without diabetes; however, it is considered an appropriate threshold because it approximates the lower limit of the physiologic fasting nondiabetic range, the normal...
Hypoglycemia in Children With Diabetes

16-9

glycemic threshold for glucose counterregulatory hormone secretion, and the highest antecedent glucose level reported to reduce sympathoadrenal responses to subsequent hypoglycemia. It has been debated that a cutoff value of less than 63 mg/dL (3.5 mmol/L) is preferable to avoid overclassification of hypoglycemia in asymptomatic patients.

In children, the risk of hypoglycemia is associated with younger age, tighter glycemic control, insulin regimens with fixed dosing (as opposed to therapy that delivers a basal insulin dose/infusion rate with intermittent boluses to cover for intake), exercise (due to increased insulin absorption, more rapid glucose utilization, and increased insulin sensitivity), acute illness (particularly when associated with nausea, vomiting, and anorexia), psychological disturbance, lower socioeconomic status, and occurrence of one or more prior hypoglycemic episodes. In children and adolescents receiving intensive therapy, the risk of severe hypoglycemia is increased more than threefold. Finally, the risk is also increased at night due to a sleep-induced blunted counterregulatory hormone response to hypoglycemia.

Clinical Features

Hypoglycemic symptoms can be adrenergic due to epinephrine (adrenaline) release and/or neuroglycopenic due to direct effects of hypoglycemia on the central nervous system (CNS). Adrenergic symptoms include tremor, pallor, tachycardia, palpitations, and diaphoresis. Neuroglycopenic symptoms include fatigue, lethargy, headaches, behavior changes, drowsiness, unconsciousness, seizures, or coma. The severity of the neuroglycopenic symptoms increases with the severity of hypoglycemia and resultant CNS energy deprivation.

The severity of hypoglycemia is classified by both symptoms and the clinical intervention required. Mild hypoglycemia is associated with adrenergic and mild neuroglycopenic symptoms, such as headaches and mood changes in older children and poor feeding, lethargy, jitteriness, and hypotonia in infants and toddlers. In such cases, oral intake of a rapidly absorbed carbohydrate is generally adequate treatment. Patients with moderate hypoglycemia are neurologically impaired to a level that requires help from a second person to administer oral therapy. In the absence of a person to aid therapy, moderate episodes could escalate in severity. Severe hypoglycemia is recognized by the presence of critical neurologic symptoms (seizures or coma) or requirement for intervention with subcutaneous glucagon and/or IV dextrose. Case reports exist of acute and transient cortical blindness and stroke-like hemiparesis associated with severe hypoglycemia. Unlike mild episodes of hypoglycemia that are relatively frequent in children with type 1 DM, severe hypoglycemic events are uncommon, occurring at a rate of approximately 5 to 19 events per 100 patient-years.

Diagnostic Studies and Management

Patients with mild and moderate hypoglycemia should be treated orally with a concentrated and rapidly absorbed simple carbohydrate source, such as glucose tablets, fruit juice, or cake frosting; 15 to 20 g of oral glucose is typically sufficient. A snack containing a mixed food source should follow to sustain normal blood glucose level. Blood glucose levels should be checked every 15 to 20 minutes for approximately 2 hours to confirm that glucose values have normalized and to determine whether further intervention is necessary. The patient might require additional carbohydrates until normal blood glucose levels are sustained.

A patient with diabetes presenting with altered mental status should have glucose concentration assessed rapidly with a bedside glucose meter. Hypoglycemia, if present, should be corrected as rapidly as possible with an IV infusion of 0.5 g/kg of dextrose. This can be accomplished by infusing 5 mL/kg of 10% dextrose in an infant, 2 mL/kg of 25% dextrose in a toddler, or 1 mL/kg of 50% dextrose in older children (note the “50 rule”: the product of the milliliters per kilogram dose and the percentage of dextrose should equal 50). In the event that IV access cannot be established rapidly, glucagon should be given via subcutaneous or intramuscular injection. The accepted dose is 0.02 to 0.03 mg/kg or 0.5 mg for children weighing less than 20 kg and 1 mg for children weighing greater than 20 kg. If neurologic or mental status
abnormalities persist for prolonged periods after correction of hypoglycemia, other possibilities should be considered, such as toxic ingestions and other intracranial disease.

**Hypoglycemia in Nondiabetic Children**

Hypoglycemia can result from excessive insulin production (insulinoma or hyperinsulinism) or decreased concentrations of counterregulatory hormones (deficiencies of growth hormone, cortisol, or both). Hypoglycemia can also result from inborn metabolic errors that impair gluconeogenesis, glycogenolysis, or fatty acid oxidation. Unsuspected hypoglycemia can be found when patients present to the ED with episodes of acute illness. A recent study revealed that a substantial percentage (28%) of these patients had previously undiagnosed fatty acid oxidation defects (19%) or endocrine disorders (9%).

**Clinical Features**

Infants with hypoglycemia can present with jitteriness, poor feeding, lethargy, hypotonia, hypothermia, apneic episodes, or seizures. Symptoms of hypoglycemia in infants might also be subtle and less obvious than those in older children. In older children, symptoms of hypoglycemia include headaches; vision changes; mental status changes, such as confusion, lethargy, irritability, or anxiety; and seizures. Adrenergic symptoms, such as palpitations, sweating, pallor, and tremulousness, are usually also present. Hypoglycemia should be considered in all patients presenting with unexplained alterations in mental status, seizure, or loss of consciousness, and a routine bedside test for hypoglycemia should be part of pediatric resuscitation procedures.

**Diagnostic Studies**

If hypoglycemia is suspected, a rapid glucose test should be performed using a bedside blood glucose meter. A glucose concentration less than 50 mg/dL should be considered abnormal and the patient treated. If the bedside test reveals a low glucose concentration, a confirmatory venous sample should be sent to the laboratory for measurement with greater accuracy. Treatment for hypoglycemia should not be delayed while awaiting results. At the time that the confirmatory sample is drawn, an additional serum sample (enough for special studies) should be obtained for future measurement of hormone concentrations and other biochemical measures. It is essential that this sample be drawn at the time of the hypoglycemic event. Without information from this sample, it is usually impossible to determine the cause of the hypoglycemic episode. If hypoglycemia is confirmed, the measurements to be obtained on the initial sample include serum insulin, cortisol, and growth hormone concentrations, as well as serum ketones, lactate, and free fatty acid concentrations.

A toxicologic evaluation for ethanol, salicylates, β-blockers, and oral hypoglycemic agents should also be considered. Remaining serum from the initial sample should be stored for additional biochemical testing if necessary. Finally, a urine sample should also be obtained and tested for ketones and reducing substances. An additional sample of urine should likewise be stored for future testing.

**Differential Diagnosis**

There are many possible causes of hypoglycemia, and a discussion of all causes is beyond the scope of this chapter. Among the more frequent causes (in patients without DM) are toxic
Adrenal Insufficiency/Congenital Adrenal Hyperplasia

Adrenal insufficiency can be related to processes directly affecting the adrenal gland (primary), or it can result from adrenocorticotropic hormone (ACTH) deficiency (secondary). Both primary and secondary adrenal insufficiency are characterized by inadequate production of corticosteroids that can culminate in “adrenal crisis,” a life-threatening cardiovascular collapse. However, in secondary adrenal insufficiency mineralocorticoid function is preserved.

The causes of adrenal insufficiency in childhood are varied. Congenital adrenal hyperplasia is the most common form of primary adrenal insufficiency in children, with an incidence of 1 in 10,000 to 18,000 live births. Congenital adrenal hyperplasia is a group of autosomal recessive inherited adrenal steroidogenesis enzyme deficiencies (most often 21-hydroxylase) that cause various degrees of adrenal cortical inability to synthesize cortisol. In childhood, acquired primary adrenal insufficiency is relatively uncommon and can result from autoimmune adrenal destruction, infectious infiltration (by tuberculosis, most commonly worldwide), or inherited adrenoleukodystrophy syndromes. Furthermore, long-term treatment with glucocorticoids can result in secondary adrenal insufficiency by the suppressive effect on the hypothalamic-pituitary-adrenal axis. In fact, the most common cause of acute adrenal insufficiency in North America today is glucocorticoid withdrawal or omission in patients being treated for a variety of disorders with pharmacologic ingestions (eg, oral hypoglycemic agents, β-blockers, and ethanol), sepsis, hypopituitarism, adrenal insufficiency, fatty acid oxidation defects, hyperinsulinism, and ketotic hypoglycemia. Analysis of the initial serum sample will differentiate among many of these entities and will indicate whether additional analyses are necessary to investigate less frequent causes of hypoglycemia.

**Management**

Hypoglycemia should be corrected as rapidly as possible with an IV infusion of 0.5 g/kg of glucose (dextrose). This can be accomplished by infusing 5 mL/kg of 10% dextrose in an infant, 2 mL/kg of 25% dextrose in a toddler, and 1 mL/kg of 50% dextrose in older children (note the “50 rule”: the product of the milliliters per kilogram dose and the percentage of dextrose should equal 50). Subsequently, an IV infusion of 10% dextrose at 1.5 times maintenance rates should be provided to maintain glucose concentrations in the normal range and reverse the catabolic state. If adrenal insufficiency is known or strongly suspected and adequate samples have been set aside for further study, IV hydrocortisone should be given (50 mg for children younger than 4 years and 100 mg for children older than 4 years).

**Your First Clue**

**Signs and Symptoms of Hypoglycemia**
- Infants: jitteriness, poor feeding, lethargy, hypotonia, hypothermia, apnea, seizures
- Children: headaches, altered mental status, diaphoresis, pallor, palpitations, tremulousness, seizure

**Key Points**

**Diagnosis and Management of Hypoglycemia**
- Perform rapid bedside glucose testing for altered level of consciousness, seizure, or lethargy.
- Obtain additional blood and urine samples at the time of the hypoglycemic event.
- Administer dextrose: 5 mL/kg of 10% dextrose in an infant, 2 mL/kg of 25% dextrose in a toddler, and 1 mL/kg of 50% dextrose in older children.
secondary adrenal insufficiency is commonly associated with signs and symptoms of additional pituitary hormone deficiencies, such as growth failure, delayed puberty, secondary hypothyroidism, and/or diabetes insipidus (DI).

Adrenal crisis continues to occur in children with known primary or secondary adrenal insufficiency during intercurrent illness because of failure to increase glucocorticoid dosing.

It is important to recognize that other hormones affect cortisol metabolism and can influence the onset or progression of adrenal insufficiency. It is well documented that initiation of thyroid hormone replacement in an individual with hypothyroidism accompanied by unrecognized adrenal insufficiency can precipitate an adrenal crisis. The mechanism that precipitates adrenal crisis is not fully understood, but it is hypothesized that hypothyroid patients have reduced cortisol requirements secondary to a reduced metabolic rate. When thyroxine therapy is initiated, the metabolic rate and cortisol requirements increase, and an adrenal crisis can ensue. Accordingly, hyperthyroidism can increase cortisol metabolism. It is suggested that in the individual with hyperthyroidism and adrenal insufficiency, cortisol replacement should be increased as much as twofold because of increased cortisol clearance. Growth hormone appears to decrease conversion of inactive cortisone to active cortisol. Therefore, after growth hormone therapy is initiated, a patient with unrecognized concomitant adrenal dysfunction might be vulnerable. Pregnancy is associated with increased corticosteroid-binding globulin and therefore...
lower free cortisol levels during the last trimester, thus necessitating an increase in hydrocortisone dosing by 50%. In addition, increasing intrapartum progesterone levels antagonize the mineralocorticoid effect, which can dictate adjustment of fludrocortisone supplementation as well.38

Certain medications interfere with cortisol metabolism as well and must be considered in patients with adrenal disorders. Some drugs inhibit cortisol biosynthesis, including amino-gluthimide, etomidate, ketoconazole, metyrapone, medroxyprogesterone, and megestrol.39,44

In addition, certain drugs accelerate cortisol metabolism, such as phenytoin, barbiturates, and rifampin.39

Diagnostic Studies
Blood should be drawn to test for cortisol, electrolytes, glucose, ACTH, plasma renin activity, and aldosterone before glucocorticoid therapy, if possible. When CAH is suspected, serum 17-hydroxyprogesterone concentration should be measured as well. Measurement of urinary sodium and potassium concentrations is helpful in assessing mineralocorticoid status and in differentiating from other hyponatremic conditions.

In primary adrenal insufficiency, testing typically reveals hyperkalemia, hyponatremia, hypoglycemia, and acidosis. However, not all patients manifest all of these laboratory abnormalities, and the diagnosis cannot be excluded based on the absence of one or more of these findings. Both BUN and creatinine concentrations can be elevated due to dehydration. In secondary adrenal insufficiency, hyperkalemia and hyponatremia are absent due to preservation of mineralocorticoid production, and hypoglycemia might be the primary biochemical abnormality.

Differential Diagnosis
Most of the symptoms of adrenal insufficiency are nonspecific, and many overlap with other, more common, diagnoses. In infancy, for example, adrenal insufficiency might be confused with other illnesses that present with lethargy, vomiting, poor weight gain, hypotension, and tachycardia, including sepsis, gastrointestinal malformations, congenital heart disease, inborn errors of metabolism, certain hematologic disorders, neurologic diseases, or child abuse. The presence of hyperkalemia, hyponatremia, acidosis, skin hyperpigmentation, and masculinized genitalia in a genetic female can help to differentiate primary adrenal insufficiency from these other entities. In an older child, mild symptoms of primary adrenal insufficiency might be confused with mononucleosis or anorexia nervosa. More severe symptoms can mimic infections (eg, sepsis), hematologic disease, psychiatric illness, or even an acute abdomen. Again, the presence of hyperpigmentation and the characteristic laboratory abnormalities serve to differentiate these entities. Secondary adrenal insufficiency can be even more difficult to differentiate from other entities because of the lack of hyperpigmentation and the lack of specific laboratory features other than hypoglycemia. In these cases, a history of CNS
tumors, neurosurgical procedures, congenital CNS malformations, other coincident pituitary hormone deficiencies (suggested clinically by short stature, inappropriately absent or delayed puberty, or polyuria, as examples), or prolonged exogenous glucocorticoid use must be relied on for the diagnosis. Secondary adrenal insufficiency can evolve over time in patients with cranial radiation, septo-optic dysplasia, autoimmune hypophysitis, and head trauma.45-47

Management
In the hypotensive patient with adrenal insufficiency, it is imperative to rapidly restore intravascular volume with isotonic sodium chloride containing glucose and to administer glucocorticoids expeditiously. An initial fluid bolus of normal saline (20 mL/kg) should be given and repeated as necessary to improve perfusion. After the initial bolus, a continuous infusion of normal saline with 5% dextrose should be given. On the basis of body surface area, the recommended stress dose of IV hydrocortisone is 50 to 75 mg/m² initially followed by 50 to 75 mg/m² per day divided into four doses.40 It is reasonable to approximate IV hydrocortisone dosing and administer immediately 50 mg for children younger than 4 years and 100 mg for children older than 4 years. The benefits of sufficient dosing greatly outweigh the risk of underdosing in such cases. Hydrocortisone can be given intramuscularly if no IV access exists, although the effects of intramuscular administration is slower and can be ineffectively absorbed if peripheral perfusion is poor. Comparable body surface area stress doses are 10 to 15 mg/m² for methylprednisolone and 1.5 to 2 mg/m² for dexamethasone; the latter two corticosteroids have minimal mineralocorticoid activity. Prednisone is not a preferred glucocorticoid because it must be converted to prednisolone for it to have glucocorticoid activity, and in patients with liver failure, this conversion might be impaired. Dexamethasone can be used if one desires to treat the patient urgently but wishes to perform a diagnostic ACTH-stimulation test because this glucocorticoid will not interfere with diagnostic laboratory assays. Treatment should never be withheld if the diagnosis of adrenal insufficiency is even suspected. If the patient has good gastrointestinal function, fludrocortisone (0.1 to 0.2 mg/d), a synthetic mineralocorticoid, can be administered orally. However, typically, administration of IV sodium chloride along with stress doses of hydrocortisone are sufficient to begin normalizing electrolyte abnormalities, making the addition of mineralocorticoid unnecessary in the initial phase of treatment.48

Severe hyperkalemia, resulting in a non-perfusing dysrhythmia, should be treated immediately with IV calcium gluconate to restore a perfusing rhythm. This should be followed by IV sodium bicarbonate, nebulized albuterol (salbutamol), and/or glucose with insulin to shift
potassium intracellularly. If there is a coexisting cardiomyopathy and/or acute renal failure prohibiting rapid rehydration, aggressive therapy of hyperkalemia might be needed.

**Diabetes Insipidus**

Under normal circumstances, plasma osmolality is maintained within a narrow range (280–295 mOsm/L). This homeostasis requires adequate water intake, regulated by an intact thirst mechanism and appropriate free water excretion by the kidneys, which is mediated by adequate posterior pituitary secretion and peripheral action of arginine vasopressin (AVP), also known as antidiuretic hormone (ADH). Diabetes insipidus is caused by a deficiency in the production or secretion of ADH (central DI) or due to resistance to ADH in the kidneys (nephrogenic DI). Symptoms of DI result from the effective inability to reabsorb free water at the level of the collecting duct in the nephrons of the kidney. Polyuria, polydipsia, and hypo-osmolar urine characterize this disorder. Hypernatremia might be present as well at the time of diagnosis, particularly in infants or children with developmental delay. An intact thirst mechanism and access to drinking water minimize the risk of dehydration and hypernatremia.

Central DI is rarely congenital and more frequently acquired. Congenital central DI can be caused by structural malformations or by autosomal dominant or recessive mutations in the gene encoding vasopressin-neurophysin II. Acquired forms of central DI can occur at any age in association with a variety of disorders in which there is destruction or degeneration of vasopressinergic neurons that can be caused by CNS tumors (craniopharyngioma or germinoma), infections (meningitis or encephalitis), head trauma, neurosurgery, vascular disorders, granuloma, and autoimmune disorders (lymphocytic infundibuloneurohypophysitis). Idiopathic DI is a diagnosis of exclusion and one that is made with decreasing frequency as a result of improved sensitivity of diagnostic technology.

Much like central DI, nephrogenic DI can be genetic or acquired. The genetic causes described are inactivating mutations of the AVPR2 gene or autosomal recessive or dominant mutations in the AQP-2 gene. These cases typically present in infancy. Acquired nephrogenic DI can be caused by various conditions, including primary renal disease, obstructive uropathy, hypokalemia, hypercalcemia, sickle cell disease, and medications such as lithium and demeclocycline (a tetracycline). In addition, prolonged polyuria of any cause can also lead to some degree of nephrogenic DI because of a reduction of tonicity in the renal medullary interstitium and a subsequent decrease in the gradient necessary to concentrate urine.

**Clinical Features**

Characteristic symptoms of DI are pronounced polyuria and polydipsia. Older children typically present without any obvious abnormalities on physical examination as long as they have an intact sense of thirst, access to fluids, and no ongoing losses, such as diarrhea. They might report a history of nocturia and secondary enuresis. Infants, in addition to polyuria and polydipsia, frequently demonstrate irritability, poor weight gain, failure to thrive, hyperthermia, and signs of dehydration. Developmental delays and arrest of variable severity can ensue after repeated episodes of dehydration if the condition remains untreated. Hydronephrosis can be detected in all age groups. Interestingly, symptoms of DI might not be apparent in patients with coexisting untreated anterior pituitary-mediated adrenal glucocorticoid insufficiency because cortisol is required to generate normal free water excretion.

**Diagnostic Studies**

Infants generally present with hypernatremia and serum hyperosmolality because they have limited access to fluids. Coincident inappropriately dilute urine (<300 mOsm/L) helps to establish the diagnosis. Older children usually do not present with hypernatremia or hyperosmolality unless their fluid intake is restricted, their thirst mechanism is abnormal, or they are experiencing excessive losses. In unclear cases, a carefully monitored “water deprivation test” is recommended, whereby the fasting patient is monitored for 8 to 10 hours with serial
The principal presenting sign of DI is polyuria, which, in addition to deficiency or impaired responsiveness to ADH, can result from an osmotic agent, such as hyperglycemia as seen in DM, or from excessive water intake (primary polydipsia). Patients with hypercalcemia or hypokalemia can also have impaired urinary concentrating ability, resulting in polyuria.

Management

Patients without hypernatremia and dehydration do not require immediate intervention for DI but should undergo evaluation to determine the underlying cause. Patients with hypernatremic dehydration and hyperosmolality should be treated with fluid resuscitation. This includes an initial 20-mL/kg fluid infusion of normal saline to restore perfusion followed by subsequent slow correction because overly aggressive free water replacement can lead to cerebral edema. In addition to correcting the fluid deficit, the management of central DI includes treating the primary disease and normalization of urine output with measurements of body weight, serum sodium and osmolality, and urine volume and osmolality. If urine osmolality of greater than 750 mOsm/L is achieved with any degree of water deprivation, DI can be excluded. The diagnosis of DI is established at any time point if serum osmolality rises above 300 mOsm/L and urine osmolality remains below 300 mOsm/L. Urine osmolality in the 300- to 750-mOsm/L range during water deprivation can indicate partial DI. During the test, if DI is suspected, an ADH plasma sample should be obtained, and then ADH, or a synthetic analog (desmopressin), should be administered to further distinguish ADH deficiency (central DI) from ADH unresponsiveness (nephrogenic DI).

If central DI is suspected, an MRI of the brain, with particular attention to the hypothalamic-pituitary region, is indicated. The posterior pituitary hyperintensity (bright spot) on T1-weighted MRIs is often absent in central DI. However, the absence of the bright spot is neither sensitive nor specific for this diagnosis because it can be absent in healthy individuals and, conversely, present in children with central DI as well. In central DI patients, a normal MRI does not exclude the possibility of an evolving occult hypothalamic-stalk lesion, and therefore follow-up with cerebrospinal fluid (CSF) tumor markers and cytology, serum tumor markers, and serial contrast-enhanced brain MRIs for early detection is critical. Intracerebral calcifications of the frontal lobes and basal ganglia can result from repeated episodes of dehydration. Ultrasonography can be helpful in detecting nonobstructive hydronephrosis, hydroureter, and megabladder, resulting from longstanding polyuria and polydipsia.

Differential Diagnosis

The principal presenting sign of DI is polyuria, which, in addition to deficiency or impaired responsiveness to ADH, can result from an osmotic agent, such as hyperglycemia as seen in DM, or from excessive water intake (primary polydipsia). Patients with hypercalcemia or hypokalemia can also have impaired urinary concentrating ability, resulting in polyuria.

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Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Syndrome of inappropriate secretion of antidiuretic hormone (ADH or AVP) is characterized by excessive kidney resorption of free water, resulting in hyponatremia and hypo-osmolar serum in association with inappropriately concentrated urine and natriuresis. Several disorders and medications are associated with SIADH: (1) CNS disorders or damage, such as meningitis or encephalitis, cerebral hemorrhage, head trauma, or after neurosurgical procedures; (2) psychiatric disorders; (3) a large variety of pharmacologic agents (eg, phenothiazines or tricyclic antidepressants); (4) various pulmonary disorders and interventions (eg, pneumonia, asthma, or positive pressure ventilation); (5) non-CNS tumors with ectopic production of ADH; (6) patients treated with desmopressin acetate who drink excessive amounts of fluids (typically habit driven); and (6) miscellaneous causes, such as AIDS, postoperative state, glucocorticoid deficiency, and severe hypothyroidism.

Clinical Features

Patients with SIADH frequently will not manifest symptoms of hyponatremia until the serum sodium concentration falls below 120 mEq/L. Below this level, symptoms can include anorexia, nausea, vomiting, lethargy, irritability, and confusion. Severe hyponatremia can culminate in seizures and loss of consciousness.

Diagnostic Studies

On the basis of criteria established by Bartter and Schwartz, the diagnosis of SIADH is made when the following constellation occurs: (1) plasma hypo-osmolality (<275 mOsm/L), (2) less than maximally dilute urine (urine osmolality >100 mOsm/L), (3) clinical euvolemia, (4) natriuresis (urine sodium >40 mEq/L), (5) normal renal function, and (6) no evidence of thyroxine or cortisol deficiency. Typically, BUN concentrations are normal or low. Causes of pseudohyponatremia should be excluded such as that due to hyperlipidemia, hyperproteinemia, and the osmotic effect of hyperglycemia. Most patients with SIADH have inappropriately measurable or elevated levels of plasma ADH relative to plasma osmolality.

Differential Diagnosis

Other causes of hyponatremia include water intoxication (primary polydipsia or iatrogenic), hyponatremic dehydration, adrenal insufficiency, renal failure, diuretic medications, nephrotic syndrome, cirrhosis, congestive heart failure, severe hypothyroidism, cystic fibrosis, and cerebral salt-wasting (CSW) syndrome. These diagnoses can generally be excluded based on the absence of corresponding diagnostic signs, such as dehydration, edema, and hyperkalemia.
Metabolic Diseases

Management
The mainstay of SIADH therapy for patients with mild or no symptoms is fluid restriction, treatment of the underlying disorder, or discontinuation of use of an offending drug. Ultimately, replacement of sodium loss might also be necessary, but it can usually be achieved through dietary salt intake. Severe hyponatremia (serum sodium <120 mEq/L), particularly when associated with CNS disturbance (lethargy, coma, or seizures), might require treatment with IV hypertonic saline (3% sodium chloride solution). The correct dosage of 3% sodium chloride solution can be calculated based on the assumption that 12 mL/kg of 3% sodium chloride solution will increase the serum sodium concentration by 10 mEq/L. It is generally recommended that plasma sodium be corrected at a rate of no greater than 0.5 mEq/L per hour, with an overall correction that does not exceed 12 mEq/L in the initial 24 hours and 18 mEq/L in the initial 48 hours of treatment. Therapy should continue until neurologic symptoms improve and a safe level of approximately 120 to 125 mEq/L is achieved. Further treatment can then be accomplished with fluid restriction.

Euvolemia in chronic SIADH is a critical distinguishing factor in the evaluation of a patient with serum hypo-osmolality; it is thought to represent an adaptation to water overload mediated, in part, at the cellular level through depletion of intracellular electrolytes (potassium) and organic osmolytes. Natriuresis, thought to be mediated in part through secretion of atrial natriuretic peptide, also contributes to volume regulation in chronic SIADH.

The CSW syndrome is particularly important to exclude because it occurs in overlapping clinical settings with SIADH. Cerebral salt-wasting syndrome is characterized by renal sodium and fluid loss. However, the hypo-osmolality, hyponatremia, and natriuresis in CSW syndrome are associated with volume contraction and clinical signs of dehydration (including elevated BUN and creatinine concentrations), helping to distinguish this syndrome from SIADH.

**YOUR FIRST CLUE**

**Signs and Symptoms of SIADH**
- Hyponatremia in association with head trauma, cerebral hemorrhage, or other intracranial conditions
- Clinical symptoms and signs of hyponatremia, including anorexia, nausea, vomiting, lethargy, irritability, altered level of consciousness, and seizures

**THE CLASSICS**

**Laboratory Findings in Patients With SIADH**
- Serum hypo-osmolality (<275 mOsm/kg)
- Urine hyperosmolality (>100 mOsm/L)
- Inappropriate natriuresis (>40 mEq/L)
- Normal renal, thyroid, and adrenal cortical function

**WHAT ELSE?**

**Differential Diagnosis of SIADH**
- Water intoxication
- CSW syndrome
- Hyponatremic dehydration
- Adrenal insufficiency
- Renal failure
- Diuretic use
- Nephrotic syndrome
- Hypothyroidism
- Cystic fibrosis
- Congestive heart failure
- Cirrhosis
to avoid excessive sodium correction. If SIADH and hyponatremia are acute (<48 hours), it is thought that hyponatremia can be corrected rapidly. However, if SIADH and hyponatremia are chronic (>48 hours), overzealous treatment can result in CNS damage, including central pontine myelinolysis.70 Concurrent use of a diuretic, such as furosemide, might be indicated if volume expansion is severe. Other therapeutic approaches include the use of agents that induce nephrogenic DI, such as demeclocycline and lithium, although both are contraindicated, particularly in younger pediatric patients, because of adverse effects. Urea has been used as an osmotic diuretic in pediatric SIADH.75 Once patient stabilization is achieved, a careful search for an underlying cause for SIADH is necessary if the cause is unknown.

**Water Intoxication**

Water intoxication occurs when daily water intake is excessive in relation to sodium. In infants, this situation occurs most frequently because of inappropriate dilution of formulas or misguided supplemental feedings of solute-free water.15,16 Excess water ingestion during infant swimming lessons has also been associated with this condition. Iatrogenic water intoxication is a well-known phenomenon, particularly in labor and delivery rooms.76 Water intoxication can be seen as a manifestation of child abuse as well. Certain psychiatric illnesses, particularly schizophrenia, can be associated with compulsive water drinking. It is presumed that a central defect in thirst regulation plays an important role in the pathogenesis of primary polydipsia in these patients.77-80 In some cases, for example, the osmotic threshold for thirst is reduced below the threshold for the release of ADH81; therefore, these patients will continue to drink until the plasma tonicity is less than the threshold level. Drug therapy can also contribute to the increase in water intake in schizophrenic patients. Many antipsychotic drugs induce the sensation of a dry mouth, which will enhance thirst.82

**Clinical Features**

Clinical manifestations of water intoxication result from hyponatremia. Infants typically present with poor feeding, vomiting, and lethargy. Hypothermia and edema might also be present. With severe hyponatremia, seizures can occur and might be prolonged. It has been suggested that hypothermia can be a specific marker for hyponatremia in infants with a new onset of seizures.83

**Diagnostic Studies**

Hyponatremia (serum sodium concentration <130 mEq/L) with coinciding dilute urine is the hallmark of this condition. Serum potassium, urea nitrogen, and creatinine concentrations are typically normal, and acidosis is not present, which helps exclude other causes of hyponatremia. Fictitious hyponatremia should be excluded which can occur with hyperlipidemia, hyperproteinemia, or due to the osmotic effect of hyperglycemia.

**Differential Diagnosis**

The differential diagnosis of hyponatremia is extensive and includes renal failure, diuretic use, renal tubular defects (renal tubular acidosis), SIADH, adrenal insufficiency, cystic fibrosis, nephrotic syndrome, cirrhosis, and congestive heart failure. Iatrogenic hyponatremia can also occur in infants or children when insensible losses are replaced with free water or other fluids deficient in sodium; this scenario differs, however, from classic water intoxication in that clinical and

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**KEY POINTS**

**Management of SIADH**

- Restrict fluids in patients with mild or no symptoms.
- Treat with 3% sodium chloride in cases of severe hyponatremia (serum sodium <120 mEq/L), particularly when associated with neurologic disturbance.
- Rapid correction of chronic hyponatremia can precipitate central pontine myelinolysis.
laboratory features of dehydration are present and the urine is concentrated. A careful history, including infant feeding practices and psychiatric illness, in addition to the detection of dilute urine can lead to the diagnosis of water intoxication.

**Management**

For infants who are asymptomatic or have mild symptoms of hyponatremia, reinstitution of normal daily sodium with more restricted fluid intake is generally all that is required. For infants with severe manifestations of hyponatremia (pronounced lethargy, seizures, or coma), treatment with 3% sodium chloride solution should be initiated with caution.

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**YOUR FIRST CLUE**

**Signs and Symptoms of Water Intoxication**
- Poor feeding
- Vomiting
- Lethargy
- Seizures
- Hypothermia

**KEY POINTS**

**Diagnosis and Management of Water Intoxication**
- Presents with hyponatremia with a history of excessive water intake (relative to sodium).
- Infant who presents with hypothermia with seizures is a specific indicator for hyponatremia.
- Free water restriction and normalization of sodium intake are sufficient treatment in most instances.
- Hypertonic 3% sodium chloride solution treatment can be used prudently in severely affected patients.

**THE CLASSICS**

**Laboratory Findings in Patients With Water Intoxication**
- Hyponatremia (sodium concentration <130 mEq/L)
- Dilute urine
- Absence of metabolic acidosis and dehydration
Metabolic Disease of the Newborn and Young Child: Inborn Errors of Metabolism

Early recognition of a possible inborn error of metabolism (IEM) in acutely ill patients is critical to minimize the high morbidity and mortality rates associated with these conditions. Although individually rare, IEMs collectively are relatively common. A diagnosis of IEM should be considered not only in the evaluation and treatment of critically ill patients but also in patients with recurrent episodes of vomiting, lethargy, and/or seizures and those with chronically progressive neurologic abnormalities and/or organ dysfunction. Usually, IEMs manifest in the neonatal period or infancy; however, presentation, can occur at any time throughout childhood and even in adulthood. Initial treatment of the critically ill child with an IEM does not require a detailed knowledge of individual IEMs or biochemical pathways but rather an understanding and early recognition of life-threatening clinical manifestations and consequences of the metabolic derangements. Prompt initiation of appropriate treatment is crucial for optimizing immediate and long-term outcome and is often lifesaving.

More than 400 IEMs have been identified since 1908. The incidence of IEMs is estimated to be as high as 1 in 1,000 live births. Inborn errors of metabolism are caused by single gene defects that result in abnormal synthesis, catabolism, and/or function of proteins, carbohydrates, fats, organelles (ie, lysosomes, mitochondria, and peroxisomes), metals, or complex molecules. Most IEMs are due to a defect in an enzyme or transport protein that results in a block in a metabolic pathway. Effects are caused by toxic accumulations of substrates before the block or from alternative metabolic pathway intermediates (disorders of protein metabolism, carbohydrate intolerance, metal metabolism, and porphyrias); defects in energy production and use within the brain, heart, liver, skeletal muscle, and other organs due to a deficiency of products beyond the block (disorders of carbohydrate metabolism [eg, gluconeogenesis, glycogenolysis, and glycogen storage disorders], fatty acid oxidation defects, and mitochondrial disorders); or disturbances in the synthesis or catabolism of complex molecules (lysosomal storage and peroxisomal disorders or defects in the metabolism of cholesterol, purines and pyrimidines, and neurotransmitters; and defects in glycosylation). Most IEMs have multiple forms that differ in age of clinical onset, severity, and even mode of inheritance. The IEMs most likely to result in acute, potentially life-threatening decompensation include disorders of protein metabolism, defects in carbohydrate metabolism, fatty acid oxidation defects, and early-onset forms of mitochondrial and peroxisomal disorders. Lysosomal storage disorders, certain glycogen storage disorders, and late-onset forms of mitochondrial and peroxisomal disorders tend to have a chronic insidious progression that results in organ dysfunction and ultimately failure. Inheritance is autosomal recessive for most IEMs (because many are enzyme deficiencies),

CASE SCENARIO

A 14-month-old girl presents to the ED with a 1-day history of tactile fever, loss of appetite, and intermittent emesis. This morning, she did not seem interested in her usual breakfast and seemed sleepier than usual. On examination, she has respirations of 40/min, a heart rate of 170/min, blood pressure of 80/40 mm Hg, and a temperature of 36.0°C (96.8°F). She appears lethargic and has mildly dry mucous membranes and no obvious source of infection. Bedside rapid glucose measurement reveals a blood glucose level of 20 mg/dL.

1. What therapeutic measures must be taken immediately?
2. What laboratory tests would you order?
3. What complications can occur as part of the disease process and secondary to therapeutic intervention?

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but there are IEMs with autosomal dominant, X-linked, and mitochondrial inheritance.

Nearly all states in the United States test newborns for at least 29, and some for more than 50, genetic diseases, most of which are IEMs.\(^{91,92}\) A table of newborn screening tests performed by state is available online.\(^{93}\) Results are usually available within days but might take weeks. In at least some states, parents can opt to not have their child screened. False-negative newborn screens can result and are most commonly due to screening too soon after birth, weight less than 1,500 g, neonatal illness, medications, transfusions, and problems related to sample collection and handling. Cutoff values are set to minimize false-negative rates, which result in relatively high false-positive rates. Neonates who test positive on newborn screens for an IEM that can result in acute, life-threatening decompensation require emergent evaluation.\(^{94}\)

**Clinical Features**

**History**

History can vary from abrupt onset of rapidly progressing illness that results in death within hours, to intermittent recurrent acute episodes of potentially life-threatening decompensation in an otherwise well child, to chronic, slowly progressive deterioration throughout decades.\(^{85,90,95,96}\) Inborn errors of metabolism that result in acutely life-threatening critical illness present most commonly within the first year of life and usually within the newborn period, those that cause intermittent decompensation most often manifest later in infancy or early in childhood, and those with insidious, progressive symptoms tend to present in older childhood, adolescence, or even throughout adulthood. In the neonate, the most important clue to an IEM is a history of deterioration after an initial period of apparent good health ranging from hours to weeks.\(^{97,98}\) In neonates and infants, a history of poor feeding, vomiting, chronic diarrhea, failure to thrive, lethargy, and seizures is common.\(^{99–101}\) Developmental delay in infants, particularly with loss of milestones, is strongly suggestive of an IEM. Symptoms can be precipitated by increased intake of protein or carbohydrate and/or by a reduction in feeds (eg, as in gastroenteritis). Unusual dietary preferences, particularly protein or carbohydrate aversion, and symptoms occurring during diet changes are often seen in patients with an IEM. By late infancy or early childhood, it is often apparent that with routine illnesses, children with an IEM become more severely symptomatic and/or require longer to recover than expected. In older children and adults, vigorous exercise, sleep deprivation, hormonal changes, intercurrent illness, anesthesia or surgery, and pregnancy or delivery commonly precipitate symptoms.

A family history of siblings and/or a history of relatives with similar findings is an important clue to possible IEM. A family history of sudden infant death or unexplained neonatal death, particularly due to sepsis or neurologic, cardiac, and/or hepatic dysfunction, should also raise concern for a possible IEM. Parental consanguinity increases the likelihood of an autosomal recessive IEM. Maternal history of HELLP (hemolysis, elevated liver enzyme, low platelet count) during pregnancy is associated with maternal heterozygosity for fatty acid oxidation defect and suggests the possibility of homozygosity for the disease in the child. Decreased fetal movement has been described with certain glycogen and lysosomal storage disorders and peroxisomal disorders. A negative family history does not rule out an IEM.

**Clinical Manifestations**

Clinical manifestations of IEMs reflect the multiorgan system involvement typical of these disorders. Common clinical presentations include a sepsis-like illness or cardiac, hepatic, and/or neurologic dysfunction.\(^{85–87,97–104}\) Physical examination findings are normal for most IEMs. Abnormal odor or hair, hearing deficit, visual dysfunction, organomegaly, and/or chronic dermatitis should prompt consideration of an IEM. Dysmorphic features are seen commonly with mitochondrial disorders, peroxisomal disorders, lysosomal storage, and other disorders of complex molecules. The risk of mortality can be very high, particularly with initial presentation of an undiagnosed IEM. Features of specific IEMs can be found in the texts referenced in this chapter\(^{85,95,96}\) and on Web sites, including Online Mendelian Inheritance in Man.\(^{88,90}\)
**Neonates**

Inborn errors of metabolism should be considered in neonates who are critically ill, particularly those with encephalopathy and/or hepatic dysfunction. Clinical manifestations of IEMs in neonates are nonspecific and most commonly include decreased feeding, hiccups, vomiting, diarrhea, dehydration, temperature instability, tachypnea or apnea, bradycardia, poor perfusion, unusual odor, jaundice, irritability, involuntary movements or posturing, abnormal tone, seizures, stroke, and/or altered level of consciousness. These same findings are also manifestations of many other causes, making the differential diagnosis extensive. Presence of one diagnosis does not rule out the possibility of a concomitant IEM. In fact, some IEMs, such as galactosemia, certain organic aminoacidopathies, and glycogen storage diseases, are associated with an increased risk of sepsis. Inborn errors of metabolism should be considered in neonates with lethal hydrops or pulmonary or intracranial hemorrhage in utero or after birth. It should also be recognized that an undiagnosed IEM is a possible cause of sudden infant death, most commonly fatty acid oxidation defects. The time to onset of symptoms for inborn errors of substrate and intermediary metabolism is dependent on significant accumulation of toxic metabolites, which for severe forms can occur within hours after the initiation of feeding. Neonates with IEMs that result in defects in energy production and use are often symptomatic at birth or within the first 24 hours of life. These neonates are less likely to have coma as an early manifestation and are more likely to have dysmorphic features, cardiopulmonary compromise, organomegaly, skeletal malformations, and hypotonia.

**Infants and Young Children**

Infants and children with IEMs can have recurrent episodes of vomiting, dehydration, hepatomegaly, ataxia, seizures, stroke, lethargy, and coma but can appear completely normal between episodes. Others have dysmorphic features, failure to thrive, microcephaly or macrocephaly, alopecia or sparse hair, hearing and vision deficits, corneal opacities, cataracts, subluxed or dislocated lens, cherry red spots, retinopathy, optic atrophy, chronic dermatoses, skin photosensitivity, nodules, dilated or hypertrophic cardiomyopathy, cardiac arrhythmia, jaundice, hepatomegaly, liver dysfunction, splenomegaly, pancreatitis, skeletal abnormalities, hypotonia, dystonia, weakness, peripheral neuropathy, and/or developmental delay, in some cases with loss of milestones. Inborn errors of metabolism most likely to present in this age group include partial enzyme deficiency urea cycle defects, disorders of carbohydrate metabolism, fatty acid oxidation defects, and lysosomal storage disorders. Reye syndrome–like symptoms are now recognized often to be due to IEMs. The differential diagnosis of IEMs in infants and young children with IEMs is extensive and, in addition to that for the neonates, includes routine illness, cyclic vomiting, diabetes, drug or toxin ingestion, malignant tumor, and Munchausen by proxy.

**Older Children, Adolescents, and Adults**

In older children, adolescents, and adults, previously undiagnosed IEMs usually manifest as neurologic and/or psychiatric abnormalities that can range from recent to longstanding and from subtle to severe. Although rare, the initial presentation of an IEM can be that of critical illness with rapid progression to death. Manifestations of life-threatening IEMs most commonly include profound lethargy, coma, encephalopathy, seizures, stroke, other thromboembolic event, cardiac or hepatic dysfunction or failure, weakness, and/or paresis. More commonly, manifestations are not acute in onset or imminently life-threatening and include learning disabilities, autism, developmental delay, visual deficits, ocular abnormalities, exercise intolerance, muscle cramps, ataxia, abnormal movements, abnormal or aggressive behaviors, and psychiatric disturbances, such as anxiety, panic attacks, hallucinations, delirium, paranoia, and/or psychosis. Findings particularly concerning for IEMs include ophthalmologic abnormalities, progressive neurologic disease, abnormal movements, cerebellar symptoms, and mixed psychiatric and neurologic symptoms. Among the most common IEMs on the growing list of recognized IEMs with late onset are partial ornithine transcarbamylase deficiency (particularly
in females), homocystinuria, certain glycogen storage disorders, mitochondrial and peroxisomal disorders, and Wilson disease.

Diagnostic Studies
In the acutely ill patient with an undiagnosed condition, results of routine laboratory tests often provide clues to IEMs and should guide further evaluation. Most patients with acute, life-threatening presentations of metabolic disease have metabolic acidosis, hyperammonemia, and/or hypoglycemia. Laboratory abnormalities can be transient; therefore, specimens should be collected as soon as possible, preferably before initiation of any therapy, including fluids and glucose. If samples were not collected before treatment, remaining pretreatment specimens are likely to be more informative than posttreatment samples and should be used if available. A metabolic specialist can be helpful in directing the evaluation of patients with suspected or known IEMs.

Metabolic Acidosis
Clinical manifestations of metabolic acidosis include tachypnea and vomiting. Initial laboratory studies to evaluate acid-base status include electrolytes and blood gas. Laboratory manifestations of primary metabolic acidosis are low pH, PCO₂, and bicarbonate level and an elevated anion gap. Severe metabolic acidosis and ketonuria, with or without hyperammonemia or hypoglycemia, are hallmarks of organic acidemias. An elevated anion gap accompanies acidosis in organic acidemias, mitochondrial disorders, aminoacidopathies, and disorders of carbohydrate metabolism. Lactate and pyruvate should also be obtained in patients with suspected or confirmed acidosis. Lactic acidosis, although seen in many IEMs, is a nonspecific finding in critically ill patients that results from hypoxia and poor tissue perfusion. An elevated lactate/pyruvate ratio (usually >20), provides an important clue to determining whether a patient has an IEM, most commonly due to a mitochondrial or cytoplasmic enzyme disorder. Urine with low specific gravity and pH of 5.0 or higher in the setting of metabolic acidosis suggests renal tubular acidosis, which, although not specific for an IEM, is a feature of many IEMs. For most patients with primary metabolic acidosis, it is appropriate to test plasma amino acids, acylcarnitine profile, urine organic acids, and acylglycines.

Hyperammonemia
An ammonia concentration greater than 100 mcg/dL (60 mcmol/L) in neonates and greater than 80 mcg/dL (50 mcmol/L) in children is abnormal and potentially neurotoxic. Early clinical manifestations of hyperammonemia are tachypnea, anorexia, and irritability. Older individuals might report headache, abdominal pain, and fatigue. Progression to vomiting, lethargy,
acidopathies or mitochondrial disorders might have ketonuria with normal glucose levels. In addition to plasma for amino acids and acylcarnitine profile and urine for organic acids and acylglycines, serum ketones, plasma free-fatty acids, and endocrine studies, including insulin and serum cortisol, should be performed.

Other Studies
Liver function tests, including bilirubin, transaminases, and coagulation studies, most commonly reveal elevated levels in patients with disorders of protein metabolism or fatty acid oxidation defects but can reveal elevated levels in IEMs within most categories. Triglycerides and uric acid levels can be elevated in glycogen storage disorders. Lactate dehydrogenase, creatine kinase, and aldolase levels are most commonly elevated in patients with disorders of carbohydrate metabolism, fatty acid oxidation defects, and mitochondrial disorders and should be tested in patients with symptoms of skeletal muscle myopathy and/or myoglobinuria. Urine test results positive for non-glucose-reducing substances suggest possible aminoacidopathy or carbohydrate intolerance disorder (eg, galactosemia).

In select cases, CSF, collected at approximately the same time as plasma, should be frozen for possible measurement of lactate, pyruvate, and IEM-specific neurometabolites, particularly neurotransmitters.

Histologic evaluation of affected tissues, most commonly liver and/or skeletal muscle, and enzyme assay or DNA analysis in leukocytes, erythrocytes, skin fibroblasts, and liver or other tissues might be appropriate but are not usually emergent. Other studies, including evaluation for bacterial or viral infection, radiography, computed tomography, MRI, ultrasonography, electrocardiography, and/or echocardiography, should be obtained emergently as clinically indicated for evaluation and management of life-threatening manifestations of IEMs.

In the child who has died, identifying an IEM might still be important because currently asymptomatic family members and/or future children might be affected. Samples of plasma, serum, urine, and possibly CSF and skin, bile, vitreous humor, bone marrow, and selected organ...
In addition to rapid assessment and aggressive management of airway, breathing, and circulation, goals of treatment of IEMs are to stop intake of harmful substances, correct metabolic abnormalities, and eliminate toxic metabolites. Even the apparently stable patient with mild symptoms can deteriorate rapidly with progression to death within hours. For an undiagnosed suspected IEM, this means initiating treatment empirically as soon as the diagnosis is considered. For patients with a known IEM, treatment should be disease and patient specific. Families should have an emergency treatment plan specifically for their child developed by their IEM specialist with them or available electronically. In addition, families might have a plan detailing their desired interventions should lifesaving resuscitation be necessary.”

**Differential Diagnosis**

Because the signs and symptoms of inborn errors of metabolism are nonspecific, IEMs are frequently not considered in the differential diagnosis. Therefore, a high index of suspicion is important because the physician must initiate appropriate therapy without delay (and without a final diagnosis in hand) to decrease morbidity and mortality. A concomitant acquired disorder can obscure the diagnosis of an inherited metabolic disease condition. For example, neutropenia can occur in organic acidemias, leading to an increased susceptibility of bacterial infection. The underlying disorder might be missed if an infection is also present and focus is directed solely toward antimicrobial therapy. *Escherichia coli* sepsis frequently supervenes in neonates with galactosemia, and the typical jaundice, liver failure, and vomiting that accompany that disorder might wrongly be ascribed solely to sepsis as well.

**Management**

In addition to rapid assessment and aggressive management of airway, breathing, and circulation, goals of treatment of IEMs are to stop intake of harmful substances, correct metabolic abnormalities, and eliminate toxic metabolites. Even the apparently stable patient with mild symptoms can deteriorate rapidly with progression to death within hours. For an undiagnosed suspected IEM, this means initiating treatment empirically as soon as the diagnosis is considered. For patients with a known IEM, treatment should be disease and patient specific. Families should have an emergency treatment plan specifically for their child developed by their IEM specialist with them or available electronically. In addition, families might have a plan detailing their desired interventions should lifesaving resuscitation be necessary.

Once airway, breathing, ventilation, and vascular access have been established, hydration, glucose as necessary to correct hypoglycemia and prevent catabolism, and therapy to correct acidosis and hyperammonemia must be initiated. Protocols for treatment of acute illness in patients with a suspected IEM and some diagnosed IEMs are available on the New England Consortium Web site. Consultation with a metabolic specialist should be initiated.
For patients with an aminoacidopathy, organic acidemia, or fatty acid oxidation defect, hyperammonemia usually improves with rehydration and the reversal of acidosis and hypoglycemia. For severe hyperammonemia in patients with urea cycle defects, hemodialysis is the mainstay of treatment. Extracorporeal membrane oxygenation–assisted hemodialysis is the most effective form of hemodialysis but has increased risks, particularly in neonates. Exchange transfusion is not effective. Recommendations of the New England Consortium are to consider dialysis for ammonia levels greater than 300 mcg/dL (175 mcmol/L) and transfer to a facility or unit with dialysis capability for ammonia levels greater than 200 to 250 mcg/dL (120–150 mcmol/L).

If dialysis is not immediately available for ammonia levels between 100 and 200 mcg/dL (60–175 mcmol/L), sodium phenylacetate and sodium benzoate (available as Ammonul) should be administered to patients with known or suspected urea cycle defect to augment nitrogen excretion.109 The combination of sodium phenylacetate and sodium benzoate is approved as adjunctive therapy for acute hyperammonemia and associated encephalopathy due to urea cycle defects but is also used to treat hyperammonemia of unknown origins. Ondansetron should be administered with sodium phenylacetate and sodium benzoate. Potassium, which can be depleted by sodium phenylacetate and sodium benzoate, should be monitored and replaced as potassium acetate, 0.5 to 1 mEq/kg per hour, as needed. In addition, 10% arginine hydrochloride, which enhances urea cycle activity, should be given for treatment of urea cycle defects with the exception of arginase deficiency. Citrulline can be administered to augment nitrogen clearance in urea cycle defects with the exception of arginosuccinic acid synthetase (citrullinemia) and argininosuccinase acid lyase deficiencies. Although data are limited, recent literature suggests hypertonic saline should be given for cerebral edema rather than mannitol. Corticosteroids increase catabolism and therefore should not be given. To assess patient response to treatment, glucose, acid-base status, ammonia, and electrolytes should be monitored serially.

if available. With appropriate therapy, patients can recover completely without sequelae.

Hydration is critical not only to restore intravascular volume but also to promote urinary excretion of toxic metabolites. For IEMs that are potentially acutely life-threatening, fluid boluses should be administered as 10% dextrose normal saline unless the patient is hypoglycemic, in which case a glucose bolus is indicated (0.5 g/kg as 10% dextrose for neonates and 10% or 25% dextrose for children; note the “50 rule” described earlier). Preferentially, colloids should be avoided because they increase nitrogen load. After bolus fluid, maintenance fluid should be administered as 10% to 12.5% dextrose half normal saline at a rate high enough to prevent catabolism by maintaining serum glucose at 120 to 170 mg/dL. Large fluctuations in serum glucose should be avoided. Although controversial, 0.1 to 0.2 U/kg per hour of insulin can be administered to prevent hyperglycemia. For a suspected IEM, stop all oral intake to ensure that potentially harmful protein or sugars are avoided. For a known IEM, dietary restriction should be disease specific.

Treatment of acidosis with bicarbonate is thought to be indicated for IEMs because of ongoing acid production; however, data regarding the degree of acidosis for which it should be initiated and dose are lacking. Recommendations for administration of bicarbonate range from pH 7.0 to 7.2 and serum bicarbonate as low as 14 to 16 mEq/L. The recommended dose range is 0.25 to 2 mEq/kg per hour, depending in part on the specific IEM. Bicarbonate should be administered cautiously in patients with hyperammonemia because alkalinization converts NH₄⁺ to NH₃, which is less readily excreted in urine and more readily crosses the blood-brain barrier, increasing the risk of brain complications. If administering sodium bicarbonate, potassium should be given as potassium acetate. For severe, intractable metabolic acidosis, hemodialysis should be considered. Acidosis must be corrected cautiously to minimize paradoxical effects on the CNS that can be caused by rapid or overcorrection.

Hyperammonemia can be acutely life-threatening and must be treated immediately.
Appropriate antibiotics should be given if there is concern about possible serious bacterial infection. As necessary, fresh frozen plasma should be administered to treat coagulopathy.

Intravenous L-carnitine, 25 to 50 mg/kg, can be administered empirically in life-threatening situations associated with known or suspected carnitine deficiency (eg, primary carnitine deficiency, certain organic aminoacidopathies, and fatty acid oxidation defects); however, because it can be harmful with some IEMs, consultation with an IEM specialist is highly recommended. Carnitine should not be administered with sodium phenylacetate and sodium benzoate. Intravenous pyridoxine (B₆), 100 mg; IV folate, 2.5 mg; and/or biotin, 10 to 40 mg, orally or via nasogastric tube can be given empirically to neonates with seizures unresponsive to conventional anticonvulsants to treat a possible vitamin or cofactor responsive IEM. Although there are other disease-specific adjunctive therapies, administration of these agents in the ED is rarely indicated.

Rapid assessment, establishment of vascular access, and administration of appropriate fluids (with glucose) are priorities in treating patients with IEMs in acute crisis. Dehydration and hypoglycemia should be treated with boluses of normal saline and dextrose solutions, respectively. Maintenance IV fluids should then be started to prevent recurrence of hypoglycemia and hypovolemia and stop the catabolic spiral. Administration of 10% dextrose (with electrolytes based on the child’s weight) at 1.5 times maintenance is usually adequate. General supportive measures (maintenance of oxygenation and acid/base balance and treatment of infection) should, of course, be provided. Intravenous carnitine (100 mg/kg) can be beneficial in certain organic acidemias and fatty acid oxidation disorders but is usually used after consultation with a metabolic specialist. The child might need immediate admission to an intensive care unit for further monitoring and other procedures (eg, hemodialysis).

In children who are already known to have an IEM, the importance of listening closely to the history provided by the parents or regular caregiver must be stressed. A child with a metabolic disorder can appear relatively well but might decompensate rapidly. If such a child is not maintaining adequate fluid and caloric intake, “does not seem to be his usual self,” or both, the metabolic specialist should be contacted, and IV fluids with dextrose should be administered even in the absence of documented hypoglycemia or other markers of metabolic imbalance. The goal in such cases is to provide therapy in a timely manner to prevent a metabolic crisis.

**THE BOTTOM LINE**

**Issues in the Diagnosis and Management of IEMs**

- Maintain a high index of suspicion, especially in the presence of hypoglycemia, metabolic acidosis, hyperammonemia, and or inappropriate ketosis.
- Although specialized tests are needed to arrive at a final diagnosis, simple laboratory studies often provide the first clues to the presence of an IEM. Obtain pretreatment specimens when possible.
- Early detection and treatment are essential to optimize immediate and long-term outcome.
KEY POINTS

Initial Treatment of Patients With IEMs

• Evaluation
  - Contact metabolic specialist immediately once diagnosis is suspected.
  - Obtain specimens, ideally before treatment.
    • Blood: venous blood gas, glucose, electrolytes, BUN, creatinine, complete blood cell count
    • If lethargic, ammonia (free flow, ice)
    • Lactate dehydrogenase, aldolase, creatinine kinase if skeletal muscle myopathy is suspected
    • Lactate, pyruvate if acidosis (free flow, special perchloric acid tube for pyruvate)
    • Plasma amino acids, acylcarnitine profile if initial evaluation supports possible IEM
    • Urine: urinalysis, urine culture if concern of infection; urine amino, organic acids, acylglycine if initial evaluation supports possible IEM

• Treatment
  - Stop all oral feedings
  - Fluid hydration with 10% dextrose normal saline
  - Glucose to treat hypoglycemia, prevent catabolism (use the “50 rule”)
  - IV bicarbonate corrects acidosis but could worsen hyperammonemia equilibrium
  - For hyperammonemia, plan for detoxification by hemodialysis and/or sodium phenylacetate and sodium benzoate (Ammonul) and arginine (except for arginase deficiency); if using sodium phenylacetate and sodium benzoate, administer ondansetron and treat hypokalemia with potassium acetate
  - Seizures: IV pyridoxine (B6), 100 mg; IV folate, 2.5 mg; and/or biotin, 10 to 40 mg, orally or via nasogastric tube
  - Suspected carnitine deficiency: IV l-carnitine, 25 to 50 mg/kg
Check Your Knowledge

1. Which of the following is most associated with the development of cerebral edema in a child with diabetic ketoacidosis (DKA)?
   A. Ketosis
   B. High fluid administration (20 mL/kg per hour)
   C. Urinary tract infection
   D. Treatment with sodium bicarbonate

2. Which of the following is a prominent finding in female newborns with congenital adrenal hyperplasia?
   A. Acanthosis nigricans
   B. Ambiguous genitalia
   C. Hyperpigmentation
   D. Midline facial defects and microphallus

3. Syndrome of inappropriate secretion of antidiuretic hormone should be treated with:
   A. intravenous hydrocortisone.
   B. oral sodium supplements.
   C. hypertonic saline, 10-mL/kg infusion if the sodium concentration is 130 mEq/L.
   D. fluid restriction unless the patient is seizing or severely lethargic or comatose.
   E. sodium restriction.

4. Which of the following statements regarding hypernatremia in patients with diabetes insipidus (DI) is correct?
   A. Never occurs in infants with DI because of high fluid intake
   B. Occurs in all patients with DI
   C. Rare in older children with DI and normal thirst mechanisms
   D. Should be treated with 3% sodium chloride solution

5. Of the following inborn errors of metabolism (IEMs), which is most likely to present with an insidious onset and progressive worsening?
   A. Organic acidemias
   B. Aminoacidopathies
   C. Fatty acid oxidation defects
   D. Lysosomal storage disorders

6. Laboratory abnormalities due to IEMs commonly include which of the following (best choice)?
   A. Metabolic acidosis, hyperammonemia, hypoglycemia
   B. Hypoglycemia, ketosis, leukopenia
   C. Hematuria, azotemia, hypercholesterolemia
   D. Proteinuria, hypercholesterolemia, hypoalbuminemia
   E. Hypocalcemia, hyponatremia, hypokalemia

7. The most appropriate initial rapid fluid infusion for a patient with a suspected IEM who is tachycardic, hypoglycemic, and acidotic is:
   A. normal saline (20 mL/kg).
   B. lactated Ringer solution (20 mL/kg).
   C. 10% Dextrose normal saline (20 mL/kg).
   D. 25% Dextrose (2 mL/kg) and normal saline (20 mL/kg).
   E. 10% Dextrose (2 mL/kg) and normal saline (20 mL/kg).

8. The most effective treatment for severe hyperammonemia due to an IEM is:
   A. hemodialysis.
   B. exchange transfusion.
   C. peritoneal dialysis.
   D. sodium phenylacetate and sodium benzoate (Ammonul).
   E. hyperventilation.
References


CHAPTER REVIEW


A 10-year-old boy presents to the emergency department (ED) with altered mental status and a 2-week history of polyuria and weight loss. He is experiencing abdominal pain. On examination, he has a respiratory rate of 36/min, a heart rate of 150/min, a systolic blood pressure of 80 mm Hg, and a temperature of 37.9°C (100.2°F). Pulse oximetry oxygen saturation is 97% on room air. On examination, he appears lethargic, has dry mucous membranes, has normal abdominal examination results, and has nonfocal neurologic examination results. Bedside rapid glucose measurement is above the upper limit of the glucose meter (>500 mg/dL).

1. **What therapeutic actions must be taken immediately?**
2. **What laboratory tests would you order?**
3. **What is the most important potential complication?**

This child is hypotensive, mainly due to dehydration. Immediate volume resuscitation with boluses of normal saline (20 mL/kg) should be administered to restore perfusion. An insulin infusion should be initiated as soon as possible after intravenous fluid therapy has been initiated.

A reasonable set of initial laboratory tests would include measurement of serum electrolytes, a venous blood gas analysis, and urinalysis for ketones. Complete blood cell counts are not usually helpful. This child must be closely monitored for the development or progression of cerebral edema. Clinically apparent cerebral edema occurs in approximately 1% of children with DKA. Therefore, frequent neurologic monitoring is indicated for all children with DKA.

A 14-month-old girl presents to the ED with a 1-day history of tactile fever, loss of appetite, and intermittent emesis. This morning, she did not seem interested in her usual breakfast and seemed sleepier than usual. On examination, she has respirations of 40/min, a heart rate of 170/min, blood pressure of 80/40 mm Hg, and a temperature of 36.0°C (96.8°F). She appears lethargic and has mildly dry mucous membranes and no obvious source of infection. Bedside rapid glucose measurement reveals a blood glucose level of 20 mg/dL.

1. **What therapeutic measures must be taken immediately?**
2. **What laboratory tests would you order?**
3. **What complications can occur as part of the disease process and secondary to therapeutic intervention?**
The child is hypoglycemic and likely volume depleted. Resuscitation with boluses of 2 mL/kg of 25% dextrose (or 5 mL/kg of 10% dextrose) to normalize blood glucose levels should be started without delay, followed by administration of volume (normal saline bolus of 20 mL/kg) until perfusion is restored. Fluids consisting of 10% dextrose and 0.45% sodium chloride at 1.5 times maintenance should be started. Appropriate potassium supplementation is added as needed. Initial studies include measurement of electrolytes, measurement of glucose, blood gas analysis, complete blood cell count, blood and urine cultures, and urinalysis for ketones. If possible, samples should be obtained before initiation of therapy, including administration of glucose and fluids. The finding of nonketotic (hypoketotic) hypoglycemia is a clue to the presence of an underlying fatty acid oxidation defect. Ammonia levels might be mildly elevated. Metabolic disorders might be unmasked by an infection severe enough to cause catabolism, but an obvious infection or clear exacerbating factor is not always present. Because of the risk of multiorgan system failure, measurement of liver enzymes, blood urea nitrogen, creatinine, and creatine phosphokinase levels can also be helpful. Metabolic studies include measurement of lactate, ammonia, plasma amino acids, carnitine, acylcarnitine profile, and urine organic acids. Freezing aliquots of serum and urine and contacting a metabolic specialist for further guidance with respect to specialized testing are appropriate alternatives if your laboratory does not routinely handle such specimens.

Fatty acid oxidation disorders can progress to multiorgan system failure (Reye-like syndrome). Seizures, cardiomyopathy, cardiac arrest, liver failure, and kidney failure might supervene. There is a significant risk of death.

Secondary to therapeutic interventions, cerebral edema of unclear pathogenesis might occur in some IEMs, particularly those with hyperammonemia. This complication can also occur if a high rate of relatively dilute dextrose solution (eg, 5% dextrose) is used. Close monitoring of fluid resuscitation and neurologic status is therefore imperative.