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Hypoglycemia is a metabolic disorder not infrequently encountered in the emergency department (ED). Up to 20% of patients with diabetes mellitus using insulin or oral hypoglycemic agents (OHA) will experience symptoms of hypoglycemia in their lifetimes, often requiring ED evaluation and therapy.[1-3] If one considers all patients with altered mentation presenting to the ED, hypoglycemia is identified as the underlying process in approximately 7% of cases. In addition to the diabetic patient, numerous other clinical scenarios may involve hypoglycemia, including toxicologic, infectious, psychiatric, and metabolic syndrome presentations.4,5

Fortunately, hypoglycemia most often is diagnosed easily and is rapidly treated with satisfactory patient outcome in the ED. The classic presentation of hypoglycemia involves a diaphoretic patient with a history of diabetes mellitus who is found to have an altered mental status; the patient is subsequently found to have used insulin or OHA and taken relatively little oral nutrition. The patient's presentation and history, however, may lead the provider to believe that the condition is due to some other condition such as a cerebrovascular accident, status epilepticus, intoxication, sepsis, or traumatic injury.[6-10]

The purpose of this review is to outline current diagnostic and management approaches to the patient suspected of having hypoglycemia.

— The Editor

Hypoglycemia: Current Strategies for Diagnosis and Management

Authors: **William J. Brady, MD, FACEP**, Associate Professor of Emergency Medicine, Department of Emergency Medicine; Associate Professor of Internal Medicine, Department of Internal Medicine; Program Director, Emergency Medicine Residency, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, VA; **Alan C. Dalkin, MD,** Associate Professor of Internal Medicine, Department of Internal Medicine; Program Director, Endocrinology and Metabolism Fellowship Program, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, VA.

Peer Reviewer: **David P. Sklar, MD,** Chair, Department of Emergency Medicine, University of New Mexico-School of Medicine, Albuquerque.

Introduction

The diagnosis of hypoglycemia is based on the presence of Whipple's triad, which consists of a low plasma glucose concentration, symptoms consistent with the diagnosis, and improvement of these symptoms following an increase in the plasma glucose level. This definition certainly has a number of problems when applied clinically. For example, diabetic patients may manifest hypoglycemic symptoms at normal or even elevated plasma glucose values due to the presence of altered glycemic thresholds. In the other extreme, apparently normal women may develop asymptomatic plasma glucose concentrations of fewer than 40 milligrams per deciliter (mg/dL) during a fast. The serum glucose value must not be considered the absolute criterion for hypoglycemia; rather, the serum sugar level must be correlated with the clinical picture.

Both the diagnosis and treatment of hypoglycemia are easily accomplished, assuming the clinician considers the possibility of such a metabolic derangement. It is imperative that the emergency physician consider hypoglycemia in all patients with any mental status abnormality, focal neurological deficit, or seizure activity—even when the findings seem to be explained initially by other etiologies. Blood glucose should be monitored in any patient with any degree of mental status abnormality, even if the altered mentation appears to be explained by other clinical findings or medical conditions. An estimate using a bedside glucose monitoring device is sufficient, with the understanding that these devices have greater error at the high and low extremes.

If bedside monitoring suggests hypoglycemia, laboratory levels should be determined, followed by rapid glucose replacement therapy. Significant medical harm to the patient and medicolegal risks for the emergency physician are issues to consider in cases involving misdiagnosis, incorrect therapy, and inappropriate disposition.[11] Although hypoglycemia is rarely fatal, significant, irreversible central nervous system (CNS) damage may occur if the blood glucose concentration is not rapidly corrected. Further, medical interventions such as neuromuscular blockade-assisted endotracheal intubation may be avoided with prompt normalization of the mental status abnormality by dextrose infusion.[8-10]

Clinical Pathophysiology

Blood glucose homeostasis is essential for maintenance of normal brain function, and involves a complex interaction of neural, metabolic, and hormonal factors. The brain requires approximately 150 grams/day of glucose, which must be continuously available.

Specific measurements of daily glucose requirements in the child are lacking; on the basis of animal studies, however, it appears that the necessary amount is two- to three-fold greater compared to the adult. The CNS depends upon glucose as its primary energy source, requiring a continuous supply of carbohydrate fuel for normal function; the CNS has a small reservoir of glucose that is sufficient for only a few minutes of normal brain function. Ketone bodies may be used by the CNS for metabolism if glucose is not available. In the acute setting, neuronal death due to hypoglycemia begins rapidly after the onset of significant mental status alteration, particularly if coma ensues. Despite these stringent demands, the body normally functions quite well in maintaining plasma glucose levels within a narrow range even with constant changes in glucose intake and/or utilization.

Glucoregulation. The primary glucoregulatory organs are the pancreas and the adrenal medulla and cortex and the pituitary gland. These organs maintain glucose control via the release and interaction of various hormonal agents, including insulin, glucagon, the catecholamines epinephrine and norepinephrine, cortisol, and growth hormone. Insulin is the major metabolic regulatory factor, acting predominantly in the liver, skeletal muscle, and adipose tissue. The secretion of insulin suppresses endogenous glucose production, stimulates glucose utilization, and increases glucose storage in the form of glycogen, thus lowering the plasma glucose concentration.

The first defense against the development of hypoglycemia is a decrease in insulin secretion. It has been clearly demonstrated, however, that additional counter-regulatory mechanisms are involved in a complex hierarchical fashion. Experimental studies have demonstrated that both glucagon and epinephrine are of primary importance in the acute protection against hypoglycemia. Both of these counter-regulatory hormones are the only agents capable of stimulating hepatic glucose production within minutes of their release into circulation, primarily via glycogenolysis (the release of glucose from its intracellular storage depot glycogen).

The effect of these two hormones, beyond the immediate period after their release, is felt predominately through their effect on gluconeogenesis (i.e., the de novo production of glucose from other metabolic substrates). Glucagon is thought to be the major counter-regulatory hormone, while epinephrine is important under certain conditions, especially during glucagon deficiency and in the generation of warning symptoms of hypoglycemia: the hyperepinephrinemic constellation of findings. Epinephrine also

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Editorial Group Head: Valerie Loner
Managing Editor: Suzanne Zunic
Marketing Manager: Schandale Kornegay

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stimulates hepatic glucose production and limits glucose utilization. In contrast to glucagon and epinephrine, glucocorticoid and growth hormone responses to the presence of hypoglycemia are thought to be of minor importance in the acute setting; in fact, cortisol and growth hormone have been shown to be largely involved in the protection against prolonged hypoglycemia which can last days to weeks.

The fasting period describes the interval between feedings, beginning approximately four hours after eating and extending up to the next meal; blood glucose concentrations can begin to decline in as little as six hours when fasted. In the fasted individual, the maintenance of normal blood glucose levels are dependent on an adequate supply of endogenous gluconeogenic substrates (amino acids, glycerol, lactate), functionally intact hepatic and renal glycogenolytic and gluconeogenic enzymatic systems, and normal endocrinologic function for integrating and modulating these processes. Hypoglycemia may result if any part of this system is disrupted.

During fasting, relatively low insulin levels initiate the mobilization of these various stored fuels from host tissue sources. The most readily and rapidly available source of glucose is hepatic glycogen that is formed via glycogenolysis. The glycogen reserve is limited and will be depleted after 24-48 hours of fasting in the healthy patient and possibly earlier in the malnourished individual (e.g., chronic alcohol abuser or patient with end stage renal disease). With continuation of fasting (approximately 4-6 hours), gluconeogenesis becomes the primary source of blood glucose required for CNS metabolism and other bodily processes.

Gluconeogenesis, which takes place primarily in the liver, uses various metabolic substrates to generate this additional glucose supply. Amino acids represent one such source of metabolic substrate for gluconeogenesis and are mobilized from muscle tissue via proteolysis, which is facilitated by low insulin levels and mediated by both cortisol and glucagon. Lactate, from recycled glucose, and glycerol, from lipolysis, represent relatively minor yet important sources of substrate for gluconeogenesis. During overnight fasting, 90% of gluconeogenesis occurs via proteolysis with conversion of amino acids to glucose.

The adult human is capable of maintaining normal blood glucose levels even when totally deprived of caloric intake for weeks, or in the case of obese subjects, for several months. In the infant, this homoeostatic process is more complex. The normal term infant exhibits an immediate drop in serum glucose concentration during the first 4-6 hours of life; this reduction ranges from approximately 45 mg/dL to a level equal to the maternal concentration. The child must quickly assume the function of blood glucose homeostasis. In the fasting state, the normal neonate and infant exhibit a progressive fall in the blood glucose content to hypoglycemic levels when fasted for relatively short periods.

This response is in marked contrast to the adult who is capable of maintaining normal serum glucose values for prolonged periods without an exogenous supply of metabolic fuel. The specific reasons for this difference are unclear, yet it is obvious that the young individual, when fasted, is unable to supply sufficient glucose to meet the obligatory metabolic demands of the body. Similar issues are encountered in the malnourished adult who has fasted for greater than 12 hours; for example, the chronic alcoholic who is managed in an ED-based observation unit.

Symptoms and Responses to Hypoglycemia

Development of low serum sugar values without the physiologic ability to react places the individual at greater risk for coma and other neurologic sequelae; the patient with such a process will not recognize the complication until lower serum sugar levels are reached. Various issues contribute to an unawareness of hypoglycemia, including age, comorbidity, medication therapy, autonomic neuropathy, and the degree of serum sugar control. It has been suggested that the elderly patient is more likely to experience hypoglycemia without an awareness of the event; the presence of past CNS injury, such as stroke, in the older patient also increases the chance of unrecognized hypoglycemia.

Beta-adrenergic receptor antagonists block the effects of epinephrine, thereby contributing to a patient being unaware of hypoglycemia. Furthermore, patients with diabetes mellitus and autonomic neuropathy demonstrate blunted counter-regulatory responses to hypoglycemia—such a blunted response may result clinically in a patient's being unaware of hypoglycemia.[12] With increasingly rigid control of the serum sugar (i.e., a lower mean serum sugar level maintained over time), it has been demonstrated that patients with diabetes mellitus without neuropathy also have reduced responses of the counter-regulatory hormones—potentiating a lack of awareness of hypoglycemia.[13] This may result from either a lack of CNS recognition of hypoglycemia or impaired autonomic response to low serum sugar.

Etiology of Hypoglycemia: Common Syndromes

A number of clinical conditions that produce hypoglycemia are recognized and frequently encountered in the ED. Please see Table 1 for a listing of such syndromes relative to patient age. Perhaps the most frequent situation involves the patient with diabetes mellitus who is maintained on either insulin or OHA. Excessive medication use and/or lack of caloric intake naturally results in hypoglycemia. Acute ethanol intoxication, chronic alcohol abuse, chronic malnutrition, liver disease, sepsis, fasting, and endocrinopathies (hypothyroidism, hypoadrenalism, and insulinoma) also are common settings in which hypoglycemia develops. Unfortunately, the clinical manifestations noted on ED presentation are not predictive of the etiology of hypoglycemia; in many instances, the ultimate etiology is not discovered in the ED. The most common clinical scenarios producing hypoglycemia in patients presenting to an urban ED were noted to occur at the following frequencies: diabetic medical therapy, 54%; ethanol use, 48%; and sepsis, 12%.[4]

Pharmacologic therapy for diabetes mellitus is the most frequently cited reason for development of hypoglycemia managed in the ED.[4] Typically, the patient has a history of diabetes mellitus and is taking physician-supervised medications for treatment of the condition; at times, however, the patient without diabetes

Table 1. Potential Etiologies of Hypoglycemia Relative to Age

AGE GROUP	CAUSE/SYNDROME
NEONATE	
	Maternal diabetes mellitus
	Maternal toxemia
	Small size for gestational age
	Sepsis
	Malnutrition/fasting
	Hyperinsulinism
	Deficiency of glycogenolytic enzyme
	Deficiency of gluconeogenic enzyme
	Hormone deficiency
	Medication/toxin effect
	Idiopathic
INFANT	
	Sepsis
	Malnutrition/fasting
	Hyperinsulinism
	Deficiency of glycogenolytic enzyme
	Deficiency of gluconeogenic enzyme
	Hormone deficiency
	Medication/toxin effect
	Idiopathic
CHILD	
	Sepsis
	Malnutrition/fasting
	Ketotic hypoglycemia
	Islet cell adenoma
	Hormone deficiency
	Medication/toxin effect
	Idiopathic
ADOLESCENT	
	Sepsis
	Malnutrition/fasting
	Islet cell adenoma
	Hormone deficiency
	Medication/toxin effect
	Idiopathic
ADULT	
	Sepsis
	Malnutrition/fasting
	Medication/toxin effect

mellitus will present with hypoglycemia resulting from an adverse reaction to such medical therapy.

The various patient scenarios include the following: 1) the diabetic patient who correctly uses anti-diabetic medications yet consumes little oral nutrition with or without significant physical exertion; 2) a similar patient who develops hypoglycemia due to incorrect medication dosing or drug interactions; 3) the patient—with or without a history of diabetes—who knowingly injects insulin or ingests an OHA in a self-harm attempt; and 4) the child who is accidentally exposed to diabetic medications.

If one considers the long-term use of insulin or OHA in the management of diabetes mellitus, hypoglycemia will occur yearly in 15-20% of patients.[1,2,4] The characteristics of the diabetic patient who is more likely to experience hypoglycemia include male gender, both adolescent and very elderly age groups, African-American heritage, a history of hypoglycemia, "intensive" diabetic medical therapy, insulin use (compared to OHA therapy), polypharmacy (more than 5 agents), and recent hospitalization.[1-3]

Pharmacologic Precipitants. Several classes of oral hypoglycemic agents used in the treatment of diabetes can cause hypoglycemia.[14,15] The sulfonylureas act to increase endogenous insulin secretion and thereby increase hepatic glucose uptake and peripheral tissue glucose disposal. Thus, sulfonylurea treatment with reduced caloric intake can result in hypoglycemia. Sulfonylureas are both metabolized by the liver and cleared by the kidneys. Therefore, progressive renal insufficiency, as is seen with diabetic nephropathy, can prolong the half-life of certain sulfonylureas and result in prolonged hypoglycemia.

The thiazolidinediones are a newer class of agents that act to reduce insulin resistance in skeletal muscle, liver, and adipose tissue via peroxisome proliferator-activated receptors (PPAR). In so doing, they do not directly alter insulin secretion; therefore, their use as single agents is not associated with hypoglycemia. The introduction of the medication metformin, a biguanide, has added another medication to the list of agents encountered in the diabetic patient. Metformin improves the end-organ sensitivity to insulin and acts via a number of mechanisms in the diabetic patient, including a reduction in hepatic glucose output and enhanced peripheral glucose uptake. Metformin is considered an anti-hyperglycemia drug rather than a hypoglycemic agent such as the sulfonylureas and insulin; hypoglycemia is rarely encountered in patients using only metformin.

Notably, current approaches to treating patients with Type II diabetes mellitus include step-wise addition of medications as glycemic control worsens. In so doing, combinations of agents such as sulfonylureas and biguanides or thiazolidinediones are often utilized. While the biguanides or thiazolidinediones when used alone do not precipitate hypoglycemia, when used with an agent that increases insulin secretion (e.g., a sulfonylurea), hypoglycemia may become a significant problem.

From the perspective of drug-induced hypoglycemia, diabetic medical therapy is the most frequent etiologic factor in the hypoglycemic patient who presents to the ED; 54% percent of hypoglycemic patients presenting to the ED developed the complication due to such adverse medication effects.[4] Among patients experiencing symptomatic low blood sugar, insulin is the most frequent specific agent, and is reportedly responsible for hypoglycemia twice as often as OHA.[3] OHAs, both in diabetic patients using such therapy and in children accidentally exposed to the medication, represent another frequent drug-related etiology of hypoglycemia.[3,16,17] Seltzer showed that 220 (47%) of 473 patients exhibited exogenous hypoglycemia resulting from the use of OHA.[5] Additionally, ethanol was involved in 36% of cases. Three percent of these patients developed hypoglycemia

due to salicylates. Interestingly, insulin was infrequently encountered as a cause of hypoglycemia in this study.

Another commonly used medication class that may be encountered in patients developing hypoglycemia is the adrenergic-blocking agents, particularly beta-blockers. Most often, the beta-adrenergic blocking agent is implicated as a co-instigator in the development of hypoglycemia, rather than the actual cause of lowered blood sugar levels. Such medications, particularly the nonselective beta-blocker agents, impair glycogenolysis and the hyperepinephrinemic response to lowered serum sugar levels, thus predisposing to hypoglycemia. Hypoglycemia resulting from the sole ingestion of such adrenergic-blocking agents is rare.[5]

Ethanol. Approximately 50% of patients treated for hypoglycemia in an urban ED were acutely intoxicated with ethanol or were chronic alcohol abusers.[4] Alcohol inhibits hepatic gluconeogenesis, which becomes problematic when the patient has not eaten for a prolonged period and the glycogen stores have been depleted by glycogenolysis. A 12-hour fast often is sufficient for alcoholics to become hypoglycemic due to pre-existing malnutrition. Hypoglycemia also has been produced in healthy adults by infusing 75 grams of alcohol after a 36-hour fast. The depressed level of consciousness found in the patient acutely intoxicated with ethanol can mask the clinical findings of hypoglycemia, making it essential for rapid bedside serum glucose determinations to be performed on all such patients with any degree of mental status abnormality or evidence of alcohol use.

Sepsis. Sepsis may cause hypoglycemia by inhibition of gluconeogenesis and/or by increased responsiveness to insulin. Systemic hypoperfusion, often associated with sepsis, increases peripheral glucose utilization, while metabolic acidosis decreases gluconeogenesis. The multiorgan failure associated with the sepsis syndrome not infrequently includes hepatic dysfunction and an increased potential for hypoglycemia.

Pediatric Patients. Considering the pediatric perspective, the vast majority of neonates developing hypoglycemia will have clinical markers (maternal diabetes mellitus or toxemia of pregnancy, small for gestational age, or prematurity) that immediately identify these patients as high-risk infants. Hypoglycemia in most newborns resolves spontaneously within hours to days of diagnosis. In that neonatal hypoglycemia is a relatively common, transient event, it is usually treated empirically without a detailed diagnostic evaluation. If hypoglycemia in the infant is persistent or severe, however, a diagnostic evaluation must be initiated. Despite the many known causes, an infant with persistent hypoglycemia is likely to have a disorder in one of four categories, including: hyperinsulinism, deficiency of a glycogenolytic or gluconeogenic enzyme, hormone deficiency, or idiopathic disorder. Similarly, the older child with an isolated, persistent finding of hypoglycemia is likely to have one of the following disorders producing primary hypoglycemia: ketotic hypoglycemia, hormone deficiency (growth hormone or glucocorticoid), or islet cell adenoma.

Secondary hypoglycemia in children has been seen in certain toxicologic syndromes (the various diabetic medical therapies, ethanol, salicylates, and beta-adrenergic blocking agents), sepsis, and fasting states. Excessive diabetic medication use and/or lack of caloric intake naturally results in hypoglycemia. In a study by Seltzer, 3% of these patients developed hypoglycemia due to salicylates;[5] of the cases involving salicylate-induced hypoglycemia, 87% were in children with a 39% death rate. Sixteen percent of hypoglycemic cases related to ethanol occurred in children, with a mortality rate of 25% in this subgroup.

Table 2. Frequency of Presenting Signs and Symptoms in Hypoglycemia[4]

CLINICAL PRESENTATION	FREQUENCY (%)
Depressed sensorium	52
Other mental status changes	30
Hyper-epinephrinemic findings	8
Seizure	7
Focal neurologic findings	2

Clinical Presentation and Evaluation

Patients with hypoglycemia may present to the ED with a range of symptoms and signs. (Please see Table 2 for a listing of the occurrence frequency of the symptoms and signs of the hypoglycemic patient seen in the ED.) The clinical manifestations of hypoglycemia can be divided into two broad categories: neuroglycopenic and hyperepinephrinemic (also known as the autonomic or sympathomimetic findings). As glucose is the main energy source for the CNS, it is not surprising that most episodes of symptomatic hypoglycemia present with neurologic dysfunction. With a decline in serum sugar, the brain quickly exhausts its reserve supply of carbohydrate fuel, resulting in CNS dysfunction, which is manifested most commonly by alterations in consciousness such as lethargy, confusion, and unresponsiveness.

Importantly, agitation and combativeness also are seen in these patients. Other neuroglycopenic manifestations include convulsive activity and the development of focal neurologic deficits. A review of 125 cases of hypoglycemia presenting to an urban ED showed that the neuroglycopenic findings predominated.[4] A depressed sensorium was noted in 52% of cases, with other mental status changes (e.g., agitation and combativeness) found in 30% of patients. Described less frequently, seizure activity and focal neurological findings were encountered in 7% and 2% of such ED patients, respectively.[4] In the absence of neuronal damage, these neurologic deficits should reverse with the administration of glucose and do not require aggressive evaluation such as the computed tomography (CT) scan of the head.

A rapid fall in blood glucose levels and/or the hypothalamic sensing of neuroglycopenia cause the release of the counter-regulatory hormones, primarily the catecholamines epinephrine and norepinephrine. The release of these counter-regulatory hormones is responsible for the hyperepinephrinemic findings, including anxiety, nervousness, irritability, nausea, vomiting, palpitations, and tremor. These findings result from the actions of the adrenergic nervous system (e.g., catecholamine release) that are triggered by hypoglycemia. Such signs and symptoms were noted in 8% of ED patients with hypoglycemia.[4] Stimulation of the cholinergic nervous system also occurs and may result in manifestations such

as sweating, changes in pupillary size, bradycardia, and increased secretion of parotid saliva.The term "hyperepinephrinemic" is a misnomer in that cholinergic factors resulting from autonomic nervous system stimulation also are noted in certain patients.

The rapidity of onset of the hypoglycemic event in part determines the presentation. A gradual onset of hypoglycemia results from a relatively slow decrease in the serum glucose and the development of the neuroglycopenic signs and symptoms. Conversely, a sudden drop in the blood sugar level will produce anxiety, diaphoresis, tremor, and the other hyperepinephrinemic findings. In most cases of hypoglycemia, however, CNS dysfunction predominates with some degree of alteration in the level of awareness, and is accompanied by diaphoresis and tachycardia.

Children. Similar symptoms and signs are encountered in the pediatric setting, especially in the older child. Although the biochemical diagnosis of hypoglycemia is rather simple in the pediatric patient, clinical manifestations in the child can sometimes be misleading. In newborns and young infants, for example, hypoglycemia frequently presents with a number of nonspecific findings usually associated with other etiologies; these presentations include feeding difficulties, irritability, lethargy, cyanosis, tachypnea, and hypothermia. In fact, Losek has shown that approximately one in five children undergoing resuscitation have hypoglycemia requiring therapy.[18] Furthermore, hypoglycemia also has been reported in the child with dehydration of various causes as occurring approximately 10% of the time; this finding, of uncertain clinical significance, may only require appropriate therapy for the underlying illness—most often, viral gastroenteritis.[19] These signs and symptoms are in marked contrast to those encountered in the older child and the adult.

Differential Diagnosis. Unsuspected hypoglycemia may masquerade as neurologic, psychiatric, traumatic, or toxicologic disorders. Hypoglycemia has been misdiagnosed as cerebrovascular accident, transient ischemic attack, seizure disorder, traumatic head injury, brain tumor, narcolepsy, multiple sclerosis, psychosis, sympathomimetic drug ingestion, hysteria, and depression. A number of reports are found in the medical literature describing hypoglycemic patients who present with mental status abnormalities and focal neurological deficits, masquerading as cerebrovascular accidents (CVA).[6,7] These patients were initially suspected of having suffered a CVA; only later in the evaluation was the diagnosis of hypoglycemia discovered. Hypoglycemia also can masquerade as traumatic head injury with varying degrees of altered mentation,[10] as well as cardiac arrhythmia with bradycardia.[20]

Patients with hypoglycemia have been misdiagnosed with decompensated psychosis, as well as acute sympathomimetic ingestion.[8] Law enforcement officials also have detained, arrested, and eventually transported patients to the ED with unrecognized hypoglycemia; out-of-hospital information provided by police personnel should not dissuade the emergency physician from the consideration of hypoglycemia.[21] Other atypical presentations of hypoglycemia also are seen in the ED, including urticaria, night terrors in children, altered sleep patterns in adults, and orthopedic injuries, particularly posterior shoulder dislocation, which most often results from hypoglycemic convulsive activity.

Misdiagnosis. The importance of these various atypical clinical presentations is found in the initial impression of an alternative, more common explanation for the patient's abnormalities. Such an approach not infrequently leads to failure of blood glucose determination early in the evaluation. This approach also results in either a delayed or missed diagnosis, with associated morbidity due to CNS injury and/or unnecessary invasive procedures and therapies. It is imperative for emergency physicians to consider hypoglycemia as a potential cause of altered mentation and rapidly screen for this metabolic abnormality with a bedside determination followed by replacement therapy, regardless of the presumed reason for the patient's condition. The use of bedside testing is preferred in that the result is immediately available to the clinician; its result may alter therapeutic and diagnostic plans. Reliance on the clinical laboratory serum sugar result may expose the patient to prolonged, unrecognized hypoglycemia and unnecessary treatments, procedures, and investigations.[22]

Glucose Testing. Beyond serum glucose determination, the ability to evaluate hypoglycemia in the ED is limited. A thorough history, physical examination, selected radiographic investigations, and laboratory studies, such as random glucose, are the main tools available to the emergency physician. Obvious infectious, toxicologic, and metabolic issues should be investigated and ruled out as necessary. Other laboratory studies, such as measurement of the levels of serum insulin, insulin antibodies, and C peptides, should be obtained in conjunction with either the patient's primary physician or the health care provider charged with outpatient responsibility. Progressive renal insufficiency should be ruled out by an analysis of the blood urea nitrogen and serum creatinine; in that insulin is significantly metabolized by the kidney, reduced renal function will prolong its active life and cause hypoglycemia.

In most instances, the diagnosis of hypoglycemia is easily and rapidly accomplished in the ED. A bedside glucose test should be performed as soon as possible after the patient arrives to the ED if the patient has an abnormal mental status. The accuracy of these bedside reflectance tests is acceptable, though less reliable at the extremes of the spectrum, i.e., extremely low and high serum sugar levels. If possible, immediately prior to IV dextrose therapy, a serum sample should be obtained and sent to the lab for definitive analysis.

The serum glucose level at which individual patients develop symptoms varies as a function of age, sex, recent dietary intake, chronic nutritional status, emotional state, comorbidity, and medication use. Hence, a single definition which defines a level at which hypoglycemia occurs in all patients is not possible. Blood glucose levels do not predict symptoms;[4] in fact, the clinical state of the patient must be correlated with the glucose value made at the determination.[4] Patients may present with profound coma and demonstrate only modestly low serum glucose levels. Conversely, a serum sugar of 20 mg/dL may be measured in an alert patient who only complains of anxiety, weakness, and extreme hunger. In the nondiabetic patient (i.e., normal patient) with the plasma glucose value dropping to approximately 50 mg/dL, epinephrine release occurs with activation of the autonomic nervous system—and the development of the hyperepinephrinemic findings.

If the process continues without curative therapy, the serum sugar will continue to decline; neuroglycopenic signs may not occur until the serum sugar concentration reaches even lower levels in the range of 20 mg/dL. Diabetic patients with poorly controlled sugar levels appear to have higher symptomatic thresholds (i.e., higher serum glucose values) for the development of symptomatic hypoglycemia, whereas well controlled diabetics and nondiabetics have significantly lower thresholds (i.e., lower serum glucose values).[23] Anorexia nervosa and other chronic starvation states produce a lower fasting serum glucose at which patients develop symptomatic hypoglycemia.[24]

Furthermore, the definition of hypoglycemia in the infant and child differs from that commonly used in the adult. Infants and children generally become symptomatic when the blood glucose drops below a concentration of 40 mg/dL. Blood glucose concentrations below 20-30 mg/dL during the first three days of life are considered hypoglycemic in pre-term or small-for-date neonates and values below 30 mg/dL in term infants. Other investigators disagree with these limits, defining the lowest acceptable levels to be between 40 and 50 mg/dL for all age groups—children and adult. This recommendation seems reasonable for the emergency physician; such an approach will insure that all hypoglycemic patients receive appropriate therapy.

Interpretation. The serum glucose value, therefore, must not be considered the absolute criterion to define hypoglycemia. Rather, the serum sugar level must be correlated with the clinical picture and the particular patient with age and comorbidity considerations. Emergency physicians, however, must establish a numerical threshold below which prompt treatment is administered even in the absence of symptoms; a plasma glucose value below 50 mg/dL is significant and sufficient to make a diagnosis of hypoglycemia, prompting treatment. Such an approach appears reasonable in most instances in that this value represents the physiologic level at which counter-regulatory systems are activated.

When interpreting serum sugar results, it also is important to consider both the methods of sample collection and storage of the blood sample. It has been shown that the glucose values of whole blood are approximately 15% less than serum or plasma. This discrepancy is due to the relatively low glucose concentration in red blood cells—with storage, equilibriation occurs. Venous blood has been found to have a 10% lower glucose concentration when compared to either capillary or arterial blood. Finally, the collecting tube should contain fluoride to inhibit glycolysis in vitro before the sample is assayed.

Endocrine Evaluation

Having fulfilled the criteria of Whipple's triad (the presence of symptoms at the time of documented hypoglycemia with resolution of those symptoms following restoration of euglycemia), it is essential to establish a specific etiology for hypoglycemia.[25] As noted above, in the diabetic patient treated with either insulin or certain oral hypoglycemic agents, the sequence of events resulting in low blood glucose values may be readily apparent. However, it should be cautioned that in the well-controlled diabetic patient with previously rare hypoglycemia, the recent appearance of recurrent low blood sugars should alert the physician to consider additional medical conditions. For example, alteration in insulin levels and subsequent hypoglycemia may be observed in progressive renal failure or hypothyroidism. Similarly, the loss of a counter-regulatory hormone (see below), as seen in adrenal insufficiency, should be considered. Addison's disease may result from an unrelated adrenal process in patients with Type I diabetes or may be part of a polyglandular autoimmune syndrome.

Differential Diagnosis. Aside from the scenarios of exogenous insulin, oral hypoglycemic agents, alcohol intoxication, or overwhelming sepsis, identification of the cause for spontaneous hypoglycemia requires a careful and rigorous medical evaluation. Three broad categories encompass the most common causes of hypoglycemia: 1) an excess of glucose lowering hormones; 2) a deficit of glucose "stores" during fasting, usually related to depletion of glycogen stores (see above); and 3) a deficit of counter-regulatory hormones. While some physicians have grouped the various diagnoses into fasting and non-fasting patterns, the distinction between these two profiles are often blurred, and patients may have episodes of hypoglycemia that do not neatly fit into either category.

Insulinoma. Three peptide hormones retain the action of reducing blood glucose levels. This includes insulin as well as insulin-like growth factor (IGF) -I and -II. Insulinomas, islet cell tumors secreting insulin in a non-regulated fashion, are the most common tumor type resulting in hypoglycemia. These tumors usually present in patients older than age 40, with symptoms becoming apparent either with fasting or several hours after a meal. Hypoglycemia commonly occurs after exercise or alcohol ingestion. Forty percent of insulinomas are smaller than 1 cm in size, rendering it difficult to image these neoplasms. The distribution of islet cell neoplasms is generally equal between the head, body, and tail of the pancreas, though a rare tumor (< 1%) is ectopic to the pancreas. Eighty percent of insulinomas are single neoplasms, with 10% of cases having multiple adenomas (often associated with the multiple endocrine neoplasia syndromes).

As the initial step in documenting the presence of an insulinoma, it is mandatory to establish an inappropriate circulating insulin level in the presence of hypoglycemia. Moreover, hormonal evaluation should precede any attempt at imaging a possible tumor. In evaluating the relationship between insulin and glucose, this must be undertaken during a fast. Following caloric intake, patterned changes in glucose and then insulin are observed, and either high or low ratios of insulin to glucose are observed in normals as well as patients with endocrine tumors. As noted above, the prolonged fast is the gold standard test, with 30% of patients with insulinoma manifesting hypoglycemia within 12 hours, 70% within 24 hours, 92% within 48 hours, and 98% within 72 hours.

Due to the need for frequent sampling of insulin and glucose levels, as well as the severity of the hypoglycemia should it occur, these studies are routinely performed in the hospital setting. Generally, glucose and insulin values are obtained simultaneously every six hours and with any symptoms of hypoglycemia. While absolute blood glucose values at which to terminate the fast may

differ between centers, we generally view values of less than 50 mg/dL in males and 40 mg/dL in females as the thresholds below which pathologic hypoglycemia is certain. However, the presence of "typical" hypoglycemic symptoms at a higher blood glucose value may be sufficient to terminate the fast.

For establishing pathologic hypoglycemia, the ratio of insulin to glucose is calculated. Simply, insulin (μU/mL) concentration is divided by glucose (mg/dL) concentration with normals having ratios less than 0.3. To improve specificity, the "amended" insulin to glucose ratio is more widely utilized and is calculated as: (insulin (μu/mL) x 100)/ (glucose (mg/dL) - 30). Normal individuals have an AIGR less than 50. During a fast, supporting evidence for an insulinoma also may include proinsulin levels greater than 22% and a failure to detect ketonuria (assessed daily), as ongoing insulin secretion will suppress ketone body production.

As a caution in interpreting insulin levels, either exogenous insulin or the administration of oral hypoglycemic drugs such as sulfonylureas will result in abnormal insulin to glucose ratios. In that light, we suggest that a serum sample for C-peptide and a urine sample be analyzed for sulfonylurea usage at the time of hypoglycemia. In a patient administering insulin, C-peptide levels are low while insulin levels are inappropriately high. Surreptitious use of sulfonylureas increases both insulin and C-peptide concentrations; hence, results may appear quite similar to those seen in a patient with an insulinoma.

Radiographic Studies. Localizing studies for pancreatic neoplasms in general and insulinomas in specific include CT scanning, magnetic resonance imaging (MRI), angiography, selective venous sampling, and octreotide scintigraphy. As many insulin-producing neoplasms are small, CT or MRI may fail to detect the tumor. Success with angiography is highly variable, with reports ranging from 30% to 90% sensitivity. Venous sampling also is difficult and carries a substantial risk in terms of complications. Recently, it has become clear that a substantial percentage of insulinomas express cell surface receptors for somatostatin. The somatostatin analog, octreotide, has therefore been used as a diagnostic (and therapeutic) tool. Radiolabled octreotide scanning has a detection rate that varies between 40% and 80%, which is likely related to the range of receptor expression in tumor tissues as well as the technical difficulty of the procedure.

Non-Islet Cell Tumors. Non-islet cell tumors also may result in hypoglycemia. While there exist a number of postulated mechanisms for low glucose concentrations, these tumors do not release insulin itself but rather produce insulin-like peptides. IGF-1 is produced primarily by the liver and is thought to be important in multiple facets of physiology, including tissue repair and linear growth. It is primarily regulated by pituitary growth hormone. While administration of IGF-1 can reduce glucose concentrations, no tumor associated with hypoglycemia that produces solely IGF-1 has been reported to date. Moreover, acromegaly with increased growth hormone and IGF-1 concentrations is associated with hyperglycemia and insulin resistance. In contrast, IGF-2 production has been associated with hypoglycemia. Physiologically, IGF-2 is thought to be involved in fetal growth and, as it is present in an array of adult tissues, function as an autocrine/paracrine signal. Neoplasms of embryonal (e.g., Wilm's tumor, nephroglastoma, rhabdomyosarcoma, hepatoblastoma) mesenchymal (fibrosarcoma, leiomyosarcoma, hemangiopericytoma, and liposarcoma), neuroendocrine (pheochromocytoma and neuroblastoma), and epithelial (colon, liver, and breast) derivation have been described to produce IGF-2.

Notably, only the mesenchymal tumors have been shown to be associated with hypoglycemia. Measurement of IGF levels is complex as the result of numerous circulating binding protein; therefore, a complete discussion is beyond the scope of this paper. However, when present, increased IGF-2 is associated with hypoglycemia and a suppressed insulin concentration. In that instance, rigorous imaging techniques are essential, as tumors such as hemangiopericytomas may be small and located in either the truncal region or in the extremities.

Four compounds are regarded as counter-regulatory hormones: glucagon, cortisol, epinephrine, and growth hormone. Practically, glucagon deficiency occurs only in the post-pancreatectomy setting and is, therefore, not a diagnostic challenge. Similarly, though beta blockade can reduce glucagon secretion and predispose a patient to hypoglycemia, true catecholamine deficiency is essentially never a clinical concern. Isolated growth hormone deficiency appears to have a minimal role in causing hypoglycemia. In contrast, pituitary insufficiency with loss of both growth hormone and adrenocorticotropic hormone clearly can present with hypoglycemia. Primary adrenal failure of any cause is associated with hypoglycemia and, as primary adrenal failure also includes the loss of aldosterone, hyperkalemia. In this regard, measurement of cortisol and growth hormone at the time of hypoglycemia may be indicated.

Management

As in any patient presenting in extremis, the emergency physician must perform a rapid, thorough review of the ABCs, insuring a stable airway and ventilatory status, as well as an adequate hemodynamic state. After stabilization of the patient with either suspected or known hypoglycemia, the next management goal involves glucose replacement therapy. In certain cases with adequate personnel in the resuscitation area, early bedside determination of the glucose status may occur in conjunction with correction of alterations in the ABC functions. Such treatment involves rapid glucose replacement using the oral, topical (mucosal), or parenteral route.

Patients who are cooperative, lack CNS abnormalities, and are able to take liquids by mouth can be treated with oral carbohydrates. Oral replacement therapy may take the form of glucose gel or various drinks (juice or soda); solid foods such as candy should only be given to the patient with an entirely normal level of consciousness. In the rare patient without IV access when glucagon therapy is not possible (i.e., not available), the emergency physician may apply a dextrose-rich solution to the buccal mucosa; extreme care must be exercised to avoid both iatrogenic aspiration by the patient and injury to the physician by accidental biting of the examiner's finger. Furthermore, the oral glucose route may be

used in patients who initially received parenteral therapy and have normalized their mental status alteration yet require additional dextrose. Finally, fructose and other complex carbohydrates should not be used to correct hypoglycemia in that these sugars do not cross the blood-brain barrier effectively and/or require extensive metabolic conversion prior to internal consumption.

Glucose Replacement. Guidelines for oral glucose replacement therapy in the hypoglycemic patient suggest the initial use of 10-20 grams glucose, delivered in either 4 ounces of orange juice or 8 ounces of milk. Five grams is usually sufficient for an infant or toddler. Commercially available formulations will provide 5 grams of glucose per tablet. In addition, there are 3 grams of glucose in a Lifesaver candy, 4 grams per teaspoon of granulated table sugar, 10-15 grams of sugar per 120 mL of orange or apple juice, or 15 grams per application of glucose gel. The initial therapy should be followed by a laboratory determination of the glucose value and reassessment of the patient's condition within 15-30 minutes. If symptoms persist, additional oral therapy is indicated. If the patient should develop any mental status alteration during the oral replacement therapy, then parenteral treatment is required.

The adult patient with an altered level of consciousness including agitation, lethargy, or frank coma should receive a bolus of 25-50 grams of glucose as a 50% dextrose solution—the "one amp of D50" approach. The symptomatic infant and young child should be given intravenous glucose at 1 g/kg of body weight. The dilution of a 50% dextrose solution to a 25% concentration is recommended in the infant due to the possibility of tissue necrosis should accidental tissue infiltration occur. The use of 50% dextrose solution will provide 50 grams of glucose in a 100 milliliter treatment. The use of D5W intravenous fluid (a 5% dextrose solution) will provide 5 grams of glucose per liter.

A continuous infusion of at least a 10% dextrose solution is recommended in cases where hypoglycemia recurs after bolus therapy and the patient is not able to take oral carbohydrate. Such constant infusion treatment can be anticipated and empirically administered in cases of massive insulin overdose, hypoglycemia related to OHA therapy, sepsis, severe malnutrition, liver failure, profound malnutrition, prolonged fasting, and known enzyme disorder. The serum glucose level with the infusion running should be maintained at least 100 mg/dL or greater with frequent monitoring (initially every 30 minutes in the early phase of ED care). Persistent hyperglycemia, maintained by slow administration of dextrose, indicates that the infusion may be reduced and eventually withdrawn. The use of 10% dextrose solution will provide 10 grams of glucose per liter infused. Five percent dextrose infusions (i.e., D5W IV solution) provide little usable calories and, therefore, are not recommended as replacement therapy in the acute setting.

Failure to respond to parenteral glucose administration should prompt consideration for other causes of altered mental status. The emergency physician, however, must realize that profound or prolonged hypoglycemia may not respond immediately to replacement therapy; the recovery from such extreme hypoglycemia may require significantly longer periods of time, approaching 5-10 minutes.[10] Other etiologies of altered consciousness must be investigated in the interim.

Glucagon. If IV access is not possible, glucagon use should be considered. Glucagon can be administered intramuscularly, subcutaneously, or intravenously. In most cases, glucagon is given via the intramuscular route at a dose of 1 mg for the adolescent and adult; the infant and larger child doses of glucagon are 0.5 mg. Response to glucagon therapy is generally slower when compared to IV dextrose, requiring 7-10 minutes prior to normalization of mental status; additionally, the response to glucagon administration may be short-lived.[26,27] Glucagon acts by stimulating glycogenolysis in the liver and therefore may not be effective in malnourished patients with little to no hepatic glycogen reserve, such as the chronic ethanol abuser. Glucagon also may be given to hypoglycemic patients who have not responded to IV dextrose; if so, it is usually administered IV along similar dosing recommendations.

In patients developing sulfonylurea-related hypoglycemia, the theoretical risk of paradoxically worsening hypoglycemia is present, though such individuals not infrequently receive glucagon with favorable clinical response. Such an event may occur via inhibition of hepatic gluconeogenesis, which has been noted with chronic use of OHA. Glucagon also may potentiate insulin release in healthy patients as well as diabetics. Nonetheless, endocrinologists recommend the use of glucagon in addition to dextrose in the treatment of patients with hypoglycemia related to most etiologies including OHA ingestion.

Octreotide. Octreotide, a synthetic analogue of somatostatin, inhibits the release of insulin and has been used in the treatment of sulfonylurea-induced hypoglycemia. One recent report describes the use of octreotide in patients who ingested excessive amounts of sulfonylurea OHA.[28] These patients, prior to octreotide administration, had experienced recurrent hypoglycemia. Soon after the initiation of octreotide therapy, serum sugar levels stabilized with a significant reduction in recurrent hypoglycemia. It is administered subcutaneously at an initial dose of 50-125 mcg; both constant infusions (125 mcg/hr) and repeat dosing (50-100 mcg) at 6- to 12-hour intervals have been employed successfully. The optimal dose, frequency of administration, and duration of therapy have not been defined. Intravenous glucose is still the most appropriate therapy for hypoglycemia. Octreotide is only recommended after initial therapy has been initiated in the sulfonylurea ingestion. Its use primarily is designed to reduce the chance of recurrent hypoglycemia.

Thiamine. Administration of parenteral thiamine at a dose of 100 mg is required in conjunction with glucose therapy (delivered by any route) in cases of suspected ethanol abuse or other nutritional deficiency states to avoid acute development of Wernicke's encephalopathy.[29] The concern with administration of glucose-containing solutions in a thiamine deficient state centers on the fact that thiamine is a co-factor in glucose metabolism. If glucose is given before thiamine, this may lead to an exacerbation of thiamine deficiency and the development of an acute Wernicke's syndrome.

Acute precipitation of the classic syndrome has been reported in four patients; it is quite rare.[29] In each instance (an ethanol user with chronic gastritis and persistent emesis; a schizophrenic with colonic pseudo-obstruction; a patient with end-stage renal

Table 3. Admission Indications in the Hypoglycemic Patient Presenting to the ED

Issue under Consideration	In-patient Location (non-critical care setting vs critical care setting*)	Indication (Relative/absolute)
Patient age: neonate/infant & very elderly	Variable	Relative
Medication etiology: non-short-acting insulins and all OHA	Variable	Absolute
Continued/recurrent mental status change	CCS	Absolute
Continued/recurrent hypoglycemia	Likely CCS	Absolute
Lack of "reactive" hyperglycemia despite adequate glucose replacement therapy	Variable	Relative
Requirement for frequent/continuous glucose administrations	CCS	Absolute
Etiology of event: sepsis, severe malnutrition, toxicologic response to ingestion with other body system failures	CCS	Absolute
Psychiatric (i.e., intentional ingestion) etiology	Variable	Absolute
Lack of: 1) responsible adult supervision, 2) motivated patient or caretaker, and 3) identified physician for outpatient care.	Variable	Absolute
Significant comorbidity	Variable	Relative
History of hypoglycemia	Variable	Relative

* CCS = Critical care setting

disease managed by chronic peritoneal dialysis; and a trauma victim receiving total parenteral nutrition), the patient was exposed to dextrose and rapidly developed manifestations of Wernicke's encephalopathy. Prompt administration of thiamine reversed the ophthalmoplegia, mental status abnormalities, and ataxia during the following 12-24 hours. The investigators theorize that by providing relatively large amounts of glucose to these patients with pre-existing thiamine deficiency, the classic findings of the syndrome appeared in a rapid manner as available supplies of thiamine were quickly depleted.

Thiamine acts as a co-enzyme in several reactions in intermediary metabolism, specifically in the conversions of pyruvate to acetyl CoA (linking glycolysis to the TCA cycle) and alpha-ketoglutarate to succinate (a reaction in the TCA cycle). As thiamine reserves disappear, the reactions halt, removing the central nervous system's main source of ATP and causing the acute development of Wernicke's syndrome.

Steroid administration should be considered in patients with hypoglycemia that is either resistant to aggressive glucose replacement therapy or associated with the signs of adrenal insufficiency. In addition to hypoglycemia, adrenal insufficiency is characterized by profound weakness, hypothermia, hypotension poorly responsive to crystalloid and vasopressor infusions, and various metabolic abnormalities (hyponatremia, hyperkalemia, and azotemia). Initial, ED steroid replacement includes the rapid administration of hydrocortisone via the IV route: 100-200 mg in the adult and 1-2 mg/kg in children.[35]

Potential Risks of Glucose Administration. The use of glucose replacement therapy is not without theoretical risk to the head injured patient, in both atraumatic and traumatic settings. Hyperglycemia at the time of hospital admission has been associated with poor neurologic recovery in stroke patients[30] and survivors of out-of-hospital cardiopulmonary arrest.[31] Similar concern has been voiced regarding the association with worsened neurologic outcome and hyperglycemia in patients with acute head injury.[32,33] These retrospective studies have proposed an association between hyperglycemia and worsened neurologic outcome; these same studies, however, have not established a cause and effect relationship.

It is theorized that hyperglycemia accentuates local tissue damage via continued or increased anaerobic metabolism, lactate production, and intracellular acidosis. This acidosis may trigger a cascade that includes calcium entry into cells, lipolysis, and cytotoxic fatty acid release, culminating in neuronal death. At the present time, no controlled, prospective studies have been performed examining these issues in the setting of acute ischemic stroke or head injury. It is a known fact, however, that hypoglycemia will worsen neurologic outcome in patients with and without CNS injury of any etiology. Hypoglycemia clearly must be avoided—the emergency physician must always consider hypoglycemia as a causative or contributing factor in patients with altered mentation—even if the etiology appears to be related to another process or event.

The empiric use of IV dextrose for the patient experiencing altered mentation in the out-of-hospital setting without prior documentation of hypoglycemia places the emergency physician in a difficult position. After the administration of dextrose by emergency medical services (EMS) personnel, the emergency physician must then interpret the post-intervention serum glucose value. Although the literature suggests that each ampule of glucose (50 grams of a 50% dextrose solution) will raise the serum sugar by 60 mg/dL,[34] this post-treatment correction does not consider the time interval from initial therapy to glucose determination; such a calculation probably does not adequately estimate the post-treatment serum glucose level. Other authorities have demonstrated that a marked variation in serum glucose values after administration of 50 grams of a 50% dextrose solution is encountered such that any prediction of post-treatment levels is impossible.[35]

Disposition. Disposition considerations must weigh a number of factors, including: 1) the patient's current mental status as well as the level of consciousness during observation in the ED; 2) serial determinations of the serum glucose; 3) both the timing and extent of the response to resuscitative therapy; 4) the need for additional replacement therapy; 5) the pathophysiology (i.e., etiology) of the hypoglycemic event; 6) any comorbidities; 7) the social situ-

ation of the particular individual; 8) any psychiatric issues; and 9) the agent ingested. These issues are listed in Table 3 along with the strength of the admission recommendation (relative vs absolute indication), as well as the suggested in-hospital destination.

Obviously, either continued or recurrent mental status alteration, recurrent hypoglycemia, or a downward trend in serial glucose values during ED observation despite adequate replacement therapy demands admission to the hospital. Also, any patient requiring large doses of dextrose in both bolus and infusion fashion should be admitted to the intensive care unit not only for ongoing therapy but also for close evaluation of the mental status and serial serum glucose samplings. An inpatient disposition in a critical care setting is likely warranted in cases involving the following etiologies: massive insulin or OHA ingestion, marked malnutrition, sepsis, acute liver failure, or any other event associated with the tendency toward profound hypoglycemia. Further, the patient without proper, outpatient supervision should be admitted to the hospital for observation.

The case suitable for outpatient observation is characterized by both a responsible adult who will monitor the patient's mental status every three hours and a motivated patient who will perform serum glucose determinations frequently; an absence of either of these features should prompt admission to the hospital. Obviously, the suspected or known intentional ingestion (i.e., the self-harm scenario) of either insulin or OHA must be admitted for ongoing medical and psychiatric care.

The particular medication ingested must be strongly weighed in disposition decisions. Short-acting insulin preparations do not always demand hospitalization; intermediate and long-acting preparations, however, likely will require admission for ongoing observation and, at times, continued supportive care. Care must be exercised in the large short-acting insulin ingestion in that the pharmacodynamics of such insulin preparations are altered in the massive exposure situation; the expected, relatively short half-life may not be encountered. OHAs also represent an indication for hospitalization due to relatively long serum half-life with a prolonged tendency toward the development of hypoglycemia. A single tablet ingestion in a child can produce significant hypoglycemia; additionally, low serum sugars may develop as much as 16 hours after ingestion, though the majority of patients will become symptomatic within eight hours of exposure.[16]

The ultimate outcome of recurrent, unrecognized hypoglycemia is catastrophic—both medically for the patient and legally/psychologically for the emergency physician;[11] if any doubt exists as to the need for inpatient observation in the hypoglycemic patient, the emergency physician should err on the cautious side and arrange for an admission for short-term observation. If an outpatient status is recommended, very close medical follow-up (i.e., within 12-24 hours) is needed for additional adjustments.

References

1. Hayward RA, Manning WG, Kaplan SH, et al. Starting insulin therapy in patients with type 2 diabetes: Effectiveness, complications, and resource utilization. *J Am Med Assoc* 1997;278:1663-1669.
2. Anonymous. Hypoglycemia in the Diabetes Control and Complications Trial: The Diabetes Control and Complications Trial Research Group. *Diabetes* 1997;46:271-286.
3. Shorr RI, Ray WA, Daugherty JR, et al. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Int Med* 1997;157:1681-1686.
4. Malouf R, Brust JCM. Hypoglycemia: Causes, neurological manifestations, and outcome. *Ann Neurol* 1985;17:421-430.
5. Seltzer HS. Drug-induced hypoglycemia: A review based on 473 cases. *Diabetes* 1972;21:955-966.
6. Wallis WE, Donaldson I, Scott RS, et al. Hypoglycemia masquerading as cerebrovascular disease (hypoglycemic hemiplegia). *Ann Neurol* 1985;18:510-512.
7. Foster JW, Hart RG. Hypoglycemic hemiplegia: Two cases and a clinical review. *Stroke* 1987;18:944-946.
8. Brady WJ, Duncan CW. Hypoglycemia masquerading as acute psychosis and acute cocaine intoxication. *Am J Emerg Med* 1999;17: 318-319.
9. Luber S, Meldon S, Brady W. Hypoglycemia presenting as acute respiratory failure in an infant. *Am J Emerg Med* 1998;16: 281-284.
10. Luber S, Brady W, Brand A, et al. Acute hypoglycemia masquerading as head trauma: A report of four cases. *Am J Emerg Med* 1996; 14:543-547.
11. Fink S, Chaudhuri TK. Iatrogenic hypoglycemia and malpractice claims. *So Med J* 1997;90:251-253.
12. Fanelli C, Pampanelli S, Lalli C, et al. Long-term intensive therapy of IDDM patients with clinically overt autonomic neuropathy: Effects on hypoglycemia awareness and counterregulation. *Diabetes* 1997;46:1172-1181.
13. Boyle PJ, Kempers SF, O'Connor AM, et al. Brain glucose uptake and unawareness of hypoglycemia in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 1995;333: 1726-1731.
14. Mahler RJ, Adler ML. Type 2 diabetes mellitus: Update on diagnosis, pathophysiology and treatment. *J Clin Endocrinol Metab* 1999;84:1165-1171.
15. Davidson MB. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med* 1997;102:99-110.
16. Quadrani DA, Spiller HA, Widder P. Five year retrospective evaluation of sulfonylurea ingestion in children. *J Toxicol Clin Toxicol* 1996;34:267-270.
17. Spiller HA, Villalobos D, Krenzelok EP, et al. Prospective multicenter study of sulfonylurea ingestion in children. *J Pediatr* 1997;131: 141-146.
18. Losek JD. Hypoglycemia and the ABC'S [sugar] of pediatric resuscitation. *Ann Emerg Med* 2000;35:43-46.
19. Losek JD, Reid S. Letter to the Editor. *Ann Emerg Med* 2000; 36:279.
20. Pollock G, Brady WJ, Hargarten S, et al. Hypoglycemia manifested by sinus bradycardia: A report of three cases. *Acad Emerg Med* 1996;3:700-707.
21. Shen F. Motorist in diabetic shock arrested in MD; Man's erratic behavior prompts beating, dog attack and multiple charges. *The Washington Post* June 22, 1998:B3.

22. Brady WJ, Butler K, Fines R, et al. Hypoglycemia in multiple trauma victims. *Am J Emerg Med* 1999;17:4-5.
23. Boyle PJ, Schwartz NA, Shah SD. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. *N Engl J Med* 1988;318: 1487-1492.
24. Rich LM, Caine MR, Findling JW, et al. Hypoglycemic coma in anorexia nervosa: Case report and review of the literature. *Arch Int Med* 1990;150:894-895.
25. Service FJ. Hypoglceic disorders. *N Engl J Med* 1995;332: 1144-1152.
26. Collier A, Steedman DJ, Patrick AW, et al. Comparison of intravenous glucagon and dextrose in treatment of severe hypoglycemia in an accident and emergency department. *Diabetes Care* 1987;10: 712-715.
27. Patrick AW, Collier A, Hepburn DA, et al. Comparison of intramuscular glucagon and intravenous dextrose in treatment of hypoglycemic coma in an accident and emergency department. *Arch Emerg Med* 1990;7:73-77.
28. MacLaughlin SA, Crandell CS, McKinney PE. Octreotide: An antidote for sulfonylurea-induced hypoglycemia. *Ann Emerg Med* 2000;36:133-138.
29. Watson AJS, Walker GH, Tomkin MMR, et al. Acute Wernicke's encephalopathy precipitated by glucose loading. *Irish J Med Sci* 1981;150:301-303.
30. Pulsinelli WA, Levy DE, Sigsbee B, et al. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. *Am J Med* 1983;74:540-544.
31. Longstreth WT, Inui TS. High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. *Ann Neurol* 1984;15:59-63.
32. Lam AM, Winn HR, Cullen BF, et al. Hyperglycemia and neurologic outcome in patients with head injury. *J Neurosurg* 1991;75:545-551.
33. Young B, Ott L, Dempsey R, et al. Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients. *Ann Surg* 1989;210:466-473.
34. Hoffman RS, Goldfrank LR. The poisoned patient with altered consciousness: Controversies in the use of a "coma cocktail." *J Am Med Assoc* 1995;274:562-569.
35. Balentine JR, Gaeta TJ, Kessler D, et al. Effect of 50 milliliters of 50% dextrose in water administration on the blood sugar of euglycemic volunteers. *Acad Emerg Med* 1998;5:691-694.

Physician CME Questions

9. Regarding the etiology of hypoglycemia in the ED patient, all of the following statements are true *except*:
   A. It most often presents with atypical features and is a difficult diagnosis.
   B. Excessive diabetic medical therapy is a frequent cause.
   C. It is most often easily treated with glucose replacement therapy.
   D. It should be suspected in all patients with altered mental status.

10. Organs most closely involved in glucose homeostasis include all of the following *except:*
   A. the pancreas.
   B. both the adrenal medulla and cortex.
   C. the kidneys.
   D. the pituitary gland.

11. The glycogen reserve is limited and will be depleted after how many hours of fasting in the healthy patient?
   A. 6-12 hours
   B. 12-24 hours
   C. 24-48 hours
   D. 48-72 hours

12. Presentations of hypoglycemia that may masquerade as other clinical syndromes include all of the following *except:*
   A. focal neurologic findings.
   B. seizure.
   C. tachypnea in newborns and infants.
   D. dyspnea.

13. According to this article, treatment of hypoglycemia may include all of the following agents *except:*
   A. octreotide.
   B. glucagon.
   C. naloxone.
   D. glucose.

14. Which of the following hypoglycemia treatments and related issues is *incorrectly* matched?
   A. Severe, chronic malnutrition — glucagon
   B. Chronic malnutrition — thiamine
   C. Acute physiologic stress in chronic steriod user — hydrocortisone
   D. Sulfonylurea ingestion — octreotide

15. The most common presentation of hypoglycemia in the ED is:
   A. convulsion.
   B. focal neurologic deficits.
   C. alterations of consciousness, such as confusion, lethargy, and unresponsiveness.
   D. isolated diaphoresis.

16. Which of the following statements regarding pitfalls in the diagnosis of hypoglycemia in the ED is *false*?
   A. Patients may present with clinical syndromes involving mental status changes and other findings which suggest another etiology.
   B. Patients with autonomic neuropathy may demonstrate blunted counter-regulatory responses to hypoglycemia.
   C. The response to glucagon is usually delayed.
   D. Glucagon is the agent-of-choice in the severely malnourished alcoholic patient.

In Future Issues: Movement Disorders