CHAPTER

18

Endocrine Alterations

Jacqueline LaManna, MSN, ARNP-BC, ADM, CDE
Christina Stewart-Amidei, PhD, RN, CNRN, CCRN, FAAN

evolve WEBSITE

Many additional resources, including self-assessment exercises, are located on the Evolve companion website at http://evolve.elsevier.com/Sole.

- Review Questions
- Mosby's Nursing Skills Procedures
- Animations
- Video Clips

INTRODUCTION

The endocrine glands form a communication network linking all body systems. Hormones from these glands control and regulate metabolic processes such as energy production, fluid and electrolyte balance, and response to stress. This system is closely linked to and integrated with the nervous system. In particular, the hypothalamus and pituitary gland play a major role in hormonal regulation. The hypothalamus manufactures and secretes several releasing or inhibiting hormones that are conveyed to the pituitary. The pituitary gland responds to these hormones by increasing or decreasing hormone secretion, thus regulating circulating hormone levels. This system is designed as a feedback control mechanism. Positive feedback stimulates release of a hormone when serum hormone levels are low. Negative feedback inhibits the release of hormones when serum hormone levels are high. Examples of how these feedback systems work to control circulating levels of cortisol are provided in Figure 18-1. This same feedback system also controls the secretion and inhibition of other hormones outside hypothalamic-pituitary control.

Changes in the Endocrine System in Critical Illness

The stress of critical illness provokes a significant response by the endocrine system. Excess glucose in the blood occurs as a result of release of *counterregulatory hormones* that promote hepatic gluconeogenesis and decreased peripheral utilization of glucose with resulting relative hypoinsulimemia. Adrenal insufficiency can occur as a result of insult or damage to the gland itself (primary) or because of dysfunction of the hypothalamus, pituitary, or both (secondary). Relative adrenal insufficiency may occur in critically ill patients whenever elevated cortisol levels are inadequate for the demand. Thyroid hormone balance is disrupted by changes in peripheral metabolism that cause a decrease in triiodothyronine (T_3) levels. Pituitary and hypothalamus dysfunction as a result of brain tumor, trauma, or surgery can cause significant fluid and electrolyte imbalances that complicate critical illness.

Disease States of the Endocrine System

Diseases involving the hypothalamus, the pituitary gland, and the primary endocrine organs (i.e., pancreas, adrenal glands, and thyroid gland) interfere with normal feedback mechanisms and the secretion of hormones. Crisis states occur when these diseases are untreated or undertreated, when the patient is stressed physiologically or psychologically, or as the result of many other factors.

This chapter describes both the endocrine response to critical illness, and the crises that occur as a result of imbalances of hormones from the pancreas, adrenal glands, thyroid gland, and posterior pituitary gland. For a summary of endocrine concerns for the older adult, see box, "Geriatric Considerations."

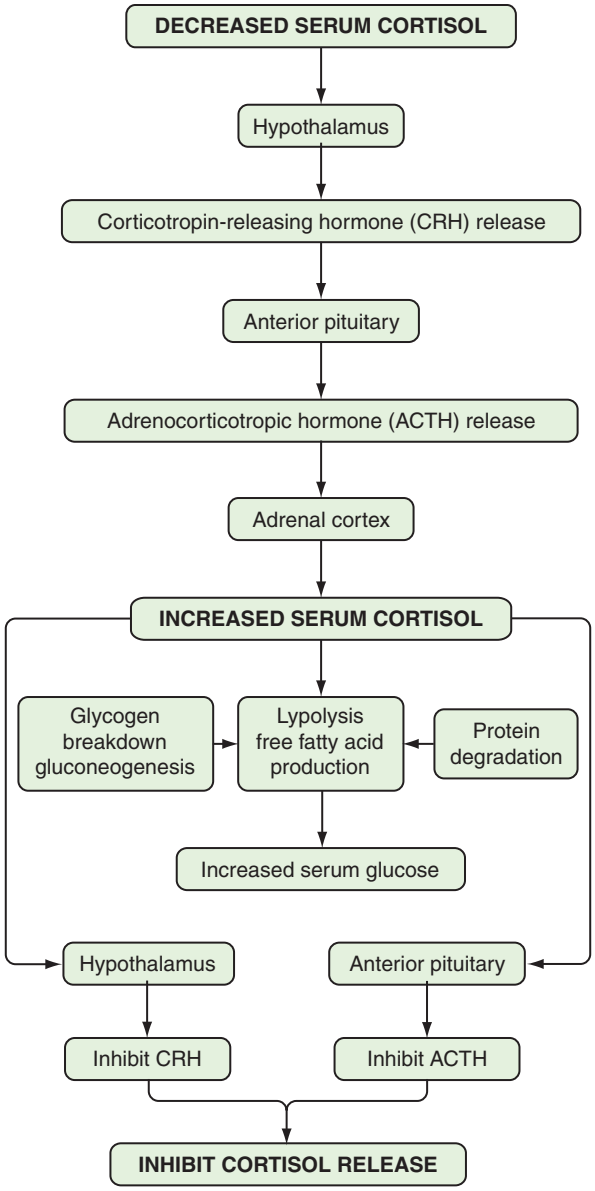


FIGURE 18-1 Feedback system for cortisol regulation.

GERIATRIC CONSIDERATIONS

Elderly patients present diagnostic and treatment challenges related to endocrine disorders. When critically ill, they are at increased risk for endocrine complications. Older adults have more comorbidities and take more medications that affect fluid and electrolyte balance. The presenting signs and symptoms of an endocrine disorder are frequently atypical and nonspecific, and the responses to dysfunction are blunted. Many of the compensatory mechanisms are lost with advanced age.

Pancreas

Over 25% of adults older than 65 years have diabetes, primarily type 2 diabetes.[6] Elderly persons are more prone to develop hyperosmolar hyperglycemic state. They are also at increased risk of being unaware of hypoglycemia. Elderly patients are more likely to have comorbid conditions, such as cardiac or renal disease, and to take medications that make them more reactive to electrolyte imbalances.[16] They are also slower to respond to treatments.

Adrenal

Utilization and clearance of cortisol decrease with age, resulting in increased serum cortisol levels. Cortisol secretion decreases because feedback systems are intact, leading to lower cortisol levels in the elderly. The absolute level of cortisol needed to maintain homeostasis is unknown. Poor nutrition and decreased albumin stores (one of cortisol's binding proteins) may compound the decline in cortisol availability and response.

Thyroid

Thyroid hormone levels decrease with age because of glandular atrophy and inflammation. Approximately 5% of people older than 60 years are affected by hypothyroidism. Detection of thyroid disease by assessment of signs or symptoms becomes more challenging. In addition, lower amounts of thyroid medication are needed as replacement, and adjustment of dosage must be slower to prevent potentially dangerous side effects. Elderly patients are less likely to tolerate urgent treatment with liothyronine sodium.

Older patients may not exhibit the typical signs of thyrotoxicosis. Anorexia, atrial fibrillation, apathy, and weight loss may already be present or misinterpreted. Goiter, hyperactive reflexes, sweating, heat intolerance, tremor, nervousness, and polydipsia are less commonly present. In the elderly, symptoms of thyroid storm may present as increasing angina or worsening congestive heart failure.

Pituitary

Decreased release of growth hormone leads to a decrease in lean body mass and increased blood glucose levels, leading to suppression of thyroid-stimulating hormone (thyrotropin), although usually not significantly. An increase in secretion of antidiuretic hormone occurs with advanced age and places the older person at risk of dilutional hyponatremia. Elderly patients are at greater risk of the syndrome of inappropriate antidiuretic hormone from any cause than are younger patients. Elderly patients can fail to recognize and respond to thirst, and therefore are at an increased risk for dehydration.

HYPERGLYCEMIA IN THE CRITICALLY ILL PATIENT

Critically ill patients are at high risk for hyperglycemia from many different stressors including their disease states, the illness-related hormonal responses to stress, and the critical care environment. Refer to Box 18-1 for risk factors associated with an increase in blood glucose levels.

Although stress-induced hyperglycemia is a normal physiological response related to the *fight-or-flight* mode, glucose elevation is associated with poor outcomes in hospitalized patients with and without a formal diagnosis of diabetes. Hyperglycemia in acutely ill patients has been linked to impaired immune function, cerebral ischemia, osmotic diuresis, poor wound healing, decreased erythropoiesis, increased hemolysis, endothelial dysfunction, increased thrombosis, vasoconstriction with resulting hypertension, decreased respiratory muscle function, neuronal damage, and impaired gastric motility.[7] Acute hyperglycemia during the course of illness has been associated with poor clinical outcomes, including mortality in

BOX 18-1 RISK FACTORS FOR THE DEVELOPMENT OF HYPERGLYCEMIA IN THE CRITICALLY ILL PATIENT

- Preexisting diabetes mellitus, diagnosed or undiagnosed
- Comorbidities such as obesity, pancreatitis, cirrhosis, hypokalemia
- Stress response release of cortisol, growth hormone, catecholamines (epinephrine and norepinephrine), glucagon, glucocorticoids, cytokines (interleukin-1, interleukin-6, and tumor necrosis factor)
- Aging
- Lack of muscular activity
- Relative insulin deficiency/insulin resistance
- Administration of exogenous catecholamines, glucocorticoids
- Administration of dextrose solutions, nutritional support
- Drug therapy such as thiazides, beta-blockers, highly active antiretroviral therapy, phenytoin, tacrolimus, cyclosporine

critically ill patients who have been treated for myocardial infarction, traumatic brain injury, burns, trauma, subarachnoid hemorrhage, and transplantation.[17]

Optimal glucose targets in critically ill patients are a matter of current debate. In 2001, Van den Berghe and colleaguespublished a landmark study showing that intensive insulin control of hyperglycemia in a critically ill surgical population decreased mortality and morbidity, including sepsis, acute kidney injury necessitating dialysis, blood transfusion requirements, and polyneuropathy.[26] Findings of this study led many hospitals to institute tight glycemic control protocols in critically ill patients as a standard of care. Subsequent studies conducted in broader populations have demonstrated higher rates of mortality in nonsurgical populations, and significantly higher rates of severe hypoglycemia, raising questions about the degree of glycemic control that should be attained in critically ill individuals.[9,18,25] In response, the American Diabetes Association and the American Association of Clinical Endocrinologists issued a joint statement on inpatient glycemic control. Current guidelines recommend an initial target glucose level of 180 mg/dL or less; targets of 140 to 180 mg/dL are appropriate for most critically ill patients. Lower targets may be desired for a select group of patients.[1,17] A summary of evidence to support this change in practice is discussed in this chapter.

Achieving Optimal Glycemic Control

To optimize patient safety, intravenous delivery using short-acting insulin as guided by an evidence-based protocol is the preferred method for treating hyperglycemia in critically ill patients (see box, "QSEN Exemplar").[1,7,17] These nurse-managed protocols include frequent glucose monitoring and insulin dosage adjustments based on patient-specific glucose targets. Frequent blood glucose monitoring is intended to ensure the appropriate insulin dosage and to minimize the incidence of hypoglycemia. The key elements for glycemic control protocols are described in Box 18-2. Effective protocols minimize complexity so there is less chance for error. Systems approaches are required to limit the patient risk associated with this complex therapy.[17] Computer decision support software is helpful in managing glucose control. Although strictly controlling insulin delivery is labor-intensive, these protocols reduce hospitalization costs secondary to fewer inpatient complications, reduce critical care and hospital lengths of stay, reduce ventilator days, and reduce charges for radiology, laboratory tests, and pharmaceuticals.[17]

The transition from intravenous to subcutaneous insulin therapy must be carefully timed to limit the risk for hyperglycemia. Most patients may be transitioned from intravenous to subcutaneous insulin when they are eating regular meals, or when their clinical conditions warrants transfer to a lower-intensity level of care.[17] Subcutaneous insulin should be administered 1 to 4 hours before discontinuation of the insulin infusion. It is recommended that the subcutaneous insulin regimen include basal and nutritional bolus insulin delivery in a dose equivalent to approximately 75% of the total daily insulin infusion dose with the addition of a bolus correction scale.[17] Adjustments to this recommendation may be required if the patient is receiving enteral feedings, parenteral nutrition, or high-dose glucocorticoids. Insulin regimens that are composed exclusively of sliding scale insulin have been associated with poor patient outcomes.

QSEN EXEMPLAR

Evidence-Based Practice and Quality Improvement

A critical care advanced practice registered nurse (APRN) attended a recent conference where findings of the NICE-SUGAR study were presented. The APRN's practice network used an intensive insulin protocol in all of its critical care units and progressive care units. The protocol was developed several years ago and used evidence provided by the Van den Berghe and colleagues trials to establish glucose targets. Following the conference, the APRN conducted a review of current literature on glycemic control of critically ill adults and additionally reviewed the most recent American Diabetes Association Clinical Practice Guidelines. The APRN noted discrepancies between current practice and the evidence and presented these findings at the critical care committee meeting. Committee members concurred that the current evidence and guidelines supported the need to amend practice, and formed a committee of stakeholders to evaluate network practice and revise the protocols using the FOCUS-PDSA approach to performance improvement. After multiple meetings, an initial draft of a revised protocol was developed and presented to appropriate physician and clinical groups. Necessary approvals were obtained, and an education program for providers, nurses, and affected disciplines such as pharmacy, nutrition, and laboratory services was developed and presented. The evidence supporting the revisions was emphasized. A formal implementation strategy was developed, and the revised protocol was introduced serially into each of the critical care units. The APRN worked with the quality and safety department to establish a follow-up monitoring plan. The APRN collected data continuously after the implementation and worked with the quality department to identify trends that suggested the need to modify the protocol. These findings were presented to appropriate parties, revisions made, and a continuous monitoring and reporting plan was established.

Hypoglycemia as a Preventable Adverse Effect of Glucose Management

Intensive insulin therapy has been associated with a significant (sixfold) increase in the risk for an episode of severe hypoglycemia (glucose 40 mg/dL or less).[9] The increased incidence of hypoglycemia in critically ill patients is associated with a reduction or discontinuation of nutrition without adjustment of insulin therapy, such as the holding of parenteral or enteral feedings during diagnostic exams; a prior diagnosis of diabetes mellitus (DM); sepsis; and the use/change in dosage of inotropic drugs, vasopressor support, and glucocorticoid therapy.[7]

BOX 18-2 KEY COMPONENTS OF A GLUCOSE MANAGEMENT PROTOCOL

- Frequent plasma blood glucose measurements
- Concentration of insulin infusion (i.e., number of units of insulin mixed in quantity of normal saline)
- Initial intravenous insulin bolus dose if appropriate
- Table with titration for increasing or decreasing insulin infusion based on glucose level
- Interventions for:
  - Hypoglycemia, should it occur
  - When feeding is interrupted, either parenteral or enteral
  - When the patient is transported from the critical care unit for diagnostic testing
  - Discontinuing the intravenous insulin infusion
  - When the patient is transferred out of the critical care unit

Based on data from Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care.* 2009;32:1119-1131; Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crisis in adult patients with diabetes. *Diabetes Care.* 2009;32:1335-1343.

Many episodes of hypoglycemia are preventable. The nurse must ensure that the glucose testing is accurate and consistent. Concurrent and shift-to-shift coordination and adjustment of all medical and nutritional therapies (including increasing, decreasing, or temporarily suspending any of them), is required to prevent hypoglycemia.

Hyperglycemia in the Critically Ill

Stress-induced hyperglycemia affects patients with and without a formal diagnosis of DM. In the critically ill, stress-induced hyperglycemia exacerbates the elevated glucose levels of patients with preexisting diabetes, predisposes them to an even higher incidence of complications and comorbidities, and impacts treatment for all disease states. Individuals with diabetes are hospitalized more frequently, are more prone to complications, and have longer hospital stays and higher hospital costs than patients without diabetes.[7] Therapy aimed at establishing euglycemic levels contributes to improved patient outcomes. Critically ill patients with diabetes are most effectively managed with insulin therapy regardless of their usual home self-management regimen.[17] Figure 18-2 and Table 18-1 provide a review of the insulin action profiles of a variety of insulin products and common insulin regimens. Additionally, Table 18-2 lists oral agents used in the management of type 2 diabetes presented by class along with information on injectable agents used to regulate blood glucose.

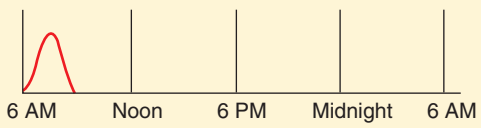
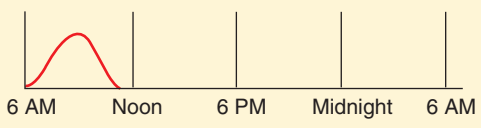
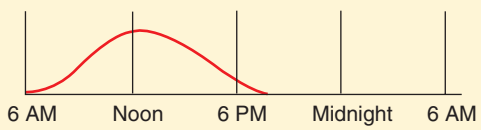
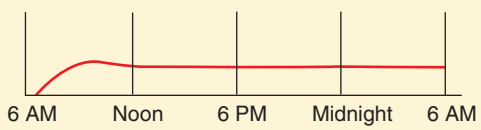
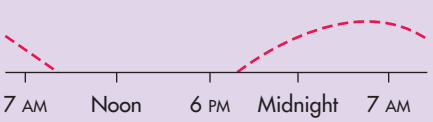
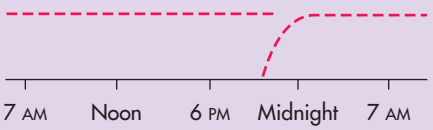
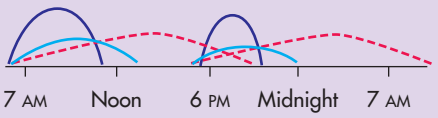
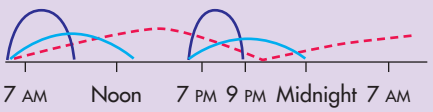
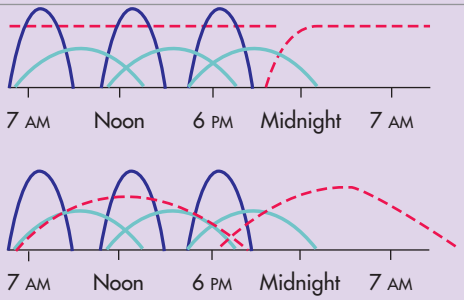
INSULIN PREPARATION	ONSET, PEAK, DURATION	EXAMPLE
Rapid-acting lispro (Humalog) aspart (NovoLog) glulisine (Apidra)	*Onset:* 15 min *Peak:* 60-90 min *Duration:* 3-4 hr	
Short-acting Regular (Humulin R, Novolin R, ReliOn R)	*Onset:* ½-1 hr *Peak:* 2-3 hr *Duration:* 3-6 hr	
Intermediate-acting NPH (Humulin N, Novolin N, ReliOn N)	*Onset:* 2-4 hr *Peak:* 4-10 hr *Duration:* 10-16 hr	
Long-acting glargine (Lantus) detemir (Levemir)	*Onset:* 1-2 hr *Peak:* no pronounced peak *Duration:* 24+ hr	

FIGURE 18-2 Commercially available insulin preparations showing onset, peak, and duration of action. (From Michel B. Nursing management of diabetes. In Lewis SL, Dirksen SR, Heitkemper MM, et al, eds. *Medical-Surgical Nursing: Assessment and Management of Clinical Problems.* 8th ed. St. Louis: Mosby. 2011.)

TABLE 18-1 COMMON INSULIN REGIMENS

REGIMEN	TYPE OF INSULIN/FREQUENCY	ACTION PROFILE	COMMENTS
Once a day Single dose	Intermediate (NPH) *At bedtime*		One injection should provide nighttime coverage.
	Or Long-acting (glargine [Lantus], detemir [Levemir]) *In AM or at bedtime*		One injection will last 24 hours with no peaks and less chance for hypoglycemia. Does not cover postprandial blood sugars.
Twice a day Split-mixed dose	NPH and regular or rapid (both regular and rapid are shown on the diagram) *Before breakfast and at dinner*		Two injections provide cover for 24 hours. Patient must adhere to a set meal plan.
Three times a day Combination of mixed and single dose	NPH and regular or rapid (both regular and rapid are shown on the diagram) *Before breakfast* + Regular or rapid *Before dinner*		Three injections provide coverage for 24 hours, particularly during early AM hours. Potential is reduced for 2-3 AM hypoglycemia.
Basal-bolus Multiple dose	Regular or rapid (both regular and rapid are shown on the diagram) *Before breakfast, lunch, and dinner* + Long-acting (glargine or detemir) *Once a day* Or Regular or rapid (both regular and rapid are shown on the diagram) *Before breakfast, lunch, and dinner* + NPH *Twice a day*		More flexibility is allowed at mealtimes and for amount of food intake. Good postprandial control. Premeal blood glucose checks and establishing and following individualized algorithms are necessary. Patients with type 1 will require basal injection to cover 24 hours. Most physiological approach, except for pump.

Key:

- Rapid-acting (lispro, aspart, glulisine) insulin.
- Short-acting (regular) insulin.
- Intermediate-acting (NPH) or long-acting (glargine, detemir) insulin.

From Michel B. Nursing management of diabetes. In Lewis SL, Dirksen SR, Heitkemper MM, eds. *Medical-Surgical Nursing: Assessment and Management of Clinical Problems.* 8th ed. St. Louis: Mosby. 2011.

TABLE 18-2 PHARMACOLOGICAL AGENTS USED IN THE MANAGEMENT OF DIABETES

CLASSIFICATION	ROUTE OF ADMINISTRATION	MECHANISM OF ACTION	SIDE EFFECTS
Sulfonylureas Glipizide (Glucotrol, Glucotrol XL) Glyburide (Micronase, DiaBeta, Glynase) Glimepiride (Amaryl)	Oral	Stimulates release of insulin from pancreatic beta cells; decreases glycogenesis and gluconeogenesis; enhances cellular sensitivity to insulin; agents are longer-acting	Hypoglycemia; weight gain; photosensitivity; cholestatic jaundice; use with caution in patients with hepatic or renal dysfunction
Meglitinides Repaglinide (Prandin) Nateglinide (Starlix)	Oral	Stimulates rapid, short-lived release of insulin from the pancreas; taken within 30 minutes of meal	Hypoglycemia; medication is held if no meal taken Weight gain
Biguanide Metformin (Glucophage, Glucophage XR, Fortamet, Riomet)	Oral	↓ Rate of hepatic glucose production; augments glucose uptake from tissues, especially muscles	Stomach upset—take with meals; Diarrhea; Lactic acidosis; medication held before IV contrast procedures and 48 hours after Withhold if creatinine ≥1.4 mg/dL in woman and ≥1.5 mg/dL in men or creatinine clearance <50 mL/min
α-Glucosidase Inhibitors Acarbose (Precose) Miglitol (Glyset)	Oral	Delays absorption of glucose from the GI tract; taken with first bite of food; withheld if meal missed	Flatulence; abdominal pain; diarrhea; avoid use in patients with chronic intestinal disorders; hypoglycemia treated with glucose only
Thiazolidinediones Pioglitazone (Actos) Rosiglitazone (Avandia)	Oral Administered at bedtime	↑ Glucose update in muscle; ↓ endogenous glucose production	Edema; contraindicated in Class III/IV congestive heart failure; hypoglycemia if used with insulin or sulfonylureas; weight gain; cardiovascular events such as myocardial infarction and stroke (Avandia: black box warning issued by FDA); increased risk of fracture in women; hepatic dysfunction – withhold if ALT >2.5 times upper limit of normal; Pioglitazone use for more than one year may be associated with increased risk for bladder cancer.
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Sitagliptin (Januvia) Saxagliptin (Onglyza)	Oral	Enhances incretin system; stimulates insulin release from pancreatic beta cells; ↓ hepatic glucose production	Upper respiratory tract infection; sore throat; GI upset; diarrhea; dose reduction for renal impairment; hypoglycemia (with sulfonylureas); hypersensitivity reactions (anaphylaxis, Stevens-Johnson Syndrome)
Incretin Mimetic Exenatide (Byetta) Liraglutide (Victoza)	Subcutaneous within 60 minutes of AM and PM meal; dose titrated	Stimulates release of insulin; ↓ glucagon secretion; ↑ satiety; ↓ gastric emptying (avoid in patients with gastroparesis); ↓ hepatic gluconeogenesis; used in treatment of type 2 DM	Hypoglycemia (with insulin-secreting agents); pancreatitis (may be fatal); nausea; vomiting; weight loss; diarrhea; headache (medullary thyroid cancer [Victoza])
Amylin Analog Pramlintide (Symlin)	Subcutaneous (abdomen or thigh)	Take with each significant carbohydrate-containing meal. ↓ glucagon secretion; ↑ satiety; ↓ gastric emptying; ↓ hepatic gluconeogenesis	Hypoglycemia, nausea; vomiting; decreased appetite; headache (May be used in type 1 and type 2 diabetes; held if no significant meal)
Combination Agents Variety of combinations available	Oral	Combine effects of each class	Combine side effects of all agents to obtain complete risk profiles. Combinations of sulfonylureas or meglitinides with other agents may increase the risk for hypoglycemia.

Adapted from Michel B. Nursing management of diabetes. In Lewis SL, Dirksen SR, Heitkemper MM, eds. *Medical-Surgical Nursing: Assessment and Management of Clinical Problems.* 8th ed. St. Louis: Mosby. 2011.

PANCREATIC ENDOCRINE EMERGENCIES

Review of Physiology

DM is a metabolic disease of glucose imbalance resulting from alterations in insulin secretion, insulin action, or both.[2] The number of people with DM has been increasing, with current incidence at more than 220 million worldwide.[27] The two most common types of DM are type 1 and type 2. Type 1 DM is primarily caused by pancreatic islet beta cell destruction, resulting in an *absolute insulin deficiency* and a tendency to develop ketoacidosis. In most cases, type 1 diabetes is an autoimmune disorder. A subset of patients, primarily of African American or Asian ancestry, may experience a genetic but nonimmunological form of type 1 diabetes.[2]

Type 2 is the most common form of diabetes and results from the combination of insulin resistance and insulin

GENETICS

Type 2 Diabetes Mellitus: A Complex Disease with Complex Genetics

Type 2 diabetes mellitus (T2DM) is an example of a complex, multifactorial, polygenic disease. *Multifactorial* means that T2DM is a result of an interaction between genes, lifestyle, and the environment. *Polygenic* means that more than one gene is implicated in the development of this common, chronic disease. Other multifactorial and polygenic disorders that occur in adults include hypertension, atherosclerosis, many cancers, and manic-depressive psychosis.[3]

Environmental factors such as high caloric intake, physical inactivity, and obesity contribute to T2DM. Offspring of parents with T2DM have a 40% chance of being diagnosed with T2DM (a sixfold increase over the general population).[4] Over 40 genetic variations are identified as contributing to the clinical manifestation of T2DM. Initial investigations linked defects in pancreatic beta cell function to T2DM, explaining about 10% of T2DM heritability. These genetic findings suggest that insulin secretion rather than insulin resistance is the primary cause of T2DM.[2,3] More recently, genome-wide association studies (GWAS) suggest that intron or noncoding regions of the genome contribute to disturbances in fasting glucose, body mass index and dysplidemia—all traits associated with T2DM.[4] Experts suggest that each genetic variation contributes 5% to 10% toward genetic susceptibility for T2DM development.[4]

People with T2DM likely have pathological variations in multiple genes. They may also experience greater lifestyle and environmental hazards. The interaction between genes, lifestyle, and the environment in patients with diagnosed T2DM has been known for many decades. Specifically, a family history that includes diabetes combined with one's food intake, body weight (specifically, obesity), and low exercise is a strong predictor of T2DM. Genetic and environmental factors influence the onset and progression of diabetes in a number of ways; findings from investigations of risk factors for T2DM are summarized here.[4]

1. *Number of pancreatic beta cells that produce insulin*. Inheriting a greater number of beta cells may be protective despite a sedentary lifestyle, whereas few beta cells may result in early-onset or more severe T2DM. For example when the *CD-KN2A* gene overexpresses its protein product, pancreatic beta cell mass is reduced in mice.[4] Environmental toxins contribute to reduction in the number of pancreatic beta cells.
2. *Production of insulin*. The efficiency or effectiveness of insulin is influenced by genes such as *UBE2E2,* which increase insulin synthesis under stress. Toxic environmental agents and viruses also influence the synthesis and secretion of insulin.
3. *Secretion of insulin from the pancreatic beta cells*. Secretion is affected by genetic factors, food intake, and exercise. In a recent study, an overexpression of melatonin receptors (*MNR1B* variants) was associated with suppression of glucose-stimulated insulin secretion.[4]
4. *Insulin-signaling pathways that regulate the uptake of glucose by fat and muscle cells*. Genes influence the response of muscle and fat cells to insulin. The size and number of fat cells and skeletal muscle cells also influence insulin responsiveness.
5. *Control of fat metabolism and storage in the body*. Some genes influence fat absorption from the gastrointestinal tract and fat deposition in the body. Diet and exercise also influence the amount of fat intake and deposition.

The genetics of T2DM are complex. T2DM is not inherited in a clearly dominant or recessive manner. Though genetic polymorphisms that increase the risk for developing diabetes are becoming better characterized, new information is emerging about other genetic variations that reduce risk for T2DM. For example, in mitochondrial DNA, a variation in one haplogroup is significantly associated with resistance against T2DM.[4]

The American Diabetic Association recommends screening for diabetes onset every 3 years in individuals with a positive family history, and in all individuals older than 45 years.[1] Elucidating the genetics of T2DM helps to identify individuals at risk who may benefit from interventions before the disease develops. Taking and recording a family history will help to identify those at higher risk for diseases influenced by genetic factors.[3]

References

1. American Diabetic Association. Standards of medical care in diabetes. *Diabetes Care*. 2008;31(Suppl 1):S13-S54.
2. Lander ES. Initial impact of the sequencing of the human genome. *Nature*. 2011;470(7333):187-197.
3. Lashley FR. *Clinical Genetics in Nursing Practice*. 3rd ed. New York: Springer. 2006.
4. Park KS. The search for genetic risk factors of type 2 diabetes mellitus. *Diabetes Metabolism Journal*. 2011;35(1):12-22.

secretory defects.[2] The net result is a *relative insulin deficiency.* A combination of cardiovascular risk factors including hypertension, atherogenic dyslipidemia, and hyperglycemia comprise the *cardiometabolic risk syndrome* and significantly increases the risk of developing type 2 DM. The other causes of DM include insulin resistance during pregnancy (gestational DM), medications such as corticosteroids, genetic disorders such as cystic fibrosis, pancreatic damage, viruses, and disorders of the pituitary gland and adrenal gland.[2] Additionally, polycystic ovary syndrome is strongly associated with the development of obesity and insulin resistance and places a woman at significant risk for development of gestational diabetes and type 2 DM later in life.

Genetic factors have a strong role in the development of type 1 DM (see box, "Genetics"). For example, rates of type 1 DM are particularly high in Scandinavia. Genetic alterations may play a role in the development of type 2 DM and related conditions, such as obesity and the cardiometabolic risk syndrome. The incidence of type 2 DM in the United States is higher in Latinos, African Americans, Native Americans, Alaska Natives, Asian Americans, and Pacific Islanders.[2]

Normally, glucose transport into cells occurs by the process of facilitated diffusion using various glucose transport channel proteins.[24] Insulin is not required for glucose to enter cells in the liver, kidney tubules, central nervous system, retina, or intestinal mucosa; beta cells in the islets of Langerhans; or into erythrocytes. In response to increased levels of serum glucose, insulin is released from the pancreas by beta cells in the islets of Langerhans. Insulin promotes uptake of glucose by muscle, liver, and adipose cells and is integral in carbohydrate, protein, and lipid synthesis.[3] The physiological activity of insulin is summarized in Box 18-3.

Control of glucose levels and insulin secretion is affected by the pancreatic hormones glucagon, amylin, and somatostatin, as well as the gut-secreted incretin hormones such as glucagon-like peptide-1 (GLP-1).[3] Amylin is cosecreted by the pancreatic beta cells in response to glucose elevation in the postfed state and acts to suppress postprandial hepatic glucose output, delay gastric emptying, and promote satiety.[3] GLP-1 is produced by the small intestines in response to glucose entry into the gut following a meal. GLP-1 has actions similar to amylin and additionally promotes first-phase insulin release by the pancreas.[4] Circulating counterregulatory hormones including catecholamines, cortisol, glucagon, and growth hormone also are integral in blood glucose regulation. These hormones are released in response to decreased glucose levels and also as an element of the physiologic response to stress. Excretion of glucose by the renal tubules additionally plays a role in blood glucose regulation. Sodium-glucose cotransporter (SGLT-2) is a compound found in the proximal tubule of the nephron that is responsible for the majority of glucose excretion by the kidney. A new class of drugs called SGLT-2 inhibitors is being developed and will augment blood glucose control in people with type 2 diabetes by enhancing renal glucose excretion by limiting tubular reabsorption of glucose. The net result is a decrease in circulating levels of glucose.

BOX 18-3 PHYSIOLOGICAL ACTIVITY OF INSULIN

Carbohydrate Metabolism
- Increases glucose transport across cell membrane in most cells including muscle and fat
- Within liver and muscle, promotes glycogenesis, the storage form of glucose
- Inhibits gluconeogenesis and glycogenolysis in the liver, thus sparing amino acids and glycerol for protein and fatty acid synthesis

Fat Metabolism
- Increases triglyceride synthesis
- Increases fatty acid transport into adipose tissue
- Inhibits lipolysis of triglycerides stored in adipose tissue
- Stimulates fatty acid synthesis from glucose and other substrates

Protein Metabolism
- Increases amino acid transport across cell membrane of muscle and liver
- Augments protein synthesis
- Inhibits proteolysis

Without insulin, glucose is unable to enter storage cells, and instead it accumulates in the blood and triggers a variety of physiological processes as the cells requiring insulin for glucose entry begin to starve. In contrast, levels of circulating insulin that exceed the body's requirement result in decreased serum glucose levels and changes in nervous system function including mental status, because glucose is the preferred substrate for the central nervous system.

Three common critical endocrine disorders associated with the pancreas are diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and hypoglycemia. An understanding of the normal physiology of insulin, as well as of the pathophysiology, critical assessments, and collaborative treatment regimens of the aforementioned disorders, is essential to the management and nursing care of these patients.

Effects of Aging

With aging, pancreatic endocrine function declines. Fasting glucose levels trend upward with age and glucose tolerance decreases. These changes are due to a combination of both decreased insulin production and increased insulin resistance, independent of any other coexisting disease states. Fifty percent of adults age 65 years and older have elevated blood glucose levels and are at increased risk for diabetes (prediabetes), and over one fourth of elders have glucose levels that meet diagnostic criteria for diabetes.[6]

Hyperglycemic Crises

Pathogenesis

DKA and HHS are endocrine emergencies. The underlying mechanism for both DKA and HHS is a reduction in the net effective action of circulating insulin coupled with a concomitant elevation of counterregulatory hormones (Figure 18-3). Together, this hormonal mix leads to increased hepatic and renal glucose production, but it prevents use of glucose in the peripheral tissues.

Historically, DKA was described as the crisis state in type 1 DM, whereas HHS was thought to occur in type 2 DM. Increasingly, DKA and HHS are seen concurrently in the same patient.[5]

Etiology of diabetic ketoacidosis. Numerous factors precipitate DKA (Box 18-4). Many patients present with DKA as the initial indication of previously undiagnosed type 1 DM. In the critically ill, the presence of coexisting autoimmune endocrine disorders of the thyroid and adrenal glands must be considered, especially in unstable patients with type 1 DM.[24] Additionally, the multiple endocrine changes that accompany pregnancy alter insulin needs that escalate rapidly in the second and third trimesters.[3] Pregnant women with type 1 DM are at increased risk for DKA. Signs and symptoms of DKA characteristically develop over a short period, and patients seek medical help early because of the associated symptoms.

The incidence of recurrent DKA is higher in females and peaks in the early teenage years. The risk of recurrent DKA is also higher in patients with DM diagnosed at an early age and in those of lower socioeconomic status. The causes of recurrent DKA are unclear but include physiological, psychosomatic, and psychosocial factors. Psychological problems complicated by eating disorders in younger patients with type 1 DM may contribute to 20% of recurrent DKA.[10]

Etiology of hyperosmolar hyperglycemic state. HHS is usually precipitated by inadequate insulin secretion or impaired action associated with rising glucose levels, and is more commonly seen in patients with who have type 2 DM or no prior history of DM.[10] Most patients who develop this condition are elderly, with decreased compensatory mechanisms to maintain homeostasis in hyperosmolar states. A major illness that mediates overproduction of glucose secondary to the stress response may contribute to the development of HHS. High-calorie parenteral and enteral feedings that exceed the patient's ability to metabolize glucose have induced HHS. Several medications are associated with the development of the disorder. The major etiological factors of HHS are included in Box 18-4.

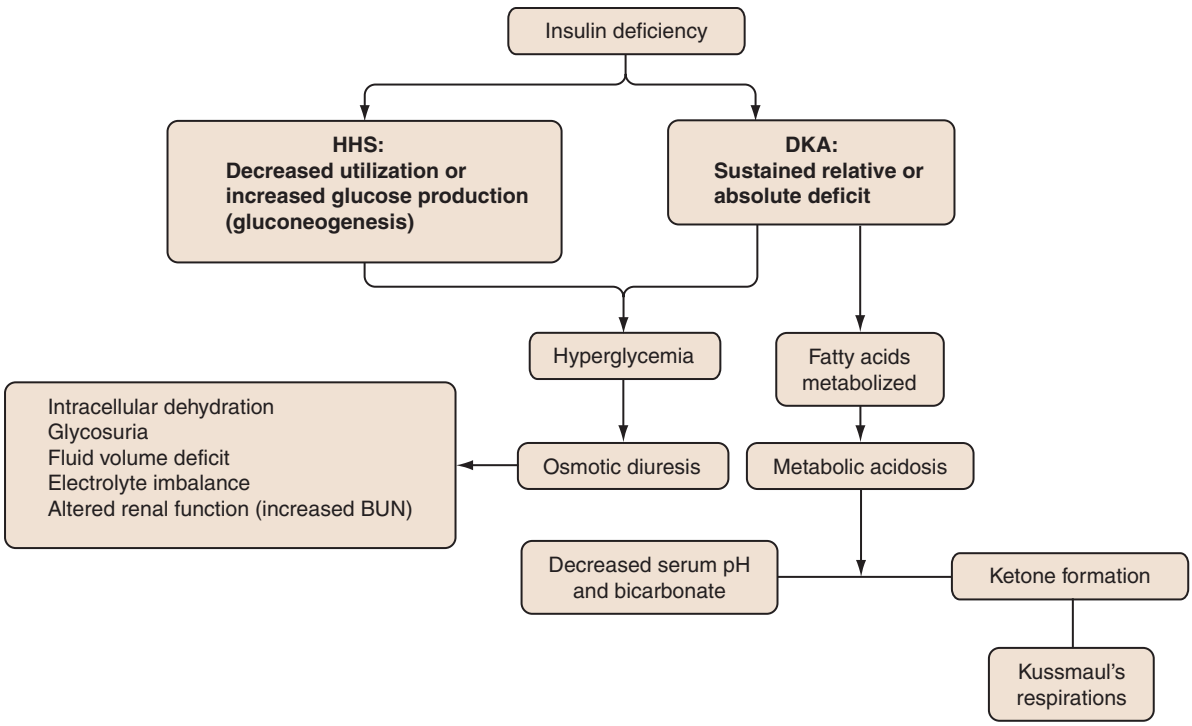


FIGURE 18-3 Pathophysiology of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS).

BOX 18-4 FACTORS LEADING TO DIABETIC KETOACIDOSIS AND HYPEROSMOLAR HYPERGLYCEMIC STATE

Common Factors
- *Infections:* pneumonia, urinary tract infection, sepsis, or abscess
- Omission of diabetic therapy or inadequate treatment
- New-onset diabetes mellitus
- *Preexisting illness:* cardiac, renal diseases
- *Major or acute illness:* MI, CVA, pancreatitis, trauma, surgery, renal disease
- *Other endocrine disorders:* hyperthyroidism, Cushing's disease, pheochromocytoma
- Stress
- High caloric parenteral or enteral nutrition

Medications
- Steroids (especially glucocorticoids)
- Beta-blockers
- Thiazide diuretics
- Calcium channel blockers
- Phenytoin
- Epinephrine
- Psychotropics, including tricyclic antidepressants
- Sympathomimetics
- Analgesics
- Cimetidine
- Calcium channel blockers
- Immunosuppressants
- Diazoxide
- Chemotherapeutic agents
- "Social drugs" such as cocaine, ecstasy

DKA-Specific Factors
- Malfunction of insulin pump
- Insulin pump infusion set site problems (infection, disconnection, catheter kinking or migration
- Increased insulin needs secondary to insulin resistant states: pregnancy, puberty, before menstruation

HHS-Specific Factors
- Decreased thirst mechanism
- Difficult access to fluids (e.g., nursing home resident)

CVA, Cerebrovascular accident; *DKA,* diabetic ketoacidosis; *HHS,* hyperosmolar hyperglycemic state; *MI,* myocardial infarction.

Pathophysiology of Diabetic Ketoacidosis

Figure 18-4 details the intracellular and extracellular shifts that occur in both DKA and HHS. In both disorders, high extracellular glucose levels produce an osmotic gradient between the intracellular and extracellular spaces, causing fluid to translocate from cells.[10] This process is called *osmotic diuresis.* When serum glucose levels exceed the renal threshold (approximately 200 mg/dL), glucose is lost through the kidneys *(glycosuria).* As glycosuria and osmotic diuresis progress, urinary losses of water, sodium, potassium, magnesium, calcium, and phosphorus occur. This cycle of osmotic diuresis causes increases in serum osmolality, further compensatory fluid shifts from the intracellular to the intravascular space, and worsening dehydration.

Typically, body water losses in DKA total 6 L.[24] The evolving hyperosmolarity further impairs insulin secretion and promotes a state of insulin resistance known as *glucose toxicity.*[3] The glomerular filtration rate in the kidney decreases in response to these severe fluid volume deficits. Decreased glucose excretion (causing increased serum glucose levels) and hemoconcentration result. The altered neurological status frequently seen in these patients is partially the result of cellular dehydration and the hyperosmolar state.

The absolute or relative insulin deficiency that precipitates DKA causes derangement of carbohydrate, protein, and fat metabolism.[10] Protein stores are depleted through the process of gluconeogenesis in the liver. Amino acids are metabolized into glucose and nitrogen to provide energy. Without insulin, the liberated glucose cannot be used, further increasing serum blood glucose and urine glucose concentrations and worsening osmotic diuresis. As nitrogen accumulates in the peripheral tissues, blood urea nitrogen (BUN) rises. Breakdown of protein stores also stimulates the shift of intracellular potassium into the extracellular serum (hyperkalemia). This additional circulating potassium may also be lost as a result of osmotic diuresis (hypokalemia). Serum electrolyte levels, particularly potassium, may be falsely elevated in relation to the actual intracellular level. Total body potassium deficits are common and must be considered in the overall management of DKA. Because of the fluid volume and potassium shifts, serum potassium values must be interpreted with caution in patients with DKA.[3]

The starvation state that accompanies DKA results in the breakdown of fat cells into free fatty acids.[10] The free fatty acids are released into the blood and are transported to the liver where they are oxidized into ketone bodies (beta-hydroxybutyrate) and acetoacetate. This leads to an increase in circulating ketone concentrations and further increases gluconeogenesis by the liver. Ketonuria and the accompanying rising glucose level contribute to osmotic diuresis. The ketoacids are transported to peripheral tissues where they are oxidized to acetone. Inadequate buffering of the excess ketone acids by bicarbonate results in metabolic acidosis as the ratio of carbonic acid to bicarbonate ions increases. As ketone and hydrogen ions accumulate and acidosis worsens, the respiratory system attempts to compensate for excess carbonic acid by "blowing off" carbon dioxide (CO_2), a weak acid. Kussmaul respirations, characterized by increases in the rate and depth of breathing, and an acetone ("fruity") breath odor are classic clinical signs of DKA associated with this compensatory process. In addition to ketonemia, patients with DKA may have an accumulation of lactic acid (lactic acidosis). The resulting dehydration may cause decreased perfusion to core organs, with consequent hypoxemia and worsening of the lactic acidosis.

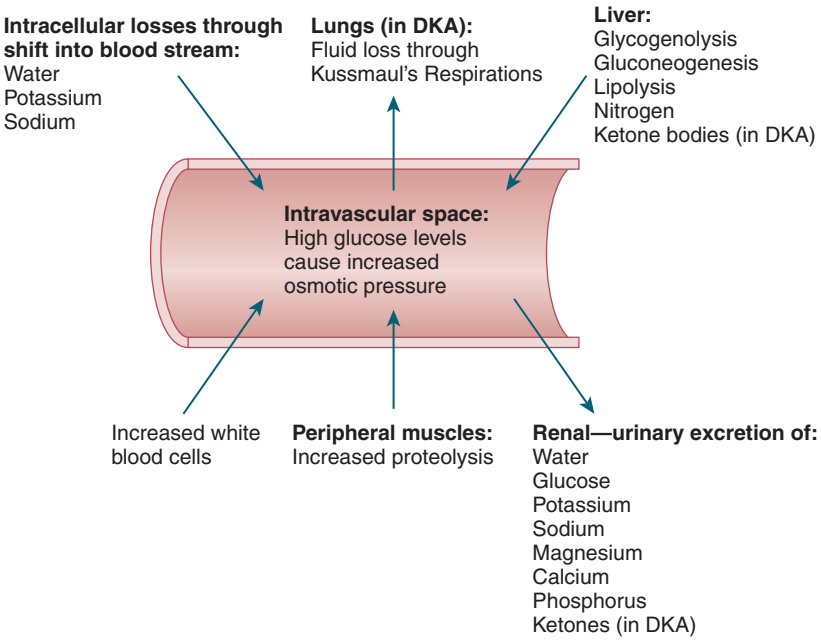


FIGURE 18-4 Intracellular/extracellular shifts in hyperglycemic crises. *DKA,* Diabetic ketoacidosis.

BOX 18-5 CALCULATION FOR ANION GAP

$(Na^+ + K^+) - (Cl^- + HCO_3^-)$

The normal value is 8 to 16 mEq/L. An elevated value indicates the accumulation of acids, such as is present in diabetic ketoacidosis.

Cl^-, Chloride; *HCO_3^-,* bicarbonate; *K^+,* potassium; *Na^+,* sodium.

Excess lactic acid results in an *increased anion gap* (increased body acids). Sodium, potassium, chloride, and bicarbonate are responsible for maintaining a normal anion gap, which is normally less than 16 mEq/L. Ketone accumulation causes an increase in the anion gap greater than 16 mEq/L. To calculate the anion gap, see Box 18-5.

Many enzymatic reactions within the body function only within a limited range of pH. As the patient becomes more acidotic and enzymes become less effective, body metabolism slows. This situation promotes further ketone formation, and acidosis worsens. The stress response associated with the progressing ketoacidosis state also contributes to metabolic alterations because the liver is stimulated by hormones (glucagon, catecholamines, cortisol, and growth hormones) to metabolize protein stores. The net result is an additional increase in serum glucose, nitrogen levels, and plasma osmolality. Some of these hormones also decrease the ability of cells to use glucose for ATP production and therefore compound the problem. The alterations in central nervous system function in DKA are thought to be influenced by the combination of acidosis and severe dehydration.

In summary, cells without glucose starve and begin to use existing stores of fat and protein to provide energy for body processes (gluconeogenesis). Fats are metabolized faster than they can be stored, resulting in an accumulation of ketone acids, a by-product of fat metabolism in the liver. Ketone acids accumulate in the bloodstream, where hydrogen ions dissociate from the ketones and cause metabolic acidosis. The more acidotic the patient becomes, the less able the body is to metabolize these ketones.

Pathophysiology of Hyperosmotic Hyperglycemic State

The pathophysiology of HHS is similar to that of DKA. However, in HHS, there are significantly lower levels of free fatty acids, resulting in a lack of ketosis, but even higher levels of hyperglycemia, hyperosmolality, and severe dehydration (see Figure 18-3).[4] HHS is referred to by many different acronyms (Box 18-6).

Hyperglycemia results from decreased utilization of glucose, increased production of glucose, or both. The hyperglycemic

BOX 18-6 HHS AND OTHER SYNONYMOUS ACRONYMS

- *HHS:* Hyperosmolar hyperglycemic state
- *HHNC:* Hyperosmolar hyperglycemic nonketotic coma
- *HNS:* Hyperosmolar nonketotic state
- *HHNK:* Hyperosmolar hyperglycemic nonketosis
- *HHNS:* Hyperosmolar hyperglycemic nonketotic state/syndrome
- *HNKDC:* Hyperosmolar nonketotic diabetic coma
- *HONK:* Hyperosmolar nonketosis
- *HNAD:* Hyperglycemic nonacidotic diabetic coma

state causes an osmotic movement of water from a lesser concentration of solutes to a higher concentration of solutes. This results in expansion of the extracellular fluid volume and intracellular dehydration. The osmotic diuresis and resultant intracellular and extracellular dehydration in HHS are generally more severe than those found in DKA, because HHS generally develops insidiously over a period of weeks to months. Alterations in neurological status are common because of cellular dehydration. The typical total body water deficit is greater in HHS, approximately 9 L.[24] By the time these patients seek medical attention, they are profoundly dehydrated and hyperosmolar. As a result, the mortality rate of HHS is higher than that of DKA.

Most commonly, patients who develop HHS are older. They are also more likely to have other medical problems such as renal insufficiency, congestive heart failure, myocardial ischemia, and chronic lung disease that may limit the ability of providers to aggressively treat the condition, particularly in regard to fluid resuscitation. Older adults that develop HHS are at very high risk for mortality.

Ketoacidosis is usually not seen in patients with HHS. It is believed that insulin levels in these patients are sufficient to prevent lipolysis and subsequent ketone formation.[4] The levels of glucose counterregulatory hormones that promote lipolysis are lower in patients with HHS than in those with DKA. However, persistence or worsening of the physiological stressor that precipitated the HHS episode may allow the hyperglycemia to progress to a state of extreme, insulin deficiency. Lipolysis occurs as a consequence of the severe insulin deficit, and ketoacidosis becomes superimposed upon the HHS.

Assessment

Clinical presentation. The presenting symptoms of DKA and HHS are similar (Table 18-3). Signs of DKA and HHS are related to the degree of dehydration present and the electrolyte

TABLE 18-3 MANIFESTATIONS OF DIABETIC KETOACIDOSIS AND HYPEROSMOLAR HYPERGLYCEMIC STATE

	DIABETIC KETOACIDOSIS	HYPEROSMOLAR HYPERGLYCEMIC STATE
Pathophysiology	Relative or absolute insulin deficiency resulting in cellular dehydration and volume depletion, acidosis, and protein catabolism	Insulin deficiency resulting in dehydration and hyperosmolality
Health history	History of type 1 diabetes mellitus (DM) or use of insulin Signs and symptoms of hyperglycemia before admission Can also occur in type 2 DM in severe stress	History of type 2 DM signs and symptoms of hyperglycemia before admission Occurs most frequently in elderly, with preexisting renal and cardiovascular disease
Onset	Develops quickly	Develops insidiously
Clinical presentation	Flushed, dry skin Dry mucous membranes ↓ Skin turgor Tachycardia Hypotension Kussmaul's respirations Acetone breath Altered level of consciousness Visual disturbances Polydipsia Nausea and vomiting Anorexia Abdominal pain	Flushed, dry skin Dry mucous membranes ↓ Skin turgor (may not be present in elderly) Tachycardia Hypotension Shallow respirations Altered level of consciousness (generally more profound and may include absent deep tendon reflexes, paresis, and positive Babinski's sign)
Diagnostics	↑ Plasma glucose (average: 675 mg/dL) pH <7.30 ↓ Bicarbonate Ketosis Azotemia Electrolytes vary with state of hydration; often hyperkalemic Plasma hyperosmolality (average: 330 mOsm/kg)	↑ Plasma glucose (usually >1000 mg/dL) pH >7.30 Bicarbonate >15 mEq/L Absence of significant ketosis Azotemia Electrolytes vary with state of hydration; often hypernatremic Plasma hyperosmolality (average: 350 mOsm/kg) Hypotonic urine

imbalances. The osmotic diuresis occurring from hyperglycemia results in signs of increased thirst (polydipsia), increased urine output (polyuria), and dehydration. Increased hunger (polyphagia) may be an early sign. Elderly persons have a decreased sense of thirst, so this sign may not be observed in these patients. Signs of intravascular dehydration are common as the physiological processes continue.

Hyperglycemia and ketosis both contribute to delayed gastric emptying. Vomiting can occur, which further worsens total body dehydration. Patients also report symptoms of weakness and anorexia. Abdominal pain and tenderness are common presenting symptoms, particularly in DKA, and are associated with dehydration and underlying pathophysiology, such as pyelonephritis, duodenal ulcer, appendicitis, and metabolic acidosis. Pain associated with DKA usually disappears with treatment of dehydration. Significant weight loss occurs because of the fluid losses and an inability to metabolize glucose.

Altered states of consciousness range from restlessness, confusion, and agitation to somnolence and coma. Visual disturbances, especially blurred vision, are common in hyperglycemia. Generally, altered levels of consciousness are more pronounced in patients with HHS. This is related to the severity of hyperglycemia, serum hyperosmolality, and electrolyte disturbances. Seizures and focal neurological signs may also be present and often lead to misdiagnosis in patients with HHS.

In DKA, ketonuria and metabolic acidosis are seen. Nausea is an early sign of DKA and is thought to be a result of retained ketones. Kussmaul's respirations and an acetone breath odor additionally are clinical signs of ketosis. Later in the disease process, the respiratory status of the patient may be influenced by the neurological status, precipitating impaired breathing patterns and gas exchange. A decreased level of consciousness is also associated with the severe acidotic state (pH less than 7.15). The flushed face associated with DKA is the result of superficial vasodilation.

Laboratory evaluation. Numerous diagnostic studies are used to evaluate for the presence of DKA and HHS, to rule out other diseases, and to detect complications (see box, "Laboratory Alert: Pancreatic Endocrine Disorders"). In addition, cultures and testing are performed to determine any precipitating factors such as infection or myocardial infarction.

! LABORATORY ALERT

Pancreatic Endocrine Disorders

LABORATORY TEST*	CRITICAL VALUE	SIGNIFICANCE
Glucose	≥200 mg/dL (2 hours postprandial or random) ≥126 mg/dL (fasting)	Combined with symptoms, establishes diagnosis of diabetes mellitus
	>250 mg/dL	Suggestive of DKA; significantly higher in HHS
	<50 mg/dL	Hypoglycemia
Potassium	>6.0 mEq/L	Potential for heart blocks, bradydysrhythmias, sinus arrest, ventricular fibrillation, or asystole
	<3.0 mEq/L	Potential for ventricular dysrhythmias
Sodium	>150 mEq/L	May be a result of stress and dehydration
BUN	>20 mg/dL	Elevated due to protein breakdown and hemoconcentration
Bicarbonate	<20 mEq/L	Decreased in DKA due to compensation for acidosis
pH	<7.3	Decreased in DKA due to accumulation of acids
Osmolality	>330 mOsm/kg H_2O	Elevated in DKA relative to dehydration, higher in HHS
Phosphorus	<2.5 mg/dL	May result in impaired respiratory and cardiac functions
Magnesium	<1.3 mEq/L	Depleted by osmotic diuresis May coincide with decreased potassium and calcium levels; may result in dysrhythmias
Beta-hydroxybutyrate	>3.0 mg/dL	Reflects blood ketosis in DKA

DKA, Diabetic ketoacidosis; *HHS*, hyperosmolar hyperglycemic state.
*Serum tests.

In DKA, an initial arterial blood gas analysis reflects metabolic acidosis (low pH and low bicarbonate level). The partial pressure of arterial carbon dioxide ($PaCO_2$) may also be low, reflecting the respiratory system's compensatory mechanism. Acidosis is subsequently monitored by venous pH, which correlates well with arterial pH but is easier to obtain and process. The severity of DKA is determined by the pH, bicarbonate level, ketone values, and the patient's mental status.[10] Severe acidosis is associated with cardiovascular collapse, which can result in death.

In HHS, the laboratory results are similar to those in DKA, but with four major differences: (1) the serum glucose concentration in HHS is generally significantly more elevated, (2) plasma osmolality is higher than in DKA and is associated with the degree of dehydration, (3) acidosis is not present or very mild compared with DKA, and (4) ketosis is usually absent or very mild in comparison with DKA.[10] Serum electrolyte concentrations may be low, normal, or elevated and generally are not reliable indicators of total body stores of electrolytes or water.

Nursing and Medical Interventions

Primary interventions in the treatment of DKA and HHS include respiratory support, fluid replacement, administration of insulin to correct hyperglycemia, replacement of electrolytes, correction of acidosis in DKA, prevention of complications, and patient teaching and support (see box, "Evidence-Based Practice").

Respiratory support. Assessment of the airway, breathing, and circulation is always the first priority in managing life-threatening disorders. Airway and breathing may be supported through the use of oral airways and oxygen therapy. In more severe cases, the patient may be intubated and placed on ventilatory support. Prevention of aspiration is accomplished by elevating the head of the bed. Nasogastric tube suction may be considered in a patient with impaired mentation who is actively vomiting.

Fluid replacement. Dehydration may have progressed to hypovolemic shock by the time of admission. Immediate intravenous (IV) access and rehydration need to be accomplished. In DKA, the typical water deficit approximates 100 mL/kg, and it may be as high as 200 mL/kg in HHS.[10] Monitoring for signs and symptoms of hypovolemic shock is a priority. Vital signs and neurological status are recorded at least every hour initially. Unstable patients require constant monitoring and recording of hemodynamic parameters at least every 15 minutes. Right atrial pressure or pulmonary artery pressure monitoring may also be instituted to evaluate fluid requirements and to monitor the

EVIDENCE-BASED PRACTICE

Tight Glycemic Control

Problem

Tight glycemic control has been advocated in critically ill patients. Issues and outcomes of achieving glycemic control need to be identified.

Clinical Question

What are the outcomes and issues associated with tight glycemic control in critically ill patients?

Evidence

Since the 2001 landmark study of Van den Berghe and colleagues demonstrated improved patient outcomes after initiation of tight glycemic control, most critical care units implemented protocols to achieve better glucose levels.[26] Many research studies have been conducted, and those cited in this box critically appraised recent evidenced—primarily from randomized controlled trials—on a variety of variables that have been studied. Findings of the NICE-SUGAR study raised important questions on the safety of tight glycemic targets in critically ill individuals.[1] The NICE-SUGAR trial included over 6000 critically ill patients, most of whom were mechanically ventilated. Those randomized to intensive control with glucose targets of 81 to 108 mg/dL experienced significantly higher 90-day mortality, primarily from cardiovascular causes, and higher rates of severe hypoglycemia than patients randomized to a target glycemic value of less than 180 mg/dL. Findings of a subsequent meta-analysis of 26 studies related to intensive glucose control in critically ill adults representing over 13,000 patients including those from the NICE-SUGAR trial concluded that intensive insulin therapy in critically ill patients does not reduce mortality and substantially increases the risk of serious hypoglycemia. But it may still provide specific benefit to surgical patients.[2] The degree of desired control remains a source of debate. Because significant hyperglycemia has been clearly associated with poor outcomes in the critically ill, current recommendations suggest that moderation of glucose targets to values between 140 and 180 mg/dL in critically ill patients should be maintained.

Implications for Nursing

Glycemic control has become a standard of practice within critical care settings. Nurses must be aware of protocols for achieving glycemic control and assist in ensuring that target glucose levels are achieved. Assessing patients for hypoglycemia is an essential nursing implication to prevent complications associated with treatment. Nurses will likely be involved in additional research over the next several years as protocols are refined based upon changing evidence.

Level of Evidence

A—Meta-analysis

References

1. NICE-SUGAR Study Investigators. Intensive verses conventional glucose control in critically ill patients. *New England Journal of Medicine*. 2011;360:1283-1297.
2. Griesdale DEG. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR data, *Canadian Medical Association Journal*. 2009; 180:821-827.

patient's response to treatment. This is particularly true of patients with HHS, who tend to be elderly and have concurrent cardiovascular and renal disease. Accurate intake, hourly recording of urine output, and measurement of daily weight are also essential. Changes in mentation may also indicate a change in fluid status. Ongoing assessment of neurological status can alert the nurse to a change in mentation.

Normal saline (0.9% NS) is the fluid of choice for initial fluid replacement because it best replaces extracellular fluid volume deficits. Fluid replacement usually starts with an initial bolus of 1 L of 0.9% NS. This is followed by an infusion of 15 to 20 mL/kg during the first hour.[10] The effectiveness of fluid replacement is evaluated by hemodynamic status, intake and output, laboratory measures, and assessment of the patient's general physical condition, particularly mental status. IV fluids are rapidly infused until the patient's blood pressure and serum sodium level normalize. If the serum sodium is elevated or normal, IV fluid is changed to hypotonic saline (0.45% NS) and infused at slower rates to replace intracellular fluid deficits. When the plasma glucose level approaches 200 mg/dL, 5% dextrose is added to fluids to prevent hypoglycemia and assist in the resolution of ketosis.[10] The goal is to replace half of the estimated fluid deficit over the first 8 hours. The second half of the fluid deficit should be replaced during the next 16 hours of therapy so that the volume is restored in most patients within the first 24 hours of treatment.[10] Significant improvements in hyperglycemia may be seen with fluid resuscitation before initiation of insulin therapy. Hyperglycemia resolves more quickly than ketosis.

The goal of fluid resuscitation is normovolemia. Hypervolemia must be prevented, especially in patients with ischemic heart disease, heart failure, or acute kidney injury. Fluid overload from overaggressive fluid replacement can be prevented by monitoring breath sounds and performing cardiovascular assessments. Hemodynamic monitoring may be used to guide fluid resuscitation. Signs and symptoms of fluid overload are reviewed in Box 18-7. Rapid fluid administration may also contribute to cerebral edema, a complication associated with DKA. A rapid decrease in the plasma glucose level, combined with rapid fluid administration and concurrent insulin therapy (see next section), may lead to movement of water into brain cells, resulting in brain edema, which may be fatal.

Insulin therapy. Replacement of insulin is definitive therapy for DKA and HHS. Before starting insulin therapy, fluid replacement therapy must be underway and the serum potassium level must be greater than 3.3 mEq/L.[10] The goal is to restore normal glucose uptake by cells while preventing complications of excess insulin administration, such as hypoglycemia, hypokalemia, and hypophosphatemia. Hyperglycemic crises are commonly treated with IV insulin infusions because absorption is more predictable. An initial IV bolus of 0.1 units/kg of regular insulin is administered, followed by a continuous infusion of 0.1 units/kg per hour to achieve a steady decrease in serum glucose levels of 50 to 75 mg/dL per hour.[10] Initial insulin infusion rates of less than 0.1 units/kg per hour are typically insufficient to inhibit ketosis. Alternatively, patients with mild to moderate DKA may be treated with hourly subcutaneous injections of rapid-acting insulin using a titration scale.

BOX 18-7 SIGNS AND SYMPTOMS OF FLUID OVERLOAD

- Tachypnea
- Neck vein distention
- Tachycardia
- Crackles
- Increased pulmonary artery occlusion or right atrial pressures
- Declining level of consciousness in cerebral edema

Serum glucose levels are monitored every 1 to 2 hours using a consistent monitoring method. While receiving an intravenous insulin infusion, patients are generally allowed nothing by mouth. When glucose values are less than 200 mg/dL, insulin infusion rates may be decreased to 0.02 to 0.05 units/kg per hour and maintained to keep the glucose value in the range of 150 to 200 mg/dL.[10] Patients may be transitioned to subcutaneous insulin when the blood glucose is 200 mg/dL or less and when two of the following criteria are met: (1) venous pH is greater than 7.30, (2) serum bicarbonate level is greater than 15 mEq/L, and (3) calculated anion gap is 12 mEq/L or less.[10] Subcutaneous insulin therapy using a basal-bolus regimen that also includes an algorithm for correction doses of rapid acting insulin may be most appropriate for patients who are not receiving nutritional support in the form of enteral feedings or total parenteral nutrition. Glucose levels are monitored at least every 6 to 8 hours while a patient is receiving subcutaneous insulin.

In patients with HHS, insulin infusion rates may be decreased to 0.2 to 0.5 units/kg per hour when the glucose values reach 300 mg/dL.[10] Target glucose values of 200 to 300 mg/dL should be maintained until the patient's mental status improves, at which time the patient may be transitioned to subcutaneous insulin therapy.

It is important that serum glucose levels not be lowered too rapidly, not more than 50 to 75 mg/dL per hour, to prevent cerebral edema, which could result in seizures and coma. Any patient who exhibits an abrupt change in the level of consciousness after initiation of insulin therapy requires frequent blood glucose monitoring and protective steps instituted to prevent harm, such as seizure precautions. Treatment of acute cerebral edema usually involves administration of an osmotic diuretic (e.g., 20% mannitol solution).

Electrolyte management. Potassium, phosphate, chloride, and magnesium replacement may be required, especially during insulin administration. Osmotic diuresis in DKA and HHS results in total body potassium depletion ranging from 400 to 600 mEq. The potassium deficit may be greater in HHS. Insulin therapy will promote translocation of potassium into the intracellular space resulting in a further decrease in serum potassium levels.

The need for potassium therapy is based on serum laboratory results. In the absence of renal disease, insulin replacement and

monitoring begins after the first liter of IV fluid has been administered, the serum potassium level is greater than 3.3 mEq/L, and the patient is producing urine. At that point, 20 to 30 mEq of potassium may be added to each liter of fluid administered. This may be augmented by additional doses of potassium as intermittent infusions.[10] Serum potassium levels should be maintained between 4 and 5 mEq/L during the course of therapy. In the event that the patient is admitted with hypokalemia, insulin therapy should be withheld until potassium values exceed 3.3 mEq/L.[10] The integrity of the IV site must be maintained to prevent extravasation. Electrocardiographic (ECG) monitoring for cardiac dysrhythmias and assessment of respiratory status is also important during potassium administration.

Total body phosphorus levels are also depleted by osmotic diuresis, but serum phosphate levels may remain in the normal range. Insulin therapy may cause further reductions in phosphate levels. Phosphate replacement occurs when there is associated respiratory or cardiac dysfunction. Potassium phosphate can be administered to treat part of the potassium deficit in a concentration of 20 to 30 mEq/L.[10] Phosphate replacement is used with extreme caution in patients with renal failure because these patients are unable to excrete phosphate and typically have underlying hyperphosphatemia.

Treatment of acidosis. Acidosis is a hallmark feature of DKA. However, multiple studies have shown that treatment with sodium bicarbonate is often not beneficial and may pose increased risk of hypoglycemia, cerebral edema, cellular hypoxemia secondary to decreased uptake of oxygen by body tissues, worsening hypokalemia, and development of central nervous system acidosis.[10] Therefore sodium bicarbonate is not routinely used to treat acidosis unless the serum pH is less than 6.9. Bicarbonate replacement is used only to bring the pH up to 7.0, but not to normal levels. When administered, 100 mEq/L of bicarbonate may be added to 400 mL of sterile water with 20 mEq of KCl at a rate of 200 mL per hour until the venous pH exceeds 7.0.[10] Serum blood gas analysis is done frequently to assess for changes in pH, bicarbonate, anion gap, $PaCO_2$, and oxygenation status. Repeat infusions of the bicarbonate solution may be required every 2 hours until the pH exceeds 7.0. Once fluid and electrolyte imbalances are corrected and insulin is administered, the kidneys begin to conserve bicarbonate to restore acid-base homeostasis, and ketone formation ceases.

Patient and family education. A primary intervention to prevent DKA is patient education. Managing blood glucose levels with diet, exercise, and medication is a priority. Monitoring of hemoglobin A1c levels three to four times per year provides an indication of the patient's long-term control of blood glucose levels, changing insulin needs, and indications of psychosocial or behavioral factors that may impact control, including coping issues such as diabetes-related distress and depression.[1] The importance of a regular eating schedule, exercise, rest, sleep, and relaxation must be emphasized. Adjustments to the usual diabetic control regimen for illness is known as "sick day management," and all patients with diabetes and their families need to be instructed in this strategy for prevention of DM complications. Patients who go into DKA while on insulin pump therapy may require reeducation on pump features, insulin pump safety, management of pump failure, and troubleshooting abnormal glucose levels.

Patient Outcomes

Outcomes for a patient with DKA or HHS are included the nursing care plan (see box, "Nursing Care Plan for the Patient with Hyperglycemic Crisis").

NURSING CARE PLAN

for the Patient with Hyperglycemic Crisis

NURSING DIAGNOSIS

Ineffective breathing pattern or impaired gas exchange related to acidosis (DKA), decreased level of consciousness

PATIENT OUTCOMES

Normal respiratory rate and pattern

- RR, 10-25 breaths/min
- Tidal volume >5 mL/kg
- ABG values WNL

NURSING INTERVENTIONS	RATIONALES
• Assess airway and breathing on admission and every 1-2 hours; correlate ABG/venous pH results with clinical examination	• Ability to protect airway and respiratory effort will stabilize as pH improves
• Assess for clinical signs of hypoxemia	• Impairment of ventilation may occur as a result of mental status or electrolyte changes
• Provide support as needed (e.g., airway, intubation, mechanical ventilation)	• Maintenance of oxygenation and ventilation are critical in maintaining cellular integrity and preventing worsening acidosis
• Assess neurological status every 1-2 hours	• Mental status changes may be first indication of hypoxemia and cerebral edema
• Prevent aspiration: elevate head of bed; NG tube for decompression may be needed	• Patients with altered level of consciousness are at higher risk for aspiration, and individuals with glycemic derangement are at higher risk for vomiting

Continued

NURSING CARE PLAN

for the Patient with Hyperglycemic Crisis—cont'd

NURSING DIAGNOSIS

Deficient fluid volume related to total body water loss secondary to osmotic diuresis, ketosis, increased lipolysis, and vomiting

PATIENT OUTCOMES

Adequate fluid volume status

- Normal serum glucose
- Hemodynamic stability: BP, HR, RAP, PAOP WNL
- Normal sinus rhythm
- Urine output >0.5 mL/kg/hr
- Balanced I&O
- Stable weight
- Warm, dry extremities
- Normal skin turgor
- Moist mucous membranes
- Serum osmolality and serum electrolyte levels WNL: sodium, potassium, calcium, phosphorus
- pH WNL

NURSING INTERVENTIONS	RATIONALES
• Assess fluid status: Vital signs every hour until stable I&O measurements every 1-2 hours Skin turgor, mucous membranes, thirst Consider insensible fluid losses Daily weight	• Provide clinical indications of hypovolemia and provide data for restoring cellular function
• Initiate fluid replacement therapy: Monitor for signs and symptoms of fluid overload Monitor effects of volume repletion Monitor neurological status closely	• Correct volume deficit and prevent/treat hypovolemic shock; neurological status should improve as electrolytes normalize Mental status changes may indicate cerebral edema if glycemic correction is too rapid
• Administer IV insulin infusion per hospital protocol; titrate therapy hourly based on glucose levels; provide a steady decrease in serum glucose levels; a decrease of 50 to 75 mg/dL per hour is desired	• Prevents cerebral edema and potentially dangerous electrolyte abnormalities
• Monitor glucose every hour via consistent method (serum or fingerstick capillary) during insulin infusion	• Assesses response to therapy and allows for immediate correction of glycemic abnormalities.
• Monitor for signs and symptoms of hypoglycemia	• Hypoglycemia may occur if the insulin dose is exceeds patient's needs
• Add dextrose to maintenance IV solutions once serum glucose level reaches 200 mg/dL in DKA and 300 mg/dL in HHS	• Prevents relative hypoglycemia and a decrease in plasma osmolality that may result in cerebral edema
• Monitor serum electrolyte levels (sodium, potassium, calcium, phosphorus); administer supplements according to protocols; assess causes of continuing electrolyte depletion such as diuresis, vomiting, NG suction	• Prevent complications of electrolyte imbalance; osmotic diuresis may result in increased excretion of potassium and hyponatremia; insulin therapy causes potassium and phosphate to shift to intracellular space
• Monitor pH	• pH is the best indicator of acidosis and response to treatment; acidosis will correct more slowly than hyperglycemia; correction of hyperglycemia without correction of ketosis may result in reoccurrence of DKA
• Administer bicarbonate only in severe acidosis (pH <6.9)	• Routine administration of bicarbonate has been associated with hypokalemia, hypoglycemia, cellular ischemia, cerebral edema, and CNS cellular acidosis

NURSING CARE PLAN

for the Patient with Hyperglycemic Crisis—cont'd

NURSING DIAGNOSIS

Risk for ineffective therapeutic management related to lack of knowledge of disease process, treatment regimen, complications, sick day management and/or ineffective coping

PATIENT OUTCOMES

Effective therapeutic management of diabetes

- Patient/family can describe the pathophysiology and causes of DKA and/or HHS; preventative interventions related to diet, exercise regimen, and medications; signs and symptoms of hypoglycemia and hyperglycemia; signs and symptoms of infections that require medical follow-up; sick day management; and emergency hypoglycemia management
- Patient/family can identify the patient's individual glucose targets
- Patient/family can demonstrate self–glucose monitoring and administration of oral hypoglycemic medications and/or insulin therapy according to glucose values

NURSING INTERVENTIONS	RATIONALES
• Assess patient/family's current diabetes self-management practices, ability to learn information, and psychomotor and sensory skills	• Allows for individualization of patient's plan of care to match physical, psychosocial and educational needs
• Implement a teaching program that includes information on pathophysiology and causes of DKA or HHS; diet and exercise restrictions; individualized target glucose values; signs and symptoms of hypoglycemia and hyperglycemia, including interventions; and signs and symptoms of infection and illness, including interventions	• Prevention of acute diabetes complications primarily rests with the patient and/or family who are capable and able to follow the self-management plan and act early on significant physiological changes
• Demonstrate methods for blood glucose monitoring; have the patient repeat the demonstration until proficient; if the patient takes insulin, demonstrate administration; for each skill, have the patient demonstrate abilities with repeat demonstration; review insulin pump use and abilities if used for treatment	• Regular glucose monitoring is essential for patient self-management; ensure that patient/family have the ability to perform these skills related to at-home monitoring, insulin delivery, and problem solving related to abnormal glucose findings before discharge
• Review administration of hypoglycemic medications and/or insulin, including dosage, frequency, action, duration, side effects, and situations when medication may need to be adjusted	• Patients and caregivers require a thorough knowledge of insulin therapy in order to optimize treatment; failure to adjust hypoglycemic medications to match changing glycemic demands may result in acute hyperglycemia or hypoglycemia
• Consult with clinical dietitian regarding disease-specific nutrition and diet needs	• Assist in identifying the appropriate diet based on the patient's condition and caloric needs
• Encourage patient to wear a form of identification for diabetes	• Assists in prompt recognition and treatment of complications should they occur
• Provide written materials for all content taught; provide means for the patient to get questions answered after discharge, and schedule follow-up diabetes self-management education after discharge	• Effective diabetes self-management education is a collaboration between the patient, family, and multiprofessional care providers; in the short term, diabetes self-management education improves glycemic control; regular reinforcement improves self-management outcomes

ABGs, Arterial blood gases; *BP,* blood pressure; *DKA,* diabetic ketoacidosis; *HHS,* hyperosmolar hyperglycemic state; *HR,* heart rate; *I&O,* intake and output; *IV,* intravenous; *NG,* nasogastric; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; *PAOP,* pulmonary artery occlusion pressure; *RAP,* right atrial pressure; *RR,* respiratory rate; *WNL,* within normal limits.

Based on data from Gulanick M and Myers JL. *Nursing Care Plans: Diagnoses, Interventions, and Outcomes.* 7th ed. St. Louis: Mosby; 2011.

Hypoglycemia

Pathophysiology

A hypoglycemic episode is defined as a decrease in the plasma glucose level to less than 70 mg/dL and is sometimes referred to as *insulin shock* or *insulin reaction.* Glucose production falls behind glucose utilization, resulting in decrease in blood glucose. Because the brain is an obligate user of glucose, the first clinical sign of hypoglycemia is a change in mental status. A hypoglycemic event activates the sympathetic nervous system causing a rise in counterregulatory hormones, including glucagon, epinephrine, cortisol, and growth hormone. Those at highest risk for hypoglycemia are patients taking insulin, children and pregnant women with type 1 DM, patients with autonomic diabetic neuropathy, and elderly persons with type 1 or type 2 DM.

Hypoglycemia unawareness, also known as hypoglycemia-associated autonomic failure, is a term used to describe a diabetes-related condition where a patient does not recognize the onset of hypoglycemic signs and symptoms.[1] In this complication, the impairment of the autonomic nervous systems results in a blunted response to critically low glucose levels (see box, "Clinical Alert"). Patients with hypoglycemia unawareness may be asymptomatic while experiencing extremely low blood glucose levels. Patients who have other forms of autonomic neuropathy such as orthostasis, gastroparesis, erectile dysfunction, and cardiac autonomic neuropathy are at higher risk for this condition. Those at highest risk of hypoglycemia unawareness include the elderly because of their impeded stress responses and those with diminished mental function resulting from dementia, concurrent illness, or other factors. Patients taking beta-blockers are at risk of decreased awareness of signs of hypoglycemia because of the drug's impact on the sympathetic nervous system. The pathophysiological mechanisms associated with acute hypoglycemia and the associated central nervous system (CNS) and sympathetic symptoms are reviewed in Figure 18-5.

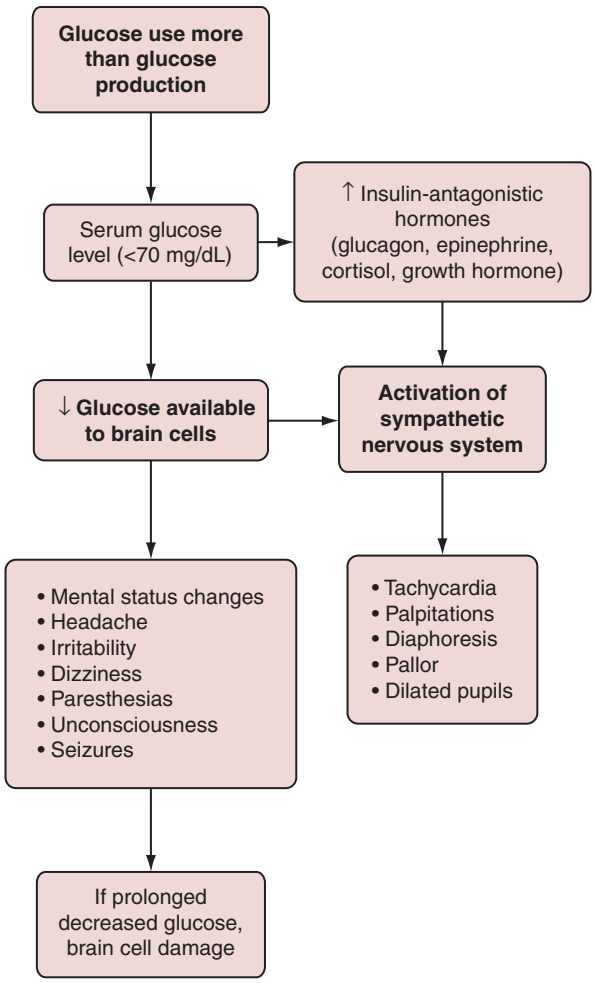


FIGURE 18-5 Pathophysiology of hypoglycemia.

! CLINICAL ALERT

Hypoglycemic Unawareness

Some patients have hypoglycemia unawareness, and remain asymptomatic despite extremely low blood glucose levels. The elderly and those taking beta-blockers are at especially high risk.

Etiology

Patients receiving insulin therapy must be closely monitored for hypoglycemia when insulin requirements are decreased because of weight loss or renal insufficiency, when insulin doses are increased, when nondiabetes medications that may impact glycemia are prescribed or adjusted, or when injection sites are rotated from a hypertrophied area to one with unimpaired absorption. Additionally, patients who use oral agents that promote production and release of endogenous insulin, such as long-acting sulfonylureas, are at risk for hypoglycemia. Amylin and agents that act on incretin hormones (exenatide and gliptins) also increase the risk for a hypoglycemic episode. Other causes of hypoglycemia in the hospitalized patient include insufficient caloric consumption because of a missed or delayed meal or snack, decreased intake because of nausea and vomiting, anorexia, and interrupted tube feedings or total parenteral nutrition. As a patient recovers from a stress event (infection illness, corticosteroid therapy, postpartum), the need for exogenous insulin decreases. Failure to adjust the insulin dose may precipitate hypoglycemia. Other major causes of hypoglycemia are reviewed in Box 18-8.

Severe hypoglycemia and hypoglycemia unawareness place a patient at risk for injury secondary to motor vehicle accidents, falls, and seizures. Patients with renal impairment or liver dysfunction are at particular risk for a severe hypoglycemic episode. Delayed degradation or excretion of hypoglycemic medications potentiates or prolongs the action of many diabetes medications. The resulting increase in circulating levels of active drug, including insulin, results in erratic glucose control. Close glucose monitoring and patient/family education on prevention, recognition, and treatment of hypoglycemia is critical in promoting safety in these very high-risk patients.

BOX 18-8 CAUSES OF HYPOGLYCEMIA

Excess Insulin or Oral Hypoglycemics
- Dose of insulin or oral hypoglycemics too high
- Islet cell tumors (insulinomas)
- Liver insufficiency or failure (impaired metabolism of insulin)
- Acute kidney injury (impaired inactivation of insulin)
- Autoimmune phenomenon
- Drugs that potentiate action of antidiabetic medications (propranolol, oxytetracycline, antibiotics)
- Sulfonylureas in elderly patients
- Amylin and incretin mimetic diabetes agents

Decreased Oral, Enteral, or Parenteral Intake

Underproduction of Glucose
- Heavy alcohol consumption
- Drugs: aspirin, disopyramide (Norpace), haloperidol (Haldol)
- Decreased production by liver
- Hormonal causes

Too Rapid Utilization of Glucose
- Gastrointestinal surgery
- Extrapancreatic tumor
- Increased or strenuous exercise

TABLE 18-4 SIGNS AND SYMPTOMS OF HYPOGLYCEMIA

DECREASE IN BLOOD SUGAR	
RAPID	**PROLONGED**
Activation of Sympathetic Nervous System	**Inadequate Glucose Supply to Neural Tissues**
Nervousness	Headache
Apprehension	Restlessness
Tachycardia	Difficulty speaking
Palpitations	Difficulty thinking
Pallor	Visual disturbances
Diaphoresis	Paresthesia
Dilated pupils	Difficulty walking
Tremors	Altered consciousness
Fatigue	Coma
General weakness	Convulsions
Headache	Change in personality
Hunger	Psychiatric reactions
	Maniacal behavior
	Catatonia
	Acute paranoia

Assessment

Clinical presentation. Common signs and symptoms of hypoglycemia are summarized in Table 18-4**.** Symptoms of hypoglycemia are categorized as (1) mild symptoms from autonomic nervous system stimulation that are characteristic of a rapid decrease in serum glucose levels, and (2) moderate symptoms reflective of an inadequate supply of glucose to neural tissues, associated with a slower, more prolonged decline in serum glucose levels.

With a rapid decrease in serum glucose levels, there is activation of the sympathetic nervous system, mediated by epinephrine release from the adrenal medulla. This compensatory fight-or-flight mechanism may result in symptoms such as tachycardia; palpitations; tremors; cool, clammy skin; diaphoresis; hunger; pallor; and dilated pupils. The patient may also report feelings of apprehension, nervousness, headache, tremulousness, and general weakness.

Slower and more prolonged declines in serum glucose levels result in symptoms related to an inadequate glucose supply to neural tissues *(neuroglycopenia)*. These include restlessness, difficulty in thinking and speaking, visual disturbances, and paresthesias. The patient may have profound changes in the level of consciousness, seizures, or both. Personality changes and psychiatric manifestations have been reported. Prolonged hypoglycemia may lead to irreversible brain damage and coma.

Laboratory evaluation. In most patients, the confirming laboratory test for hypoglycemia is a serum or capillary blood glucose level less than 70 mg/dL. Adults with a history of hypoglycemia unawareness, cognitively impaired elders, and older adults at high risk for falls may have higher target glucose ranges and an individualized protocol for management of lower glucose values.[1] The glucose level should be checked in all high-risk patients with the aforementioned clinical signs before initiating treatment. It is important to know baseline values before treatment because patients who have experienced elevated glucose levels for some time may complain of hypoglycemia-like symptoms when their glucose levels are brought into normal range. In patients with a known history of DM, a thorough history of past experiences of hypoglycemia, including patient-specific associated signs and symptoms, is essential. It is important to identify the glucose level at which symptoms appear because this may vary with individuals. Additionally, renal function is evaluated in patients with long-standing diabetes who have a new history of recurrent hypoglycemia. Decreased renal function may result in impaired clearance of insulin and result in erratic glucose control in patients who are on short-acting insulins, long-acting insulins, or oral insulin secretagogues.

Nursing Diagnoses

The nursing diagnoses applicable to a patient with a hypoglycemic episode include the following:
- Unstable blood glucose related to excess circulating insulin as in relation to available plasma glucose
- Acute confusion related to decreased glucose delivery to the brain and nervous tissue
- Risk for injury (seizures and falls) related to altered neuronal function associated with hypoglycemia
- Deficient knowledge related to hypoglycemia: prevention, recognition, and treatment of hypoglycemia

Nursing and Medical Interventions

After serum or capillary glucose levels have been confirmed, carbohydrates must be replaced. The patient's neurological

BOX 18-9 TREATMENT OF HYPOGLYCEMIA

Mild Hypoglycemia

- Patient is completely alert. Symptoms may include pallor, diaphoresis, tachycardia, palpitations, hunger, or shakiness. Blood glucose is less than 70 mg/dL. Patient is able to drink.
- Treatment: 15 g of carbohydrate by mouth

Moderate Hypoglycemia

- Patient is conscious, cooperative, and able to swallow safely. Symptoms may include difficulty concentrating, confusion, slurred speech, or extreme fatigue. Blood glucose is usually less than 55 mg/dL. Patient is able to drink.
- Treatment: 20 to 30 g of carbohydrate by mouth

Severe Hypoglycemia

- Patient is uncooperative or unconscious. Blood glucose is usually less than 40 mg/dL or patient is unable to drink
- Treatment with intravenous access: 12.5 g of dextrose as $D_{50}W$
- Treatment without intravenous access: 1 mg of glucagon subcutaneously

$D_{50}W$, 50% dextrose in water.

BOX 18-10 SOURCES OF 15 GRAMS OF CARBOHYDRATES

- 4 oz sweetened carbonated beverage
- 4 oz unsweetened fruit juice
- 1 cup skim milk
- Glucose gels or tablets (follow manufacturer's instructions)
- 2 tablespoons raisins
- 4 or 5 saltine crackers
- 6 to 7 hard candies
- ½ roll of Life Savers type of candy

status and ability to swallow without aspiration determine the route to be used. Box 18-9 details a protocol for treatment of mild, moderate, and severe hypoglycemia. Common food substances that contain at least 15 g of carbohydrate are listed in Box 18-10. Glucose levels should be reassessed 15 minutes after treatment. If the blood glucose level remains lower than 70 mg/dL, treatment is repeated.

In the event of hypoglycemia, rapid-acting and short-acting insulin should be withheld temporarily. If the patient has an insulin pump, it should be suspended for moderate or severe hypoglycemia, but the infusion catheter should not be removed. The patient should determine whether to discontinue the infusion for mild hypoglycemia. Longer-acting basal insulins should typically not be withheld in patients on subcutaneous insulin therapy who are experiencing hypoglycemia, because this will increase the risk for both DKA in patients with type 1 diabetes and hyperglycemia in all insulin-treated patients with diabetes. Patients should be instructed to notify their diabetes care provider if two or more events of hypoglycemia are experienced within a week because the medication regimen may require adjustment.

Neurological assessments are done to detect any changes in cerebral function related to hypoglycemia. It is important to document baseline neurological status, including mental status, cranial nerve function, sensory and motor function, and deep tendon reflexes. There is a potential for seizure activity related to altered neuronal cellular metabolism during the hypoglycemic phase, so patients should be assessed for seizure activity. Descriptions of the seizure event and associated symptoms are important to note. Seizure precautions should be instituted, including padded side rails, oxygen, oral airway, and bedside suction, as well as removal of potentially harmful objects from the environment. Neurological status is the best clinical indicator of effective treatment for hypoglycemia.

Patient and family education about hypoglycemic episodes may also be appropriate in the critical care setting. The patient and family members need to be instructed on the causes, symptoms, treatment, and prevention of hypoglycemia. The relationship of carbohydrate intake, actions of insulin or oral hypoglycemic agents, excessive alcohol intake, and activity changes or exercise with hypoglycemia should be incorporated into the teaching plan. Instruction on the use of home blood glucose monitoring techniques, schedule, and pattern recognition may also be needed. Patients at risk for severe hypoglycemia should be prescribed a glucagon emergency kit, and family and significant regular contacts should be instructed in its use. The patient is encouraged to wear emergency medical identification and encouraged to perform a blood glucose test before driving. Patients at risk for nocturnal hypoglycemia are encouraged to store glucose gel at the bedside. Childbearing women with diabetes are at very high risk for hypoglycemia after delivery as the levels of insulin-resistant hormones drop quickly. Lactating women also may be at particular risk and may be encouraged to drink milk while nursing. Additionally, patients need to be instructed on the relationship between alcohol ingestion and hypoglycemia.

Patient Outcomes

Outcomes for a patient with a hypoglycemic episode include the following:

- Serum or capillary glucose levels within the patient's target range
- No acute signs and symptoms of hypoglycemia
- Mental status returned to baseline
- Absence of seizure activity
- Ability of the patient and family to identify causes of hypoglycemia, state symptoms of hypoglycemia, state type and amount of foods that may be used to treat hypoglycemia, and perform home blood glucose monitoring.

ACUTE AND RELATIVE ADRENAL INSUFFICIENCY

Etiology

Hypofunction of the adrenal gland results from either primary or secondary mechanisms that suppress secretion of cortisol, aldosterone, and androgens. Primary mechanisms, resulting in Addison's disease, are those that cause destruction of the adrenal gland itself. At least 90% of the adrenal cortex must be destroyed before clinical signs and symptoms appear. Primary disorders result in deficiencies of both glucocorticoids and mineralocorticoids. Primary adrenal insufficiency (AI) has a variety of causes including idiopathic autoimmune destruction of the gland, infection and sepsis, hemorrhagic destruction, and granulomatous infiltration from neoplasms, amyloidosis, sarcoidosis, or hemochromatosis.

Idiopathic autoimmune destruction of the adrenal gland is the most common cause of AI, accounting for 50% to 70% of cases. Autoimmune adrenal destruction may have a genetic component that leads to atrophy of the gland. Genetic adrenal disease may affect just the adrenal gland or be part of a constellation of autoimmune problems, such as autoimmune polyglandular disorder.[13] Young women with spontaneous premature ovarian failure are at increased risk of developing the autoimmune form of adrenal insufficiency.[13] In addition to sepsis, HIV infection and tuberculosis are significant infectious causes of AI.[12]

Secondary mechanisms that can produce adrenal insufficiency are those that decrease adrenocorticotropic hormone (ACTH) secretion, resulting in deficiency of glucocorticoids alone, because mineralocorticoids are not primarily dependent on ACTH secretion. Mechanisms that can produce secondary adrenal insufficiency include abrupt withdrawal of corticosteroids, pituitary and hypothalamic disorders, and sepsis. A more detailed listing of possible causes of primary and secondary adrenal insufficiency is given in Box 18-11.

The most common cause of acute adrenal insufficiency is abrupt withdrawal from corticosteroid therapy. Long-term corticosteroid use suppresses the normal *corticotropin-releasing hormone (CRH)-ACTH-adrenal feedback systems* (see Figure 18-1) and result in adrenal suppression. It is difficult to accurately predict the degree of adrenal suppression in patients receiving exogenous glucocorticoid therapy. Longer-acting agents such as dexamethasone are more likely to produce suppression than are shorter-acting corticosteroids such as hydrocortisone. Once corticosteroid use has been tapered off, it may take several months for these patients to resume normal secretion of corticosteroids. Thus it is important to be familiar with disorders that may be treated with corticosteroids, because the resulting adrenal suppression may prevent a normal stress response in these patients and may put them at risk of an adrenal crisis. Other drugs may contribute to adrenal suppression. For example, administration of the drug etomidate to facilitate endotracheal intubation is associated with significant but temporary adrenal dysfunction and increased mortality.[23]

Infection, sepsis, or both are among the most common causes of adrenal insufficiency in the critical care setting.[14] The proinflammatory state commonly seen in critical illness is thought to produce AI by suppressing the hypothalamic-pituitary-adrenal axis. Glucocorticoid resistance and suppression of feedback mechanisms are postulated to contribute to low cortisol levels commonly seen in critical illness. Sepsis and septic shock can also cause thrombotic necrosis of the adrenal gland.[15] The concept of relative adrenal insufficiency has been debated for several years. The hypermetabolic state of critical illness may increase cortisol levels by as much as tenfold over baseline.[14] Patients with an inadequate physiological response to the demands of this hypermetabolic state have an increased mortality rate. The degree of response, how to best measure the response, and optimum treatment continue to be investigated.[11]

BOX 18-11 CAUSES OF ADRENAL INSUFFICIENCY

Primary

- *Autoimmune disease:* idiopathic and polyglandular
- *Granulomatous disease:* tuberculosis, sarcoidosis, histoplasmosis, blastomycosis
- Cancer
- *Hemorrhagic destruction:* anticoagulation, trauma, sepsis
- *Infectious:* meningococcal, staphylococcal, pneumococcal, fungal (candidiasis), cytomegalovirus
- Acquired immunodeficiency syndrome
- *Drugs:* ketoconazole, aminoglutethimide, trimethoprim, etomidate, 5-fluorouracil (suppress adrenals); phenytoin, barbiturates, rifampin (increase steroid degradation)
- Irradiation
- Adrenalectomy
- Developmental or genetic abnormality

Secondary

- Abrupt withdrawal of corticosteroids
- Pathology affecting the pituitary, such as tumors, hemorrhage, radiation, metastatic cancer, lymphoma, leukemia, sarcoidosis
- Systemic inflammatory states: sepsis, vasculitis, sickle cell anemia
- Postpartum pituitary hemorrhage (Sheehan's syndrome)
- Trauma, especially head trauma, or surgery
- Hypothalamic disorders

Review of Physiology

The manifestations of adrenal insufficiency result from a lack of adrenal cortical secretion of glucocorticoids (primarily

BOX 18-12 PHYSIOLOGICAL EFFECTS OF GLUCOCORTICOIDS (CORTISOL)

- *Protein metabolism:* promotes gluconeogenesis, stimulates protein breakdown, and inhibits protein synthesis
- *Fat metabolism:* ↑ lipolysis and free fatty acid production, promotes fat deposits in face and cervical area
- *Opposes action of insulin:* ↓ glucose transport and utilization in cells
- *Inhibits inflammatory response:*
  - Suppresses mediator release (kinins, histamine, interleukins, prostaglandins, leukotrienes, serotonin)
  - Stabilizes cell membrane and inhibits capillary dilation
  - ↓ Formation of edema
  - Inhibits leukocyte migration and phagocytic activity
- *Immunosuppression:*
  - ↓ Proliferation of T lymphocytes and killer cell activity
  - ↓ Complement production and immunoglobulins
- Circulating erythrocytes
- *Gastrointestinal effects:* ↑ appetite; increases rate of acid and pepsin secretion in stomach
- ↑ Uric acid excretion
- ↓ Serum calcium
- Sensitizes arterioles to effects of catecholamines; maintains blood pressure
- ↑ Renal glomerular filtration rate and excretion of water

cortisol), mineralocorticoids (primarily aldosterone), or both. The deficiency of glucocorticoids is especially significant because their influence on the defense mechanisms of the body and its response to stress makes them essential for life.

Cortisol is normally released in response to ACTH stimulation from the anterior pituitary gland (see Figure 18-1). ACTH is stimulated by CRH from the hypothalamus, which is influenced by circulating cortisol levels, circadian rhythms, and stress. Circadian rhythms affect ACTH and cortisol levels, creating peak levels of cortisol in the morning and the lowest levels around midnight. This normal diurnal rhythm can be overridden by stress. During stress, plasma cortisol may increase as much as 10 times its normal level. Release of cortisol increases the blood glucose concentration by promoting glycogen breakdown and gluconeogenesis in the liver, increases lipolysis and free fatty acid production, increases protein degradation, and inhibits the inflammatory and immune responses. Cortisol also increases sensitivity to catecholamines, producing vasoconstriction, hypertension, and tachycardia (Box 18-12).

Aldosterone is a mineralocorticoid synthesized in the adrenal cortex that regulates the body's electrolyte and water balance in the renal tubules. Secretion of aldosterone is regulated primarily by the renin-angiotensin-aldosterone system. Renin is an enzyme stored in the cells of the juxtaglomerular apparatus (JGA) in the kidneys. It is released in response to stimulation of beta receptors on the JGA surface. Factors that stimulate the release of renin include low plasma sodium, increased plasma potassium levels, decreased extracellular fluid volume, decreased blood pressure, and decreased sympathetic nerve activity. Once released, renin cleaves angiotensinogen in the plasma to form angiotensin I. Angiotensin I is then converted to angiotensin II in the lungs under the influence of angiotensin-converting enzyme. Angiotensin II stimulates the secretion of aldosterone by the adrenal cortex while causing vasoconstriction of the arterioles. Aldosterone acts in the kidneys on the ascending loop of Henle, the distal convoluted tubule, and the collecting ducts to increase sodium ion reabsorption and to increase potassium and hydrogen ion excretion. Because reabsorption of sodium creates an osmotic gradient across the renal tubular membrane, antidiuretic hormone (ADH) is activated, causing water to be reabsorbed with sodium. The physiology of aldosterone release is summarized in Figure 18-6.

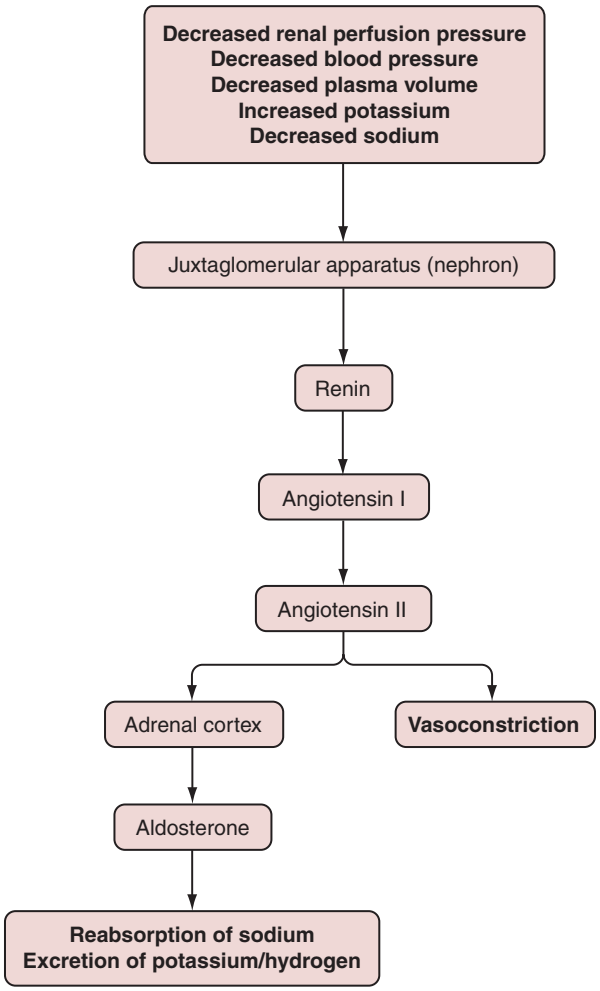


FIGURE 18-6 Physiology of aldosterone release.

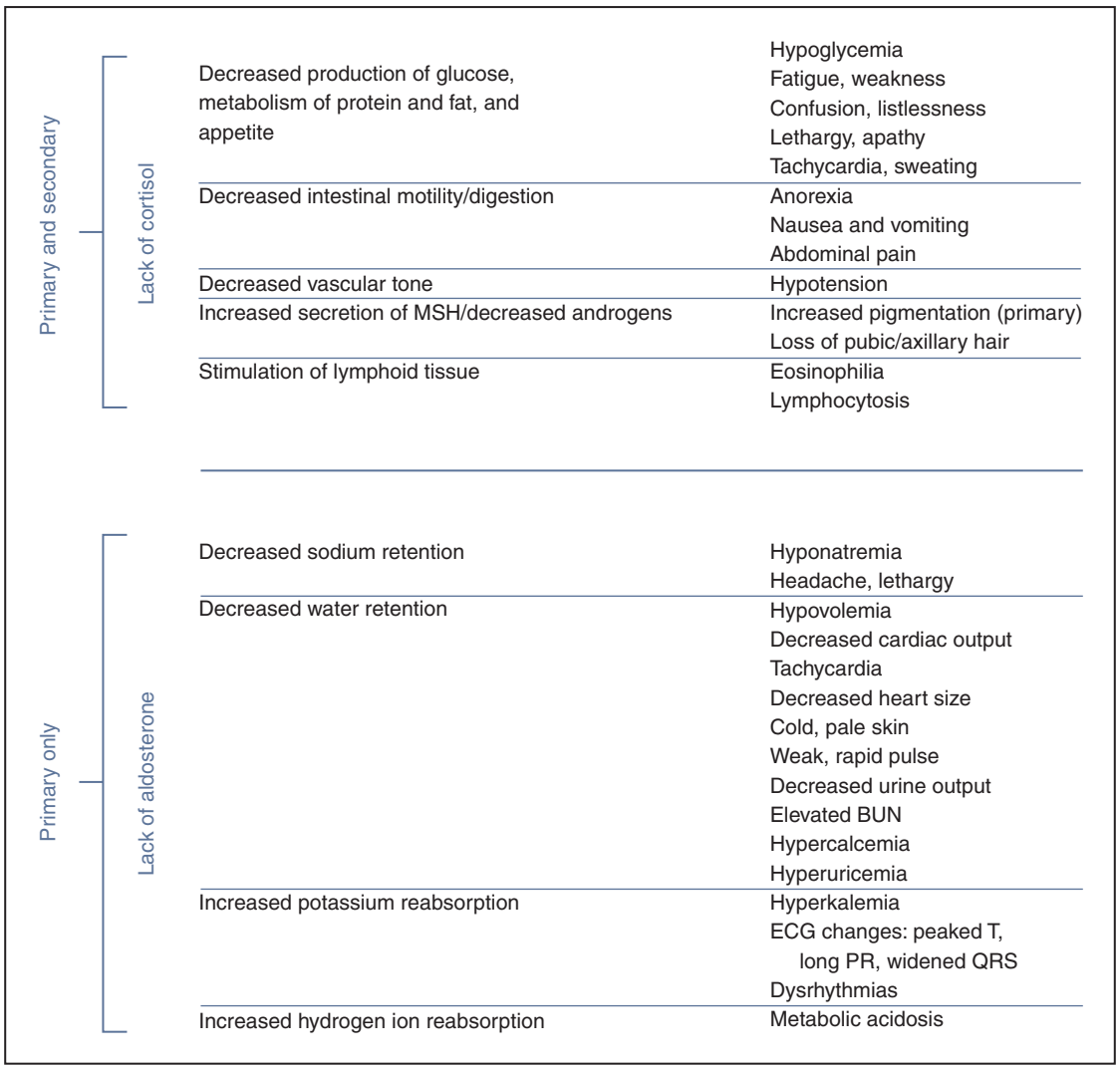


FIGURE 18-7 Pathophysiological effects of adrenal insufficiency. *BUN,* Blood urea nitrogen; *ECG,* electrocardiogram; *MSH,* melanocyte-stimulating hormone.

Pathophysiology

Adrenal crisis is a life-threatening absence of cortisol (glucocorticoid) and aldosterone (mineralocorticoid). A deficiency of cortisol results in decreased production of glucose, decreased metabolism of protein and fat, decreased appetite, decreased intestinal motility and digestion, decreased vascular tone, and diminished effects of catecholamines. If a patient with deficient cortisol is stressed, this deficiency can produce profound shock due to significant decreases in vascular tone caused by the diminished effects of catecholamines.[11,15]

Deficiency of aldosterone results in decreased retention of sodium and water, decreased circulating volume, and increased potassium and hydrogen ion reabsorption. These effects are seen in patients with underlying primary adrenal insufficiency but not secondary adrenal insufficiency, because aldosterone secretion is not primarily dependent on ACTH. A summary of pathophysiological effects of adrenal insufficiency can be found in Figure 18-7.

Assessment

Clinical Presentation

Adrenal crisis requires astute and rapid data collection. Box 18-13 identifies risk factors for adrenal crisis. Features of adrenal crisis are nonspecific and may be attributed to other medical disorders. Signs and symptoms vary (see Figure 18-6). Because this condition is a medical emergency, the diagnosis should be considered in any patient acutely ill with fever, vomiting, hypotension, shock, decreased serum sodium level, increased serum potassium level, or hypoglycemia (see box, "Laboratory Alert: Adrenal Disorders"). Specific system disturbances are widespread.

BOX 18-13 ASSESSMENT OF RISK FACTORS FOR ADRENAL CRISIS

Assess carefully for patients who are at risk, have predisposing factors, or have physical findings associated with chronic adrenal insufficiency. Risk factors include:

- *Drug history:* steroids in the past year, phenytoin, barbiturates, rifampin
- *Illness history:* infection, cancer, autoimmune disease, diseases treated with steroids, radiation to head or abdomen, human immunodeficiency virus–positive status
- *Family history:* autoimmune disease, Addison's disease
- *Nutrition:* weight loss, decreased appetite
- *Miscellaneous:* fatigue, dizziness, weakness, darkening of skin, low blood glucose that does not respond to therapy, salt craving (dramatic craving such as drinking pickle juice or eating salt from the shaker)

! LABORATORY ALERT

Adrenal Disorders

LABORATORY TEST	CRITICAL VALUE	SIGNIFICANCE
Serum		
Glucose	<50 mg/dL	Hypoglycemia
Cortisol	<10 mcg/dL	In severely ill patient or stressed patient, indicates insufficiency
Potassium	>6.6 mEq/L	Potential for heart blocks, bradydysrhythmias, sinus arrest, ventricular fibrillation, or asystole
	<3.0 mEq/L	Potential for ventricular dysrhythmias
Sodium	>150 mEq/L	May be a result of stress and dehydration
	<130 mEq/L	Due to lack of aldosterone
BUN	>20 mg/dL	↑ From protein breakdown and hemoconcentration
pH	<7.3	↓ From accumulation of acids and dehydration

BUN, Blood urea nitrogen.

Cardiovascular system. Cardiovascular signs and symptoms in adrenal crisis are related to hypovolemia (decreased water reabsorption), decreased vascular tone (decreased effectiveness of catecholamines), and hyperkalemia. The most common presentation of adrenal crisis in the intensive care unit is hypotension refractory to fluids and requiring vasopressors. The patient may also have symptoms of decreased cardiac output; weak, rapid pulse; dysrhythmias; and cold, pale skin. The chest x-ray study may show decreased heart size due to hypovolemia. Changes in the ECG may result if accompanied by significant hyperkalemia. Hypovolemia and vascular dilation may be severe enough in crisis to cause hemodynamic collapse and shock.

Neurological system. Neurological manifestations in adrenal crisis are related to decreases in glucose levels, protein metabolism, volume and perfusion, and sodium concentrations. Patients may complain of headache, fatigue that worsens as the day progresses, and severe weakness. They may also suffer from mental confusion, listlessness, lethargy, apathy, psychoses, and emotional lability.

Gastrointestinal system. The gastrointestinal signs and symptoms in adrenal crisis are related to decreased digestive enzymes, intestinal motility and digestion. Anorexia, nausea, vomiting, diarrhea, and vague abdominal pain are present in the majority of patients.[7]

Genitourinary system. Decreased circulation to the kidneys from diminished circulating volume and hypotension decreases renal perfusion and glomerular filtration rate. Urine output may decline and acute kidney injury may occur as a result.

Laboratory Evaluation

Laboratory findings in a patient with acute adrenal crisis include hypoglycemia, hyponatremia, hyperkalemia, eosinophilia, increased BUN level, and metabolic acidosis (see box, "Laboratory Alert: Adrenal Disorders"). Hypercalcemia or hyperuricemia is possible as a result of volume depletion.

The diagnosis of adrenal crisis is made by evaluating plasma cortisol levels. These levels vary diurnally in healthy individuals, but this pattern is lost in the critically ill, making the timing of the test unimportant. In crisis, plasma cortisol levels are less than 10 mg/dL. Differentiating between primary and secondary adrenal insufficiency is accomplished by evaluating serum ACTH levels. ACTH levels will be elevated in primary insufficiency and normal or decreased in secondary insufficiency.

The diagnosis of relative adrenal insufficiency is less clear. A "normal" cortisol level in a critically ill patient may actually be abnormal and indicate an inadequate response.[22] Because these tests are difficult to interpret, corticosteroid replacement should begin as soon as insufficiency is suspected. The technique for performing a cosyntropin (a synthetic ACTH) stimulation is outlined in Box 18-14. The test determines baseline levels as well as response to stimulation. A standard dose of 250 mcg cosyntropin is given, and the expected response is an increase in cortisol level of 7 to 9 mcg/dL from the baseline. A patient whose cortisol level does not increase

BOX 18-14 COSYNTROPIN STIMULATION TEST

Standard Method

- Obtain baseline serum cortisol level
- Administer cosyntropin, either 250 mcg or 1 mcg (low dose) IV
- Obtain serum cortisol level 30 and 60 minutes after cosyntropin

In emergency situations, may treat with dexamethasone (Decadron), 2 to 8 mg IV (will not interfere with cortisol levels)

Test Response

- *Expected response:* cortisol >20 mcg/dL, or increase from baseline of >9 mcg/dL
- *Primary aldosterone insufficiency:* a total level >20 mcg/dL and/or a change from baseline of >7 mcg/dL
- *Relative aldosterone insufficiency:* a change from baseline <9 mcg/dL regardless of baseline level

by this amount is deemed a nonresponder and has an increased risk of mortality.[11,19]

Nursing Diagnoses

The nursing diagnoses that may apply to a patient with adrenal crisis based on the assessment data include the following:

- Deficient fluid volume related to deficiency of aldosterone hormone (mineralocorticoid) and decreased sodium and water retention
- Ineffective tissue perfusion related to cortisol deficiency, resulting in decreased vascular tone and decreased effectiveness of catecholamines
- Disturbed thought processes related to decreased glucose levels, decreased protein metabolism, decreased perfusion, and decreased sodium levels
- Imbalanced nutrition (less than body requirements) related to cortisol deficiency and resultant decreased metabolism of protein and fats, decreased appetite, and decreased intestinal motility and digestion
- Deficient knowledge related to adrenal disorder: proper long-term corticosteroid management
- Activity intolerance related to use of endogenous protein for energy needs and loss of skeletal muscle mass as evidenced by early fatigue, weakness, and exertional dyspnea.

Nursing and Medical Interventions

Adrenal crisis requires immediate recognition and intervention if the patient is to survive. Primary objectives in the treatment of adrenal crisis include identifying and treating the precipitating cause, replacing fluid and electrolytes, replacing hormones, and educating the patient and family.

Fluid and Electrolyte Replacement

Fluid losses should be replaced with an infusion of 5% dextrose and NS until signs and symptoms of hypovolemia stabilize. This not only reverses the volume deficit but also provides glucose to minimize the hypoglycemia. The patient may need as much as 5 L of fluid in the first 12 to 24 hours to maintain an adequate blood pressure and urine output and to replace the fluid deficit.

Hyperkalemia frequently responds to volume expansion and glucocorticoid replacement and may require no further treatment. In fact, the patient may become hypokalemic during therapy and may require potassium replacement. The acidosis also usually corrects itself with volume expansion and glucocorticoid replacement. However, if the pH is less than 7.1 or the bicarbonate level is less than 10 mEq/L, the patient may require sodium bicarbonate.

Hormone Replacement

Initially, glucocorticoid replacement is the most important type of hormone replacement. If adrenal insufficiency has not been previously diagnosed and the patient's condition is unstable, dexamethasone phosphate (Decadron), 4 mg by IV push, then 4 mg every 8 hours, is given until the cosyntropin test has been done. This drug does not significantly cross-react with cortisol in the assay for cortisol and therefore can be administered to patients pending adrenal testing results.

Hydrocortisone sodium succinate (Solu-Cortef) is the drug of choice after diagnosis is confirmed by the cosyntropin test, because it has both glucocorticoid and mineralocorticoid activities in high doses. After a bolus dose, IV doses are administered for at least 24 hours or until the patient has stabilized. Cortisone acetate may be given intramuscularly if the IV route is not available.

Once the patient improves, the dose of hydrocortisone is decreased 10% to 20% daily until a maintenance dose is achieved. The patient can be switched to oral replacement once oral intake is resumed. At lower doses (less than 100 mg/day of hydrocortisone), a patient with primary adrenal insufficiency may also require mineralocorticoid replacement. Fludrocortisone, 0.05 to 0.2 mg daily is added. A nutritional consideration if the patient is experiencing excessive sweating or diarrhea is to increase sodium intake to 15 mEq/day. Table 18-5 describes the drugs used in the treatment of acute adrenal crisis.

Patient and Family Education

In a patient with known adrenal insufficiency and/or receiving corticosteroid therapy, adrenal crisis is preventable. Education of patients, family, and significant others is the key to prevention.

TABLE 18-5 **PHARMACOLOGY**

Medications Used to Treat Adrenal Crisis

MEDICATION	ACTION/USES	DOSAGE/ROUTE	SIDE EFFECTS	NURSING IMPLICATIONS
Hydrocortisone sodium succinate (Solu-Cortef)	Antiinflammatory and immunosuppressive effects Salt-retaining (mineralocorticoid) effects in high doses	Individualized: adrenal crisis: 100 mg IV bolus; 50-100 mg every 6-8 hours	Vertigo, headache, insomnia, menstrual abnormalities, fluid and electrolyte imbalance, hypertension, HF, peptic ulcers, nausea and vomiting, immunosuppression, impaired wound healing, increased serum glucose levels, cushingoid state	Institute prophylaxis against GI bleeding Be aware of multiple drug-drug interactions, especially with IV route: oral contraceptives, phenytoin, digoxin, phenobarbital, theophylline, insulin, anticoagulants, salicylates Avoid abrupt discontinuation Monitor serum glucose and electrolyte levels Watch for signs of fluid overload Observe for signs of infection (may be masked) Maintain adequate nutrition to avoid catabolic effects Provide meticulous mouth care
Cortisone acetate (Cortone)	Same as hydrocortisone	Individualized: adrenal crisis: 50 mg IM every 12 hours	Same as hydrocortisone	Same as for hydrocortisone
Dexamethasone (Decadron)	Has only glucocorticoid effects	Individualized doses PO, IM, IV	Same as hydrocortisone	Same as for hydrocortisone
Fludrocortisone acetate (Florinef)	Increases sodium reabsorption in renal tubules and increases potassium, water, and hydrogen loss	0.05-0.2 mg/day PO	Increased blood volume, edema, hypertension, HF, headaches, weakness of extremities	Assess for signs of fluid overload, HF Monitor serum sodium and potassium levels Use only in conjunction with glucocorticoids Restrict sodium intake if the patient has edema or fluid overload Not used to treat acute crisis; added as glucocorticoid dose is decreased

GI, Gastrointestinal; *HF,* heart failure; *IM,* intramuscular; *IV,* intravenous; *PO,* orally.

THYROID GLAND IN CRITICAL CARE

Review of Physiology

Thyroid hormones play a role in regulating the function of all body systems. Box 18-15 lists the physiological effects of thyroid hormones. The thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) are secreted by the thyroid gland under the influence of the anterior pituitary gland via secretion of thyroid-stimulating hormone (TSH, also thyrotropin), which in turn is influenced by thyroid-releasing hormone (TRH, also called thyrotropin-releasing hormone) from the hypothalamus. Thyroid hormones are highly bound to globulin, T_4-binding prealbumin, and albumin. Only the unbound (or free) fraction of the circulating hormone is biologically active. Regulation of these hormones occurs via positive and negative feedback mechanisms (Figure 18-8).

T_4 accounts for more than 95% of circulating thyroid hormones, but half of all thyroid activity comes from T_3. T_3 is five times more potent, acts more quickly, and enters cells more easily than T_4. T_3 is derived from conversion of T_4 in nonthyroid tissue. Certain conditions and drugs can block the conversion of T_4 to T_3, creating a potential thyroid imbalance. Possible causes for blocked conversion are listed in Box 18-16.

BOX 18-15 PHYSIOLOGICAL EFFECTS OF THYROID HORMONES

Major Effects

- ↑ Metabolic activities of all tissues
- ↑ Rate of nutrient use/oxygen consumption for ATP production
- ↑ Rate of growth
- ↑ Activities of other endocrine glands

Other Effects

- Regulate protein synthesis and catabolism
- Regulate body heat production and dissipation
- ↑ Gluconeogenesis and utilization of glucose
- Maintain appetite and gastrointestinal motility
- Maintain calcium metabolism
- Stimulate cholesterol synthesis
- Maintain cardiac rate, contractility, and output
- Affect respiratory rate, oxygen utilization, and carbon dioxide formation
- Affect red blood cell production
- Affect central nervous system affect and attention
- Produce muscle tone and vigor and provide normal skin constituents

BOX 18-16 FACTORS THAT BLOCK CONVERSION FROM THYROXINE TO TRIIODOTHYRONINE

- *Severe illness:* chronic renal failure, cancer, chronic liver disease
- Trauma
- Malnutrition, fasting
- *Drugs:* glucocorticoids, propranolol, propylthiouracil, amiodarone
- Radiopaque dyes
- Acidosis

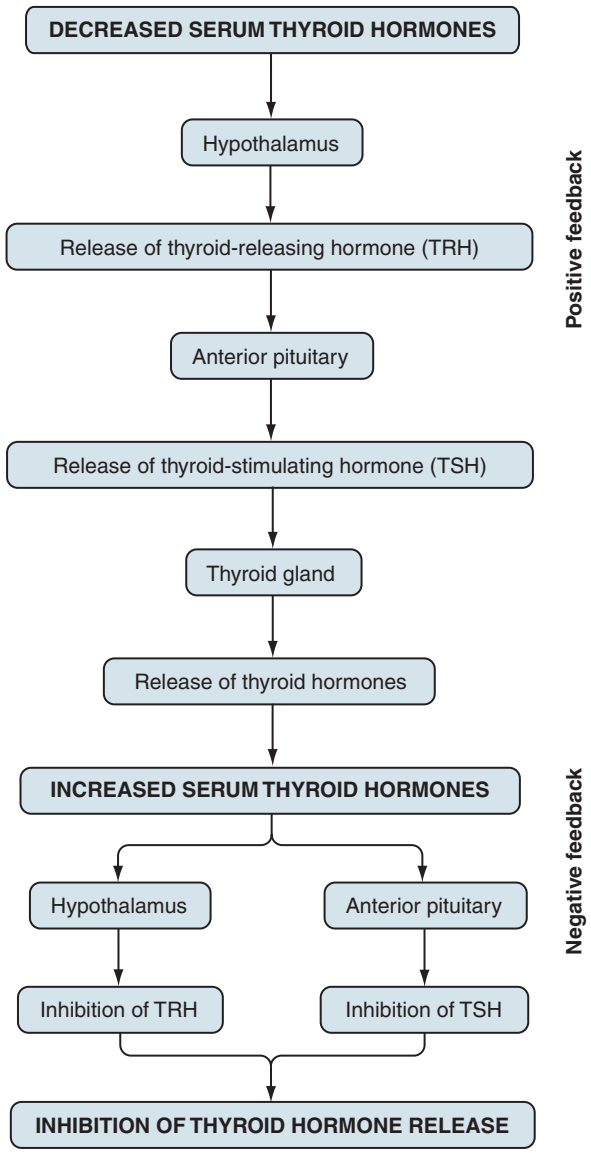


FIGURE 18-8 Feedback systems for thyroid hormone regulation.

Effects of Aging

With aging, thyroid function declines. Hypothyroidism occurs in the elderly, frequently with an insidious onset. The decrease in energy level; the feeling of being cold; the dry, flaky skin; and other signs are often mistakenly assumed to be part of aging, whereas they may be signs of decreased thyroid function. Thyroid function should be assessed in any elderly patient with a "sluggish" response to treatments.

Thyroid Function in the Critically Ill

During critical illness, stress-related changes occur in thyroid hormone balance. Initially, there is a decrease in plasma T_3 levels, known as *low T_3 syndrome* or *euthyroid sick syndrome.* These changes are thought to result from alterations in the peripheral metabolism of thyroid hormones, which may be an adaptation to severe illness in which the body attempts to reduce energy expenditure.[8] Generally, these changes are considered to be beneficial and do not require intervention. Within approximately 3 days, T_3 levels return to low-normal levels. In severe illness, T_3 levels may fail to normalize, and T_4 levels may also decrease.[19]

In the chronically critically ill, additional thyroid hormone changes occur. Both T_3 and T_4 levels are reduced as is TSH secretion. The changes in chronic critical illness are not

well understood but are thought to also include central neuroendocrine dysfunction.[22] Low T_4 levels may serve as a poor prognostic indicator for patient recovery.

THYROID CRISES

Thyroid disorders that have been previously diagnosed and adequately treated do not generally result in crisis states. However, if patients with thyroid disorders, especially undiagnosed thyroid disorders, are stressed either physiologically or psychologically, the results can be life-threatening. Hyperthyroidism must be explored as a causative factor in new-onset, otherwise unexplained rapid heart rates.

Etiology

Hyperthyroidism is common. The most frequent form of hyperthyroidism is *toxic diffuse goiter,* also known as *Graves' disease.* It occurs most frequently in young (third or fourth decade), previously healthy women. A family history of hyperthyroidism is often present. Graves' disease is an autoimmune disease, and affected patients have abnormal thyroid-stimulating immunoglobulins that cause thyroid inflammation, diffuse enlargement, and hyperplasia of the gland.

Toxic multinodular goiter is the second most common cause of hyperthyroidism. It also occurs more commonly in women, but these patients are generally older (fourth to seventh decades). Crises in patients with toxic multinodular goiter are more commonly associated with heart failure or severe muscle weakness.

Hyperthyroidism also occurs secondary to exposure to radiation, interferon-alpha therapy for viral hepatitis, and other events. Administration of amiodarone, a heavily iodinated compound, can result in either hyperthyroidism or hypothyroidism.[20] Other possible causes of hyperthyroidism are listed in Box 18-17.

Low levels of thyroid hormones disrupt the normal physiology of most body systems. Hypothyroidism produces a hypodynamic, hypometabolic state. *Myxedema coma* is a magnification of these disruptions initiated by some type of stressor. This condition takes months to develop and should be suspected in patients with known hypothyroidism, with a surgical scar on the lower neck, or in those who are unusually sensitive to medications or narcotics.

The underlying causes of myxedema coma are those that produce hypothyroidism. Most cases occur either in patients with long-standing autoimmune disease of the thyroid (Hashimoto's thyroiditis) or in patients who have received surgical or radioactive iodine treatment for Graves' disease and have received inadequate hormone replacement.[23] Approximately 5% of adults have hypothyroidism as a result of a pituitary (secondary) or hypothalamic (tertiary) disorder. These and other less common causes of hypothyroidism are listed in Box 18-18.

BOX 18-17 CAUSES OF HYPERTHYROIDISM

Most Common
- Toxic diffuse goiter (Graves' disease)
- Toxic multinodular goiter
- Toxic uninodular goiter

Other Causes
- Triiodothyronine
- Exogenous iodine in patient with preexisting thyroid disease: exposure to iodine load from radiographic contrast dyes, medications (amiodarone)
- Thyroiditis (transient)
- Postpartum thyroiditis

Rare Causes
- Toxic thyroid adenoma—more common in the elderly
- Metastatic thyroid cancer
- Malignancies with circulating thyroid stimulators
- Pituitary tumors producing thyroid-stimulating hormone (thyrotropin)
- Acromegaly

Associated with Other Disorders*
- Pernicious anemia
- Idiopathic Addison's disease
- Myasthenia gravis
- Sarcoidosis
- Albright's syndrome

*The presence of these disorders in a patient in thyroid crisis increases the likelihood that the patient has underlying hyperthyroidism.

BOX 18-18 CAUSES OF HYPOTHYROIDISM

Primary Thyroid Disease
- Autoimmune (Hashimoto's thyroiditis)
- Radioactive iodine treatment of Graves' disease
- Thyroidectomy
- Congenital enzymatic defect in thyroid hormone biosynthesis
- Inhibition of thyroid hormone synthesis or release
- Antithyroid drugs
- Iodides
- Amiodarone
- Lithium carbonate
- Oral hypoglycemic agents
- Dopamine
- Idiopathic thyroid atrophy

Secondary (Pituitary) or Tertiary (Hypothalamus) Disease
- Tumors
- Infiltrative disease (sarcoidosis)
- Hypophysectomy
- Pituitary irradiation
- Head injury
- Strokes
- Pituitary infarction

Thyrotoxic Crisis (Thyroid Storm)

Pathophysiology

Thyroid storm occurs in untreated or inadequately treated patients with hyperthyroidism; it is rare in patients with normal thyroid gland function. The crisis is often precipitated by stress related to an underlying illness, general anesthesia, surgery, or infection. Thyroid hormones play a major role in regulating most body systems. Uncontrolled hyperthyroidism produces a hyperdynamic, hypermetabolic state that results in disruption of many major body functions, and without treatment, death may occur within 48 hours. The specific mechanism that produces thyroid storm is unknown but includes high levels of circulating thyroid hormones, an enhanced cellular response to those hormones, and hyperactivity of the sympathetic nervous system. Thyroid hormones normally increase the synthesis of enzymes that stimulate cellular mitochondria and energy production. When excess thyroid hormones are present, the increased activity of these enzymes produces excessive thermal energy and fever. It is believed that the rapidity with which hormone levels rise may be more important than the absolute levels.

Assessment

Clinical presentation. The excess thyroid hormone activity of hyperthyroidism affects the body in many ways. Box 18-19 gives signs associated with progressive hyperthyroidism. Common findings in patients with thyroid storm, their significance, and the actions nurses can take to address each of these findings are listed in Table 18-6.

BOX 18-19 PROGRESSIVE SIGNS OF HYPERTHYROIDISM

- *Cardiovascular:* Increased heart rate and palpitations. Hyperthyroidism may present as sinus tachycardia in a sleeping patient or as atrial fibrillation with a rapid ventricular response.
- *Neurological:* Increased irritability, hyperactivity, decreased attention span, and nervousness. In an elderly patient, these signs may be masked, and depression or apathy may be present.
- *Temperature intolerance:* Increased cold tolerance; heat intolerance; fever; excessive sweating; and warm, moist skin. Older patients may naturally lose their ability to shiver and may be less comfortable in the cold.
- *Respiratory:* Increased respiratory rate, weakened thoracic muscles, and decreased vital capacity are evident.
- *Gastrointestinal:* Increased appetite, decreased absorption (especially of vitamins), weight loss, and increased stools. Diarrhea is not common. Elderly patients may be constipated.
- *Musculoskeletal:* Fine tremors of tongue or eyelids, peripheral tremors with activity, and muscle wasting are noted.
- *Integumentary:* Thin, fine, and fragile hair; soft friable nails; and petechiae. Young women generally have the more classic findings. Young men may notice an increase in acne and sweating. An elderly patient with dry, atrophic skin may not have significant skin changes.
- *Hematopoietic:* Normochromic, normocytic anemia and leukocytosis may occur.
- *Ophthalmic:* Pathological features result from edema and inflammation. Physical findings may include upper lid retraction, lid lag, extraocular muscle palsies, and sight loss. Exophthalmos is found almost exclusively in Graves' disease.

TABLE 18-6 THYROID CRISES

CLINICAL CONCERNS	SIGNIFICANCE	NURSING ACTIONS
Thyroid Storm		
Alterations in level of consciousness	Symptoms can be confused with other disorders (e.g., paranoia, psychosis, depression), especially in the elderly	Provide a safe environment. Assess for orientation, agitation, inattention. Control environmental influences. Implement seizure precautions.
↑ Cardiac workload due to hypermetabolic state; ↓ cardiac output	Can lead to heart failure and collapse	Assess for chest pain, palpitations. Monitor for cardiac dysrhythmias (e.g., atrial fibrillation or flutter) and tachycardia. Monitor blood pressure for widening pulse pressure. Auscultate for the development of S_3. Monitor hemodynamic status: SVO2, SI, PAOP, RAP. Assess urine output. Evaluate response to therapy.
↑ Oxygen demand due to hypermetabolic state; ineffective breathing pattern	↑ Respiratory rate and drive can lead to fatigue and hypoventilation	Provide supplemental oxygen or mechanical ventilation as needed. Monitor respiratory rate and effort. Monitor oxygen saturation via pulse oximeter. Minimize activity.

Continued

TABLE 18-6 **THYROID CRISES—cont'd**

CLINICAL CONCERNS	SIGNIFICANCE	NURSING ACTIONS
Loss of ability to regulate with temperature	Inability to respond to fever exacerbates hypermetabolic demands	Monitor temperature and treat with acetaminophen and/or a cooling blanket as needed.
Myxedema Coma		
↓ Cardiac function	Hypotension and potential to develop pericardial effusion	Perform ECG monitoring (look for ↓ voltage in the QRS complexes, indicating effusion). Auscultate for diminished heart sounds. Monitor blood pressure for signs of hypotension.
Muscle weakness, hypoventilation, pleural effusion; ineffective breathing	Potential for respiratory acidosis and hypoxemia	Auscultate the lungs frequently. Monitor respiratory effort (rate and depth) and pattern. Maintain I&O (probable need for fluid restriction). Monitor ABGs/pulse oximetry and CBC (for anemia). Position for optimum respiratory effort.
Alteration in level of consciousness	Ranges from difficulty concentrating to coma Seizures can occur	Assess and maintain patient safety.
Loss of ability to regulate temperature	Inability to respond to cold	Monitor temperature Control room temperature, provide rewarming measures.

ABGs, Arterial blood gases; *CBC,* complete blood count; *I&O,* intake and output; *PAOP,* pulmonary artery occlusion pressure; *RAP,* right atrial pressure; *SI,* stroke index; *SVO2,* mixes venous oxygen consumption.

Thyroid storm has an abrupt onset. The most prominent clinical features of thyroid storm are severe fever, marked tachycardia, heart failure, tremors, delirium, stupor, and coma.

The patient's ability to survive thyroid storm is determined by the severity of the hyperthyroid state and the patient's general health. The severity of the hyperthyroid state is not necessarily indicated by the serum levels of thyroid hormones but rather by tissue and organ responsiveness to the hormones.

Thermoregulation disturbances. Temperature regulation is lost. The patient's body temperature may be as high as 106° F (41.1° C). The increase in heat production and metabolic end products also causes the blood vessels of the skin to dilate. This enhances oxygen and nutrient delivery to the peripheral tissues and accounts for the patient's warm, moist skin.

Neurological disturbances. Thyroid hormones normally maintain alertness and attention. Excess thyroid hormones cause hypermetabolism and hyperactivity of the nervous system causing agitation, delirium, psychosis, tremulousness, seizures, and coma.

Cardiovascular disturbances. Thyroid hormones play a role in maintaining cardiac rate, force of contraction, and cardiac output. The increase in metabolism and the stimulation of catecholamines produced by thyroid hormones cause a hyperdynamic heart. Contractility, heart rate, and cardiac output increase as peripheral vascular resistance decreases. These effects are magnified by the body's increased demand for oxygen and nutrients. In thyroid storm, the increased demands on the heart produce high-output heart failure and cardiovascular collapse if the crisis is not recognized and treated.

Patients experience palpitations, tachycardia (out of proportion to the fever), and a widened pulse pressure. Atrial fibrillation is common. A prominent third heart sound may be heard as well as a systolic murmur over the pulmonic area, the aortic area, or both. Occasionally, a pericardial rub may be heard. In the absence of atrial fibrillation, frequent premature atrial contractions or atrial flutter may be present. In an elderly patient with underlying heart disease, worsening of angina or severe heart failure may herald thyroid storm.

Pulmonary disturbances. Thyroid hormones affect respiratory rate and depth, oxygen utilization, and CO_2 formation. Tissues need more oxygen as a result of hypermetabolism. This increased need for oxygen stimulates the respiratory drive and increases respiratory rate. However, increased protein catabolism reduces protein in respiratory muscles (diaphragm and intercostals). As a result, even with an increased respiratory rate, muscle weakness may prevent the patient from meeting the oxygen demand and may cause hypoventilation, CO_2 retention, and respiratory failure.

Gastrointestinal disturbances. Excess thyroid hormones increase metabolism and accelerate protein and fat degradation.

Thyroid hormones also increase gastrointestinal motility, which may result in abdominal pain, nausea, and jaundice. Vomiting, and diarrhea can occur, contributing to volume depletion during thyrotoxic crises.

Musculoskeletal disturbances. Muscle weakness and fatigue result from increased protein catabolism. Skeletal muscle changes are manifested as tremors. Thoracic muscles are weak, causing dyspnea. In thyrotoxic crises, patients are placed on bed rest to reduce metabolic demand.

Laboratory evaluation. The determination of thyroid storm is a clinical diagnosis. Thyroid hormone levels are elevated; however, these levels are generally no higher than those normally found in uncomplicated hyperthyroidism. In any event, the patient must be treated before these results are available. See "Laboratory Alert: Thyroid Disorders" for possible laboratory abnormalities that may occur in thyroid storm.

Nursing Diagnoses

The nursing diagnoses that may apply to a patient with thyroid storm are based on assessment data and include the following:

- Hyperthermia related to loss of temperature regulation, increased metabolism, increased heat production
- Disturbed thought processes related to hypermetabolism and increased cerebration, agitation, delirium, psychosis
- Decreased cardiac output related to increased metabolic demands on the heart, extreme tachycardia, dysrhythmias, congestive heart failure
- Ineffective breathing pattern related to muscle weakness and decreased vital capacity resulting in hypoventilation and CO_2 retention, increased oxygen need from hypermetabolism

! LABORATORY ALERT

Thyroid Disorders

LABORATORY TEST	CRITICAL VALUE	SIGNIFICANCE
Thyroid Storm		
T_3, free (triiodothyronine)	>0.52 ng/dL	Hyperthyroidism
T_3, resin uptake	>35% of total	
T_4 (thyroxine)	>12 mcg/dL	
TSH	<0.01 milliunits/L	
Glucose	≥200 mg/dL (2 hours postprandial or random); >140 mg/dL (fasting)	↑Insulin degradation
Sodium	>150 mEq/L	May be a result of stress, dehydration, and/or hypermetabolic state
BUN	>20 mg/dL	↑Due to protein breakdown and hemoconcentration
CBC	↓ RBCs ↑ WBCs	Normocytic, normochromic anemia
Calcium	>10.2 mg/dL	Excess bone resorption
Myxedema Coma		
T_3, free	<0.2 mg/dL	Hypothyroidism
T_3, resin uptake	<25% of total	
T_4	<5 mcg/dL	
TSH	>25 milliunits/L	
Sodium	<130 mEq/L	Dilutional from increased total body water
Glucose	<50 mg/dL	Hypoglycemia due to hypermetabolic state
CBC	↓ RBCs	Anemia due to vitamin B_{12} deficiency, inadequate folate or iron absorption
Platelets	<150,000 cells/microliter	Risk for bleeding
pH	<7.35	Respiratory acidosis from hypoventilation

BUN, Blood urea nitrogen; *CBC,* complete blood count; *RBCs,* red blood cells; *TSH,* thyroid-stimulating hormone (thyrotropin); *WBCs,* white blood cells.

- Imbalanced nutrition: less than body requirements related to increased requirement, increased peristalsis, decreased absorption
- Activity intolerance related to muscle weakness, tremors, anemia, fatigue, and extreme energy expenditure
- Deficient knowledge related to thyroid disorder: disease process, therapeutic regimen, prevention of complications

Nursing and Medical Interventions

Thyroid storm requires immediate intervention if the patient is to survive. The primary objectives in the treatment of thyroid storm are antagonizing the peripheral effects of thyroid hormone, inhibiting thyroid hormone biosynthesis, blocking thyroid hormone release, providing supportive care, identifying and treating the precipitating cause, and providing patient and family education. Box 18-20 details the treatment of thyroid storm.

Antagonism of peripheral effects of thyroid hormones. Because it may take days or longer to impact circulating thyroid hormones, immediate action is necessary to minimize the systemic effects of thyroid storm. The mortality rate of thyroid storm has been significantly reduced with the introduction of beta-blockers to inhibit the effects of thyroid hormones. The drug used most frequently is propranolol (Inderal). Other beta-blockers such as esmolol hydrochloride (Brevibloc) or atenolol (Tenormin) may also be used. Results are seen within minutes using the IV route and within 1 hour after the oral route. IV effects last 3 to 4 hours. In addition, high-dose glucocorticoids are administered to block the conversion of T_4 to T_3 and thereby decreasing the effects of thyroid hormone on peripheral tissues.

Inhibition of thyroid hormone biosynthesis. Two drugs may be administered to inhibit thyroid hormone biosynthesis: propylthiouracil and methimazole (Tapazole). Neither of these drugs is available in IV form. In high doses, propylthiouracil inhibits conversion of T_4 to T_3 in peripheral tissues and results in a more rapid reduction of circulating thyroid hormone levels. Methimazole may be used because of its longer half-life and higher potency.

The disadvantage to both propylthiouracil and methimazole is that they lack immediate effect. They do not block the release of thyroid hormones already stored in the thyroid gland and may take weeks to months to lower thyroid hormone levels to normal.

Blockage of thyroid hormone release. Iodide agents inhibit the release of thyroid hormones from the thyroid gland, inhibit thyroid hormone production, and decrease the vascularity and size of the thyroid gland. Serum T_4 levels decrease approximately 30% to 50% with any of these drugs, with stabilization in 3 to 6 days.

Saturated solution of potassium iodide (SSKI) or Lugol's solution may be given orally or sublingually. These drugs must be administered 1 to 2 hours after antithyroid drugs (propylthiouracil or methimazole) to prevent the iodide from being used to synthesize more T_4. Ipodate (Oragrafin) and iopanoic acid (Telepaque) are radiographic contrast media that may be used to block thyroid hormone release. Lithium carbonate inhibits the release of thyroid hormones but is more toxic, so it is used only in patients with an iodide allergy. Lithium carbonate is given orally or by nasogastric tube and the dose is adjusted to maintain therapeutic serum levels.

Supportive care. Symptoms are aggressively treated. Acetaminophen is used as an antipyretic. Cooling blankets and ice packs may be used. Cardiac complications are treated with pharmacotherapy. Oxygen is administered to support the respiratory effort. The large fluid losses are replaced. Hemodynamic monitoring may be required. Nutritional support is provided. Precipitating factors are identified and treated and/or removed.

BOX 18-20 TREATMENT OF THYROID STORM

Antagonize Peripheral Effects of Thyroid Hormone
- Propranolol (Inderal): 1 to 2 IV boluses every 10 to 15 minutes up to 15 to 20 mg IV, or 640 mg maximum daily PO; individualized to response
- If beta-blocker contraindicated, give reserpine 0.1 to 0.25 mg PO or guanethidine 25 to 50 mg PO every 6 to 8 hours

Inhibit Hormone Biosynthesis
- Propylthiouracil: PO loading dose of 400 mg, then 200 mg, then every 4 hours until thyrotoxicosis controlled, or
- Methimazole (Tapazole): 60 mg PO loading dose; 20 mg PO every 4 hours

Block Thyroid Hormone Release
Give 1-2 Hours after Propylthiouracil or Methimazole Loading Dose
- Saturated solution of potassium iodide: 5 drops every 6 hours, mixed in 240 mL of water, juice, milk, or broth, or
- Potassium iodide tablets: 250 mg PO three times per day

Secondary Options
- Iopanoic acid: 1 g every 8 hours for 24 hours, 0.5 g PO twice daily
- Ipodate (Oragrafin): 500 to 1000 mg PO daily
- Lithium carbonate: 300 mg PO or NG every 6 hours

Supportive Therapy
- Hydrocortisone: 100 mg IV every 8 hours; or dexamethasone: 0.5 mg PO every 6 hours
- Pharmacotherapy for heart failure or tachydysrhythmia
- Correct fluid and electrolyte imbalance
- Treat hyperthermia (avoid aspirin)
- High-calorie, high-protein diet

Identify and Treat Precipitating Cause

Patient and Family Education

Doses are approximate and may vary based on the individual situation.
IV, Intravenous; *NG,* nasogastric (tube); *PO,* orally.

Patient and family education. Education of patients, families, and significant others is crucial in identifying and preventing episodes of thyroid storm. Teaching varies depending on the long-term therapy chosen for each patient (e.g., drugs versus radioactive iodine or surgery).

Patient Outcomes

Outcomes for a patient with thyroid storm include the following:

- Temperature within normal range
- Return to baseline mentation and personality
- Stable hemodynamics within normal limits
- Effective breathing pattern
- Nutritional needs met and weight maintained
- Return to baseline activity level
- Verbalization by the patient and significant others of an understanding of the patient's illness, anticipated treatment, and potential complications

Myxedema Coma

Pathophysiology

Myxedema coma is the most extreme form of hypothyroidism and is life-threatening. Myxedema coma in the absence of an associated stress or illness is uncommon, with infection being the most frequent stressor. The addition of stress to an already hypothyroid patient accelerates the metabolism and clearance of whatever thyroid hormone is present in the body. Thus the patient experiences increased hormone utilization but decreased hormone production, which precipitates a crisis state. Common findings in patients with thyroid storm are presented with those of myxedema coma in Table 18-6.

Etiology

Myxedema coma is the end stage of improperly treated, neglected, or undiagnosed hypothyroidism. It is a life-threatening emergency with a mortality rate as high as 50% despite appropriate therapy. Much of this mortality can be attributed to underlying illnesses. Most patients who develop myxedema coma are elderly women; it is rarely seen in young persons. It occurs more frequently in winter as a result of the increased stress of exposure to cold in a person unable to maintain body heat. Known precipitating factors include hypothermia, infection, stroke, trauma, and critical illness. Medications that may precipitate myxedema coma include those that affect the central nervous system, such as analgesics, anesthesia, barbiturates, narcotics, sedatives, tranquilizers, lithium, and amiodarone.

Assessment

Clinical presentation. Many patients may have had vague signs and symptoms of hypothyroidism for several years (Box 18-21). Many of the manifestations are attributable to the development of mucinous edema. This interstitial edema is the result of water retention and decreased protein. Fluid collects in soft tissue such as the face and in joints and muscles. It can also produce pericardial effusion. The clinical picture of myxedema coma varies with the rate of onset and severity. Diagnosis is based on the clinical signs and symptoms, a high index of suspicion, and a careful history and physical examination.

BOX 18-21 PROGRESSIVE SIGNS OF HYPOTHYROIDISM

- *Earliest signs:* Fatigue, weakness, muscle cramps, intolerance to cold, and weight gain.
- *Cardiovascular:* Bradycardia and hypotension.
- *Neurological:* Difficulty concentrating, slowed mentation, depression, lethargy, slow and deliberate speech, coarse and raspy voice, hearing loss, and vertigo.
- *Respiratory:* Dyspnea on exertion.
- *Gastrointestinal:* Decreased appetite, decreased peristalsis, anorexia, decreased bowel sounds, constipation, and paralytic ileus. However, the decreased metabolic rate also leads to weight gain.
- *Musculoskeletal:* Fluid in joints and muscles results in stiffness and muscle cramps.
- *Integumentary:* Dry, flaky, cool, coarse skin; dry, coarse hair; and brittle nails. The face is puffy and pallid, the tongue may be enlarged. The dorsa of the hands and feet are edematous. There may be a yellow tint to the skin from depressed hepatic conversion of carotene to vitamin A. Ecchymoses may develop from increased capillary fragility and decreased platelets.
- *Hematological:* Pernicious anemia and jaundice. Splenomegaly occurs in about 50% of patients. About 10% of patients have a decrease in neutrophils.
- *Ophthalmic:* Generalized mucinous edema in the eyelids and periorbital tissue.
- *Metabolic:* Elevated creatine phosphokinase, aspartate aminotransferase, lactate dehydrogenase, cholesterol, and triglyceride levels. Elevated cholesterol and triglyceride levels predispose persons with hypothyroidism to the development of atherosclerosis

Cardiovascular disturbances. Cardiac function is depressed, resulting in decreases from baseline in heart rate, blood pressure, contractility, stroke volume, and cardiac output. The patient may develop a pericardial effusion, making heart tones distant. The ECG has decreased voltage because of the pericardial effusion.

Pulmonary disturbances. Respiratory system responsiveness is depressed, producing hypoventilation, respiratory muscle weakness, and CO_2 retention. CO_2 narcosis may contribute to decreased mentation. As part of the picture of generalized mucinous edema and fluid retention, these patients may also develop pleural effusions or upper airway edema, further restricting their breathing.

Neurological disturbances. The low metabolic rate and resulting decreased mentation produce both psychological and physiological changes. The patient in hypothyroid crisis may present with somnolence, delirium, seizures, or coma. Personality changes such as paranoia and delusions may be evident.

Patients with hypothyroidism are unable to maintain body heat because of the decreased metabolic rate and decreased production of thermal energy. Because of this, patients may present in crisis after being stressed by exposure to cold. Hypothermia is present in 80% of patients in myxedema coma, with temperatures as low as 80° F (26.7° C). Patients with temperatures less than 88.6° F (32° C) have a grave prognosis. If a patient with myxedema coma has a temperature greater than 98.6° F (37° C), underlying infection should be suspected.

Skeletal muscle disturbances. Slowed motor conduction produces decreased tendon reflexes and sluggish, awkward movements.

Laboratory evaluation. Serum T_4 and T_3 levels and resin T_3 uptake are low in patients with myxedema coma. In primary hypothyroidism, TSH levels are high. If hypothyroidism is the result of disease of the pituitary gland or hypothalamus (secondary and tertiary hypothyroidism), TSH levels are inappropriately normal or low. As in patients with thyroid storm, if myxedema coma is suspected, treatment should not be delayed while awaiting these results to confirm the diagnosis.

Serum sodium levels may be low as a result of impaired water excretion from inappropriate ADH secretion and cortisol deficiency that frequently accompany hypothyroidism. The patient should be monitored for signs and symptoms related to hyponatremia such as weakness, muscle twitching, seizures, and coma.

Hypoglycemia is common and may be related to pituitary or hypophyseal disorders and/or adrenal insufficiency. Adrenal insufficiency may result in serum cortisol levels that are inappropriately low for stress. Laboratory manifestations of myxedema coma are summarized in "Laboratory Alert: Thyroid Disorders."

Nursing Diagnoses

The nursing diagnoses that apply to a patient in myxedema coma are based on assessment data and include the following:

- Decreased cardiac output related to decreased contractility, decreased heart rate, decreased stroke volume, pericardial effusion, dysrhythmias
- Ineffective breathing pattern related to hypoventilation, muscle weakness, decreased respiratory rate, ascites, pleural effusions
- Disturbed thought processes related to slowed metabolism and cerebration, hyponatremia
- Hypothermia related to inability of body to retain heat
- Excess fluid volume related to impaired water excretion
- Risk for injury related to edema, decreased platelet count
- Activity intolerance related to muscle weakness
- Imbalanced nutrition: less than body requirements related to decreased appetite, decreased carbohydrate metabolism, hypoglycemia
- Deficient knowledge related to myxedema coma: disease process, therapeutic regimen, and prevention of complications

BOX 18-22 TREATMENT OF MYXEDEMA COMA

- Identification and treatment of underlying disorder
- *Thyroid replacement:* levothyroxine sodium, 200 to 500 mcg IV loading dose, then 50 mcg/day IV; or liothyronine sodium, 25 mcg IV every 8 hours for 24 to 48 hours, then 12.5 mcg every 8 hours
- Restoration of fluid and electrolyte balance
- Cautious administration of vasopressors
- *Hyponatremia:* <115 mEq/L, hypertonic saline; <120 mEq/L, fluid restriction
- *Hypoglycemia:* IV glucose
- Supportive care
- Passive warming with blankets (do not actively warm)
- Ventilatory assistance
- Avoidance of narcotics and sedative drugs
- Adrenal hormone replacement: hydrocortisone, 100 mg IV bolus, then 50 to 100 mg every 6 to 8 hours for 7 to 10 days, then wean to maintenance dose over 3 to 7 days
- Chest x-ray or ultrasound study of the chest possibly needed to assess pleural effusion
- Echocardiogram possibly needed to assess cardiac function and/or pericardial effusion
- Patient and family education

Doses are approximate and may vary based on the individual situation.
IV, Intravenous.

Nursing and Medical Interventions

Myxedema coma requires immediate intervention if the patient is to survive. The primary objectives in the treatment of myxedema coma are identifying and treating the precipitating cause, providing thyroid replacement, restoring fluid and electrolyte balance, providing supportive care, and providing patient and family education. Box 18-22 details the treatment of myxedema coma. It is important to achieve physiological levels of thyroid hormone without incurring the adverse effects of excess thyroid hormones.

Thyroid replacement. The best method of thyroid replacement is controversial. Either levothyroxine sodium (Synthroid; T_4) or liothyronine sodium (Cytomel; T_3) can be used. Levothyroxine ultimately provides the patient with both T_4 and, through peripheral conversion, T_3 replacement; whereas liothyronine sodium provides only T_3.

Levothyroxine sodium is a commonly used for treatment. It has a smoother onset and a longer duration. The preferred route is IV because absorption of oral or intramuscular levothyroxine is variable. The initial dose may be decreased if the patient has underlying factors such as angina, dysrhythmias, or other heart disease.

Liothyronine sodium has more pronounced metabolic effects, a more rapid onset (6 hours), and a shorter half-life (1 day) than levothyroxine. Because of liothyronine's potency,

its administration may be complicated by angina, myocardial infarction, and cardiac irritability. Thus it is generally avoided in older populations.

The effects of levothyroxine are not as rapid as those of liothyronine, but its cardiac toxicity is lower. Serum levels of T_4 reach normal in 1 to 2 days. Levels of TSH begin to fall within 24 hours and return to normal in 10 to 14 days.

Fluid and electrolyte restoration. If the patient is hypotensive or in shock, thyroid replacement usually corrects this, but cautious volume expansion with saline also helps. Vasopressors are used with extreme caution because patients in myxedema coma are unable to respond to vasopressors until they have adequate levels of thyroid hormones available. Simultaneous administration of vasopressors and thyroid hormones is associated with myocardial irritability.

Hyponatremia usually responds to thyroid replacement and water restriction; the patient can resume water intake once thyroid hormones are replaced. If hyponatremia is severe (less than mEq/L) or the patient is having seizures, hypertonic saline with or without a loop diuretic may be administered, but only until symptoms disappear or the sodium level is at least 120 mEq/L.

If a patient has hypoglycemia, adrenal insufficiency, or both, glucose is added to IV fluids. Glucocorticoid administration is recommended for all patients in the event that hypoadrenalism coexists with hypothyroidism. Hydrocortisone, 100 mg, is given initially, followed by 50 to 100 mg every 6 to 8 hours for 7 to 10 days. The adrenal abnormality may last several weeks after thyroid replacement is begun, so this support is continued during that period.

Supportive care. Symptoms are aggressively treated. Hypothermia is treated by keeping the room warm and using passive rewarming methods. Drugs that depress respirations, such as narcotics, are avoided. Mechanical ventilation is frequently required. Cardiac function is assessed and treated.

Patient and family education. The education of patients, family, and significant others is critical in identifying and preventing episodes of myxedema coma.

Patient Outcomes

Outcomes for a patient with myxedema coma include the following:

- Stable hemodynamics within normal limits
- Effective breathing pattern
- Return to baseline mentation and personality
- Maintenance of temperature within normal range
- Normal fluid volume balance and absence of edema
- Intact skin without edema or bleeding
- Return to baseline activity level
- Adequate nutrition and stable body weight
- Verbalization by the patient and significant others of an understanding of the disease, therapeutic regimen, and prevention of complications

ANTIDIURETIC HORMONE DISORDERS

Review of Physiology

The primary function of ADH is regulation of water balance and serum osmolality. ADH (also known as arginine vasopressin [AVP]) is produced in the supraoptic nuclei and paraventricular nuclei of the hypothalamus. These nuclei are positioned near the thirst center and osmoreceptors in the hypothalamus (Figure 18-9). Once produced, ADH is stored in neurons in the posterior pituitary. Stimulation of the supraoptic and paraventricular nuclei causes release of ADH from nerve endings in the posterior pituitary. Nuclei are stimulated in several ways (Figure 18-10). Osmoreceptors in the hypothalamus respond to changes in extracellular osmolality. Stretch receptors in the left atrium and baroreceptors in the carotid sinus and aortic arch respond to changes in circulating volume and blood pressure and stimulate the hypothalamus. Primary triggers for ADH release are increased serum osmolality decreased blood volume (by more than 10%), or decreased blood pressure (5% to 10% drop). Other factors that stimulate ADH release are elevated serum sodium levels, trauma, hypoxia, pain, stress, and anxiety. Certain drugs such as narcotics, barbiturates, anesthetics, and chemotherapeutic agents also stimulate ADH release (see Figure 18-10).

Once released, ADH acts on the renal distal and collecting tubules to cause water reabsorption. In high concentrations, ADH also acts on smooth muscles of the arterioles to produce vasoconstriction.

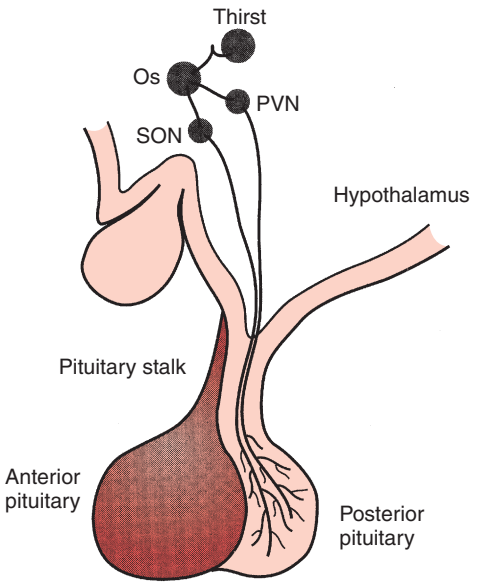


FIGURE 18-9 Hypothalamic–posterior pituitary system. *Os,* Osmoreceptor; *PVN,* Paraventricular nuclei; *SON,* Supraoptic nuclei.

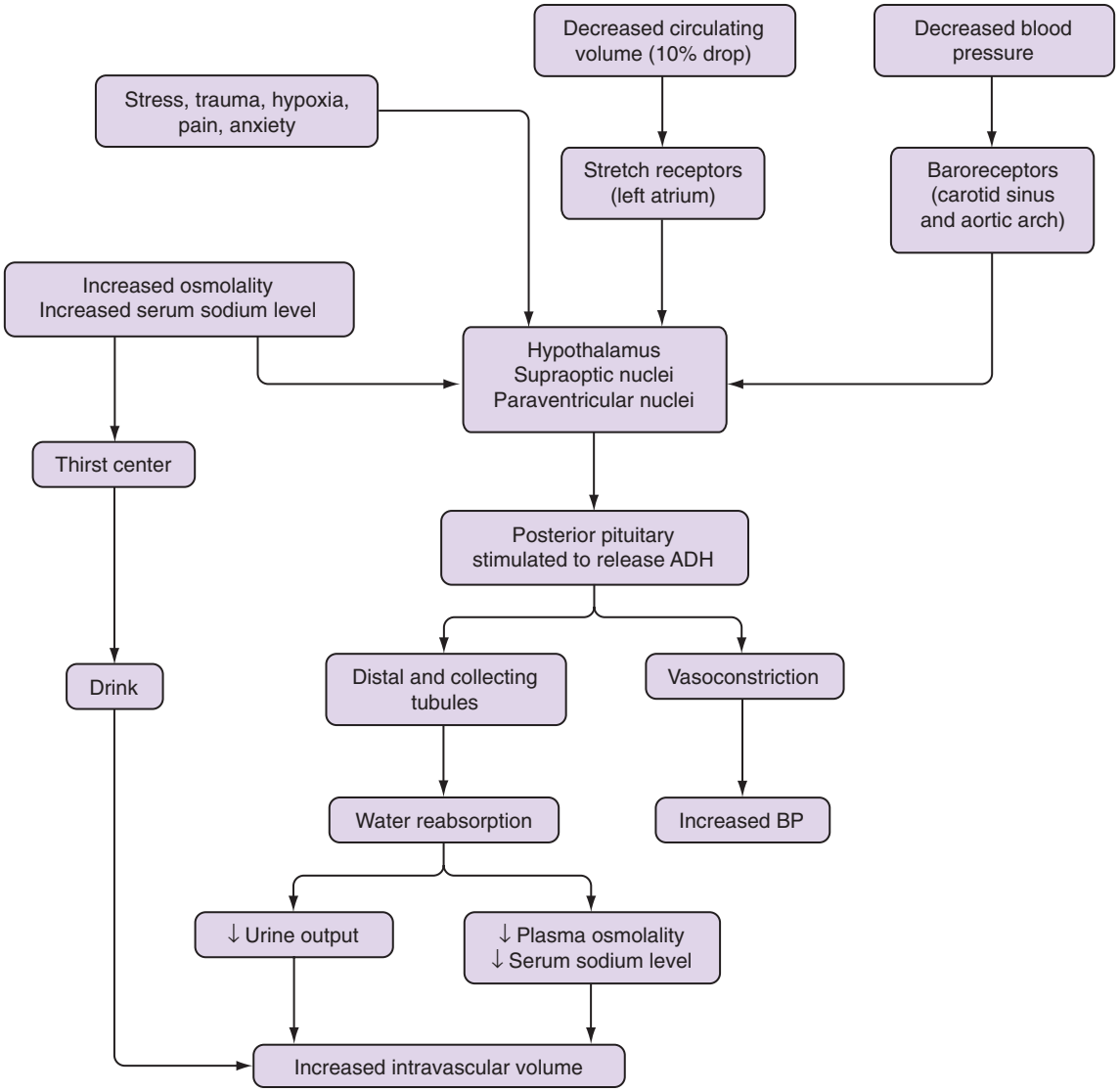


FIGURE 18-10 Physiology of antidiuretic hormone (ADH) release. *BP,* Blood pressure.

Two common disturbances of ADH are diabetes insipidus (DI) and the syndrome of inappropriate ADH (SIADH). A less common disorder is cerebral salt wasting (CSW), which is similar to SIADH but with important differences. CSW is a disorder of sodium and fluid balance that occurs in patients with a neurological insult. Differentiating CSW from SIADH is crucial because of opposing management strategies. Table 18-7 compares the electrolyte and fluid findings associated with DI, SIADH, and CSW.[21,28]

Diabetes Insipidus

Etiology

Various disorders produce neurogenic DI (Box 18-23), but the primary cause is traumatic injury to the posterior pituitary or hypothalamus as a result of head injury or surgery. Transient DI may caused by trauma to the pituitary, manipulation of the pituitary stalk during surgery, or cerebral edema. Permanent DI occurs when more than 80% to 85% of hypothalamic nuclei or the proximal pituitary stalk is destroyed.

Nephrogenic DI may occur in genetically predisposed persons. It also may be acquired from chronic renal disease, drugs, or other conditions that produce permanent kidney damage or inhibit the generation of cyclic adenosine monophosphate in the tubules.

Pathophysiology

DI results from an ADH deficiency *(neurogenic or central DI),* ADH insensitivity *(nephrogenic DI),* or excessive water intake *(secondary DI).* Regardless of the cause, the effect is impaired renal conservation of water resulting in polyuria (more than 3 L in 24 hours). As long as the thirst center remains intact and the person is able to respond to this thirst,

TABLE 18-7 ELECTROLYTE AND FLUID FINDINGS IN ADH DISORDERS

FINDING	DIABETES INSIPIDUS	SYNDROME OF INAPPROPRIATE ADH	CEREBRAL SALT WASTING
Plasma volume	Decreased	Increased	Decreased
Serum sodium	Increased	Decreased	Decreased
Serum osmolality	Increased	Decreased	Normal or increased
Urine sodium	Normal	Increased	Increased
Urine osmolality	Decreased	Increased	Normal or increased

ADH, Antidiuretic hormone.

BOX 18-23 CAUSES OF DIABETES INSIPIDUS

Antidiuretic Hormone Deficiency (Neurogenic Diabetes Insipidus)
- *Idiopathic:* familial, congenital, autoimmune, genetic
- Intracranial surgery, especially in region of pituitary
- *Tumors:* craniopharyngioma, pituitary tumors, metastases to hypothalamus
- *Infections:* meningitis, encephalitis, syphilis, mycoses, toxoplasmosis
- *Granulomatous disease:* tuberculosis, sarcoidosis, histiocytosis
- Severe head trauma, anoxic encephalopathy, or any disorder that causes increased intracranial pressure

Antidiuretic Hormone Insensitivity (Nephrogenic Diabetes Insipidus)
- Hereditary; idiopathic
- *Renal disease:* pyelonephritis, amyloidosis, polycystic kidney disease, obstructive uropathy, transplantation
- *Multisystem disorders affecting kidneys:* multiple myeloma, sickle cell disease, cystic fibrosis
- *Metabolic disturbances:* chronic hypokalemia or hypercalcemia
- *Drugs:* ethanol, phenytoin, lithium carbonate, demeclocycline, amphotericin, methoxyflurane

Secondary Diabetes Insipidus
- Idiopathic
- Psychogenic polydipsia
- Hypothalamic disease: sarcoidosis
- Excessive intravenous fluid administration
- *Drug-induced disease:* anticholinergics, tricyclic antidepressants

fluid volume can be maintained. If the patient is unable to respond, severe dehydration results if fluid losses are not replaced.

Neurogenic DI occurs because of disruption of the neural pathways or structures involved in ADH production, synthesis, or release. Absent or diminished release of ADH from the posterior pituitary produces free water loss and causes serum osmolality and serum sodium to rise. The posterior pituitary is unable to respond by increasing ADH levels; thus the kidneys are not stimulated to reabsorb water, and excessive water loss results.

In nephrogenic DI, the kidney collecting ducts and distal tubules are unresponsive to ADH; thus adequate levels of ADH may be synthesized and released, but the kidneys are unable to conserve water in response to ADH. In patients with secondary DI, compulsive volume consumption causes polyuria.

Assessment

Clinical presentation. Neurogenic DI usually occurs suddenly with an abrupt onset of polyuria, as much as 5 to 40 L in 24 hours. The onset of nephrogenic DI is more gradual. In both types, the urine is pale and dilute. The thirst mechanism is activated in conscious patients, and polydipsia occurs. If the patient is unable to replace the water lost by responding to thirst, signs of hypovolemia develop: hypotension, decreased skin turgor, dry mucous membranes, tachycardia, weight loss, and low right atrial and pulmonary artery occlusion pressures. Neurological signs and symptoms are seen with hypovolemia and hypernatremia.

Laboratory evaluation. The classic signs of DI are an inappropriately low urine osmolality, decreased urine specific gravity, and a high serum osmolality. Corresponding with the low urine osmolality is a decreased urine specific gravity. Serum osmolality is greater than 295 mOsm/kg, and the serum sodium level is greater than 145 mEq/L. The presence of hypokalemia or hypercalcemia suggests nephrogenic DI. Other values such as BUN may be elevated as a result of hemoconcentration. Further testing to differentiate neurogenic and nephrogenic DI includes water deprivation studies. However, these tests are inappropriate in the critically ill population (see box, "Laboratory Alert: Pituitary Disorders").

! LABORATORY ALERT

Pituitary Disorders

LABORATORY TEST	CRITICAL VALUE	EXPLANATION
Diabetes Insipidus		
Sodium (serum)	>145 mEq/L	Free water loss due to absent or diminished release of ADH or lack of response by the kidneys results in hemoconcentration of sodium
Osmolality (serum)	>295 mOsm/kg	Free water loss due to absent or diminished release of ADH or lack of response by the kidneys increases serum osmolality; will be normal in secondary DI
Osmolality (urine)	<100 mOsm/kg	Free water loss into urine decreases urine osmolality
Sodium (urine)	40-200 mEq/L	Urine sodium is not affected
Syndrome of Inappropriate Antidiuretic Hormone		
Sodium (serum)	<135 mEq/L	Free water retention due to oversecretion of ADH dilutes sodium
Osmolality (serum)	<280 mOsm/kg	Free water retention due to oversecretion of ADH decreases osmolality
Osmolality (urine)	>100 mOsm/kg	Lack of water excretion increases urine osmolality
Sodium (urine)	>200 mEq/L	Sodium excretion in an attempt to excrete excess water
Cerebral Salt Wasting		
Sodium (serum)	<135 mEq/L	Inability of kidneys to conserve sodium
Osmolality (serum)	>295 mOsm/kg	Inability of kidneys to conserve water
Osmolality (urine)	<100 mOsm/kg	Free water loss into urine decreases urine osmolality
Sodium (urine)	>200 mEq/L	Sodium wasting through renal tubules

ADH, Antidiuretic hormone, *HF,* heart failure.

Nursing Diagnoses

The nursing diagnoses that may apply to a patient with DI include the following:

- Deficient fluid volume related to deficient ADH, renal cells insensitive to ADH, polyuria, and inability to respond to thirst
- Disturbed thought processes related to decreased cerebral perfusion, cerebral dehydration, and hypernatremia

Nursing and Medical Interventions

The primary goals of treatment are to identify and correct the underlying cause and to restore normal fluid volume, osmolality, and electrolyte balance. Identifying the underlying cause is a necessary part of determining appropriate treatment, particularly drug therapy.

Volume replacement. Monitoring for signs and symptoms of hypovolemia is a priority. Vital signs must be recorded at least every hour, along with urine output. Hemodynamic monitoring may be instituted to evaluate fluid requirements and to monitor the patient's response to treatment. This is particularly important in elderly patients who are likely to have concurrent cardiovascular and renal disease. Accurate intake and output and daily weights are essential. Measurement of plasma sodium and volume status assists in evaluating the patient's response to treatment.

Patients who are alert and able to respond to thirst generally drink enough water to avoid symptomatic hypovolemia. However, critically ill patients who develop DI and elderly patients with cognitive impairments are frequently unable to recognize or respond to thirst, so fluid replacement is essential.

If the patient has symptoms of hypovolemia, the volume already lost must be replaced. In addition, fluid is replaced every hour to keep up with current urine losses. Correction of hypernatremia and replacement of free water are achieved by using hypotonic solutions of dextrose in water. If the patient has circulatory failure, isotonic saline may be administered until hemodynamic stability and vascular volume have been restored.

Frequent monitoring of the patient's neurological status is also critical because changes may indicate a change in fluid status, electrolyte status (e.g., sodium), or both. It is important to avoid fluid overload from overaggressive fluid replacement, particularly once hormone replacement therapy has been instituted.

Hormone replacement. Because of the decreased secretion of ADH, neurogenic DI is controlled primarily with exogenous ADH preparations. These drugs replace ADH and enable the kidneys to conserve water. They can be administered intravenously, intramuscularly, subcutaneously, intranasally, or

orally. Injectable forms are generally more potent than the intranasal or oral routes. Absorption is more reliable through the IV route.

The drug most commonly used for management is desmopressin (DDAVP), a synthetic analogue of vasopressin. Unlike aqueous vasopressin and lysine vasopressin, desmopressin is devoid of any vasoconstrictor effects and has a longer antidiuretic action (12 to 24 hours). Side effects are usually mild and include headache, nausea, and mild abdominal cramps; but overmedication can produce water overload. The patient is monitored for signs of dyspnea, hypertension, weight gain, hyponatremia, headache, or drowsiness.

Nephrogenic diabetes insipidus. Nephrogenic DI is treated with sodium restriction, which decreases the glomerular filtration rate and enhances fluid reabsorption. Administration of thiazide diuretics may increase tubular sensitivity to ADH.

Patient and family education. Patients who have a permanent ADH deficit require education regarding the following:

- Pathogenesis of DI
- Dose, side effects, and rationale for prescribed medications
- Parameters for notifying the physician
- Importance of adherence to medication regimen
- Importance of recording daily weight measurements to identify weight gain
- Importance of wearing a MedicAlert identification bracelet
- Importance of drinking according to thirst and avoiding excessive drinking

Patient Outcomes

Outcomes for a patient with DI include the following:

- Serum osmolality, 275 to 295 mOsm/kg
- Stable weight and balanced intake and output
- Serum sodium level, 135 to 145 mEq/L
- Return to baseline mentation

Syndrome of Inappropriate Antidiuretic Hormone

Etiology

Central nervous system disorders such as head injury, infection, hemorrhage, surgery, and stroke stimulate the hypothalamus or pituitary, producing excess secretion of ADH. A common cause of SIADH is ectopic production of ADH by malignant disease, especially small cell carcinoma of the lung. The malignant cells synthesize, store, and release ADH and thus place control of ADH outside the normal pituitary-hypothalamus feedback loops. Other types of malignancies known to produce SIADH include pancreatic and duodenal carcinoma, Hodgkin's lymphoma, sarcoma, and squamous cell carcinoma of the tongue.

Nonmalignant pulmonary conditions such as tuberculosis, pneumonia, lung abscess, and chronic obstructive pulmonary disease can also produce SIADH. As with malignant cells, it is believed that benign pulmonary tissue is capable of synthesizing and releasing ADH in certain disease states.

Many medications are associated with development of SIADH (Box 18-24). Of recent concern are reports of the effects of the widely prescribed selective serotonin reuptake inhibitors on ADH levels and function.[23] The mechanisms involved include increasing or potentiating the action of ADH, acting on the renal distal tubule to decrease free water excretion, or causing central release of ADH.

BOX 18-24 CAUSES OF SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE

Ectopic Antidiuretic Hormone Production

- Small cell carcinoma of lung
- Cancer of prostate, pancreas, or duodenum
- Hodgkin's disease
- Sarcoma, squamous cell carcinoma of the tongue, thymoma
- *Nonmalignant pulmonary disease:* viral pneumonia, tuberculosis, chronic obstructive pulmonary disease, lung abscess

Central Nervous System Disorders

- Head trauma
- *Infections:* meningitis, encephalitis, brain abscess
- Intracranial surgery, cerebral aneurysm, brain tumor, cerebral atrophy, stroke
- Guillain-Barré syndrome, lupus erythematosus

Drugs

- Angiotensin-converting enzyme inhibitors
- Amiodarone
- Analgesics and narcotics: morphine, fentanyl, acetaminophen

Drugs—cont'd

- *Antineoplastics:* vincristine, cyclophosphamide, vinblastine, cisplatin
- Barbiturates
- Carbamazepine (Tegretol) and oxcarbazepine (Trileptal)
- Ciprofloxacin
- General anesthetics
- Haloperidol (Haldol)
- Mizoribine
- Nicotine
- Nonsteroidal antiinflammatory drugs
- Pentamidine
- *Serotonergic agents:* 3,4-methylenedioxymethamphetamine (MDMA; Ecstasy), selective serotonin reuptake inhibitors
- Thiazide diuretics
- Tricyclic antidepressants

Positive-Pressure Ventilation

Pathophysiology

SIADH occurs when the body secretes excessive ADH unrelated to plasma osmolality. This occurs when there is a failure in the negative feedback mechanism that regulates the release and inhibition of ADH. The results are an inability to secrete a dilute urine, fluid retention, and dilutional hyponatremia. The primary treatment of SIADH is to restrict or withhold fluids.

Assessment

Clinical presentation. The clinical manifestations are primarily the result of water retention, hyponatremia, and hypo-osmolality of the serum. The severity of the signs and symptoms is related to the rate of onset and the severity of the hyponatremia.

Central nervous system. Manifestations such as weakness, lethargy, mental confusion, difficulty concentrating, restlessness, headache, seizures, and coma may occur in response to hyponatremia and hypo-osmolality. Hypo-osmolality disrupts the intracellular-extracellular osmotic gradient and causes a shift of water into brain cells, leading to cerebral edema and increased intracranial pressure. If the serum sodium level decreases to less than 120 mEq/L in 48 hours or less, there are usually serious neurological symptoms and a mortality rate as high as 50%. If hyponatremia develops more slowly, the body is able to protect against cerebral edema, and the patient may remain asymptomatic even with a very low serum sodium level.

Gastrointestinal system. Congestion of the gastrointestinal tract and decreased motility occur because of hyponatremia. This is manifest by nausea and vomiting, anorexia, muscle cramps, and decreased bowel sounds.

Cardiovascular system. Water retention produces edema, increased blood pressure, and elevated central venous and pulmonary artery occlusion pressures.

Pulmonary system. Fluid overload in the pulmonary system produces increased respiratory rate, dyspnea, adventitious lung sounds, and frothy, pink sputum.

Laboratory evaluation. The hallmark of SIADH is hyponatremia and hypo-osmolality in the presence of concentrated urine. A low serum osmolarity should trigger inhibition of ADH secretion, resulting in the loss of water through the kidneys and a dilute urine (see box, "Laboratory Alert: Pituitary Disorders").

High urinary sodium levels (higher than 20 mEq/L) help to differentiate SIADH from other causes of hypo-osmolality, hyponatremia, and volume overload (such as congestive heart failure). In SIADH, renal perfusion (a major stimulus for sodium reabsorption) is usually adequate, so sodium is not conserved, resulting in urinary sodium excretion. In a disorder such as heart failure, renal perfusion is low because of decreased cardiac output, triggering reabsorption of sodium.

Hemodilution may decrease other laboratory values such as BUN, creatinine, and albumin. SIADH should be suspected in a patient with evidence of hemodilution and urine that is hypertonic relative to plasma.

Nursing Diagnoses

The nursing diagnoses that may apply to a patient with SIADH include the following:

- Excess fluid volume related to excess water retention from excess ADH
- Disturbed thought processes related to brain swelling and fluid shift into cerebral cells

Nursing and Medical Interventions

The primary goals of therapy are to treat the underlying cause, to eliminate excess water, and to increase serum osmolality. In many instances, treatment of the underlying disorder (e.g., discontinuation of a responsible drug) is all that is needed to return the patient's condition to normal.

Fluid balance. In mild to moderate cases (serum sodium level, 125 to 135 mEq/L), fluid intake is restricted to 800 to 1000 mL/day, with liberal dietary salt and protein intake. The patient's response is evaluated by monitoring serum sodium levels, serum osmolality, and weight loss for a gradual return to baseline.

In severe, symptomatic cases (coma, seizures, serum sodium level less than 110 mEq/L), very small amounts of hypertonic 3% saline may be given following rigorous guidelines and with careful monitoring (Box 18-25). Correction of the serum sodium level must be done slowly, no more than 12 mEq within the first 24 hours. Administering hypertonic saline too rapidly, correcting the serum sodium level too rapidly, or both, can result in central pontine myelinolysis, a severe neurological syndrome that can lead to permanent brain damage or death.[28] The risk of heart failure is also significant. A diuretic such as furosemide may be given during hypertonic saline administration to promote diuresis and free water clearance. Treatments for chronic or resistant SIADH are listed in Box 18-26.

Nursing. Prevention of SIADH may not be possible, but early detection and treatment may prevent more serious sequelae from occurring. Being aware of the populations at risk and monitoring at-risk populations for clinical signs are key roles for the critical care nurse.

Close monitoring of fluid and electrolyte balance is required. Daily weight, intake and output, and urine specific gravity are measured. Fluid overload may occur from hypervolemia or too rapid administration of hypertonic saline. Cardiovascular symptoms such as tachycardia, increased blood pressure, increased hemodynamic pressures, full bounding pulses, and distended neck veins are all indicators of fluid overload. Respiratory function is monitored for signs of tachypnea, labored respirations, shortness of breath, or fine crackles. Careful monitoring of potassium and magnesium levels is necessary to replace diuresis-induced losses.

Adherence to fluid restrictions is critical but difficult for patients. The nurse should ensure that the patient and the family understand the importance of the restriction and that

BOX 18-25 NURSING CONSIDERATIONS FOR ADMINISTRATION OF 3% SODIUM CHLORIDE

- Administer via central rather than peripheral access
- Administer via pump only
- Rate should not exceed 50 mL/hour
- Monitor serum sodium levels every 4 hours; hold infusion if serum sodium level exceeds 155 mEq/L
- Wean solution rather than stopping abruptly
- Monitor level of responsiveness for evidence of decline (could indicate cerebral edema or worsening hyponatremia)
- Monitor lungs sounds for crackles indicating pulmonary edema
- Monitor intake and output every hour

BOX 18-26 TREATMENTS FOR CHRONIC OR RESISTANT SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE

- Water restriction of 800 to 1000 mL/day.
- Administration of loop diuretics in conjunction with increased salt and potassium intake is the safest method for treating chronic hyponatremia. The diuretic prevents urine concentration, and the increased salt and potassium intake increases water output by increasing delivery of solutes to the kidney.
- Demeclocycline is an antibiotic that decreases renal tubule responsiveness to ADH. Doses of 600 to 1200 mg are given PO in divided doses twice a day. Its onset is delayed for several days, and it may not be completely effective for 2 weeks, evidenced by a decrease in urine osmolality to therapeutic range. This drug is rarely used. The major side effects are nephrotoxicity and risk of infection.

Doses are approximate and may vary based on the individual situation.
ADH, Antidiuretic hormone; *PO,* orally.

they are included in planning types and timing of fluids. Patients should be encouraged to choose fluids high in sodium content such as milk, tomato juice, and beef and chicken broth. Measures to relieve some of the discomfort caused by fluid restriction include frequent mouth care, oral rinses without swallowing, chilled beverages, and sucking on hard candy.

Assessment of the patient's neurological status is also critical to monitor the effects of treatment and to watch for complications. The patient is assessed for subtle changes that may indicate water intoxication, such as fatigue, weakness, headache, or changes in level of consciousness. Strict adherence to administration rates of hypertonic (3%) saline solutions and measurement of serial serum sodium levels are essential to prevent neurological sequelae. Seizure precautions are instituted if the patient's sodium level decreases to less than 120 mEq/L.

Patient and family education. In some patients, SIADH may require long-term treatment, ongoing monitoring, or both. These patients and their families require instruction regarding the following:

- Early signs and symptoms to report to the healthcare provider: weight gain, lethargy, weakness, nausea, mental status changes
- The significance of adherence to fluid restriction
- Dose, side effects, and rationale for prescribed medications
- Importance of daily weights

Patient Outcomes

Outcomes for a patient with SIADH include the following:

- Serum osmolality, 275 to 295 mOsm/kg
- Serum sodium level, 135 to 145 mEq/L
- Hemodynamic measurements within normal limits
- Return of vital signs to patient baseline
- Return of mental status to patient baseline
- Ability of the patient and family to verbalize an understanding of SIADH, the therapeutic regimen, and prevention of complications

Cerebral Salt Wasting

Etiology

Patients with any type of serious brain insult may develop CSW. Brain trauma, subarachnoid hemorrhage and other types of stroke, and meningitis are associated with development of CSW.[28]

Pathophysiology

The exact pathophysiology of CSW is unknown. A defect in renal sodium transport has been suggested, and a change from cerebral to renal salt wasting has been suggested as a more accurate term. Natriuretic peptides, commonly released in severe brain injury, and impaired aldosterone have been implicated as factors in defective renal sodium transport. However, research has produced conflicting data.

Assessment

Clinical presentation. The findings associated with CSW are related to hypovolemia and hyponatremia. Signs of hypovolemia include decreased skin turgor, dry mucous membranes, tachycardia, weight loss, and hypotension. Signs of hyponatremia include weakness, lethargy, mental confusion, difficulty concentrating, restlessness, headache, seizures, and coma. Neurological signs and symptoms are seen with both hypovolemia and hyponatremia.

Laboratory evaluation. An increased serum osmolality, decreased serum sodium, and increased urine sodium characterize CSW. Hemoconcentration may increase other laboratory values such as BUN, creatinine, and albumin (see box, "Laboratory Alert: Pituitary Disorders").

Nursing Diagnoses

The nursing diagnoses that may apply to a patient with CSW include the following:

- Deficient fluid volume related to lack of renal sodium retention and diuresis
- Disturbed thought processes related to decreased cerebral perfusion, cerebral dehydration, and hyponatremia

Nursing and Medical Interventions

The primary goals of treatment are to simultaneously restore both sodium and fluid volume. Replacing fluids without sodium may worsen the hyponatremia, resulting in life-threatening consequences. Both isotonic saline and hypertonic saline (3%) are used. Isotonic saline is administered to replace volume at a rate to match urine output, and 3% saline is given so that sodium levels increase at a rate of no more than 12 mEq/hr. Oral or intravenous fludrocortisone, 0.05 to 0.2 mg daily may be given to increase sodium retention in the renal tubules.

Patient Outcomes

Outcomes for the patient with CSW include the following:

- Serum osmolality, 275 to 295 mOsm/kg
- Stable weight and balanced intake and output
- Serum sodium level, 135 to 145 mEq/L
- Return to baseline mentation

CASE STUDY

Mr. F., a 68-year-old man, is admitted to the critical care unit from the emergency department with respiratory failure and hypotension. His history is significant for type 2 diabetes mellitus, steroid-dependent chronic obstructive pulmonary disease, peripheral vascular disease, and cigarette and alcohol abuse. His medications at home include glipizide, prednisone, and a metered dose inhaler with albuterol and ipratropium (Combivent). In the emergency department he received a single dose of ceftriaxone and etomidate for intubation.

On exam he is intubated, on pressure-controlled ventilation, and receiving normal saline at 200 mL/hr and dopamine at 8 mcg/kg/min. His blood pressure is 86/50 mm Hg; heart rate, 126 beats/min; oxygen saturation, 88%; and temperature, 39.6° C. His cardiac rhythm shows sinus tachycardia and nonspecific ST-T wave changes. Arterial blood gas values are as follows: pH, 7.21; PaO_2, 83 mm Hg; $PaCO_2$, 50 mm Hg; and bicarbonate, 12 mEq/L. Other laboratory values are as follows: serum glucose, 308 mg/dL; serum creatinine, 2.1 mg/dL; and white blood cell count, 19,000/microliter.

Questions

1. What disease state do you suspect this patient is experiencing and why?
2. What potential endocrine complications do you anticipate?
3. What further laboratory studies would you want? What results do you anticipate?
4. What treatment goals and strategies do you anticipate?
5. In providing patient and family education and support, what issues need to be addressed immediately and which can be delayed?

SUMMARY

The stress of critical illness affects the endocrine system. Control of blood glucose levels is an essential component of critical care because of the adverse outcomes associated with hyperglycemia. Low-dose corticosteroid therapy is a component of managing the inflammatory response seen in many critical illnesses.

Various endocrine disorders are seen in critical care. Patients may be admitted to the critical care unit for treatment of an endocrine disorder or develop an endocrine disorder secondary to another problem. Preexisting disorders may become secondary during treatment of a critical illness.

The critical care nurse must be knowledgeable about the endocrine system, its feedback mechanisms, and its role in maintaining homeostasis. Nursing assessments and interventions can assist in prevention, detection, and early treatment of endocrine imbalances.

CRITICAL THINKING EXERCISE

1. How can the hazards of hypoglycemia be prevented?
2. Insulin therapy is a critical intervention in the treatment of DKA. What crucial parameters must be monitored to ensure optimal patient outcomes?
3. In a patient with neurological injury, how do lab values help to differentiate DI, SIADH, and CSW?
4. In which patient population would the nurse expect to administer a cosyntropin stimulation test? What factors affect the interpretation of the test results?

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes – 2011. *Diabetes Care*. 2011;34(Suppl 1):S11-S61.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2011;34(Suppl 1):S62-S69.
3. American Diabetes Association. *Medical Management of Type 1 Diabetes*. 5th ed. Alexandria, VA: American Diabetes Association. 2008.
4. American Diabetes Association. *Medical Management of Type 2 Diabetes*. 6th ed. Alexandria, VA: American Diabetes Association. 2008.
5. Brenner ZR. Management of hyperglycemic emergencies. *AACN Clinical Issues*. 2006;17:56-65.
6. Centers for Disease Control and Prevention. National diabetes fact sheet: National estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 2011.
7. Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004;27:553-591.
8. Golombek SG. Nonthyroidal illness syndrome and euthyroid sick syndrome in intensive care patients. *Seminars in Perinatology*. 2008;32(6):413-418.
9. Griesdale DEG, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *Canadian Medical Association Journal*. 2009;180:821-827.
10. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crisis in adult patients with diabetes. *Diabetes Care*. 2009; 32:1335-1343.
11. Lipiner-Friedman D, Sprung CL, Laterre PF, et al. Adrenal function in sepsis: the retrospective Corticus cohort study. *Critical Care Medicine*. 2007;35(4):1012-1018.
12. Lo J, Grinspoon SK. Adrenal function in HIV infection. *Current Opinion in Endocrinology, Diabetes & Obesity*. 2010;17(3):205-209.
13. Majeroni BA, Patel P. Autoimmune polyglandular syndrome, type II. *American Family Physician*. 2007;75(5):667.
14. Marik PE. Critical illness-related corticosteroid insufficiency. *Chest*. 2009;135(1):181-193.
15. Maxime V, Lesur O, Annane D. Adrenal insufficiency in septic shock. *Clinics in Chest Medicine*. 2009;30(1):17-27.
16. McCloskey B. Diabetes in the elderly. In Childs BP, Cypress M, Spollett G, eds. *Complete Nurse's Guide to Diabetes Care*. Alexandria, VA: American Diabetes Association. 2005;311-318.
17. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care*. 2009;32:1119-1131.
18. NICE-SUGAR Study Investigators. Intensive verses conventional glucose control in critically ill patients. *New England Journal of Medicine*. 2009;360:1283-1297.
19. Nylen ES, Seam N, Khosla R. Endocrine markers of severity and prognosis in critical illness. *Critical Care Clinics*. 2006;22:161-179.
20. Porsche R, Brenner ZR. Amiodarone-induced thyroid dysfunction. *Critical Care Nurse*. 2006;26(3):34-42.
21. Rivkees SA. Differentiating appropriate antidiuretic hormone secretion, inappropriate antidiuretic hormone secretion and cerebral salt wasting: the common, uncommon, and misnamed. *Current Opinion in Pediatrics*. 2008;20(4):448-452.
22. Sakharova OV, Inzucchi SE. Endocrine assessments during critical illness. *Critical Care Clinics*. 2007;23(3):467-490.
23. Thomas Z, Bandali F, McCowen K, et al. Drug-induced endocrine disorders in the intensive care unit. *Critical Care Medicine*. 2010; 38(6):S219-230.
24. Turina M, Christ-Cain M, Polk HC. Diabetes and hyperglycemia: strict glycemic control. *Critical Care Medicine*. 2006;34: S291-S300.
25. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *New England Journal of Medicine*. 2006;354:449-461.
26. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *New England Journal of Medicine*. 2001;345:1359-1367.
27. World Health Organization. *Diabetes Fact Sheet No. 312*. http://www.who.int/mediacentre/factsheets/fs312/en/; 2011.
28. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting: pathophysiology, diagnosis, and treatment. *Neurosurgery Clinics of North America*. 2010;21(2):339-352.