# Endocrine Emergencies

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**Objectives**:

- To recognize the etiologies and clinical manifestations of endocrine crises involving the pancreas, thyroid, adrenal, and pituitary glands
- To review the optimal confirmatory laboratory tests for these disorders in the acute care setting
- To delineate the initial treatment for each specific endocrine emergency
- To cover important pearls and selected caveats related to the diagnosis and management of endocrine emergencies

**Key words:** adrenal insufficiency; diabetes insipidus; diabetic ketoacidosis; hyperosmolar-nonketotic dehydration syndrome; hypoglycemia; myxedema coma; pheochromocytoma; thyroid storm

## Hypoglycemia

Hypoglycemia has numerous etiologies. Common causes in the ICU setting include sepsis, severe hepatic dysfunction, renal failure, and adrenal insufficiency. Administration of excessive exogenous insulin is another common cause. Parenteral nutrition formulas contain a high concentration of dextrose, which stimulates high insulin levels. Abruptly stopping infusions of such formulas can therefore induce hypoglycemia. Uncommon causes include pancreatic islet-cell tumors, various nonpancreatic neoplasms (*eg*, hepatoma, sarcoma, lymphoma, leukemia, and carcinoid tumors) that secrete insulin-like factors, hereditary fructose intolerance, and glycogen storage disease. Certain drugs, (*eg*, ethanol, sulfonylurea agents, β-adrenergic blocking agents, pentamidine, quinidine, and disopyramide) can potentially cause hypoglycemia.

The classic diagnostic criteria for hypoglycemia are exemplified by Whipple's triad, which consists of hypoglycemia (blood glucose concentration < 50 mg / dL) accompanied by classic symptoms of hypoglycemia, with resolution of these symptoms after administration of dextrose. The clinical findings of hypoglycemia are mainly either manifestations of the resulting hyperadrenergic state or the effects of neuroglycopenia. The latter include headache, visual disturbances, confusion, behavioral changes, delirium, stupor, coma, or seizures. Among the hyperadrenergic manifestations are tremulousness, anxiety, diaphoresis, palpitations, tachycardia, nausea, vomiting, and weakness. These signs and symptoms can be absent or blunted in patients taking β-adrenergic blocking agents. In most cases the etiology is apparent or the episode represents an isolated event. Less commonly, repetitive unexplained episodes of hypoglycemia necessitate exclusion of obscure causes using assays for insulin levels and C-peptide levels, provocative testing, and in some cases drug testing.

If severe and prolonged, hypoglycemia can potentially result in devastating and permanent neurologic injury. For this reason, it is always considered a medical emergency requiring acute treatment. Initial treatment consists of IV injection of concentrated dextrose (usually 50 mL of 50% dextrose solution). Blood can first be sampled for glucose analysis, if it does not delay dextrose administration for more than about a minute, but dextrose should then be administered without waiting for the glucose assay result. IV administration of 25 g of dextrose is safe, even if the patient is subsequently found to not have hypoglycemia, or found to have hyperglycemia. This treatment is temporizing. Whatever caused the hypoglycemia is likely to still be present and the hypoglycemia is expected to recur once the 25 g of dextrose administered has been metabolized. Therefore, a continuous IV infusion of dextrose should be started. The final aspect of acute management is to provide for serial blood or serum glucose testing to detect possible recurrences and tailor the rate of ongoing dextrose administration. Serial glucose monitoring is especially critical in patients who are sedated or otherwise already have altered mentation or a depressed sensorium that can interfere with clinical detection of neuroglycopenic manifestations.

## Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) occurs when there is a complete or near-complete lack of insulin. It is uncommon in older adults but is seen commonly

in children and young adults with new-onset or previously diagnosed type I diabetes mellitus. The two most common precipitating factors are noncompliance with insulin therapy and intercurrent medical illnesses, especially infection. Subjective manifestations include malaise, fatigue, polyuria, thirst, polydipsia, nausea, vomiting, and abdominal pain. Physical examination may reveal Kussmaul respirations, tachycardia, orthostatic or frank hypotension, acetone breath odor, abdominal tenderness, and alterations in the sensorium.

Laboratory findings include hyperglycemia, metabolic acidosis, ketonemia, ketonuria, and an elevation of the serum anion gap. The metabolic acidosis is due to production of excessive amounts of acetoacetic and β-hydroxybutyric acid. The former can be semiquantitatively assayed in the laboratory colorimetrically by reaction of serum or urine with nitroprusside. Acetone, a metabolic end-product of the these two organic acids, also reacts with nitroprusside. Dissociation of loosely bound hydrogen ions on these acids forms β-hydroxybutyrate and acetoacetate, anions that are responsible for the elevated anion gap. Glycosuria produces an osmotic diuresis and leads to depletion of potassium from the body. However, serum potassium levels are usually high in DKA at presentation, as a result of shifting of potassium from the intracellular compartment to the extracellular space caused by insulin deficiency. This hyperkalemia usually abates shortly after insulin treatment is initiated and can lead to rapid development of marked hypokalemia. Therefore, close monitoring of serum potassium is necessary. Hypophosphatemia can occur, either at presentation or, more commonly, during insulin administration. Specific diagnostic studies are used to rule out suspected precipitating factors, such as infection or myocardial infarction.

Treatment is initiated with vigorous isotonic fluid administration IV using normal saline solution initially. Hypotonic saline solution is substituted once intravascular volume has been adequately replenished. Regular insulin is given first as an IV bolus at 0.15 U/kg, followed by a continuous IV infusion at 0.1 U/kg/h, which is titrated against serial blood glucose measurements obtained at 1- to 2-h intervals. This monitoring is needed to minimize the risk of hypoglycemia, and to allow its prompt detection should it occur. Potassium supplementation is almost always necessary and is typically started as soon as the serum potassium concentration falls to within the normal range. Phosphate is administered if hypophosphatemia is present. No systematic clinical trials have shown that sodium bicarbonate therapy has an effect on outcome.

When blood glucose concentration falls below ~ 250 mg/dL, 5% dextrose is added to the IV fluid prescription, but the IV insulin infusion is continued until the ketoacidosis resolves. Resolution of ketoacidosis is demonstrated by normalization of the serum anion gap and near-normalization of serum total $CO_2$ content. Once the ketoacidosis has resolved, the IV insulin infusion can be stopped and subcutaneously administered insulin substituted. Parenteral dextrose administration is then stopped and an appropriate oral diet prescribed.

## Hyperosmolar-Nonketotic Dehydration Syndrome

Hyperosmolar-nonketotic dehydration syndrome (HONK) occurs in patients who have insulin deficiency that results in hyperglycemia, but still secrete enough insulin to prevent ketoacidosis from developing. Unlike DKA, it occurs more frequently in the elderly. Like DKA and other endocrine crises, an intercurrent illness frequently precipitates this disorder. Among the more common precipitating factors are sepsis, myocardial infarction, and stroke. Common subjective manifestations include polyuria and polydipsia, but marked sensorial depression can occur due to hyperosmolality caused by sometimes extreme degrees of hyperglycemia.

In DKA, the blood glucose concentration is typically between 400 and 800 mg/dL. HONK is characterized by blood glucose levels > 800 mg/dL by definition, often well over 1,000 mg/dL, and on rare occasions > 2,000 mg/dL. Ketoacidosis is not present in classic cases of HONK, but mild degrees of ketosis or slight degrees of ketoacidosis are sometimes seen. Pure HONK and pure DKA can be thought of as poles of a spectrum, with many patients represented in the overlap region of the spectrum such that some cases of DKA are associated with higher than typical blood glucose levels, and some cases of HONK have a degree of ketoacidosis.

As with DKA, glycosuria results in an osmotic diuresis, depleting extracellular water. In HONK, the marked elevations in blood glucose result in hyperosmolality and cause osmotic shifting of water from the intracellular space to the extracellular

compartment. This can result in severe intracellular dehydration. In the brain, this dehydration is responsible for the sensorial depression or coma. Brain shrinkage occurs and can lead to stretching of blood vessels between the skull and the surface of the brain, potentially leading to cerebral parenchymal hemorrhages.

Renal losses of hypotonic fluid can lead to associated hypernatremia. On the other hand, the osmotic shifting of water from the cells to the extracellular space tends to lower plasma sodium by dilution. Although this latter effect by itself would tend to expand intravascular volume, the associated osmotic diuresis more than countervails and leads to volume depletion. The net effect of these forces determines actual plasma sodium concentration. The degree of hypernatremia is commonly used by clinicians as a means of estimating free-water deficits in acutely ill patients, but its use for this purpose can be misleading in patients with HONK. Free-water deficits are proportional to effective plasma osmolality, which, in the absence of hyperglycemia, is normally proportional to changes in plasma sodium concentration. In HONK, however, the sodium concentration may be normal or decreased (as described above) even though the plasma is hyperosmolar because of hyperglycemia. Even if the patient is hypernatremic, the degree of hypernatremia will underrepresent the free-water deficit insofar as hyperglycemia tends to temper the plasma sodium concentration.

One way to estimate free-water deficits in this situation is to consider the adjusted serum concentration, after accounting for the expected effect of hyperglycemia on serum sodium concentration. This is conventionally done by adjusting the serum sodium concentration downward by 1.6 mmol/L for every 100-mg/dL elevation in glucose concentration. Applying this factor to the patient's reported serum sodium concentration allows the clinician to abstractly consider what the patient's sodium level would be if the same free-water deficit were present but in the absence of hyperglycemia.

Treatment of HONK is similar to that of DKA. Because the degree of dehydration is often much more severe than in DKA, more vigorous fluid replacement is usually required. Administering insulin before beginning fluid resuscitation can precipitate or worsen circulatory shock by driving glucose into cells, thereby lowering plasma osmolality and causing osmotic shifting of water from the intravascular compartment to the intracellular space, worsening hypovolemia. The choice of IV fluid composition initially is always normal saline solution. Even though hypotonic IV fluids can ameliorate the hyperosmolar state more rapidly, they are less effective at expanding intravascular volume. Treatment priority is given to correcting hypovolemia because hypoperfusion associated with the latter represents a greater immediate threat to life than does hyperosmolality.

## Myxedema Coma

Myxedema coma is the most severe expression of hypothyroidism. Etiologies of hypothyroidism include autoimmune thyroiditis, certain drugs (*eg*, propylthiouracil amiodarone, lithium), thyroidectomy or radioactive iodine ablation with inadequate thyroid replacement therapy, and iodine deficiency. An intercurrent acute illness or injury (*eg*, an infection, trauma, or surgery) frequently provokes the transition from a compensated to life-threatening state. Subjective manifestations of hypothyroidism can include fatigue, daytime somnolence, difficulty concentrating, cold intolerance, constipation, and myalgias. Objective findings may include goiter, an apathetic affect, lethargy or depressed sensorium, bradycardia or cardiac conduction disturbances, hypothermia, alopecia, dry skin, puffy facies, motor weakness, hoarseness, distant heart sounds, and absent or hypoactive deep tendon reflexes. For the hypothyroidism to be considered severe enough to be categorized as myxedema coma, a depressed level of consciousness is necessary. Hypoventilation is common in myxedema coma and a high proportion of patients progress, sometimes rapidly, to frank respiratory failure.

Arterial blood gas analysis demonstrates hypercapnia and hypoxemia in many patients with this disorder. Other nonspecific blood tests include hyponatremia, hypoglycemia, hyperlipidemia, and elevated creatine phosphokinase activity. Elevation of circulating thyroid-stimulating hormone (TSH) and depression of circulating free thyroxin ($T_4$) levels are diagnostic. Patients who are severely ill but have no thyroid disease often have abnormal thyroid function test results. Differentiating these false-positive findings, also referred to as the sick euthyroid syndrome, from true hypothyroidism can therefore be difficult in critically ill patients. Most patients with have low levels of free $T_4$ and

tri-iodothyronine ($T_3$). $T_3$ is usually low early in the course of acute illness, but $T_4$ levels can also fall if the illness becomes more severe. Although less common, free $T_4$ levels are elevated in some patients with this syndrome. TSH is usually unaffected in sick euthyroid syndrome. The syndrome is characterized by high circulating levels of reverse $T_3$, the inactive stereoisomer of the physiologically active form of $T_3$. Most authorities advise against therapeutic thyroid hormone administration to patients with euthyroid sick syndrome.

Specific treatment consists of hormone replacement. This can be accomplished using a loading dose of thyroxine (*eg*, 300 to 500 $\mu$g IV), followed by daily doses of 50 to 200 $\mu$g. Stress doses of hydrocortisone are recommended to cover the possibility of coexistent adrenal insufficiency. Passive rewarming is preferred over active methods to avoid hypotension precipitation by cutaneous vasodilation. Endotracheal intubation and mechanical ventilation are frequently required, either for overt respiratory failure or airway protection due to deep coma.

## Thyroid Storm

Thyroid storm is life-threatening thyrotoxicosis due to supraphysiologic circulating concentrations of free $T_4$ or $T_3$. This is an uncommon medical emergency. The cause is usually Graves' disease, an autoimmune disorder that represents the most common etiology of hyperthyroidism, or toxic nodular goiter. Thyroid storm is rarely due to other etiologies of hyperthyroidism, although it can result from intentional overdose of thyroid replacement pharmaceuticals.

The distinction between thyrotoxicosis and thyroid storm is that the former can exist in a compensated state with mild to moderate symptoms, while the latter implies life-threatening manifestations such as cardiac or serious central nervous system manifestations. Decompensation of thyrotoxicosis to thyroid storm is often triggered by an acute illness or injury. Subjective findings reported in thyrotoxicosis include nervousness, palpitations, fatigue, heat intolerance, dyspnea, anorexia, diarrhea, and weight loss. Physical examination may reveal a goiter, supraventricular tachydysrhythmias (particularly atrial fibrillation or flutter), systolic hypertension with a widened pulse pressure, signs of congestive heart failure, tremors, hyperreflexia, and changes in mentation. Proptosis and pretibial myxedema may be present if the underlying etiology is Graves' disease. Signs of congestive heart failure or the presence of tachydysrhythmias, respiratory failure, or sensorial changes are common prominent features of thyroid storm.

TSH levels are low in nearly all cases of thyrotoxicosis due to feedback suppression of hypothalamic TSH secretion by high circulating levels of free $T_4$. Older TSH assays were unable to detect abnormally low TSH levels and could only be used for diagnosis of hypothyroidism, but more sensitive assays are now routinely available and allow measurement of extremely low TSH concentrations. Plasma free $T_4$ levels are elevated in thyrotoxicosis, although there is a very rare form of hyperthyroidism in which free $T_4$ levels can be within normal range but plasma $T_3$ concentrations are abnormally high. While there are no specific threshold biochemical levels that serve to demarcate thyroid storm from compensated thyrotoxicosis, thyroid function test results tend to be more severely abnormal in patients with thyroid storm. Other laboratory abnormalities sometimes observed in patients with hyperthyroidism are hypercalcemia and hyperbilirubinemia.

Because this condition can be rapidly progressive and life-threatening, patients with thyroid storm are treated in the ICU. This allows close cardiac and neurologic monitoring and early recognition of dehydration, cardiac dysrhythmias, heart failure, and respiratory failure. Thyroid ablation using radioactive iodine or thyroidectomy are options for treating thyrotoxicosis, but are not used in treating thyroid storm. The use of pharmacologic agents to inhibit thyroid hormone synthesis is another long-term therapeutic option in hyperthyroidism, but it represents the primary specific treatment of thyroid storm. Propylthiouracil and methimazole are available for this purpose. These drugs stop ongoing synthesis of thyroid hormones; however, there can be enough preformed hormone stored within the thyroid gland to allow continued release into the circulation for days or weeks.

Lugol's iodine solution is traditionally administered as adjunctive therapy to block release of this stored hormone. Other iodine-containing agents, such as the oral radiocontrast agent sodium ipodate, oral potassium iodide solution, or IV sodium iodide, can also be used for this purpose. It is important not to administer any of these iodine-containing

preparations until at least 1 h after propylthiouracil has been started. If iodine is given first, it will augment thyroid hormone synthesis.

β-Adrenergic blocking drugs are routinely administered to patients with thyroid storm. Their primary purpose is to blunt the cardiovascular effects of thyrotoxicosis, including tachycardia and hypertension. Propranolol is traditionally used for this purpose, given initially in incremental doses by slow IV injection. High doses are often required to control atrial tachydysrhythmias. If there are relative contraindications to propranolol, a cardioselective β-blocker (*eg*, metoprolol) may be employed. Another alternative is the use of esmolol, which is given by continuous IV infusion. Because the drug has a short half-life, it has the advantage of rapid resolution of β-blockade after discontinuation of the infusion. Propranolol, sodium ipodate, and corticosteroids are known to inhibit conversion of $T_4$ to $T_3$ in peripheral tissues. Routine hydrocortisone administration has been recommended in thyroid storm because of the possibility of coexisting adrenal insufficiency.

## Diabetes Insipidus

Diabetes insipidus (DI) occurs when water reabsorption at the distal renal tubules and collecting ducts is curtailed. In central DI, the mechanism is lack of antidiuretic hormone (ADH) secretion by the posterior pituitary (ADH normally acts on the distal nephron to increase its permeability to water, resulting in reabsorption of water and production of concentrated urine). In nephrogenic DI, the mechanism is intrinsic unresponsiveness of the distal nephron to the action of ADH. Both forms of the disorder result in obligatory urinary dilution leading to polyuria and manifestations of volume depletion, including polydipsia. Other manifestations are a reflection of the underlying cause.

Central DI can be idiopathic or acquired. Acquired forms are caused by head trauma, hypophysectomy, brain tumors, intracranial hemorrhage, anoxic encephalopathy, meningitis, encephalitis, granulomatous diseases of the brain, cerebrovascular aneurysm, and cerebral thromboembolic disease. Nephrogenic DI is associated with polycystic kidney disease, sickle-cell disease, medullary sponge disease, sarcoidosis, hypercalcemia, and prolonged hypokalemia. The drugs lithium, amphotericin B, demeclocycline, and vinblastine can also cause nephrogenic DI.

There are congenital forms of both types of DI.

Although it is not specific for DI, hypernatremia is common in hospitalized patients with DI, particularly in the ICU setting. On the other hand, hypernatremia is usually absent in patients with DI who are not acutely ill. Patients who have an intact thirst mechanism, a normal sensorium, and free access to water will drink sufficient water to prevent the development of hypernatremia, whereas critically ill patients often have blunted thirst perception or an abnormal sensorium, and lack independent access to water. These factors lead to dehydration and hypernatremia even in the absence of DI, with more rapid development of dehydration and hypernatremia in patients with DI.

Polyuria occurs in DI but it is not specific for DI. Other causes of polyuria include excess fluid administration, diuretic use, hyperglycemia, and the polyuria that can occur after acute renal failure or relief of obstructive uropathy. Another cause is loss of the normal solute concentration gradient between the renal medulla and cortex (*ie*, "medullary washout"), which can occur after prolonged polyuria of any cause.

The diagnosis of DI is classically made by depriving the patient of water to provoke mild dehydration and hypernatremia, and then examining the effect on urine output and concentrating ability. However, water deprivation testing should not be utilized in the ICU setting because of the risk of provoking hypovolemia in acutely ill and unstable patients. In addition, most critically ill patients with DI develop hypernatremia spontaneously, making the provocation unnecessary. The diagnosis can be made in these patients simply by demonstrating an inappropriately low urine osmolality in the face of hypernatremia.

Water deprivation results in hypernatremia and elaboration of hyperosmolar urine with a total solute concentration exceeding 800 milliosmols (mosm) per kilogram $H_2O$. In complete central DI, the urine osmolality is $<300$ mosm/kg $H_2O$, whereas in partial central DI, it ranges between 300 and 800 mosm/kg $H_2O$. In the face of water deprivation, plasma ADH concentration is normally $>2$ pg/mL; however, in complete central DI, ADH is undetectable. In partial central DI, ADH levels may reach 1.5 pg/mL. Plasma ADH levels can exceed 5 pg/mL in nephrogenic DI. Discriminating between central and nephrogenic DI can also be accomplished by assaying urine osmolality before and after subcutaneous administration of 1 mg of desmopressin,

an ADH analog. Normally this results in no more than a 5% increase in urine osmolality, but in complete central DI, an increase of ≥ 50% is observed. An intermediate rise (*ie*, between 10 and 50%) is consistent with partial central DI. In nephrogenic DI, no change is expected because the nephron is refractory to both ADH and desmopressin.

Severe polyuria can occur in DI, in some cases exceeding 20 L/day. Careful monitoring of fluid intake and output, frequent measurement of serum sodium concentration, and judicious titration of IV fluids are important to prevent severe volume depletion. IV normal saline solution should be administered to patients who have or develop hypovolemia or signs of circulatory embarrassment, even though the patient is hypernatremic, because it will expand intravascular volume more effectively than hypotonic fluids, and because correction of hypovolemia takes priority over correction of hyperosmolality. Once intravascular volume has been normalized, hypotonic fluids can be substituted, targeting correction of half of the free-water deficit during the first 24 h of therapy, and the remaining deficit over the next 48 h or so. It is imperative to take ongoing urinary fluid losses into account. Overhydration should be avoided because it can induce a water diuresis that increases the risk of medullary washout, potentially leading to sustained polyuria even if the DI is corrected or ADH replacement therapy is given. Frequent monitoring of serum electrolytes is necessary because hypokalemia, hypomagnesemia, and hypophosphatemia can develop rapidly in some polyuric patients.

IV fluid administration and close monitoring may be adequate treatment for mild cases of DI in the ICU. For patients with central DI and marked polyuria, ADH replacement therapy is indicated to limit the polyuria and decrease the risk of dehydration. Aqueous vasopressin has a short duration of action that allows close titration. However, it can have potent vasoconstricting effects, particularly in critically ill patients and those with sepsis. If given subcutaneously or intramuscularly to these patients, it can result in soft-tissue necrosis. It can provoke coronary ischemia in susceptible patients. Desmopressin is a safer alternative because it acts only on $V_2$ receptors in the nephron and not on $V_1$ receptors located on vascular smooth muscle, and therefore it lacks the vasoconstrictive effect of vasopressin. Desmopressin is typically dosed as 2 to 4 μg/d subcutaneously or IV in two divided doses. It is also available in an intranasal formulation, which is typically dosed as 10 to 40 μg/d in two to three divided doses.

As with central DI, the treatment of nephrogenic DI requires the same careful attention to fluid and electrolyte balance. However, ADH analogs are generally of no benefit in nephrogenic DI. Treatment for this variant otherwise consists of stopping any drugs that could be implicated as causative, and controlling polyuria with hydrochlorothiazide. Thiazides limit polyuria in nephrogenic DI by inducing mild volume contraction, stimulating sodium and water reabsorption in the proximal renal tubule and thereby diminishing water delivery to the distal nephron.

## Adrenal Failure

Adrenal failure is the relative or absolute lack of adrenal corticosteroid production due to primary adrenal gland failure or secondary to insufficient adrenocorticotropic hormone elaboration by the anterior pituitary. Primary adrenal failure most commonly arises from autoimmune destruction of the adrenal glands, but it is also caused by various infiltrative diseases involving the glands (*eg*, sarcoidosis, amyloidosis, malignancy), including infectious diseases (*eg*, meningococcemia, pseudomonal infection, tuberculosis, or viral infections). An association between adrenal insufficiency and AIDS has been documented. Other causes include drug-induced adrenal impairment (*eg*, etomidate, ketoconazole) and hemorrhage or infarction affecting the glands. The most common cause of secondary failure is sudden withdrawal of chronic corticosteroid therapy. Other secondary causes include head trauma, brain tumors, stroke, pituitary surgery, infiltrative brain diseases, anoxic encephalopathy, and cranial radiation therapy.

Subjective manifestations of the disorder include anorexia, fatigue, nausea, vomiting, abdominal pain, diarrhea, myalgia, arthralgia, orthostatic lightheadedness, and salt craving. Physical examination may reveal orthostatic or frank hypotension, tachycardia, weight loss, abdominal tenderness, confusion, and hyper- or hypopigmented skin. An intercurrent illness or surgery can provoke adrenal crisis in patients with otherwise compensated adrenal insufficiency.

A variety of nonspecific laboratory abnormalities can be seen in adrenal insufficiency, including hyponatremia, hyperkalemia, hypercalcemia, hypoglycemia, prerenal azotemia, and a normal-an-

ion-gap metabolic acidosis. Anemia, neutropenia, lymphocytosis, and eosinophilia can also be seen. Plasma cortisol levels < 15 μg/dL are clearly abnormal in a severely stressed patient. In the acute setting, the diagnosis is conventionally confirmed by stimulation testing using synthetic adrenocorticotropic hormone. Blood is first sampled for baseline plasma cortisol assay, and then resampled 30 and 60 min after IV administration of 250 μg of cosyntropin. If warranted, treatment can be started after the poststimulation samples are obtained without waiting for the assay results. Starting treatment with hydrocortisone before obtaining the poststimulation blood samples will result in falsely elevated plasma cortisol results. In highly unstable patients in whom a 1-h delay in therapy could be compromising, treatment can be initiated with one dose of dexamethasone at the time stimulation testing is begun. Unlike hydrocortisone, dexamethasone does not cross-react with laboratory cortisol assays. Adrenal failure is likely if the highest poststimulation cortisol level is < 15 μg/dL. Levels > 18 μg/dL are conventionally accepted as excluding most cases of adrenal insufficiency, but levels up to 25 μg/dL may represent an inadequate response in patients who are profoundly stressed.

Patients with adrenal crisis are fluid-resuscitated and admitted to the ICU. Rapid initiation of fluid resuscitation is critical because most patients are severely volume-depleted. The preferred IV solution is 5% dextrose in isotonic saline solution, which expands intravascular volume and corrects or prevents hypoglycemia. The definitive treatment for adrenal crisis is IV hydrocortisone. The initial dose is 200 mg, followed by 300 mg/d given as either 100 mg IV every 8 h or 12.5 mg/h by continuous IV infusion.

## Pheochromocytoma

Pheochromocytoma is an uncommon disorder caused by a usually benign tumor arising from the adrenal medulla and consisting of catecholamine-producing chromaffin cells. The tumor less commonly arises from extra-adrenal sites, particularly the organ of Zuckerkandl adjacent to the aortic bifurcation. The disorder is also associated with von Recklinghausen's disease, as well as with types IIa and IIb multiple endocrine neoplasia syndrome. Manifestations are usually paroxysmal, typically lasting about 30 min, and most commonly consist of anxiety, headache, cutaneous flushing, tremors, and palpitations associated with hypertension. In some cases, the hypertension is severe enough to be classified as a hypertensive emergency; *ie*, it can be accompanied by end-organ derangements such as acute left ventricular dysfunction and pulmonary edema. Diaphoresis, chest pain, nausea, vomiting, abdominal pain, tachydysrhythmias, and orthostatic hypo- or hypertension can also occur. Sustained hypertension occurs in some cases.

The manifestations of pheochromocytoma are the result of acute release of excessive amounts of catecholamines. Thus, the diagnosis is made by demonstrating increased production or circulating levels of these hormones. This is conventionally performed by assaying 24-h urinary excretion of the catecholamines epinephrine and norepinephrine, as well as their metabolic byproducts, the metanephrines and vanillylmandelic acid, and by assaying plasma catecholamine levels. However, the finding of normal plasma catecholamines and urinary metanephrines levels does not reliably exclude pheochromocytoma. More recent investigations have shown that the single best biochemical screening test is the plasma metanephrine assay. Normal plasma metanephrine results effectively exclude the diagnosis of pheochromocytoma.

In critically ill patients in whom pheochromocytoma is suspected, definitive diagnostic testing is best accomplished after the patient has been stabilized and no longer needs intensive care. Definitive diagnostic testing is problematic in the ICU setting because many acute physiologic derangements that are common among critically ill patients interfere with the relevant biochemical assays. Examples of these physiologic derangements include congestive heart failure, myocardial infarction, respiratory failure, renal failure, sepsis, hypoglycemia, hypothyroidism, anemia, peptic ulcer disease, neurologic abnormalities, dehydration, and a variety of drugs (*eg*, catecholamines, adrenergic blocking agents, vasodilators, and diuretics). Thus, biochemical confirmation is best deferred until after the patient is stabilized and transferred out of the ICU. After the diagnosis of pheochromocytoma has been biochemically confirmed, the tumor is then localized using noninvasive imaging studies. These can include MRI, CT, and radiolabeled *m*-iodobenzylguanidine scintigraphy.

Surgical removal of the tumor is usually curative, but it entails considerable risk because of the

prospect of provoking hypertensive crisis. To minimize this complication, surgery is delayed until the patient is stabilized, blood pressure is controlled, volume status is optimized, and any accompanying acute medical conditions are treated. In an acute episode of hypertensive crisis, the conventional pharmacologic agent of choice is phentolamine mesylate. This drug is a short-acting a-adrenergic blocking agent that is initiated as sequential IV bolus doses (typically 2 to 5 mg) at intervals of 5 min or more until the desired blood pressure is reached. An alternative agent is sodium nitroprusside. Neither of these agents can be given chronically. For chronic α-adrenergic blockade, phenoxybenzamine can be used. β-Adrenergic blocking drugs are usually not necessary, but may be used adjunctively to control tachydysrhythmias. However, β-blockers are contraindicated in patients who have not already received adequate α-adrenergic blockade because unopposed α-adrenergic stimulation can precipitate a hypertensive emergency.

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# Notes