Hypothyroidism
Causes, Killers, and Life-Saving Treatments

Sarah B. Dubbs, MDa,*, Ryan Spangler, MDb

KEYWORDS
• Thyroid • Hypothyroidism • Myxedema • Levothyroxine
• Thyroid-stimulating hormone • Coma

KEY POINTS
• Iodine deficiency is the most common cause of hypothyroidism worldwide.
• Hashimoto thyroiditis is the most common cause in the United States.
• Hypothyroidism is more common in elderly, white women.

INTRODUCTION
Hypothyroidism is one of the most frequently encountered endocrinology disorders. Although most of the time this disease does not require immediate emergency evaluation and treatment, the emergency department is often the first point of care for many patients. This truth makes it essential that emergency physicians have an understanding of basic thyroid function, pathophysiology of thyroid-related disorders, and treatment methodology.

The overarching disease of hypothyroidism can have multiple causes and several presentations (thus its reputation as a mimic, but treatment is rather straightforward. The mainstay of treatment is thyroid hormone supplementation. Outpatient follow-up and treatment are necessary for complete and accurate treatment of these patients, but early intervention and referral from the emergency department can be easy to initiate, and in some severe cases lifesaving.

Myxedema coma, otherwise known simply as myxedema, is the rare but deadly manifestation of severe hypothyroidism. The extremely high mortality rate (historically as high as 80%, but still up to 60%) associated with myxedema makes it necessary for early recognition and treatment by emergency physicians.1 Although it is not commonly encountered, a healthy degree of suspicion of the “worst first” mentality must be maintained to prevent poor outcomes in these patients.

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In a study by Chen and colleagues, it was noted that in a series of patients admitted to the hospital with overt hypothyroidism only 21% was diagnosed on admission. Perhaps more concerning was that 50% of patients in the study ultimately diagnosed with myxedema went undiagnosed. This study indicates that hypothyroid crisis is not well recognized by emergency physicians. In fact, it can be argued that the main job of the emergency physician is to identify thyroid disorders whenever possible. Higher-risk populations include elderly patients and those with cardiovascular and neuropsychiatric illness because thyroid function can be closely tied to these entities.

EPIDEMIOLOGY

In the developed world, thyroid disease is often found to be associated with autoimmune disease and is approximately 5 to 10 times more common in women than in men. In Europe, studies have shown that the incidence of hypothyroidism may also be increasing, although it is unclear if this is from increased awareness or an overall increase in autoimmune disorders. The National Health and Nutrition Examination Survey III found subclinical hypothyroidism to be present in 4.3% and overt hypothyroidism in 0.3% of the US population. Other studies indicate that up to 15% of older women may have subclinical hypothyroidism. Higher thyroid-stimulating hormone (TSH) and antithyroid antibodies are found in women, the elderly, whites, and Mexicans (compared with African Americans). A trend has also been found in increased prevalence of autoimmune disorders and subsequently hypothyroidism. Much of these studies focused on chart review and treatment of hypothyroidism, suggesting that an even higher number of subclinical and unidentified patients may be present.

Hypothyroidism can be classified into three categories: (1) primary (thyroid gland), (2) secondary (pituitary gland), or (3) tertiary (hypothalamus). Causes of primary hypothyroidism vary by location, but it is the most common type of hypothyroidism. Worldwide, iodine deficiency is the most common cause. However, in the United States and other iodine-replete areas, chronic thyroiditis, also known as Hashimoto thyroiditis, is the most common cause. Central hypothyroidism has even lower rates, and is thought to be approximately 1 in every 1000 cases of hypothyroidism, most frequently caused by pituitary adenoma. It is a common side effect of treatment of several other conditions and can be seen in 20% to 50% of patients irradiated for nasopharyngeal and paranasal sinus tumors. However, the affects tend to show up several years later rather than immediately. Sheehan syndrome and traumatic brain injury can also cause central hypothyroidism through direct or indirect mechanisms. Table 1 summarizes the types and etiologies of hypothyroidism.

PATHOPHYSIOLOGY

Overall, the production and regulation of thyroid hormones is a relatively simple feedback system. The biochemical synthesis at a cellular and molecular level is somewhat more complex and not as immediately relevant to an emergency physician’s goals. The process begins in the hypothalamus with the production of thyrotropin-releasing hormone (TRH). TRH then stimulates the anterior pituitary to secrete TSH. After TSH is released, this stimulates the thyroid to release synthesizes, and secrete trioiodothyronine (T3) and thyroxine (T4) from the thyroid itself. T3 and T4 both feed back to the hypothalamus and the pituitary to inhibit TRH and TSH. This feedback mechanism allows for very tight control of TSH levels in the serum. Fig. 1 shows the relationships between the hormones.

Centrally, TRH and TSH are secreted according to a circadian rhythm, with a nocturnal surge in the early nighttime hours. This can be affected by derangements
in gonadal hormones, leptin, and other feeding- and sleep-related hormones, which can affect hypothalamic-pituitary feedback. This results in the condition of central hypothyroidism, which can be difficult to detect, because TSH can be normal, or even slightly elevated in some patients. This is because it is not always a matter of decreased quantity, but also secretion of dysfunctional TSH.4

Most T4 produced is stored in the bloodstream and body attached to thyroxine-binding globulin (TBG), albumin, transthyretin (prealbumin), and other lipoproteins. While attached to these molecules, the T4 is not biochemically active but provides

<table>
<thead>
<tr>
<th>Causes of hypothyroidism</th>
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<tr>
<td><strong>Primary (thyroid gland dysfunction)</strong></td>
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<tr>
<td>Iodine deficiency</td>
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<td>Autoimmune thyroiditis</td>
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<tr>
<td>• Hashimoto thyroiditis</td>
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<td>Medication-induced (see Table 2)</td>
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<td>Congenital hypothyroidism</td>
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<td>• Thyroid aplasia or hypoplasia</td>
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<td>• Defective synthesis of thyroid hormones</td>
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<td>• Thyroidectomy</td>
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<td>• Cancer treatments</td>
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| **Central** |
| **Secondary (pituitary dysfunction)/tertiary (hypothalamic dysfunction)** |
| Pituitary adenoma |
| Craniopharyngioma |
| Traumatic brain injury |
| Sheehan syndrome |
| Iron overload |
| Sarcoidosis |
| Syphilis |
| Tuberculosis |


Fig. 1. Thyroid feedback loop.
a reservoir of stored T4, capable of maintaining function for days even if thyroid function were to cease. The protein binding further provides buffer against overactivity of thyroid hormones.\textsuperscript{11}

Although T3 is also produced in the thyroid, only a small percentage of T3 is actually made in the thyroid itself. About 80\% is produced in extrathyroidal tissues by deiodination of T4. The primary sites of conversion occur in the liver and the kidneys, but most tissues are capable of performing this. T3 is also bound by TBG, albumin, and transthyretnin, ready for immediate use and storage as needed.\textsuperscript{11}

When T4 is released and peripherally converted into the bioactive T3, the overall effect is to increase metabolism. There is a direct action of increased peripheral oxygen consumption and thermogenesis. Also, T3 has direct cardiovascular effects to increase ionotropy and chronotropy. Increased cardiac output is somewhat of an indirect result. In hypothyroidism, the end result is the opposite. The exaggerated responses of hypothermia, bradycardia, and hypotension seen in myxedema are an example of this.\textsuperscript{1}

Primary hypothyroidism, as seen in Hashimoto thyroiditis, is the result of cell and antibody-mediated destruction of thyroid tissue. Antibodies to thyroperoxidase, thyroglobulin, TSH receptors, and TSH blocking antibodies can all contribute. Because the thyroid needs iodine to build T4 and T3, iodine deficiency causes thyroid deficiency. A transient hypothyroidism can be seen with iodine excess, and is known as Wolff-Chaikoff effect. Frequently, medications can cause hypothyroidism. Frequently cited medications are amiodarone and lithium, with incidence of hypothyroidism of 14\% to 18\% and 10\%, respectively. Overuse of antihyperthyroid medications propothiouracil and methimazole can lead to hypothyroidism. Other common causes are thyroidectomy or radioactive iodine treatment (see Table 1; Table 2).\textsuperscript{7}

**EMERGENCY DEPARTMENT PRESENTATION**

The hypothyroid patient most frequently presents to the emergency department with multiple, vague complaints of insidious onset, and has a nonspecific physical examination. These circumstances can make the diagnosis elusive even to the attentive physician. The presenting symptoms and signs often vary with age and gender, and the severity of these clinical features varies greatly. Despite the difficulty of diagnosis, routine screening is not recommended in the emergency department because of the effects of nonthyroidal illnesses on thyroid function tests, and national guidelines vary on how best to approach screening in the United States.\textsuperscript{4,12}

**CLINICAL FEATURES**

The hypothyroid state’s multitude of manifestations is a result of every organ system relying on thyroid hormone for normal function. The insufficient level of the hormone causes a spectrum of depression in the function of these systems. See Table 3 for

<table>
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<th>Table 2 Medication effects on native thyroid function</th>
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<tr>
<td>Decreased TSH secretion</td>
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<td>Dopamine, glucocorticoids, octreotide, metformin, opiates</td>
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<tr>
<td>Decreased thyroid hormone secretion</td>
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<tr>
<td>Lithium, iodine/iodinated contrast, amiodarone</td>
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<tr>
<td>Increased thyroid hormone metabolism</td>
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<tr>
<td>Phenobarbital, rifampin, phenytoin, carbamazepine</td>
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a summary of the signs and symptoms of hypothyroidism. **Box 1** lists some examples of common presentations of hypothyroidism. The most extreme end of this spectrum is myxedema coma. Although it is rare, myxedema coma is life-threatening and must be recognized and treated emergently.

**Symptoms**

Symptoms of progressive fatigue and malaise are almost always present with hypothyroidism. Weight gain is another frequent and typical symptom, caused by decreased metabolic rate and oxygen consumption. Other common symptoms include cold intolerance, voice changes, dry skin, hair loss, constipation, irregular menses, difficulty concentrating, memory problems, and depression. Patients also report myalgias, arthralgias, and paresthesias. Some may even present with sexual dysfunction or impaired fertility. A child may manifest hypothyroidism with impaired growth or delayed puberty.

**Box 1**

**Common patient presentations associated with hypothyroidism**

- Elderly patients
  - With new psychiatric complaints
  - With cramping, constipation
- Patient with combination of weakness, weight gain, and/or hyponatremia
- History of depression, weight gain, hoarseness
- Young “anemic” woman with frequent episodes of heavy vaginal bleeding
- Patient with history of hypertension who develop sudden hypotensive episodes, even after reduction of medication
- Refractory hypotension not responsive to routine treatments

**Physical Examination Findings and Signs**

**Head and neck**
The hypothyroid patient presents with coarse facial features, dry skin, and pallor. His or her hair may be coarse as well, with visible thinning. Facial edema, especially periorbital, can be caused by hypothyroidism. Some patients have macroglossia, which can affect their speech, in addition to a hoarse, deep voice. Finally, goiter, if present, is a fairly obvious and sensitive sign of thyroid dysfunction.

**Cardiovascular**
Vital signs reveal bradycardia, diastolic hypertension, and in severe cases hypotension as a result of depressed cardiac output. Diastolic hypertension is attributable to increased systemic vascular resistance. Overall cardiac output is decreased, secondary to the slower heart rate and decreased contractility.\(^{13,14}\)

Signs of pericardial effusion, such as muffled heart sounds, rubs, and jugular venous distention, pulsus paradoxus may be present on physical examination. Bedside ultrasound examination quickly confirms the presence or absence of effusion and tamponade physiology.

**Respiratory**
Breath sounds may be decreased or abnormal because of hypoventilation and/or pleural effusions.

**Abdominal**
As with the cardiovascular and respiratory examinations, the abdominal examination may reveal effusion in the form of ascites. Abdominal ascites is relatively rare, occurring in approximately 4% of patients with thyroid disease.\(^{15}\) Hypothyroidism may also cause constipation and ileus. Thus, bowel sounds may be hypoactive on auscultation and the patient may have mild, diffuse tenderness on palpation.

**Dermatologic**
Hypothyroid patients have fluffy, nonpitting edema, also known as myxedema. Myxedema derives from the Greek word for mucous, describing the glycosaminoglycans deposition that causes this distinctive edema.\(^{16}\)

The skin may also take on a pallor appearance caused by hypothyroid-induced anemia. The skin is dry and coarse, nails brittle as well, and hair is coarse with areas of alopecia. There have been some reports of psoriasiform lesions related to severe hypothyroidism.\(^{17}\)

**Neurologic**
Many of the neurologic findings associated with hypothyroidism center around cognitive functions, such as orientation, memory, and higher-order thinking.

Patients may also display muscle hypertrophy, proximal muscle weakness, and easy fatigability of strength.\(^{18}\) Nerve entrapment syndromes, such as carpal tunnel syndrome, can occur as a result of edema. This finding is revealed on examination when pain and paresthesias are reproduced with maneuvers, such as with the Tinel test and Phalen sign.\(^{19}\) A delayed relaxation phase in deep tendon reflexes (also known as the myxedema reflex or Woltman sign) has also been reported frequently in the literature.\(^{20,21}\)

**Psychiatric**
Hypothyroid patients may suffer from depression, reflecting in the physical examination as a slow, flat affect. Some may even display signs of psychosis by responding to internal stimuli or expressing delusional thoughts, a state often referred to as...
“myxedema madness.” In general, laboratory evaluation in psychiatric patients is guided by the history and physical examination. However, with the possibility of subclinical hypothyroidism and the subtlety of symptoms, a screening TSH should be considered in this patient population. See Box 1 for several examples of clinical scenarios that should trigger a hypothyroidism work-up.

LABORATORY FINDINGS

Diagnosis of Hypothyroidism

This difficulty in diagnosing hypothyroidism does not lie in the laboratory studies themselves; it lies in the shrewdness of the physician to include it on the list of differential diagnoses despite the vague and nebulous symptoms and signs with which patients present.

The first-line diagnostic tool to diagnose hypothyroidism in the emergency department is serum thyrotropin testing. Most facilities are able to perform an ultrasensitive monoclonal antibody test for TSH. These have been shown to be quick, reliable, and reproducible. An abnormal TSH should lead to further testing of the active thyroid hormones T4 and T3. Free thyroxine levels can be measured in two ways. Total thyroxine refers to the combined amount of protein-bound and nonbound hormone. The free T4 level (FT4) refers only to the unbound form, and as the metabolically active moiety is preferred over the total thyroxine level.

High TSH

An elevated TSH indicates some level of hypothyroidism, determined by the level of circulating T4 and T3. When the FT4 level is low, the disease process is classified as primary hypothyroidism.

When the FT4 and T3 levels are normal in the setting of low TSH, the disease is classified as subclinical hypothyroidism. Subclinical hypothyroidism has multiple etiologies. It can stem from an incomplete autoimmune process that will eventually lead to total thyroid failure. Inadequate dosing or absorption in patients who are on thyroxine replacement medications may also be the cause of these abnormal laboratory values; however, it must be noted that the TSH can be persistently elevated for up to 6 weeks after initiating thyroxine therapy. Other times, it can be part of the normal recovery phase in nonthyroidal illness as the body tries to compensate for low thyroid hormone synthesis during the illness. Finally, the TSH can be elevated with normal T4 and T3 levels during acute psychiatric illness and with abuse of amphetamines.

Elevated TSH with elevated FT4 and T3 points to a primary TSH problem, usually a TSH-secreting adenoma in the pituitary gland causing hyperthyroidism.

Normal TSH

A normal TSH level is a fairly reliable indicator of normal thyroid function. Therefore, other nonthyroidal etiologies must be investigated for the patient’s symptoms when TSH levels are normal. In the rare case of central hypothyroidism, TSH levels can be inappropriately normal, accompanied by low levels of T4.

Low TSH

Low TSH is almost always associated with hyperthyroidism. In the setting of hypothyroid symptoms, an abnormally low level of TSH can result from overall reduced TSH production, called secondary hypothyroidism. In patients who are on thyroxine therapy for hypothyroidism, it can be caused by a dose that is too high. Finally, certain
medications, such as dopamine and corticosteroids, have been shown to depress TSH levels.27

Associated Laboratory Findings

The global effects of thyroid dysfunction cause a wide variety of other laboratory abnormalities in hypothyroid patients. Anemia is frequently encountered in association with hypothyroidism. Depressed red blood cell production causes a normochromic, normocytic anemia. If significant menorrhagia is playing a role, the patient may display an iron-deficiency anemia with a hypochromic, microcytic picture. Many hypothyroid patients also have an autoimmune-related pernicious anemia, resulting in a macrocytic anemia.

Severely hypothyroid patients may also develop coagulopathy, with abnormal clotting times and international normalized ratio. Platelet counts may be normal despite abnormal function.

Renal free water secretion is reduced in hypothyroidism, causing hyponatremia.28,29 Renal insufficiency is also present in severe hypothyroidism, reflected in elevated brain urea natriuretic peptide and creatinine levels.

Decreased gluconeogenesis and reduced insulin clearance leads to hypoglycemia. This process may be solely caused by the hypothyroid state; however, it may be attributed to a more serious process, adrenal insufficiency. Hypoglycemia (and the concurrent hypotension and other symptoms and signs) related to adrenal insufficiency must be identified as such to be treated appropriately.

Increased muscle membrane permeability allows muscle enzymes to leak into the serum. Creatine kinase levels are elevated to reflect this process.

Decreased respiratory drive is reflected on an arterial blood gas analysis as hypercapnia and hypoxemia with respiratory acidosis.

Other abnormal laboratory values associated with hypothyroidism are elevated transaminases, lactate, and cholesterol. When lumbar puncture is performed as part of the diagnostic process, elevated opening pressure and cerebrospinal fluid protein levels can be present with profound hypothyroidism.30

TREATMENT

Hypothyroidism

Although there are many causes of hypothyroidism, the main goal of treatment is to replace the thyroid hormones that are lacking, T3 and T4. Generally, this involves a synthetic compound levothyroxine. Levothyroxine is identical to T4, and is converted to T3 in extrathyroidal tissue the same way endogenously produced T4 is converted. Levothyroxine has a half-life of 7 days so it reaches a steady state rapidly when started on 1.6 μg/kg/day dosing as recommended. Special note should be taken for patients older than age 60 and those with ischemic cardiovascular disease, and should start at a lower dose. There is some discussion of combination therapy with T4 and T3, but there has been no demonstrated benefit over simple levothyroxine therapy.6

This one medication approach seems very simple and straightforward; however, different brand preparations of this medication tend to vary slightly in available drug concentrations and switching manufacturers can result in inadequate or overtreatment based on prior regimens. In addition, in one study 40% to 48% of patients on levothyroxine were either overtreated or undertreated.6 For patients with a known history of hypothyroidism presenting with worsening symptoms, a thorough medication history should be obtained for possible recent pharmacy changes.23,31
The American Association of Clinical Endocrinologists suggests a mean dose of 1.6 μg/kg of ideal body weight. However, each individual may be different depending on the degree of thyroid dysfunction, concurrent medications, and general responsiveness. Titration of medication is based on normalization of TSH levels, and should be first analyzed at approximately 6 weeks, with slow titration of 12.5 to 25 μg adjustments and repeat TSH every 1 to 2 weeks. Obviously 6-week follow-up in the emergency department is not a feasible plan for continued care, but it may be important to take into account for patients recently started on levothyroxine with possible overtreatment or undertreatment.

Patients starting levothyroxine or being prescribed new medications need to be aware of possible drug interactions and their effect on levothyroxine dosing. Many drugs can affect levothyroxine at various aspects of its therapeutic course. Common drugs, such as aluminum hydroxide, ferrous sulfate, and calcium, can potentially affect absorption of levothyroxine in the gastrointestinal tract. Other drugs, such as rifampin and sertraline, can affect metabolism and require a higher dosing. Anticonvulsants, birth control pills, and other protein-bound medications can affect the binding of levothyroxine to TBG, albumin, and other proteins that can alter the amount of active drug in the bloodstream. Table 4 summarizes the effects that some common medications have on levothyroxine.

**Subclinical Hypothyroidism**

Although in the emergency department it is rare to order screening tests, the chance of identifying subclinical hypothyroidism may still occur (elevated TSH, normal T3/T4). Treatment of subclinical hypothyroidism is controversial, because with normal T4 levels there are generally no symptoms as this is the bioactive compound. The American Association of Clinical Endocrinologists recommends treatment of TSH levels greater than 10, with presence of goiter, or antithyroid peroxidase antibodies because these patients have been shown to be the most likely to progress to true hypothyroidism. It is recommended that a lower dose be used to treat subclinical levels, starting at 35 to 50 μg daily, with standard follow-up.

**Pregnancy**

Treatment of hypothyroidism in pregnant patients is of particular importance, and TSH screening is recommended as a routine prepregnancy and prenatal work-up. In pregnancy some women may develop thyroid antibodies that can increase the chance for spontaneous abortion regardless of treatment. Untreated hypothyroidism, even mild, in pregnant women increases the risk of several complications including preeclampsia, anemia, postpartum hemorrhage, fetal death, low birth weight, and others. Studies do suggest that cognitive dysfunction of offspring can be prevented with treatment. Levothyroxine is pregnancy class A (also safe in lactation) and it is recommended to initiate, or continue appropriate treatment in pregnant patients. It is also important to note that in general the course of a patient's hypothyroidism during pregnancy is unpredictable. In those with chronic hypothyroidism, some improve their symptoms and some get worse.

**DISPOSITION**

In general, the disposition status of the hypothyroid patient presenting to the emergency department is straightforward. Many of these patients can be discharged home, with the caveat that follow-up is required, particularly if long-term levothyroxine therapy has been started. The recommended follow-up window is 6 weeks after
initiation to reevaluate TSH levels. Some patients exhibiting severe hypothyroidism may require admission to the hospital if it is believed by the physician that the patient is unsafe to be discharged home to reliably follow-up and take medication. If the patient’s disease is thought to be medication-induced, the risks and benefits of continuing or discontinuing the offending medication must be carefully considered. As always, the patient’s mental status and psychological status is an important factor in the disposition decision.

**MYXEDEMA COMA**

Myxedema coma, or simply myxedema, is the most severe manifestation of hypothyroidism with a mortality rate of 30% to 60%, a decrease from almost 80% in the past. Its incidence is rare, and exact numbers are not known based on difficulty of specific

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<th>Mechanism of Effect</th>
<th>Agents</th>
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<tbody>
<tr>
<td>Interference with absorption</td>
<td>Bile acid sequestrants, Sucralafate, Cationexchange resins (Kayexelate), Oral bisphosphonates, Proton pump inhibitors, Raloxifene, Ferrous sulfate, Phosphate binders, Calcium, Chromium picolinate, Charcoal, Orlistat, Ciprofloxacin, H₂ receptor antagonists, Grapefruit juice, espresso coffee, high fiber, soy products</td>
</tr>
<tr>
<td>Increased clearance</td>
<td>Phenobarbitol, Primidone, Phenytoin, Carbamazepine, Oxacarbazepine, Rifampin, Growth hormone, Sertraline, Tyrosine kinase inhibitors, Quetiapine, Stavudine, Nevirapine</td>
</tr>
<tr>
<td>Peripheral metabolism</td>
<td>Glucocorticoids, Amiodarone, Propylthiouracil, ß-Blockers, Iodinated contrast, Interleukin-6, Clomipramine</td>
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Agents that are frequently used in the emergency department are shown in boldface.

definition and possible underrecognition. A frequently cited contributory clue is change in weather, with up to 90% of cases occurring during winter months. It is theorized that this is caused by altered temperature regulation in the severely hypothyroid patient. Myxedema coma is more common among older women and almost never occurs in individuals younger than age 60. Also, there are little data on incidence of myxedema in the equatorial regions, which may be the result of underreporting, but it is hypothesized that the lack of seasonality may play a role.34,35

The cardinal signs of myxedema coma are depressed mental status and hypothermia. If a history is available, the patient or family may report the signs and symptoms of undiagnosed hypothyroidism, as described previously; or, the patient may even already carry the diagnosis. The cardiovascular, respiratory, gastrointestinal, renal, and hematologic manifestations of hypothyroidism are at the severe end of the spectrum. Severe hypotension and shock may be the result of depressed cardiac contractility, tamponade, or bradydysrhythmias. Myxedema has even been reported to cause prolongation of the Q-T interval, predisposing patients to torsades de pointes.36 Hypoventilation can be so profound that acid-base status is disturbed. Patients may have associated gastrointestinal bleeding caused by myxedema-associated coagulopathy.37 The physical findings associated with myxedema coma are, again, on the extreme end of the hypothyroid symptoms described previously: dough-like nonpitting edema, dry and brittle skin and hair, delayed reflexes, and of course altered sensorium. Some of the most common precipitating events of myxedema coma are listed in Box 2.

Laboratory testing should not only focus on diagnosing the hypothyroidism with TSH and thyroxine levels; it should include investigation into the wide differential of altered mental status. Furthermore, a wide net should be cast to identify possible precipitating and aggravating factors in the myxedema state. Common precipitators of myxedema coma are infections, strokes, congestive heart failure, exposure to low ambient temperature, trauma, gastrointestinal bleeding, and metabolic disturbances. Medications, such as anesthetics, sedatives, narcotics, amiodarone, lithium, and changes to levothyroxine-replacement therapy, are also known to precipitate myxedema coma.38

Treatment of patients with myxedema coma can vary among practitioners and there is not a consistent or proved method of treatment. Largely because of the rarity of the

<table>
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<td><strong>Precipitating events causing myxedema coma</strong></td>
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<tr>
<td>Infection or sepsis</td>
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<tr>
<td>Gastrointestinal hemorrhage</td>
</tr>
<tr>
<td>Hypoglycemia</td>
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<tr>
<td>Hypothermia</td>
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<tr>
<td>CO₂ retention</td>
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<td>Burns or trauma</td>
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<tr>
<td>Medications</td>
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<tr>
<td>Stroke</td>
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illness, there are no large studies, and certainly no randomized controlled trials investigating this treatment. Controversy exists in treatment with T4 versus T3, intravenous (IV) versus oral based on bioavailability of each drug. However, there is some literature present noting that using T3 can result in increased mortality, although the cause is not clear and most studies are small case reports. Most sources, because of this, recommend treatment of IV or oral levothyroxine, because evidence does not seem to indicate significant difference between the two.39

General recommendations suggest the use of 100 to 500 μg of IV levothyroxine. Dosing tends to vary based on different studies, some recommending lower dosing for older, frailer patients, especially those with cardiovascular disease. Other sources recommend a size-base dosing calculating total body distribution of levothyroxine and administering a distribution size dose of 6 μg/dL (70-kg man, 7-L distribution area, 420–μg dose of levothyroxine). This initial loading dose should be followed by 50 to 100 μg of IV levothyroxine daily until the patient is able to be converted to an oral formulation.40

Those in favor of using T3 suggest a loading dose of 10 to 20 μg followed by 10 μg every 4 hours for 24 hours, then 10 μg every 6 hours for 1 to 2 days until the patient can continue with oral medication. An eight-patient case series by Yamamoto and co-workers41 suggests that although dosing ranges are large, overdosing should be avoided because doses of levothyroxine greater than 500 μg and T3 greater than 75 μg were both associated with increased mortality. Combination therapy of levothyroxine and T3 may be useful, with a loading dose of 4 μg/kg ideal body weight of levothyroxine, followed by 100 μg in 24 hours, then 50 μg daily, IV or orally. T3 would be started simultaneously with doses of 10 μg every 8 to 12 hours until the patient can take oral maintenance doses of levothyroxine.41

Although the initial loading dose and exact medication to be used for thyroid replacement is not well established, the use of IV hydrocortisone is consistently recommended throughout the literature. Because of the potential of secondary hypothyroidism and concurrent hypopituitarism, there is strong potential for associated adrenal insufficiency. A dose of 100 mg every 8 hours IV hydrocortisone is suggested to be continued until adrenal insufficiency is ruled out. Some sources suggest a random cortisol level be drawn before treatment to assess adrenal function, and if necessary a corticotropin stimulation test can be performed later. Most recommend discontinuing the hydrocortisone without taper needed once adrenal insufficiency is ruled out.33

Further treatment of myxedema coma is necessary to treat the precipitating cause. This can be environmental, infectious, medication induced, or otherwise. Many recommendations suggest immediate septic work-up up including broad-spectrum antibiotics after cultures have been sent. Lumbar puncture is also likely to be necessary in these patients to rule out meningitis as a cause of altered mental status and hypothermia. Special thought needs to be given to finding the precipitating event because this in and of itself can potentially be life threatening.

Critical care treatment of patients with myxedema coma is often necessary because of the severity of illness. Intubation in these patients may be necessary, and has the potential of being a difficult procedure. Patients with hypothyroidism can often be overweight, coupled with the potential for airway myxedema, making airway management difficult. The patients may also have already developed hypercapnia caused by hypoventilatory effects of their illness, have reduced lung volumes, and in severe cases, pleural and pericardial effusions, which can lead to cardiovascular and respiratory collapse if not managed appropriately.42 Furthermore, external airway anatomy, such as a large goiter, may cause tracheal deviation, and certainly obstruct normal
cervical anatomy needed to easily perform an emergent cricothyrotomy if necessary. These recommendations are summarized in Box 3.

Patients with suspected myxedema coma by definition have altered mental status and should always be admitted to the hospital with strong consideration for an intensive care unit level admission. These patients can present very sick because their inherent compensatory mechanisms are dysfunctional due to the severe hypothyroid state. In addition, the precipitating factor for their myxedema can be severe, such as sepsis, myocardial infarction, or stroke. Mortality for myxedema tends to increase in hypothermic patients based on the severity of their hypothermia.43 A study by Dutta and colleagues44 also noted that patients that were noncompliant with previously prescribed thyroid-replacement medication tended to have higher mortality than those with first-time diagnoses. This study also found that an elevated sequential organ failure assessment (SOFA) score was shown to predict higher mortality.44

**SUMMARY**

Hypothyroidism, one of the most common endocrine disorders encountered, is likely to be directly or indirectly related to frequent patient visits to primary care physicians. 

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**Box 3**

**Summary of recommendations for patients with suspected myxedema coma**

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
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<tbody>
<tr>
<td>Airway control</td>
</tr>
<tr>
<td>Fluid resuscitation</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
</tr>
<tr>
<td>Basic metabolic panel</td>
</tr>
<tr>
<td>TSH and free T4 levels</td>
</tr>
<tr>
<td>Blood/urine/sputum cultures</td>
</tr>
<tr>
<td>Lumbar puncture</td>
</tr>
<tr>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Chest radiograph</td>
</tr>
<tr>
<td>Head computed tomography</td>
</tr>
<tr>
<td>Echocardiogram</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levothyroxine, 100–500 µg IV loading; then 50–100 µg IV daily (until patient can take oral medication)</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>Triiodothyronine, 10–20 µg loading; then 10 µg q 4 hours for 24 hours, then 10 µg q 6 hours for 1–2 days until the patient can take oral medication and</td>
</tr>
<tr>
<td>Hydrocortisone, 100 mg IV q 8 hours</td>
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<tr>
<td>Broad-spectrum antibiotics</td>
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<tr>
<td>Vasopressors as needed</td>
</tr>
</tbody>
</table>
and emergency physicians. The clinical signs and symptoms can be broad, nonspecific, and subtle at times. Myxedema coma can be equally ambiguous but much more deadly. Early suspicion, recognition, and treatment can improve patient outcomes for any range of the hypothyroid disorders.

REFERENCES