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Identifying And Treating Thyroid Storm And Myxedema Coma In The Emergency Department

Case #1: A 65-year-old woman is brought to the emergency department (ED) with altered level of consciousness and hypotension. Her neighbor found her on the kitchen floor. He checked on her because he hadn't seen her for 3 days. The patient is unable to provide any verbal history. Her vital signs are respiratory rate of 10 respirations per min, blood pressure of 90/60 mm Hg, temperature 35°C (95°F), and heart rate 50 beats per min. On physical examination, you see an obtunded woman in no apparent distress. You note a well-healed surgical scar on her anterior neck and that her left leg is shortened and externally rotated. The differential diagnosis of the presentation is long and complex, and you keep wondering if that scar on the neck has a bearing on her management.

Case #2: A 50-year-old man presents with complaints of a fever and "feeling anxious." The patient has had a productive cough, subjective fever, and myalgias for 7 days. Yesterday, he began to "feel anxious" and like his "heart was racing." His past medical history is significant for a goiter that is still being evaluated. His vital signs are respiratory rate of 18 respirations per min, blood pressure of 160/80 mm Hg, temperature 38°C (100.4°F), and heart rate 140 beats per min. On physical examination, you note that the patient appears nontoxic. He has a tender goiter, a fine tremor of his hands, and an irregular heart rhythm. On his lung examination, there are left midfield rales. You suspect community-acquired pneumonia, but the tender goiter introduces management concerns.

August 2009
Volume 11, Number 8

Authors

Lisa Mills, MD
Director, Emergency Medicine Ultrasound, Associate Professor, Emergency Medicine, Louisiana State University at New Orleans, New Orleans, LA

Stephen Lim, MBBS
Staff Physician, Department of Emergency Medicine, Leonard J. Chabert Medical Center, Houma, LA

Peer Reviewers

Michael S. Radeos, MD, MPH
Assistant Professor of Emergency Medicine, Weill Medical College of Cornell University, New York, NY

Corey M. Slovis, MD, FACP, FACEP
Professor and Chair, Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN

CME Objectives

Upon completion of this article, you should be able to:
1. Identify presenting signs and symptoms of a thyroid crisis.
2. Discuss the treatment of myxedema coma.
3. Discuss the treatment of thyroid storm.
4. Name the groups at risk for myxedema coma.
5. Name inciting events for thyroid crises

Date of original release: August 1, 2009
Date of most recent review: May 26, 2009
Termination date: August 1, 2012
Medium: Print and online
Method of participation: Print or online answer form and evaluation
Prior to beginning this activity, see "Physician CME Information" on page 22.

Accreditation: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of EB Medicine. EB Medicine is accredited by the ACCME to provide continuing medical education for physicians. **Faculty Disclosure:** Dr. Mills, Dr. Lim, Dr. Slovis, Dr. Radeos, and their related parties report no significant financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in this educational presentation. **Commercial Support:** This issue of *Emergency Medicine Practice* did not receive any commercial support.

Although thyroid-related medical conditions are relatively common in the general population, the acute life-threatening thyroid emergency rarely presents. Both hyper- and hypothyroidism can contribute to the etiology of a number of critical ED presentations, ranging from acute psychosis to frank coma. With reported mortality rates ranging from 20% to 80% for the life-threatening, decompensated forms of hypo- and hyperthyroidism, myxedema and thyroid storm, respectively, it remains crucial that the emergency clinician be versed in their diagnosis and treatment.[1,2]

This issue of *Emergency Medicine Practice* reviews the fundamental principles of the management of thyroid emergencies using a focused, evidenced-based approach to the literature. Although thyroid disorders constitute a wide-ranging clinical spectrum, this review will focus on the common final pathway of acutely decompensated hyper- and hypothyroidism, myxedema, and thyroid storm. Accurate diagnosis and the application of proven emergent treatments are critical in reducing the profound mortality rates related to both conditions.

Critical Appraisal Of The Literature

We performed a literature review through Ovid MEDLINE and PubMed using the terms hyperthyroidism, thyrotoxicosis, thyroid storm, hypothyroidism, and myxedema. We then performed a manual search of the resulting articles to find further relevant articles. The Endocrine Society has published an excellent clinical management guideline for hyperthyroidism and hypothyroidism as well as for the pregnant and postpartum population, but this does not address emergent intervention.[3] Recent meta-analyses and randomized control trials tend to focus on the ideal pharmacological, radiotherapeutic, or surgical regimens for long-term therapy of hyperthyroidism, all of which are of limited importance to the emergency clinician. A number of case reports and case reviews exist as well for the more esoteric presentations associated with thyroid disorders.

Aside from the relatively recent development of intravenous thyroxine, the management of myxedema and thyroid storm has changed little since the mid twentieth century. Perhaps the most relevant papers to the practicing emergency clinician are the focused clinical reviews available on subtopics within the thyroid disease literature, including neonates, children, the elderly, antithyroid drugs, and mechanical ventilation principles.

Epidemiology, Etiology, And Pathophysiology

Epidemiology

The occurrence of thyroid storm or myxedema coma is rare. The National Health and Nutrition Survey III reported the incidence of subclinical and clinical hyperthyroidism to be approximately 1%, with a roughly equal distribution between the two. Hypothyroidism is more prevalent, with a reported incidence of approximately 1% to 2% overall.[4] Although overt hypothyroidism may be present in less than 0.5% of the population, the incidence of subclinical hypothyroidism is more prevalent and may affect up to 10% of elderly women.[4-6] Both hyper- and hypothyroidism are more common in women.

The incidence of thyroid storm and myxedema coma is unknown. However, mortality rates for both are exceedingly high. Untreated thyroid storm is fatal, and even with treatment, mortality ranges from 20% to 50%.[7] Myxedema coma mortality rates as high as 80% have historically been reported, but even with current treatments, mortality rates remain at 30% to 60%.[8,9] Eighty percent of myxedema coma patients are women, and most of these women are older than 60 years.[10]

Definitions And Etiology

Hyperthyroidism and hypothyroidism represent a clinical spectrum of disease. The terms hyperthyroidism and hypothyroidism in the strictest sense refer to hyperfunction and hypofunction of the thyroid gland, respectively. These conditions exist in a full spectrum ranging from clinically controlled disease to grossly decompensated, life-threatening conditions.

Thyrotoxicosis refers to any state characterized by a clinical excess of thyroid hormone. Thyroid storm represents the most extreme presentation of thyrotoxicosis. Both may be life threatening. Clinical judgment on the part of the emergency clinician determines which patients with thyrotoxicosis require intensive intervention and which are less acutely ill.

Myxedema coma is used to describe the severe life-threatening manifestations of hypothyroidism. The term myxedema coma itself is a misnomer, as patients do not usually present with frank coma but more commonly have altered mental status or mental slowing. Myxedema actually refers to the nonpitting puffy appearance of the skin and soft tissues related to hypothyroidism.

Decompensation of chronic thyroid disorders leads to myxedema and thyroid storm. Patients may have had a known history of a thyroid disorder and their conditions may have been well controlled, or patients may have had subclinical cases with no prior diagnosis. Factors precipitating thyroid decompensation include cold weather, infection, medication nonadherence, acute congestive heart failure, myocardial infarction, stroke, new medications, intoxication, and thyroid ablation. Infection is the most common precipitant of thyroid storm.[11] Myxedema coma can be triggered by cold weather, with more than 90% of cases occurring during winter months.[10]

Pathophysiology

Thyroid hormone production is closely regulated via a negative feedback loop through the hypothalamic-pituitary-thyroid axis. Thyroid hormone production begins with the oxidation of trapped serum iodide within the follicular cell membrane. This intermediate compound reacts with specific tyrosine residues to form the compounds monoiodotyrosine and diiodotyrosine. Various combinations of these molecules form triiodothyronine (T3) and thyroxine (T4). Release of the formed T4 and T3 are regulated by thyroid-stimulating hormone (TSH). Roughly 80% of the formed thyroid hormone within the thyroid is T4.[12] In the bloodstream, T4 is more than 99% protein bound; that is, 1% is free in the circulation. Free T4 (FT4) is responsible for the negative feedback inhibition affecting TSH release. During thyroid hormone production, only about 20% of T3 is produced within the thyroid follicular cells themselves. The remaining 80% is produced in the peripheral tissues from the deiodination of T4.[12]

Although the underlying pathophysiological mechanisms surrounding the body's shift from a compensated hyper- or hypothyroid state into a thyroid crisis is poorly defined, it seems intuitive. A mismatch between supply and demand of thyroid hormone secondary to some insult pushes the body into a state of severe decompensation, affecting the multiple systems that are regulated by thyroid hormone.

Cardiovascular effects of thyroid hormone include a direct increase in peripheral tissue oxygen consumption and tissue thermogenesis, indirectly increasing cardiac output, and direct chronotropic and inotropic effects on the heart. A resting sinus tachycardia is the most common cardiovascular sign in hyperthyroidism and exhibits a circadian rhythm more pronounced than in euthyroid patients.[13,14] Thyroid hormone effectively decreases systemic vascular resistance by dilating the resistance arterioles of the peripheral circulation. The clinical end result is the tachycardia, widened pulse pressure, and increased cardiac output typical of hyperthyroidism. Although this clinical picture may resemble a state of hyperadrenergic activity, serum catecholamine levels are actually low to normal. However, the concept of a hyperadrenergic state is useful for the practicing physician, as adrenergic blockade is one of the main components of management in thyroid storm. Conversely, in myxedema coma, patients exhibit bradycardia, hypotension, and hypothermia due to the lack of cardiovascular support from the thyroid hormone.[15]

Thyroid hormone also has important effects on pulmonary, neuromuscular, and renal physiology. Hyperthyroidism contributes to respiratory muscle weakness, decreased cardiopulmonary efficiency, and reduced exercise capacity as measured by spirometry and spiroergometry (direct breath-to-breath gas exchange measurements during exercise).[16] Hypothyroidism alters ventilation, as manifested by a decreased central response to hypoxia and hypercapnia resulting in a respiratory acidosis. This blunted response results in an attenuated increase in minute ventilation to rising CO_2 levels. Conversely, these patients are susceptible to respiratory alkalosis, most commonly seen after overaggressive mechanical ventilation. The pathophysiology behind this particular phenomenon lies in the reduced basal metabolic rate and diminished CO_2 production secondary to low levels of circulating thyroid hormone.[17] As a result, although intubation and mechanical ventilation may be life saving in the hypoxic, hypercapneic patient, clinicians should be cautious about overly aggressive correction of the hypercapnia, as this may induce respiratory alkalosis.[18]

In addition to directly affecting ventilatory drive, hypothyroidism affects both respiratory and skeletal muscle function. Investigators report diaphragmatic weakness and fatigue as measured by inspiratory pressures and cycle times compared with maximum transdiaphragmatic pressures and total respiratory cycle times. In concert with delayed phrenic nerve conduction velocities, the end clinical result is diaphragmatic dysfunction causing a restrictive respiratory pattern that contributes to hypoxia and hypercapnia. Significant skeletal muscle atrophy, up to 50% of total muscle mass, is also related to chronic hypothyroidism, secondary to increased skeletal muscle cell permeability and decreased adenosine triphosphate (ATP) production. Thyroid hormone replacement improves all of these conditions, but full recovery may take months.

The renal effects of thyroid hormone are an increase in blood volume and preload, which contributes to further increases in cardiac output. In addition, thyroid hormone can stimulate erythropoietin secretion.

Differential Diagnosis

The varied and diverse clinical presentations of thyroid storm and myxedema coma make them difficult to identify in the emergent setting. In addition, the frequent coexistence of an inciting illness makes a dual diagnosis likely. However, including a thyroid crisis in the differential diagnosis is crucial to appropriately manage the life-threatening conditions.

A number of serious illnesses mimic and coexist with thyroid storm. The differential diagnosis is broad and includes delirium of any etiology. Sympathomimetic and anticholinergic toxidromes and withdrawal syndromes (ethanol, narcotics, and sedative-hypnotics) resemble thyroid storm. Hypoglycemia initially presents with a hyperadrenergic state and agitation, like thyroid storm. Hypoxia of

any etiology can cause a hyperadrenergic state and altered mental status. Any infection that progresses to sepsis can cause fever, tachycardia, and mental status changes. Central nervous system infections causing encephalitis or meningitis closely resemble thyroid storm. Heat stroke may accompany tachycardia, altered mental status, and, less commonly, hypertension. Drug-induced hypertensive crises usually lack the tachycardia that is present in thyroid storm. It is crucial to recognize that any of these entities may exist concurrently with thyroid storm. Indeed, any of these disease processes may incite thyroid storm. **Table 1** lists the key diagnoses in the differential diagnosis of thyroid storm.

With a clinical picture as varied as hypotension, hypothermia, coma, and altered mental status, a similarly broad differential exists for myxedema coma. (**See Table 2.**) In addition, a broader endocrine disorder such as panhypopituitarism or adrenal insufficiency may be present. Sepsis with hypotension, altered mental status, and hypothermia can closely mimic myxedema coma. Acute heart failure with peripheral edema, cardiomegaly, pleural effusions, and hypotension can be confused with myxedema coma. Ingestions of sedative-hypnotics, narcotics, anesthetics, and heavy metals such as lithium can produce coma. Gastrointestinal bleeding and metabolic disorders must always be in the differential diagnosis.

As with thyroid storm, concomitant illness occurs commonly with myxedema coma and may be the cause of a patient's deterioration into severe life-threatening hypothyroidism. Common precipitants of myxedema coma include cold exposure, trauma that prevents access to medication, and infections, usually genitourinary or pulmonary. Consider disorders of the thyroid in all patients with systemic illness who have a history of thyroid disease or who are older than 60 years.

Prehospital Care

Prehospital interventions should focus on the ABCs. The prehospital provider is faced with clinical presentations as varied as acute psychosis and frank coma. Prehospital protocols should stress support of airway, breathing, and circulation with emergent transport to the ED, as with all critically ill patients. Altered mental status protocols should be followed with determination of blood glucose and administration of naloxone and thiamine as appropriate. One must be prepared to provide gentle passive external rewarming for hypothermic patients, consider warm humidified oxygen to provide volume support for hypotensive patients, and consider chemical and physical restraints for those patients actively psychotic and combative. All patients should be placed on a cardiac monitor and have continuous pulse oximetry. Defer starting specific treatments, such as β-blockers and steroids, until a more thorough evaluation can be performed in the ED. **Table 3** lists emergent diagnostic tests and therapeutic interventions that should be performed immediately on patients with a clinical picture of myxedema coma or thyroid storm.

Table 1. Differential Diagnosis In Thyroid Storm

- Hypoglycemia
- Hypoxia
- Sepsis
- Encephalitis/meningitis
- Hypertensive encephalopathy
- Alcohol withdrawal
- Benzodiazepine/barbiturate withdrawal
- Opioid withdrawal
- Heat stroke

ED Evaluation

Initial Approach

When the patient arrives at the ED, the emergency clinician's initial efforts should focus on respiratory and cardiovascular stabilization. Concomitant with the initial assessment, start cardiac monitoring, begin continuous pulse oximetry, determine blood glucose levels and core temperature, and establish intravenous access. Patients presenting with an altered level of consciousness may require emergent, definitive airway control. Hypotensive patients warrant initial treatment with an isotonic intravenous solution before beginning vasopressors. Hypothermic patients need gentle external rewarming, unless core temperatures are critically low. Consider chemical restraint for the extremely agitated, combative patient. Straining against physical restraints can worsen hyperthermia, rhabdomyolysis, and dehydration in hyperthyroidism. Sudden cardiovascular collapse

Table 2. Differential Diagnosis In Myxedema Coma

- Hypoglycemia
- Hypoxia
- Sepsis
- Hypothermia due to environmental exposure
- Cerebrovascular accident
- Acute myocardial infarction
- Intracranial hemorrhage
- Panhypopituitarism
- Adrenal insufficiency
- Hyponatremia
- Gastrointestinal bleeding
- Conversion disorder

may result. Investigate and intervene in conditions such as systemic infections, acute myocardial infarction, trauma, stroke, intoxication, and other sources of physiologic stress that may exacerbate hypo- and hyperthyroidism.

Important Historical Questions (From Patient, Medics, Witnesses, Family, And Other People)

Patients with thyrotoxicosis report hyperadrenergic symptoms that include palpitations, nervousness, agitation, and tremor. A focused review of systems may reveal a history of weight loss, dyspnea, fever, agitation, anxiety, restlessness, proximal myopathy, menstrual irregularity, and heat intolerance. Considered together, these common symptoms point to a diagnosis of underlying hyperthyroidism. Include a thorough past medical history, including questions about recent medication changes, recent anesthesia, infectious prodromes, radiologic imaging that required an oral or intravenous iodinated contrast agent, and thyroid manipulation. (**See Table 4.**)

Patients in a hypothyroid state may present with diverse complaints. Hypothyroidism mimics a number of common disease processes presenting to the ED. A lack of thyroid hormone results in a depressed metabolic state, and many of the most common patient complaints reflect this. Patients with hypothyroidism may report fatigue, weight gain, cold intolerance, constipation, dry skin, paresthesia, hair loss, voice change, constipation, menstrual irregularity often with amenorrhea, and depression. (**See Table 5.**) It is important to elicit a medication history with special attention to recent changes. Some medications known for exacerbation of hypothyroidism include phenothiazines, phenobarbital, narcotics, anesthetics, benzodiazepines, lithium, phenytoin, and rifampin. As with thyroid storm, in ferreting out the presence of myxedema coma, some of the most important historical facts to elicit are recent precipitants, such as exposure to cold, infection, major life stress, and trauma.

Table 3. Field Diagnostic/Therapeutic Interventions In Thyroid Crises

Diagnostic	Therapeutic
Evaluation of airway and breathing	Respiratory support if indicated
Capillary blood glucose	Administer glucose if hypoglycemic
Pulse oximetry	Administer oxygen if hypoxic
Blood pressure	
Symptomatic bradycardia or tachycardia	Discuss with medical control and provide intravenous fluids if hypotensive

Important Physical Findings

The physical examination should target essential concerns. The patient with profound thyrotoxicosis classically presents febrile, tachycardic, and tremulous. In a retrospective review of 58 patients newly diagnosed with thyrotoxicosis who were not clinically decompensated, weakness (50%), weight loss (40%), and palpitations (35%) were the most common clinical characteristics reported.[19,20]

A hyperdynamic cardiovascular state manifests with a persistent resting tachycardia, widened pulse pressure resulting in a bounding pulse, and a normal to elevated blood pressure. Atrial fibrillation is the second most common dysrhythmia following sinus tachycardia in thyrotoxicosis. The reported incidence of atrial fibrillation in acute thyrotoxicosis varies from 5% to 15.5%. A retrospective review of thyroid function test result abnormalities reported that approximately 5% of all admitted patients with new onset atrial fibrillation or flutter had either subclinical or overt hyperthyroidism.[21] Atrial fibrillation with rapid ventricular response decreases the time of ventricular diastole. This allows less filling time for the ventricles, leading to high output heart failure.

A patient's age plays a significant role in the clinical signs likely to be present. In a prospective cohort study of 152 patients, tachycardia, fatigue, and weight loss were found in more than 50% of older patients (mean age 80.2 years), whereas only anorexia (32%) and atrial fibrillation (35%) were found significantly more frequently in younger patients.[22] Another prospective study, with 880 patients, identified weight loss and atrial fibrillation as

Table 4. Historical Questions In The Evaluation Of Thyroid Storm

- History of thyroid disease?
- Symptoms of hyperthyroidism: tremor, agitation, weight loss, nervousness, heat intolerance, proximal weakness, palpitations, menstrual irregularity?
- Thyroid manipulation?
- Medication changes?
- Physiologic stressors: trauma, infections, exertion?
- Recent anesthesia?
- Recent iodinated contrast?
- Infectious syndromes?

Table 5. Historical Questions In The Evaluation Of Myxedema Coma

- History of thyroid disease?
- Symptoms of hypothyroidism: weight gain, hair loss, fatigue, weight gain, dry skin, voice change, depression, constipation, menstrual irregularity?
- Medication changes often with menometrorrhagia
- Physiologic/psychological stressors: infection, trauma, cold exposure, major life changes?

the most common clinical findings of hyperthyroidism in patients older than 50 years.[23] Goiters were significantly more likely to be present in younger patients (94%; mean age 37.4 years) than older patients (50%). The clinical signs of hyperactive reflexes, increased sweating, heat intolerance, tremor, nervousness, polydipsia, and increased appetite were found significantly less frequently in older patients. Older patients had significantly fewer clinical signs then younger patients did. As compared with older controls, the clinical signs of apathy, tachycardia, and weight loss were highly associated with thyrotoxicosis in non-geriatric patients.[22]

Patients with thyrotoxicosis are typically nervous and anxious. There may be a fine tremor at rest and movement. Behavioral changes may be profound and present as paranoia, although acute affective disorders such as depression and mania are reportedly more common.[24] Increased CO_2 production secondary to the rise in basal metabolic rate causes tachypnea. Proximal muscle weakness in the pelvic girdle and shoulder muscles may be evident if there has been a history of untreated hyperthyroidism. Significant muscle atrophy and loss of 40% of muscle strength may be evident, especially in the larger proximal muscles.[25] Profound muscle weakness may affect the muscles of respiration, and this, in combination with the tachypnea, predisposes patients to acute respiratory failure. Rarely, an entity described as hypokalemic periodic paralysis, which is found commonly in Asian men, results in muscle stiffness, cramps, weakness, and flaccid paralysis.[26] Significant weight loss may precede thyroid storm, with 25% to 50% of patients reporting more than 40 pounds (18.14 kg) weight loss in the preceding months.[27,28] Burch et al devised a clinical scoring system to differentiate thyroid storm, "impending thyroid storm," and uncomplicated thyrotoxicosis, although it is unclear whether it has been validated. (**See Table 6.**)[29,30] Ultimately, however, the distinction between thyroid storm and severe but "compensated" thyroid storm complicated by other serious disease is immaterial in the ED. Treatment should be initiated as soon as the diagnosis is suspected because of the high mortality rate related to thyroid storm.

Severe hypothyroidism presents typically with skin changes, hypothermia, pseudomyotonic deep tendon reflexes, and depressed mental function. As mentioned earlier, coma is rare even in profound life-threatening hypothyroidism. However, the critical life-threatening signs associated with profound hypothyroidism include respiratory insufficiency, hypotension, hypothermia, and coma. Look for a thyroidectomy scar as a marker of hypothyroidism.

Although blood pressure changes range from low to elevated, 50% of those with myxedema coma are hypotensive and have systolic pressures less than 100 mm Hg.[31]

Pleura- and pericardial effusions, though rare, may be present. These effusions tend to accumulate slowly and are unlikely to produce clinically significant cardiovascular effects.[32,33] A nonpitting edema, termed myxedema, secondary to chronic hypothyroidism, may be present and is especially noticeable in the face, hands and pretibial region. A husky, deep voice may be present and has been attributed to mucopolysaccharide infiltration of the vocal cords, a mechanism similar to nonpitting edema that is present in other areas of the body due to chronic hypothyroidism.[34] A preceding weight gain of 7 to 8 pounds (3.2-3.6 kg) is common as is a history of menorrhagia with irregular menses stemming from chronic hypothyroidism.[35]

The depressed metabolic state resulting from a lack of thyroid hormone affects all the major organ systems. Pseudomyotonic deep tendon reflexes are almost universally present. The relaxation phase is classically twice as long as the contraction phase and may best be elicited with the Achilles reflex. Parathesia, especially a mononeuropathy involving the median nerve, is present in about 50% of cases.[36-39] Reduced intestinal motility results in constipation and abdominal distention, potentially even mimicking an acute abdomen.

Hypothermia in myxedema coma is so common that an elevated temperature suggests an underlying infection. A core body temperature of less than 35.50ºC (95.90ºF) is found in 80% of severely hypothyroid comatose patients, with reported temperatures as low as 24ºC (75.2ºF).[40,41] Neurological changes may be accompanied by seizures, ataxia, positive Romberg's sign, slowed speech, short-term memory loss, intention tremors, nystagmus, and poor coordination. These changes may be secondary to increased muscle tone and prolonged muscle contraction, as opposed to any primary cerebellar cause. There is 1 case report of a patient presenting with status epilepticus due to myxedema.[42] A depressed central respiratory drive response to hypoxia and hypercapnia secondary to the metabolic derangements related to hypothyroidism, in concert with a depressed mental status, necessitates emergent airway management.[43]

Most patients with thyroid storm and myxedema coma are significantly hypovolemic. Hypovolemia can be a result of decreased oral intake due to an underlying illness or injury. The progression toward altered mental status with myxedema coma results in decreased oral intake. The hypermetabolic state in thyroid storm causes increased insensible fluid loss.

Diagnostic Studies

Although the diagnosis of myxedema coma or thyroid storm is a clinical diagnosis, laboratory test

confirmation can assist in narrowing the broad differential associated with both entities primarily by excluding other etiologies. There are no published studies of significant numbers of patients that report common laboratory test findings in patients with thyroid emergencies.

In a case series of 8 people with myxedema coma, hyponatremia as low as 110 mEq/L was seen. It is attributed to a syndrome of inappropriate secretion of antidiuretic hormone and decreased renal blood flow.[44] Only 5% to 10% of myxedema coma patients have an associated hypoglycemia.[44] When present in myxedema coma, hypoglycemia should raise suspicions for an associated adrenal insufficiency and other causes of hypoglycemia.

Both hyper- and hyponatremia are related to hyperthyroid states and are typically not associated with clinical findings. Hyperglycemia is present in up to half of all patients with hyperthyroidism. Serum potassium levels are generally unchanged but may be severely low in the rare cases of thyrotoxic periodic paralysis. Asymptomatic hypercalcemia is present in hyperthyroid states.

TSH, T4, T3

TSH, T3, total T4, and FT4 levels are not affected during the acute phase of myxedema coma and thyroid storm. When drawn at the time of crisis, the laboratory test findings reflect the patient's chronic thyroid state. A study comparing patients with thyroid storm with patients with uncomplicated hyperthyroidism showed that thyroxine levels were the same in the 2 groups.[45,46] Although these laboratory tests may be helpful to the consultant at a later date, they are generally not a part of the ED evaluation of patients with suspected thyroid crisis. An understanding of thyroid laboratory tests will give the emergency clinician insight into a patient's chronic thyroid state.

Normal TSH levels virtually exclude hyperthyroidism, except in the very rare case of a pituitary adenoma. A low value by itself, however, is not diagnostic of a hyperthyroid state. A number of conditions are associated with low TSH levels: chronic nonthyroid illnesses, such as liver disease or renal failure, and adverse drug effects, as seen with glucocorticoids and dopamine. The new generation of extremely sensitive TSH tests redefine the normal range of TSH to 0.3 to 0.5 mU/L.[47] To confirm a diagnosis of hyperthyroidism, the TSH should be less than 0.1 mU/L.[47] Concurrent evaluation with a FT4 and total T3 is recommended.[48]

A low TSH level with an elevated FT4 level is seen in 95% of patients with hyperthyroidism.[49] Less than 5% of patients have normal FT4 levels with elevated T3 levels, which are diagnostic of a T3 thyrotoxicosis. Total T4 levels, although commonly available, are difficult to interpret because the level is affected by serum thyroid binding proteins. These protein levels are altered by multiple conditions, including pregnancy, medications, and chronic liver disease.

The TSH and FT4 levels are central to the diagnosis of hypothyroidism. Expect to find elevated TSH levels with low levels of FT4 and T3 in primary hypothyroidism. In patients with secondary or tertiary causes of hypothyroidism, expect to find low TSH levels and low FT4 levels. An elevated TSH level is the most sensitive indicator of a hypothyroid state, and changes in its level will precede any changes in serum FT4. Early in the disease process, elevations in TSH levels may maintain normal FT4 and T3 levels. As with hyperthyroid cases, the total T4 level is difficult to interpret and may be elevated or depressed, depending on changes in serum thyroxine binding globulin levels.

Thyroid laboratory tests are affected by many physiologic states and medications. Importantly, acute illness can alter thyroid tests to give the impression of a hypothyroid state by altering T3 levels. Low T3 levels with low or normal TSH and T4 levels are typically seen in patients who are acutely ill. This is the sick euthyroid syndrome. In addition, dopamine in doses used for shock causes a low serum TSH.[49] A multitude of factors can retard the peripheral conversion of T4 to T3, resulting in a low T3 level in patients who are physiologically euthyroid. These factors include glucocorticoids, high doses of propanolol, and radiocontrast agents amiodarone.[48,50-55] T4 is decreased in patients treated with phenytoin, rifampin, and carbamazepine. Serum TSH levels remain normal in these patients.[56,57]

Other Diagnostic Tests

Given the broad differential associated with severe hyper- and hypothyroidism, consider a broad initial laboratory evaluation. Obtain cardiac markers and B-type natriuretic peptide levels to assess for cardiac ischemia or acute cardiac failure. Serum lactate levels assess perfusion status in the hypotensive patient. Consider drawing a random cortisol level if the possibility of adrenal insufficiency exists. Urinalysis is critical in assessing for an infectious source. A urine pregnancy test or β-hCG (human chorionic gonadotropin) in all women of childbearing age is mandatory as the management of thyroid storm and myxedema coma in the pregnant patient requires unique considerations. (**See the Special Circumstances: Pregnancy section, page 16.**)

An arterial blood gas is useful to quantify the level of hypercapnia and hypoxemia in severely hypothyroid patients and to identify acidosis in hypermetabolic patients with thyrotoxicosis. In a severely obtunded patient, expect to find a respiratory acidosis with hypoxemia and hypercapnia,

both secondary to a decreased ventilatory drive in myxedema coma.[58]

See Table 7 for thyroid laboratory tests in thyroid disease.

Electrocardiogram

The electrocardiogram (ECG) may reveal alternate diagnoses and concomitant illness as well as the cardiac effect of the thyroid crisis. The emergency clinician should assess for dysrhythmias and signs of cardiac ischemia. Acute cardiac ischemic events can precipitate thyroid emergencies, especially myxedema coma.

In hyperthyroidism, sinus tachycardia is the most common dysrhythmia, followed by atrial fibrillation. A retrospective review of 58 patients with thyrotoxicosis in an outpatient setting reported incident rates for sinus tachycardia and atrial fibrillation of 65.5% and 15.5%, respectively.[20] Up to 15% of patients with hyperthyroidisms develop atrial fibrillation.[59] The sinus tachycardia is typically out of proportion to the fever.[60] Atrial fibrillation with rapid ventricular response due to hyperthyroidism is typically refractory to digitalis and reverts to sinus in 20% to 50% of patients after antithyroid therapy.[60,61] Supraventricular tachycardia (defined as 10 supraventricular contractions in a row with a heart rate > 130 beats per minute) is also more common in patients with thyrotoxicosis than in matched controls.[62] Ventricular tachycardia and ventricular fibrillation, however, are not typically associated with thyrotoxicosis and, if present, are usually related to heart failure due to ischemic disease.[63]

Sinus bradycardia is the most common dysrhythmia in the patient with hypothyroidism. ECG changes consistent with a pericardial effusion, low voltage, electrical alternans, and diffuse ST-segment and T-wave changes are present in 50% of patients with myxedema coma.[32] These ECGs are nonspecific and poorly sensitive and should neither rule in nor rule out the diagnosis.

Chest Radiography

A chest X-ray (CXR) is best used to evaluate alternate and coexisting diagnoses in the severely ill patient. Assess for cardiomegaly, pleural effusions, and pericardial effusions. Assess for pneumonia, a common precipitating event in myxedema coma. CXR is an insensitive and nonspecific tool for assessing the presence of pericardial effusions. CXRs demonstrate a 30% false negative rate and a 40% false positive rate in detecting hypothyroid-related pericardial effusions.[32,33]

Echocardiography

A rapid transthoracic echocardiogram gives vital information to the emergency clinician and should be performed if there is concern for significant pericardial effusion or cardiac dysfunction. All emergency clinicians should be provided 24-hour access to a bedside ultrasonography machine.

Computerized Tomography Head

Consider the need for computerized tomography of the head without contrast to assess for other potential causes of a depressed or altered mental status in the patient with severe hyper- or hypothyroidism.

Lumbar Puncture

Lumbar puncture may be necessary to evaluate the patient for an intracranial infectious process. However, this procedure is not always feasible in an acutely altered or unstable patient. The emergency clinician must weigh the risks and benefits of this procedure. Nonspecific cerebrospinal fluid findings associated with myxedema coma include an increased opening pressure and an elevated protein level.[36]

Treatment

In both forms of thyroid crisis, support the patient's cardiovascular status and airway as indicated. Treat coexistent diagnoses as appropriate, including empiric antibiotics. Pay particular attention to the ventilation of the patient with hyperthyroidism, so as not to overventilate the patient to the point of alkalosis. Slow normalization of elevated pCO_2 is the goal (**see the "Pathophysiology" section, page 3**).

Patients with thyroid crisis almost universally need fluid resuscitation. Mindfully replace fluid with careful attention to the patient during the resuscitation.

Table 7. Thyroid Laboratory Tests In Thyroid Disease

	Thyroid-Stimulating Hormone Levels	Free T4 Levels	T3 Levels	Total T4 Levels
Hyperthyroidism	Low	High		Variable
Thyroid storm	Normal to low	Normal to high	Normal to high	Variable
Hypothyroidism	High	Low	Low	Variable
Myxedema coma	High	Low	Low	Variable
Sick euthyroid syndrome	Normal or low	Normal or low	Low	Variable

Myxedema Coma

Myxedema coma is a critical physiologic state. Mortality is high, even with early recognition and aggressive treatment. In multiple case series, patients older than 60 years and patients with cardiovascular decompensation had higher mortality rates.[8,64-66]

The treatment of myxedema coma is intravenous replacement of thyroxine.[66] Intravenous preparations of T4 and T3 are available. T4 has been considered the safer preparation, as intravenous T3 classically has been related to cardiac ischemia and arrhythmias. However, there is little published research in the past 30 years to support this concern. One recent case series of 8 patients treated with high-dosage intravenous T3 (75-175 µg initially, followed by 150 µg) showed a high mortality, with 7 of 8 patients dying.[65] These researchers also performed a case review in which they determined that high-dosage intravenous T3 and T4 are related to increased mortality. Recent research on cardiac patients treated with intravenous T3 raises questions about the concerns regarding giving intravenous T3. Studies of patients with cardiac disease have not supported the concern for adverse cardiac effects of intravenous T3. One study in which intravenous T3 was administered to 23 patients with congestive heart failure showed no cardiac ischemia or arrhythmias.[67] In another study, 30 patients undergoing coronary artery bypass grafting were administered T3 intravenously (IV) without evidence of ischemia or arrhythmia.[68] Importantly, these patients were not in decompensated hypothyroid states, so the data cannot be directly extrapolated.

T4 is administered in a dosage of 200 to 500 µg IV (pediatric dosage 10 mcg/kg/d IV divided q6-8). It has been well established by multiple classic studies and a recent study that the administration of T4 achieves therapeutic levels of T3 and clinical reversal of myxedema.[69,70] A study done in 1976 showed 100% survival of 7 patients with myxedema who were treated with high-dosage intravenous T4 (300-500 µg).[71] Yamamoto's case survey suggests that high-dosage intravenous T4 is related to higher mortality.[72] A more recent, prospective, randomized study of 11 patients compared an intravenous high-dosage (500 µg) load of T4 followed by the standard 100 µg dosage intravenous maintenance with a 100 µg maintenance dosage without a loading dose.[8] In this study, 3 of the 4 deaths were patients who did not receive a loading dose. The numbers were not sufficient to reach statistical significance. One case report describes the successful treatment of a patient with myxedema coma with oral doses of T4 given via nasogastric tube.[73] Debate continues regarding the optimum intravenous dosage of T4.

Researchers are revisiting the role of combination T4 and T3 therapy in stable patients with hypothyroidism. To date, most studies have not shown a measurable physiologic or emotional improvement with combination therapy.[70,74,75] However, 2 prospective studies, conducted by the same group, show improved reversal in symptoms of hypothyroidism with combined T4 and T3 therapy.[76,77] It is unclear how these recent studies will affect recommendations for the treatment of the patient with myxedema. One group proposes combination therapy of intravenous T3 and T4 for the patient with myxedema.[78]

Empiric glucocorticoids are recommended by some groups, as hypopituitarism and hypoadrenalism can mimic myxedema coma. In addition, thyroxine supplementation can leave a patient with relative adrenal insufficiency.[79,80] However, there is little research to support this recommendation. A stress dose of hydrocortisone at 100 mg IV (pediatric dosage 0.5-1 mg/kg IV q8) is the recommended dose. Send a random serum cortisol before administration of glucocorticoids to help in the subsequent endocrinologic evaluation of the patient. Hypothermia corrects with the normalization of basal metabolic rate. In the ED, warmed blankets are generally sufficient therapy for a mildly hypothermic patient.

Decreased oral intake due to slowed metabolism and secondary processes such as sepsis cause dehydration in most patients with myxedema coma. However, the associated bradycardia and any underlying cardiac disease make fluid replacement a complex endeavor. The physician should carefully monitor the patient's response to fluid with invasive monitoring, frequent physical examination, bedside ultrasonography, or a combination of the above to prevent hypervolemia and pulmonary edema.

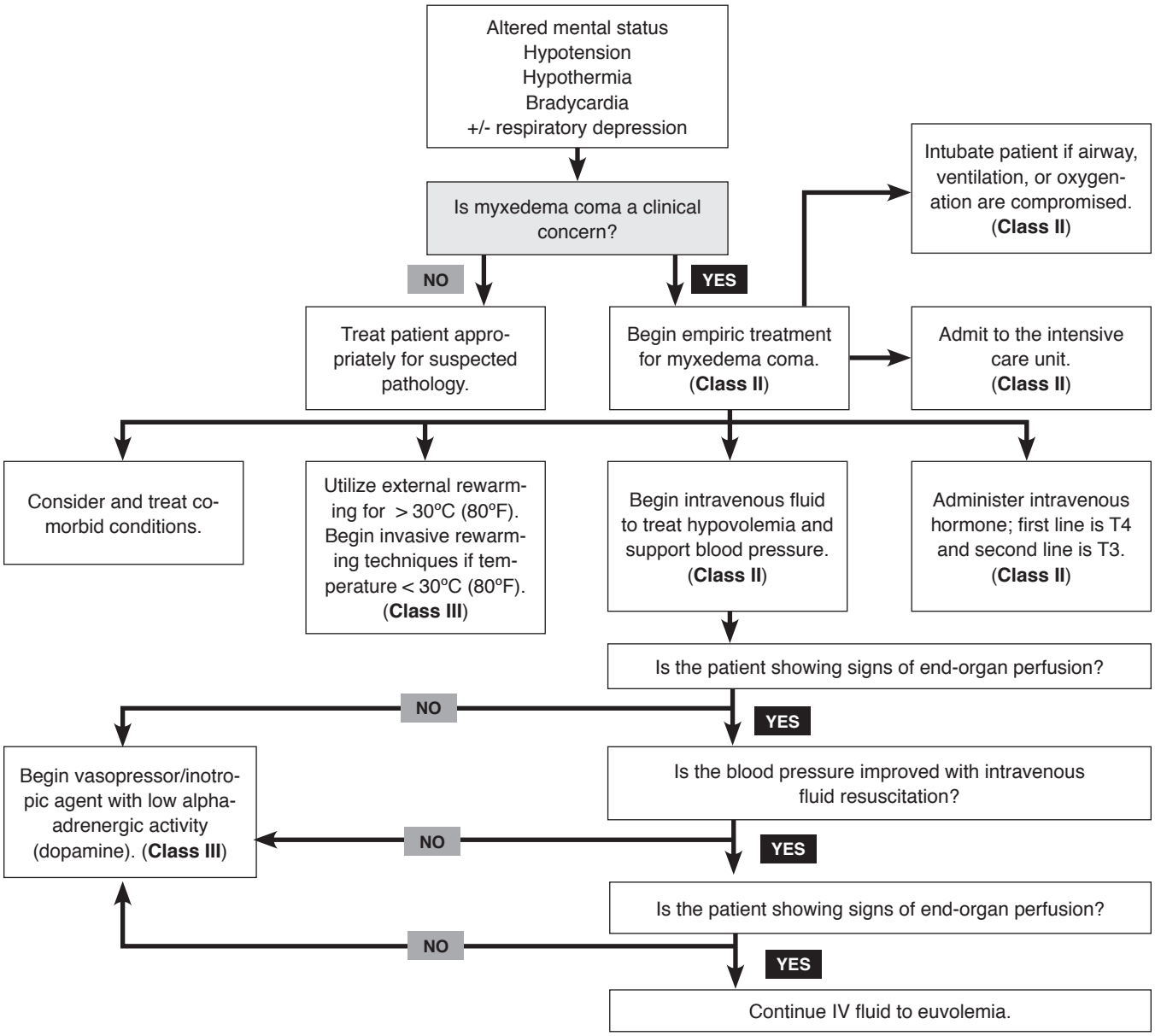
Patients with myxedema coma may require intravenous vasopressors to support their cardiovascular status. When possible, avoid vasopressors with strong α-adrenergic effects (phenylephrine and norepinephrine). The chronic state of hypothyroidism is believed to result in reduced β-adrenergic receptors. The result is a β- to α-adrenergic receptor misbalance.[81] Dopamine, because it has a lower α-effect, is the recommended first-line vasopressor.[138] There is no evidence to support this recommendation.

Thyroid Storm

Intervention in thyroid storm requires a three-step treatment approach. First, treat the peripheral effects of the hyperthyroidism. Second, prevent further synthesis of thyroid hormone with antithyroid medications. And third, prevent further release of thyroid hormone. (**See Table 7.**)

β-blocking agents reduce the systemic effects of excess thyroid hormone. If the patient shows cardiovascular stability and has mild symptoms, such as mild tachycardia and tremor, an oral β-blocking agent can be chosen. If the patient has a

Clinical Pathway For Treatment Of Myxedema Coma



Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

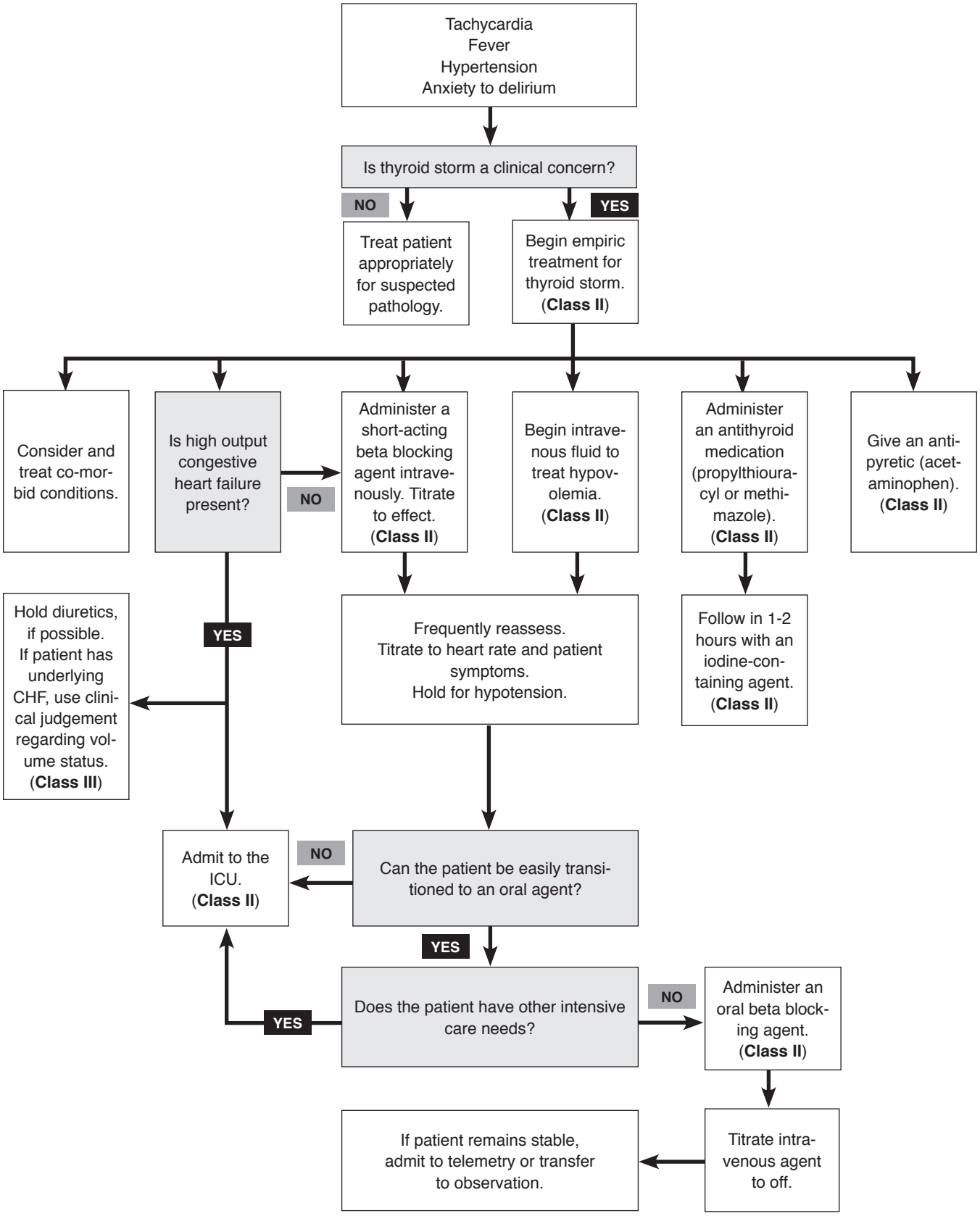
Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA*. 1992;268(16):2289-2295.

Clinical Pathway For Treatment Of Thyroid Storm



more dramatic presentation, such as signs of cardiovascular instability, chest pain, or altered mental status, intravenous β-blockers are required. Based on case reports, initial stabilization with short-acting β-blocking agents that are titrated to effect is the preferred method of treatment.[82,83] Although the use of propanolol for β-blockade has been related to bad outcomes, it does have the physiologic advantage of decreasing peripheral conversion of T4 to T3 that other β-blocking agents have not been demonstrated to possess.[52]

The fever related to thyroid storm and underlying infection contributes to tachycardia. This can worsen cardiovascular dynamics, and it complicates the physician's assessment of the patient's volume status. Antipyretics are indicated to treat fever. Acetaminophen is the antipyretic of choice. Textbooks recommend avoiding aspirin, as it increases free T3 and T4 concentrations because of protein binding. Although aspirin overdose has been linked to thyroid storm, there is little research on the clinical effect of therapeutic doses of aspirin.[84]

High output failure poses one of the most difficult treatment scenarios in thyroid storm. The patient has pulmonary edema usually in the setting of volume depletion. For this reason, diuretics should be avoided. The patient needs increased intravascular volume. Diuretics would reduce intravascular volume, possibly precipitating a hypotensive event. The inciting event in high output heart failure is tachycardia. To improve hemodynamics, the heart rate must be slowed to allow increased cardiac filling time. β-blockade of the heart will slow the heart and allow the appropriate filling time. The decision to use β-blockers can be difficult in a patient who has pulmonary edema and hypovolemia and may have underlying cardiac hypomotility. A continuous infusion of a short-acting β-blocker is preferred for this reason. The starting dose and decision to use a loading bolus is controversial. Ventilation with noninvasive positive airway pressure can facilitate the redistribution of pulmonary edema without the use of diuretics. It is difficult to balance pulmonary edema and fluid replacement. Judicious replacement of fluid while monitoring the patient's response to fluid with invasive monitoring, frequent physical examination, and bedside ultrasonography is the best approach.

Thioureas, propylthiouracil (PTU), and methimazole block the synthesis of thyroid hormone in the thyroid. PTU is the only thioureas approved for use in pregnancy. PTU is loaded in a dosage of 600 to 1000 mg orally, then 200 to 300 mg orally every 4 to 6 h for a total of 1200 mg per day (pediatric dosage 5-7 mg/kg per day divided q8). The methimazole dosage is 20 mg orally or rectally every 4 h (pediatric dosage 0.4-0.7 mg/kg per day divided q8 to q24). There is no parenteral dose of thioureas. PTU is the less expensive thiourea and has the added therapeutic benefit of inhibiting the conversion of inactive T4 to physiologically active T3 in the serum.

Corticosteroids also block the peripheral conversion of T4 to T3. Dexamethasone is the most effective corticosteroid, administered in a dosage of 2 mg IV every 6 h. An alternative is hydrocortisone 100 mg IV every 8 h.[51] Dexamethasone offers the advantage of not affecting subsequent adrenal testing. There is no significant cost differential.

Prevention of further thyroid hormone synthesis is the final step in the intervention in thyroid storm. Inorganic iodine is used to block the synthesis of thyroid hormone. The timing of this therapy is important. This treatment must follow the administration of thiourea by at least 1 h. If iodine is administered earlier than this, it stimulates the release of thyroid hormone from the thyroid, worsening the hyperthyroidism. Iodine is available in many oral forms. Saturated solution of potassium iodide or Lugol solution in doses of 6 to 8 drops every 6 to 8 h are effective. (The dosage of potassium iodide and Lugol solution is the same in the pediatric patient.) The contrast dyes can be administered. Iohexol is an intravenous formulation administered 600 mg IV every 12 h. Oral iodinated contrasts can also be administered; these have a safer renal side effect profile. An example of an oral contrast agent is iopanoic acid; it is administered 500 mg orally twice daily. Consult a pediatric endocrinologist for appropriate dosing of contrast agents in pediatric patients.[85-88] In the setting of an iodine allergy, use lithium carbonate 300 mg orally every 6 h (pediatric dosage 15-60

Table 7. Three-Step Treatment Of Thyroid Storm

	Goal	Treatment	Effect
Step 1	Block peripheral effect of thyroid hormone	Provide continuous intravenous infusion of β-blocking agent.	Slows heart rate, increases diastolic filling, and decreases tremor.
Step 2	Stop the production of thyroid hormone	Provide antithyroid medication (propylthiouracyl or methimazole) and dexamethasone.	Antithyroids decrease synthesis of thyroid hormone in the thyroid. Propylthiouracil slows conversion of T4 to T3 in periphery. Dexamethasone decreases conversion of T4 to T3 in periphery.
Step 3	Inhibit hormone release	Give iodide 1-2 h after antithyroid medication	Decreases release of thyroid hormone from thyroid.

mg/kg divided q8 orally). The optimum agent is the agent that is most readily available and familiar to the pharmacist mixing the drug.

Special Circumstances

Respiratory Failure

Airway assessment and protection comprise the basis of ED stabilization. Emergently intubate patients with respiratory failure, those unable to protect their own airway, and those for whom the predicted clinical course is poor.

Large goiters and a hyperdynamic state present special considerations in the patient with hyperthyroidism. Upper airway edema and a large anterior neck mass causing direct tracheal compression inhibit direct laryngoscopy and passage of the endotracheal tube.[115-117] One literature review cites that approximately 80% of substernal goiters cause tracheal deviation and tracheal compression on preoperative radiographs.[118]

Once the patient has been successfully intubated, special considerations apply in managing the ventilator.[58] Decreased ventilation has been written about but rarely studied in the patient with myxedema. One study of 17 patients with hypothyroidism on a ventilator concluded that the patients had depressed hypoxic ventilatory response. The study concluded that the hypercapnic ventilatory drive was not clinically significant.[119] Be aware that hypothyroidism also affects the neuromuscular system, which results in direct diaphragmatic muscle weakness and delayed conduction velocity within the phrenic nerve and causes skeletal muscle atrophy.

Pediatrics

The majority of pediatric patients with hyperthyroidism have autoimmune thyroid disease; Graves' disease encompasses 95% of this patient population.[120] The incidence of thyrotoxicosis ranges from 0.1 per 100,000 in young children to 3 per 100,000 in adolescents.[120] The preponderance of patients is women, and incidence increases in relation to other autoimmune conditions. The diagnosis of hyperthyroid disease, unless discovered during neonatal screening, is typically delayed.[121] Nontoxic prepubertal hyperthyroidism presents with long-standing complaints of weight loss and diarrhea. Pubertal children may present with irritability, heat intolerance, and neck swelling.[122] Children are typically tall but not necessarily thin.[123] Eye signs may be present in 25% to 63% of pediatric patients.[124,125] Patients with known hyperthyroidism are typically on regimens similar to adults, β-blockers for symptom control, and thioamides for thyroid hormone control.

Thyroid storm is rare in the pediatric population. As with thyroid storm in adults, precipitants include surgery, infection, radioiodine therapy, and nonadherence with antithyroid medications.[126,127] Physical findings include fever, diaphoresis, widened pulse pressure, and hypertension. Tachycardia may progress to high-output cardiac failure. Management principles are the same: treat symptoms, resuscitate, diagnose, and manage precipitating factors.

Neonatal Hypothyroidism

In the preterm infant and in the fetus of similar gestational age, the thyroid axis is immature, resulting ultimately in a physiological hypothyroid state.[85,89] T4 levels in the premature infant are low, correlating with gestational age and birth weight, whereas TSH and T3 levels are low to normal.[85,90] The more premature the infant, the more pronounced is the hypothyroidism. Although the reasons for hypothyroidism are multifactorial, the loss of maternal T4 contribution, immaturity of the hypothalamic-pituitary axis, responsiveness of the thyroid gland to TSH, and immaturity of peripheral tissue deiodination contribute significantly.[85] Ultimately, the importance of the hypothyroid state lies in its relation to increased in-perinatal mortality and morbidity, prolonged supplemental oxygen demand, mechanical ventilation, longer hospital stay, and increased occurrence of intraventricular hemorrhage.[91-94] Despite the serious short- and long-term morbidity and mortality related to neonatal hypothyroidism, the evidence to date does not support the routine use of supplemental thyroid hormone in this population.[95-100] In the rare instance of a hypothyroid neonatal patient presenting to the ED, emergency clinicians should not be concerned with emergent intervention or diagnosis of hypothyroidism. It would not be feasible for this diagnosis to be made in the ED. The emergency clinician's responsibility is to provide supportive care for the neonate as indicated by presentation. Diagnosis and definitive treatment of neonatal hypothyroidism is the purview of the neonatal service.

Neonatal Thyrotoxicosis

Neonatal thyrotoxicosis presents rarely but carries a high mortality rate. Maternal severity of the disease directly relates to the occurrence of thyrotoxicosis in infants as well as infant morbidity and mortality due to thyrotoxicosis. In mothers with Graves' disease, the incidence of neonatal hyperthyroidism ranges from 1% to 12.5%. In women requiring treatment with antithyroid drugs to term, the incidence is as high as 22% of children affected.[101-108] Mortality rates range from 12% to 20% in overt neonatal thyrotoxicosis. Mortality typically results from heart failure, tracheal compression, infectious complication, and thrombocytopenia.[109-112] Clinical signs and symptoms of neonatal thyrotoxicosis are similar

to those in adults and may present at birth or be delayed up to 10 days. The delay is related to the effects of maternal antithyroid drugs or the effect of coexistent blocking antibodies.[113,114] Neonates typically present with goiter, irritability, exophthalmos, tachycardia, arrhythmias, hypertension, voracious appetite, weight loss, and diarrhea. The diagnosis in the ED is presumptive and based predominately on history of hyperthyroidism in the mother and physical examination findings in the infant.

Management goals in the thyrotoxic neonate are identical to goals in all other patients: symptomatic control and control of thyroid function. β-blockers effectively control symptoms and inhibit deiodination of T4 to T3, as they do in adults. There are no studies comparing the efficacy of different β-blockers in the neonatal population. Propranolol has been traditionally used in doses of 0.27 to 0.75 mg/kg orally every 8 h. There is a risk of hypoglycemia and cardiovascular collapse with bradycardia and hypotension. Intravenous dosing should be discussed with the neonatologist.

The thioamides, PTU and carbimazole, block further thyroid synthesis and in the case of PTU, inhibit peripheral conversion of T4 to T3. Start PTU at 5 to 10 mg/kg/day orally divided q8 or methimazole at 0.4 to 0.7 mg/kg/day orally divided q8. Consider adding iodine solution, as there may be a delayed clinical response to the thioamides until intrinsic thyroid hormone stores are depleted. Also consider the use of prednisolone at a dose of 2 mg/kg/day orally in the severely thyrotoxic neonate. Prednisolone suppresses deiodination of T4 to T3 and replaces endogenous glucocorticoids lost in the hypercatabolic state induced by T3 and T4.[85] Sedatives may be necessary to manage irritability and restlessness. All critically ill patients require admission to an intensive care unit (ICU). Consult with a neonatologist or pediatric intensivist.

Pregnancy

Myxedema coma is exceedingly rare in the pregnant population. Hypothyroidism is generally related to low fertility rates and high rates of first trimester fetal loss. Fewer than 40 cases in the literature have been reported since 1897.[129] Untreated hypothy-

Pitfalls To Avoid For Thyroid Emergencies (Continued on page 15)

1. **"I thought she was hypothermic because it was cold outside."**
   The vast majority of cases of myxedema coma occur in the winter. The differential diagnosis of hypothermia includes myxedema coma. Do not dismiss all hypothermia to environmental causes.

2. **"I didn't want to start thyroxine until I had laboratory test confirmation of her thyroid status."**
   The use of IV thyroxine has not been shown to be harmful in euthyroid patients. Many facilities batch test their thyroid panels, and results may not be available for several days. If the clinical suspicion exists for myxedema coma, start treatment early. Delays in treatment result in increased mortality.

3. **"She was hypotensive, so I started norepinephrine."**
   Patients with myxedema coma tend to be hypotensive. The first therapy is fluid resuscitation, as these patients are hypovolemic. If patients remain hypotensive after fluid resuscitation, evaluate perfusion. If the patient is perfusing the end organs, continue supportive therapy. Evidence of impaired perfusion indicates the need for vasopressors. The vasopressor of choice is one with low α-adrenergic activity, such as dopamine. α-adrenergic vasopressors, such as norepinephrine and phenylephrine, can precipitate cardiovascular collapse in myxedema coma.

4. **"She had altered mental status because she was septic."**
   Although this is true in many cases, an ED physician should remember to consider the presence of decompensated thyroid conditions in patients with systemic illness. The diagnoses of myxedema coma and thyroid storm are clinical diagnoses. Therefore, the physician must suspect them to diagnose them.

5. **"I sent a TSH. If it's low, I will treat him for thyroid storm."**
   The acute decompensation of thyroid storm is not reflected in the laboratory tests for many hours after the onset of the clinical syndrome. Thyroid storm is a clinical diagnosis. The physician must diagnose thyroid storm based on history and physical examination findings.

6. **"She's confused because she's old and sick."**
   Systemic illness can cause decompensation in a geriatric patient's mental status. The ED physician should always consider the complicating factor of an underlying thyroid disorder in confused patients. This is especially true in geriatric women.

roidism in pregnancy is related to a multitude of maternal and fetal complications, with a literature review showing 44% of pregnant women with untreated hypothyroidism progress to preeclampsia and increased incidence of placental abruption, fetal demise, and perinatal mortality.[130]

Symptoms and signs of hypothyroidism in pregnancy are similar to those of nonpregnant women. Management goals in the pregnant patient presenting in myxedema coma are similar to those in nonpregnant adults. Obstetric guidelines recommend aggressive replacement of thyroid hormone in hypothyroid pregnant women, regardless of the degree of thyroid function, to minimize the time the fetus is exposed to a hypothyroid environment.[131] These recommendations are based on expert opinion.

Hyperthyroidism can be a challenging diagnosis in pregnant women. Low TSH levels with high FT4 levels is diagnostic of hyperthyroidism. However, approximately 15% of pregnant women who are euthyroid have a low TSH in the first trimester.[132, 137]

Controversies/Cutting Edge

Cardiovascular Collapse

There have been numerous case reports of acute hemodynamic collapse after the administration of oral propranolol in patients with diagnosed thyroid storm.[83] Although no specific mechanisms have been elucidated, it is presumed that these particular patients had an associated low output heart failure before the administration of β-blockers. No prospective trials on the use of β-blockers in patients with thyroid storm and concurrent low output heart failure exist. Therefore, one must be cautious when using intravenous, short-acting, titratable β-blockers, such as esmolol, in these patients.

Radiation Emergencies

Widespread existence of nuclear power has drawn the attention of disaster specialists. Preparation for radiation emergencies sparks controversy. The current literature supports the use of a single oral dose of 38 mg iodide for thyroid stabilization in radiation emergencies.[133]

Pitfalls To Avoid For Thyroid Emergencies (Continued from page 14)

7. **"I treated the patient as though she was septic because she had fever, tachycardia, hypertension, and altered mental status."**
   This clinical picture is consistent with both thyroid storm and sepsis. Hypertension can be present in early sepsis, but hypotension is the hallmark of late sepsis. As the conditions can coincide, the ED physician should always consider the role of the thyroid in systemically ill patients.

8. **"I gave the patient T3 for presumed myxedema coma because it works faster than T4."**
   The onset of action is faster with T3 than T4. However, T3 has a higher risk of complications, including cardiac arrhythmias. The standard of care in myxedema coma is to administer T4 intravenously. If the physician only has access to T3, this can be administered.

9. **"The patient has atrial fibrillation and congestive heart failure from thyroid storm. I gave the patient a diuretic for the heart failure and a calcium channel blocker for the heart rate."**
   Patients with a fast heart rate and signs of heart failure may have high output heart failure, which means the heart rate is too fast for the heart to fill in diastole. So, the cardiac output is decreased. The left ventricle may have normal function or may be depressed in these instances. The treatment is to slow the heart rate and reassess the patient. In this sense, the calcium channel blocker is a good choice. However, a β-blocker is the preferred agent in thyroid storm, as it also treats the patient's symptoms of agitation and anxiety and other peripheral effects of thyroid hormone. Patients with thyroid storm are hypovolemic, even if they have pulmonary edema. The administration of a diuretic should be avoided if possible, as this worsens the dehydration and also worsens the cardiac output. When the heart rate has slowed, reassess the patient's oxygenation and ventilation status before administering a diuretic. In patients with underlying cardiac dysfunction complicating the case, the physician must use clinical judgment as to which agent to administer first.

10. **"The patient has thyroid storm, so I gave iodine immediately to stop the production of thyroid hormone."**
    Iodine is an important therapy in thyroid storm, but it must be given 2 h after an antithyroid medication (methimazole or PTU). If given before these medications, iodine will worsen the clinical picture by stimulating the release of increased amounts of thyroid hormone. A patient may not be in the ED long enough for the ED physician to administer this medication.

Screening

Recent recommendations support screening for hypothyroidism in all geriatric women who have respiratory distress, confusion, or hypothermia and all geriatric patients who are admitted to the hospital, as the incidence is high in these populations.[50,55] This diagnosis may be outside the role of the emergency clinician.

Disposition

Most patients with myxedema coma or thyroid storm require intensive care admission. Myxedema coma is by definition an alteration in mental status and thus requires admission. Patients require intensive cardiovascular monitoring for worsening of the thyroid crisis as well as for adverse effects of the treatment. Continuous intravenous infusions generally require ICU admission. In addition, mortality rates for myxedema coma and thyroid storm still exceed 20% despite modern therapies. Prognostic factors for those in thyroid storm have not been reported. A number of poor prognostic factors in myxedema coma have been reported in the literature.[64,66,134] (**See Table 8.**).

Although the prognosis of patients with myxedema coma is difficult to determine, case series demonstrate consistently poor predictors of outcome, as reported in the literature, including bradycardia, persistent hypothermia, altered level of consciousness, a high APACHE II score at presentation, hypotension, need for mechanical ventilation, precipitation of myxedema coma by use of sedatives, accompanying sepsis, and baseline and mean SOFA scores greater than or equal to 6. Advanced age was not consistently reported as predictive of increased mortality in myxedema coma when survivors and nonsurvivors were compared.[135,136]

Patients who are stable, have mild symptoms that improve in the ED, and do not require continuous infusions of cardiovascularly active medications are candidates for admission to a telemetry unit. This is more commonly seen in thyroid storm because of the rapid effects of β-blocking agents. Myxedema coma patients rarely have an accelerated recovery.

No formal admission or discharge criteria for those with mild to moderate thyroid disease have been reported to the author's knowledge. Patients with clinical signs and symptoms of hypothyroidism may be discharged from the ED for evaluation and treatment by the primary care physician. Patients with minor symptoms of hyperthyroidism, such as subjective palpitations, heat intolerance, anxiety, and weight loss, may be discharged if no signs of cardiac instability are present. Patients with tachycardias that respond to β-blockers in the ED without other cardiovascular manifestations of thyrotoxicosis are also candidates for discharge from the ED. Patients with atrial fibrillation that is controlled in the ED who have a known diagnosis of hyperthyroidism may be candidates for discharge if appropriate follow-up can be arranged.

Summary

Thyroid crises masquerade as many illnesses. Iden-

Cost- And Time-Effective

1. If myxedema coma is likely based on available history and physical examination, start thyroid replacement therapy. The clinical improvement in patients with myxedema coma is prolonged. Delaying treatment not only increases the risk of mortality but also increases the duration of the stay in the ICU.
2. Avoid ordering complex endocrinologic tests from the ED. A TSH, FT4, T3, and random cortisol level ordered from the ED may assist consultants. However, these tests will need to be repeated in the course of the patient's hospitalization. Most tests of endocrine function are not time sensitive and can await consultation and recommendation by the endocrinologist.
3. Aggressively control the peripheral effects of thyroid hormone in thyroid storm. Quickly titrating a continuous intravenous infusion of a β-blocking agent to control symptoms and signs of hyperthyroidism saves physician and nursing time and more rapidly improves patient symptomatology. The more quickly the patient is stabilized, the more quickly the patient can be transitioned to oral medication to avoid an ICU admission. A stepwise approach with repeated boluses or a trial of oral medication before intravenous medication delays the alleviation of patient symptoms, delays disposition of the patient, and requires multiple changes in therapy. Although the oral or repeated intravenous bolus is less expensive from a pure drug cost, the increased nursing time and prolonged ED stay make this a non–cost-effective strategy.
4. Appropriately address the patient's volume status. Most patients with a thyroid crisis are hypovolemic. Beginning appropriate fluid resuscitation early in the patient evaluation expedites the patient's recovery. Reassess the patient often to gauge the response to fluid therapy.

tification of these processes is difficult and requires a high index of suspicion. Clinical diagnosis is necessary in the ED, as no emergent confirmatory test exists. The treatment is unique and can be intimidating because of the severity of possible adverse effects. The replacement of thyroid hormone and inhibition of thyroid hormone production has not changed much in the past 2 decades. Choices of vasopressor agents and β-blocking agents have broadened. However, a clear "correct" choice cannot be defined, as thyroid crises often coexist with other acute and chronic diagnoses. The emergency clinician should focus on treatment of the thyroid, supportive care, and identification of coexistent acute processes.

Case Conclusions

Case #1: You identify a left femoral neck fracture in the patient. With little clinical history, you try to determine the events of the past 3 days. You evaluate the patient for acute processes that may have caused a fall, such as intracranial hemorrhage, ischemic stroke, and myocardial infarction. You also evaluate the patient for sequelae of a simple trip and fall that may have left her with altered mental status, including intracranial hemorrhage and withdrawal from chronic medications. The well-healed scar on her anterior neck suggests that the patient had a thyroidectomy. Perhaps the patient fell, broke her hip, and subsequently was unable to access her levothyroxine to maintain her euthyroid state. The patient requires intubation because of her respiratory failure (respiratory rate of 10) and predicted clinical course, which is likely a prolonged recovery. After intubation, you evaluate her cardiac function and inferior vena cava with bedside ultrasound to assess her fluid status and her ability to tolerate a fluid bolus. She is hypovolemic but has reasonable left ventricular function. The ultrasound suggests that fluid resuscitation should improve her blood pressure without the use of vasopressors at this time. You administer levothyroxine intravenously. You notify the intensivist of a suspicion of myxedema coma due to the inability to access medications following a trip and fall with a resultant hip fracture. The intensivist promptly admits the patient and will contact the orthopedist to plan a repair when the patient is stable.

Case #2: The clinical presentation in this patient suggests pneumonia, which is confirmed by a focal infiltrate on his CXR. Treatment of the fever with acetaminophen has little effect on his tachycardia. An ECG reveals atrial fibrillation. You suspect that the goiter is a thyroiditis, and this infection has worsened his hypothyroidism. A continuous intravenous infusion of a β-blocking agent rapidly improves the patient's tremor, anxiousness, and heart rate. You administer PTU orally. After about 1 h on a continuous infusion, the cardiac rhythm converts to a sinus rhythm at a rate of 88 beats per min. You wean the intravenous infusion, starts oral iodide, and begins an oral β-blocking agent. You demonstrate prompt response to therapy and has no comorbidities to require admission to the hospital for community-acquired pneumonia. The patient is a good candidate for discharge if appropriate follow-up can be arranged. You contact the primary care physician, who will see the patient tomorrow and who tells the emergency clinician that the patient is also in the care of an endocrinologist with whom the primary physician works closely. The patient is comfortable with the plan for outpatient management and happy with the dramatic improvement in his symptoms.

Both of these cases allow reflection on the common occurrence of dual diagnoses in thyroid crises. Without a good index of suspicion, the thyroid crises could have been overlooked. These cases reinforce the importance of taking in the entire clinical picture and looking beyond the obvious initial diagnosis.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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Table 8. Poor Prognostic Factors In Myxedema Coma

- Persistent hypothermia lasting > 3 days despite therapy
- Initial body temperature < 93°F (33.88°C)
- Bradycardia < 44 beats per min
- Associated sepsis
- Associated myocardial infarction
- Persistent hypotension
- High APACHE II score at presentation
- Need for mechanical ventilation
- Precipitation of myxedema coma by use of sedatives
- Baseline and mean SOFA scores ≥ 6

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CME Questions

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1. **The differential diagnosis of thyroid storm includes all of the following EXCEPT:**
   a. Hypoglycemia
   b. Hypoxia
   c. Sepsis
   d. Heat stroke
   e. Gastrointestinal bleeding

2. **The differential diagnosis of myxedema coma includes all of the following EXCEPT:**
   a. Conversion disorder
   b. Cerebrovascular accident
   c. Acute myocardial infarction
   d. Hyponatremia
   e. Opioid withdrawal

3. **Symptoms of profound thyrotoxicosis include:**
   a. Fever
   b. Tachycardia
   c. Tremors
   d. All of the above

4. **Which medication is contraindicated in thyroid storm?**
   a. Aspirin
   b. Acetaminophen
   c. Metoprolol
   d. Propanolol

5. **When is the most common time of occurrence of myxedema coma?**
   a. Summer
   b. Fall
   c. Spring
   d. Winter

6. **The disposition of patients with suspected myxedema coma is best summarized as:**
   a. Admission to the ICU is most commonly required.
   b. The patient can be discharged with close follow-up.
   c. The patient can be transitioned to an observation unit from the ED.
   d. The patient can be discharged with routine follow-up.

7. **Which thyroid hormone is the most physiologically active?**
   a. T4
   b. T3
   c. TSH
   d. Progesterone

June 2009 Errata

In the June 2009 issue of *Emergency Medicine Practice,* "The Diagnosis And Treatment Of STEMI In The Emergency Department," Table 7 has a dosing error. The correct dosing for enoxaparin is as follows.

Patients < 75 y with serum Cr < 2.5 mg/dL (men) or < 2.0 mg/dL (women): 30-mg IV bolus, followed by 1.0-mg/kg SC injection q12h

Patients ≥ 75 y: 0.75-mg/kg SC injection q12h

Patients with serum CrCl < 30 mL/min: 1.0-mg/kg SC injection every day

We regret this error and apologize for any confusion.

Physician CME Information

Date of Original Release: August 1, 2009. Date of most recent review: May 26, 2009. Termination date: August 1, 2012.

Accreditation: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of EB Medicine. EB Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals & Objectives: Upon completion of this article, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Discussion of Investigational Information: As part of the newsletter, faculty may be presenting investigational information about pharmaceutical products that is outside Food and Drug Administration-approved labeling. Information presented as part of this activity is intended solely as continuing medical education and is not intended to promote off-label use of any pharmaceutical product. **Disclosure of Off-Label Usage:** This issue of *Emergency Medicine Practice* discusses contrast agents in thyroid storm as well as esmolol and metoprolol.

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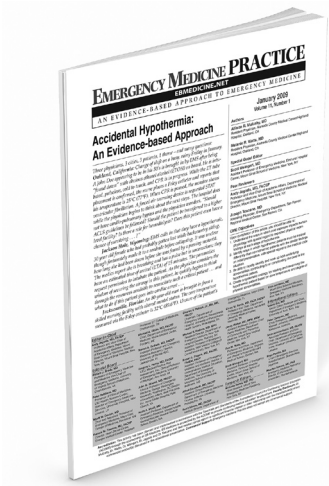

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Identifying And Treating Thyroid Storm And Myxedema Coma In The Emergency Department

Mills L. August 2009; Volume 11, Number 8

This issue of Emergency Medicine Practice reviews the fundamental principles of the management of thyroid emergencies using a focused, evidence-based approach to the literature. For a more detailed discussion of this topic, including figures and tables, clinical pathways, and other considerations not noted here, please see the complete issue at www.ebmedicine.net/topics.

Key Points	Comments
Keep myxedema coma in mind in patients with underlying thyroid disease, geriatric patients, and women with respiratory distress, hypothermia, or altered mental status.[2]	Myxedema coma has a broad differential diagnosis, including hypoglycemia, hypoxia, sepsis, hypothermia, conversion disorder, cerebrovascular accident, acute myocardial infarction, intracranial hemorrhage, panhypopituitarism, adrenal insufficiency, hyponatremia, and gastrointestinal bleeding.
Search for a precipitating event.[30] Dual diagnoses are common.	Factors precipitating thyroid decompensation include cold weather, infection, medication nonadherence, acute congestive heart failure, myocardial infarction, stroke, new medications, intoxication, and thyroid ablation.
Myxedema coma and thyroid storm are clinical diagnoses. Take action based on the history and constellation of signs and symptoms.	If myxedema coma is based on available history and physical examination, start thyroid replacement therapy.[64] The clinical improvement in patients with myxedema coma is prolonged. Delaying treatment not only increases the risk of mortality but also increases the duration of the stay in the ICU.
Patients may deteriorate quickly despite critical interventions. Be prepared for hemodynamic and respiratory compromise despite aggressive supportive care.	Emergently intubate patients with respiratory failure, those unable to protect their own airway, and those for whom the predicted clinical course is poor. In patients with large goiters and a hyperdynamic state, upper airway edema and a large anterior neck mass inhibit direct laryngoscopy and passage of the endotracheal tube, presenting special considerations.[114-116]
In thyroid storm, initial thyroid laboratory test results will be normal.[43,44]	Ordering complex endocrinologic tests from the ED should be avoided as these tests will be repeated in the course of the patient's hospitalization.
Keep in mind that a number of serious illnesses mimic and coexist with thyroid storm.	The differential diagnosis includes delirium of any etiology, hypoglycemia, hypoxia, sepsis, encephalitis/meningitis, hypertensive encephalopathy, alcohol withdrawal, benzodiazepine/barbiturate withdrawal, opioid withdrawal, and heat stroke.
Focus initial efforts in the emergency department on respiratory and cardiovascular stabilization. In addition, start cardiac monitoring, begin continuous pulse oximetry, determine blood glucose levels and core temperature, and establish intravenous access.	Note that patients presenting with an altered level of consciousness may require emergency definitive airway control.
Include a thorough past medical history, including questions about recent medication changes, recent anesthesia, infectious prodromes, radiologic imaging that required an oral or intravenous iodinated contrast agent, and thyroid manipulation.	Some of the most important historical facts to elicit are recent precipitants, such as exposure to cold, infection, major life stress, and trauma.
Target essential concerns during the physical examination. Patients with profound thyrotoxicosis classically present febrile, tachycardic, and tremulous.	The patient's age plays a significant role in the clinical signs likely to be present. Weight loss and atrial fibrillation have been found to be the most common clinical findings of hyperthyroidism in patients older than 50 years.[19,20,22,23]

** See reverse side for reference citations.*

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These references are excerpted from the original manuscript. For additional references and information on this topic, see the full text article at ebmedicine.net.

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