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High risk and low prevalence diseases: Thyroid storm

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ABSTRACT

Introduction: Thyroid storm is a rare but serious condition that carries a high rate of morbidity and even mortality.
Objective: This review highlights the pearls and pitfalls of thyroid storm, including presentation, diagnosis, and management in the emergency department (ED) based on current evidence.
Discussion: Thyroid storm is a challenging condition to diagnose and manage in the ED. It is characterized by exaggerated signs and symptoms of thyrotoxicosis and evidence of multiorgan decompensation, usually occurring in the presence of an inciting trigger. Clinical features of thyroid storm may include fever, tachycardia, signs of congestive heart failure, vomiting/diarrhea, hepatic dysfunction, and central nervous system disturbance. There are several mimics including sympathomimetic overdose, substance use disorders, alcohol withdrawal, acute pulmonary edema, aortic dissection, heat stroke, serotonin syndrome, and sepsis/septic shock. Ultimately, the key to diagnosis is considering the disease. While laboratory assessment can assist, there is no single laboratory value that will establish a diagnosis of thyroid storm. Clinical criteria include the Burch-Wartofsky point scale and Japan Thyroid Association diagnostic criteria. ED treatment focuses on diagnosing and managing the trigger; resuscitation; administration of steroids, thionamides, iodine, and cholestyramine; and treatment of hyperthermia and agitation. Beta blockers should be administered in the absence of severe heart failure. The emergency clinician should be prepared for rapid clinical deterioration and employ a multidisciplinary approach to treatment that involves critical care and endocrinology specialists.
Conclusions: An understanding of thyroid storm can assist emergency clinicians in diagnosing and managing this potentially deadly disease.

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1. Introduction

This article series addresses high-risk, low-prevalence diseases that are encountered in the emergency department (ED). Much of the primary literature evaluating these conditions is not specific to emergency medicine. By their nature, many of these diseases and presentations have little useful evidence available to guide the emergency physician in diagnosis and management. The format of each article defines the disease or clinical presentation to be reviewed, provides an overview of the extent of what we currently understand, and finally discusses pearls and pitfalls using a question-and-answer format. This article will discuss thyroid storm. This condition's low prevalence but high morbidity and mortality, as well as its variable atypical presentations and challenging diagnosis, makes it a high-risk and low-prevalence disease.

1.1. Definition

It is important to distinguish between the terms hyperthyroidism and thyrotoxicosis, which are often inappropriately conflated. Hyperthyroidism occurs as the result of excessive synthesis and secretion of thyroid hormone from the thyroid gland, whereas thyrotoxicosis refers to the clinical manifestation of symptoms due to excess T3 and T4 in peripheral tissues regardless of the source [1]. Thyrotoxicosis is a condition with a spectrum of severity that ranges from subclinical to overt thyrotoxicosis; at its most extreme, with severe end organ dysfunction, is thyroid storm [2].

Thyroid storm was first defined in 1926 as a crisis of exophthalmic goiter [3], seen as an exacerbation of Graves' disease with exaggerated findings of hyperthyroidism. Although thyroid storm most commonly occurs in patients with untreated or uncontrolled Graves' disease [4], there are a variety of etiologies, and it can affect patients with previously unrecognized hyperthyroidism [5]. The modern definition of thyroid storm is a life-threatening condition characterized by (1) exaggerated signs and symptoms of thyrotoxicosis and (2) evidence of multiorgan decompensation [5]. Patients typically demonstrate some alteration in

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mental status, along with hyperpyrexia and cardiovascular dysfunction [2-4]. This pathologic state often arises in the presence of a precipitating event, which can include interruption in drug therapy for hyperthyroidism or medication non-adherence, infection, thyroid/non-thyroid surgery, parturition, trauma, exposure to exogenous iodine, or use of a medication such as amiodarone [5-10]. To add to the complexity of this disease process, 24–43% of cases have no identifiable trigger [5,11].

1.2. Pathophysiology

The hypothalamus produces thyrotropin-releasing hormone (TRH) which stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH) [11]. TSH then binds to specific receptors on the thyroid gland to prompt a cascade of intracellular processes to generate thyroxine (T4) and triiodothyronine (T3). This cascade begins with the transport of iodide into the thyroid follicular cell. Thyroid peroxidase (TPO) then iodinates tyrosine residues on thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) molecules. The coupling of one MIT and one DIT molecule forms triiodothyronine (T3), and the coupling of two DIT molecules forms thyroxine (T4)[10]. T3 is the more potent, biologically active thyroid hormone [12]. Approximately 10–20% of circulating T3 is secreted by the thyroid gland, but the remainder is the result of peripheral conversion of T4 to T3 via 5′-deiodinases (D1 and D2) [13]. In a normal state, 99% of T3 and T4 is bound to thyroid binding globulin (TBG), transthyretin, and albumin; free hormone is available for uptake by tissues [14]. T3 and T4 possess negative feedback control on both the hypothalamus and the pituitary [11] (Fig. 1).

Thyrotoxicosis results from any cause of excessive thyroid hormone concentration, with thyroid storm representing an extreme manifestation of thyrotoxicosis [10]. However, the process by which thyroid storm arises is not as well understood. Thyroid storm may arise from a heightened tissue response to thyroid hormone, enhanced binding to thyroid receptors, decreased affinity of thyroid-binding proteins for thyroid hormone, and/or an abrupt increase in free thyroid hormone availability [5,7,10,15]. Absolute values of circulating thyroid hormone may be similar in patients with thyroid storm and in those with uncomplicated hyperthyroidism [11]. Therefore, the rate of thyroid hormone level increase is likely more important than the absolute values themselves [5,11,16].

The loss of homeostatic interaction between thyroid hormone and the sympathoadrenal system is also implicated in thyroid storm [17]. In hyperthyroid states, increased beta-adrenergic receptor density and upregulation of L-type dihydropyridine-sensitive calcium channels and plasma membrane calcium ATP-ase lead to enhanced responsiveness to endogenous catecholamines [18]. This results in tachycardia, increased cardiac contractility, and rise in metabolic demand that are central to the cardiovascular manifestations of thyroid storm [18].

1.3. Epidemiology

The prevalence of hyperthyroidism in the U.S. is 1.2% [19]. The incidence of thyroid storm ranges between 0.20 and 0.76 per 100,000 persons per year, with an incidence of 4.8–5.6 per 100,000 hospitalized patients [6,7,20]. Of those hospitalized with thyrotoxicosis in the U.S., thyroid storm is diagnosed in 16% [20,21]. Prior studies suggested a

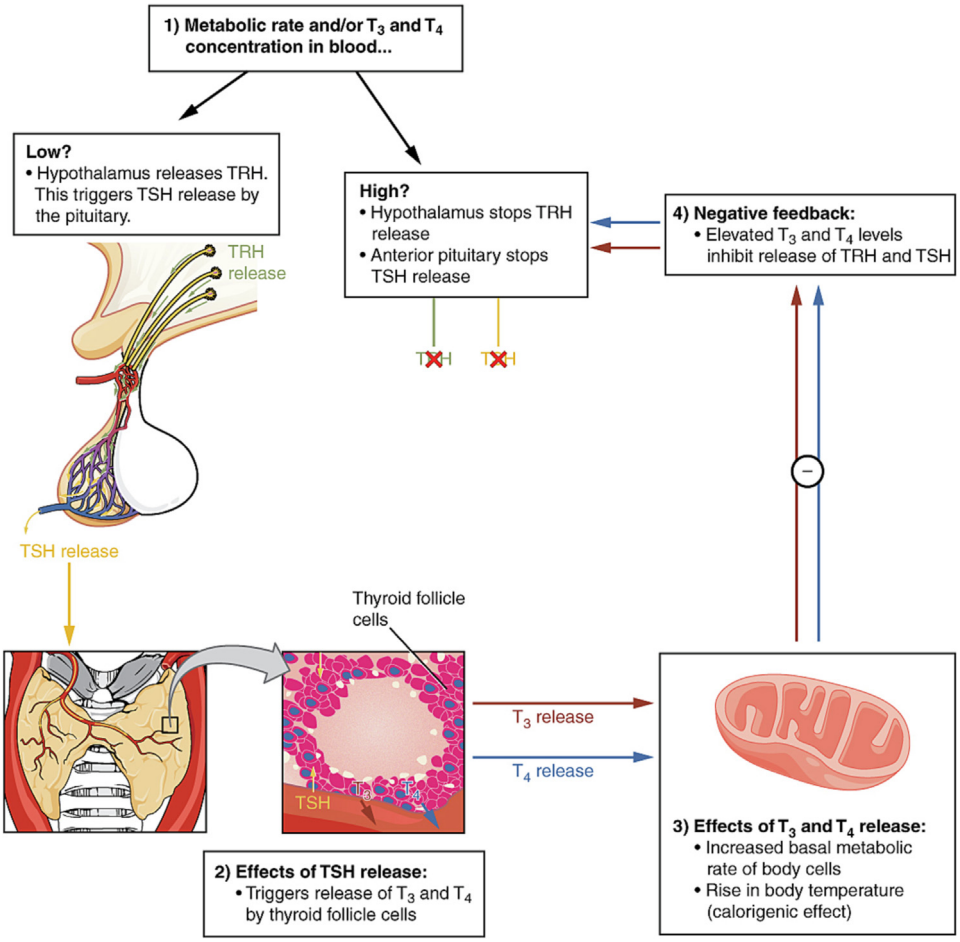

Fig. 1. Thyroid hormone activity and feedback loops. https://commons.wikimedia.org/wiki/File:1813_A_Classic_Negative_Feedback_Loop.jpg.

mortality rate ranging between 8 and 30% for those with thyroid storm [6], but more recent literature suggests the rate is 1.2%–3.6% in the U.S., which may be due to high-quality, aggressive intensive care [20]. Thyroid storm occurs most commonly in patients with underlying Graves' disease and those who are non-adherent with treatment for hyperthyroidism [11,22,23]. The majority of cases occur in women, with an average age of 50 years [20]. The most common cause of death in thyroid storm is multisystem organ failure, followed by congestive heart failure, respiratory failure, dysrhythmia, disseminated intravascular coagulation (DIC), gastrointestinal (GI) perforation, hypoxic brain injury, and sepsis [4,6].

2. Discussion

2.1. Presentation

Thyroid hormone receptors are ubiquitous in the human body, and deiodinases that are responsible for converting T4 to T3 are expressed in every organ system. This, in addition to the adrenergic hyperactivity of a profound thyrotoxic state, accounts for the vast array of clinical manifestations of thyroid storm. The most common of these are summarized in Table 1, with hyperpyrexia, cardiovascular dysfunction, and altered mental status present in almost all cases [5,7].

In addition to the presentations above, there exist case reports of thyroid storm presenting as a multitude of other disease entities, including severe abdominal pain with peritonitis, status epilepticus, rhabdomyolysis, hypoglycemia, lactic acidosis, and DIC [24–27].

2.2. ED evaluation

Thyroid storm poses a diagnostic challenge due to its varied and nonspecific presentation. Evaluation including complete blood count (CBC), electrolytes, renal and liver function, creatine kinase, coagulation panel, TSH, free T4 and T3, electrocardiogram (ECG), and urinalysis are recommended. Although laboratory testing will not diagnose thyroid storm in isolation, it serves as an important adjunct. TSH is most commonly suppressed with elevated T4 and T3 levels, although critical illness itself may lower T3 levels [28]. Furthermore, there is often no difference in thyroid hormone levels between patients with thyroid storm and those with uncomplicated hyperthyroidism [5,7,11,15]. Leukocytosis is common and can be present with or without underlying infection [5]. Patients with thyroid storm may also have decreased renal function, liver function test (LFT) derangements, hypercalcemia due to increased bone resorption, or abnormal serum glucose (usually hyperglycemia and rarely hypoglycemia) [5,10,27,29]. Further testing is based on clinical presentation. Patients presenting with altered mental status should receive head computed tomography (CT) noncontrast, while blood cultures and chest radiograph should be obtained in those with concern for infection. If toxic ingestion is suspected, acetaminophen and salicylate levels should be obtained.

Diagnosis of thyroid storm is based on the presence of severe signs and symptoms with evidence of thyrotoxicosis. There is no single set of clinical criteria, laboratory testing, or thyroid hormone threshold that will establish a diagnosis of thyroid storm, though there are two scoring systems that may assist, including the Burch-Wartofsky scale and the Japan Thyroid Association criteria. In 1993, Burch and Wartofsky formulated a novel scoring system in an effort to standardize the diagnosis (Table 2) [4,6,15]. The other most often-used set of diagnostic criteria was proposed by the Japan Thyroid Association in 2012 (Table 3) [6]. Unlike Burch and Wartofsky's scale, thyrotoxicosis is a prerequisite condition when applying the Japan Thyroid Association diagnostic criteria.

2.3. ED management

With the high morbidity and mortality associated with thyroid storm, emergent resuscitation while determining and treating the underlying trigger is necessary. Infection is the second most common trigger for thyroid storm, and thus early administration of broad-spectrum antibiotics is recommended [4]. Management of thyroid storm includes cardiovascular stabilization; administration of steroids, thionamides, iodine, and cholestyramine; and treatment of hyperthermia and agitation [5,7,30]. Beta blockers are recommended as well in the majority of patients with thyroid storm. Beyond the insensible fluid losses from fever, patients with thyroid storm often have vomiting and diarrhea resulting in severe dehydration. However, IV fluids should be

Table 1
Common presentations of thyroid storm.[5]

System	Signs and symptoms
Systemic	• Fever is nearly universal (may reach 104-106F) • Diaphoresis • Weight loss
Cardiovascular	• Tachycardia (sinus tachycardia, atrial fibrillation, ventricular fibrillation) • Systolic heart failure with pulmonary and peripheral edema • High-output heart failure (vasodilated, warm peripheral extremities) • Wide pulse pressure with systolic hypertension
Gastrointestinal	• Nausea, vomiting, diarrhea • Abdominal pain • Jaundice, hepatic injury/failure
Neurologic	• Tremor, restlessness • Agitation, anxiety, delirium, emotional lability, hallucinations • Confusion, stupor, coma
Other	• Goiter • Scar from partial thyroidectomy • Exophthalmos

Table 2
Burch-Wartofsky point scale for diagnosis of thyroid storm.[15]

Criteria	Points
Thermoregulatory dysfunction	
Temperature (°C)	5
37.2–37.7	10
37.8–38.3	15
38.4–38.8	20
38.9–39.3	25
39.4–39.9	30
≥40.0	
Cardiovascular	
Tachycardia (bpm)	5
90–109	10
110–119	15
120–129	20
130–139	25
≥140	
Atrial fibrillation	
Absent	0
Present	10
Congestive heart failure	
Absent	0
Mild	5
Moderate	10
Severe	15
Gastrointestinal dysfunction	
Absent	0
Moderate (diarrhea, abdominal pain, nausea/vomiting)	10
Severe (jaundice)	20
Central nervous system disturbance	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
Precipitating event	
Absent	0
Present	10
Total Score	
≥45	Thyroid storm
25–44	Impending storm
<25	Storm unlikely

Table 3
Japanese Thyroid Association diagnostic criteria for thyroid storm.[4,6]

Prerequisite for diagnosis
Presence of thyrotoxicosis with elevated levels of free triiodothyronine (FT3) or free thyroxine (FT4)

Symptoms
1. Central nervous system (CNS) manifestations: restlessness, delirium, mental aberration/psychosis, somnolence/lethargy, psychosis (≥1 on the Japan Coma Scale or ≤14 on the Glasgow Coma Scale)
2. Fever (≥38 °C)
3. Tachycardia: ≥130 beats per minute or heart rate ≥ 130 in atrial fibrillation
4. Congestive heart failure (CHF): pulmonary edema, moist rales over more than half of the lung field, cardiogenic shock, or class IV by the New York Heart Association or ≥Class III in the Killip classification
5. Gastrointestinal (GI)/hepatic manifestations: nausea, vomiting, diarrhea, or a total bilirubin ≥3.0 mg/dL

Grade of thyroid storm (TS)	Combinations of features	Requirements for diagnosis
TS1 (definite thyroid storm)	First combination	Thyrotoxicosis + at least 1 CNS manifestation + fever, tachycardia, CHF, or GI/hepatic manifestation
	Alternate combination	Thyrotoxicosis + at least 3 combinations of fever, tachycardia, CHF, or GI/hepatic manifestations
TS2 (suspected thyroid storm)	First combination	Thyrotoxicosis + a combination of 2 of the following: fever, tachycardia, CHF, or GI/hepatic manifestations
	Alternate combination	Patients who met the diagnosis of TS1 except that serum FT3 or FT4 level are not available

Exclusion and provisions:
Cases are excluded if other underlying diseases clearly causing any of the following symptoms: fever (i.e., pneumonia and malignant hyperthermia), impaired consciousness (i.e., psychiatric disorders and cerebrovascular disease), heart failure (i.e., acute myocardial infarction), and liver disorders (i.e., viral hepatitis and acute liver failure). Therefore, it is difficult to determine whether the symptom is caused by thyroid storm or simply a manifestation of an underlying disease; the symptom should be regarded as being due to a thyroid storm that is caused by these precipitating factors. Clinical judgment in this matter is required.

administered with caution, with frequent assessments of fluid-responsiveness due to concern for decompensated heart failure and fluid overload. If the patient appears dehydrated on history and examination, IV fluids are recommended [5,7,30]. Vasopressors may be needed to improve peripheral perfusion. Beta blockers may be administered in thyroid storm to manage adrenergic hyperactivity, often manifested as profound tachycardia. Propranolol has traditionally been used due to its ability to decrease peripheral conversion of T4 to T3. Of note, there is a risk of beta blockers precipitating cardiogenic shock in those with severe, overt heart failure. However, if there is no evidence of severe heart failure, beta blockers are recommended. If beta blockers are administered, short-acting intravenous agents like esmolol are preferred [4].

Steroids play an integral role in blocking T4 release from the thyroid and conversion of T4 to T3, and they also treat any concomitant adrenal insufficiency [30,31]. Hydrocortisone 300 mg IV loading dose followed by 100 mg every 8 h is recommended, though dexamethasone (8 mg/day) may also be used [4,30].

Thionamides such as propylthiouracil (PTU) and methimazole reduce new thyroid hormone synthesis. While both inhibit TPO, PTU also has the added benefit of inhibiting peripheral conversion of T4 to T3 [4,30]. PTU is the preferred agent in the first trimester of pregnancy due to its lower risk of teratogenicity [32]. However, methimazole may be safer overall with fewer adverse effects compared to PTU and is recommended in the second and third trimesters of pregnancy [4,33]. Inorganic iodine inhibits new thyroid hormone production and blocks release of preformed T3 and T4 from thyroglobulin [4,34,35]. Iodine should be given 1 h after the thionamide to avoid it being used as a substrate for new thyroid hormone production [30]. Cholestyramine may be used, as it binds thyroid hormone in the intestinal system and reduces enterohepatic absorption [36-38].

Patients may demonstrate severe hyperthermia and agitation. Hyperthermia is primarily due to increased tissue heat generation and results in increased cardiac demand and end organ damage. Management includes acetaminophen, along with peripheral cooling techniques (i.e., ice packs in groin/axillae, cooling blankets) [4,5,19]. However, non-steroidal anti-inflammatory drugs or salicylates should be avoided [5,39]. Agitation may also worsen hyperthermia. Options for treatment include benzodiazepines or olanzapine [4].

Early consultation with critical care, endocrinology, and potentially the cardiology specialists is an integral component of management. Patients with thyroid storm should be admitted to an intensive care unit. Depending on severity of illness and end organ dysfunction, this may require transfer to a facility that is capable of managing advanced heart, renal, and/or liver failure.

3. Pearls and pitfalls

3.1. What are common and uncommon triggers of thyroid storm?

There are many potential triggers of thyroid storm, and diagnosing and managing the trigger are essential to improving patient outcomes. Abrupt discontinuation of antithyroid medications and infection are the most common underlying triggers [5,6,10,15]. However, when

Table 4
Precipitants of thyroid storm.[6,40]

Most common causes	• Underlying Graves' disease • Infection • Treatment non-adherence, or interrupted treatment, with antithyroid medications
Other common causes	• Amiodarone • Emotional stress • Non-thyroid surgery • Preeclampsia • Pregnancy/labor • Psychosis • Trauma
Rarer causes	• Thyroid surgery (previously a common trigger but is now rare given advances in adequate preoperative preparation) • Postpartum thyroiditis • Struma ovarii • Molar pregnancy • Toxic multinodular goiter (most common in low- and middle-income countries due to associated dietary iodine deficiency) • Metastatic thyroid cancer • Radioiodine exposure or treatment • Thyroid hormone overdose (either intentional or accidental) • Treatment with checkpoint inhibitors • Vigorous palpation of the thyroid gland • Post-viral thyroiditis • Suppurative thyroiditis (more common in the immunocompromised) • Salicylate toxicity • Organophosphate toxicity • Neurotoxins • Cytotoxic chemotherapy (i.e., interferon) • Burns • Myocardial infarction • Pulmonary embolism • Stroke • Diabetic ketoacidosis • Hypoglycemia • H1N1 infection • Intense exercise

considering precipitants of thyroid storm, 25%–43% of patients will not have an identifiable trigger [5,11]. Table 4 lists both the most common triggers and rarer precipitants of thyroid storm.

3.2. When should thyroid storm be considered?

Due to the variety of presenting signs and symptoms, rarity of thyroid storm, and severe morbidity and mortality, diagnosis is vital but can be challenging. One of the main components of diagnosis is first considering the disease. Thyroid storm should be considered in any patient with known hyperthyroidism plus any acute illness/deterioration, new-onset atrial fibrillation and/or dilated cardiomyopathy, new-onset delirium/psychosis plus abnormal vital signs, hyperthermia (temperature above ~40 °C), sepsis without a focus of infection (i.e., distributive shock of unknown etiology), and advanced age, as elderly patients may present with apathetic thyroid storm.

Elderly patients warrant special consideration. The majority of thyrotoxic patients over 61 years have fewer than three classic presenting symptoms [41]. A condition called apathetic thyrotoxicosis, or masked hyperthyroidism, has been described in older patients, characterized by apathy, depression, profound weight loss, muscle weakness and wasting, ptosis, dry skin, mild tachycardia, and often congestive heart failure [42]. Although it may present atypically, apathetic thyrotoxicosis remains just as potentially fatal [3]. In these cases, thyroid studies may provide helpful information to establish a diagnosis. Of the signs and symptoms that are commonly associated with thyrotoxicosis, elderly patients often present with atrial fibrillation, shortness of breath, and weight loss [41].

3.3. What conditions may mimic thyroid storm?

Thyroid storm is a difficult diagnosis, in part because there are multiple conditions which mimic it. Table 5 describes several of these conditions and considerations that can assist in differentiating them from thyroid storm.

Table 5
Thyroid storm mimics [43-52].

Diagnosis	Considerations
Acute pulmonary edema	• Typically occurs in the context of established structural cardiac disease; history of coronary artery disease and/or myocardial infarction • History may include paroxysmal nocturnal dyspnea, orthopnea, exertional dyspnea, peripheral edema, decreased exercise tolerance • Examination may reveal rales, wheezing, peripheral edema, dyspnea, hypoxia, S3 gallop, jugular venous dissension may be present on examination • Chest x-ray with pulmonary venous congestion, interstitial edema, and/or cardiomegaly; point-of-care ultrasound with sonographic B lines • Treatment includes airway management with supplemental oxygen and noninvasive positive pressure ventilation as needed, preload and afterload reduction with nitroglycerin, diuresis
Aortic dissection	• History may include sudden onset tearing/ripping chest pain radiating to between the scapulae, sense of impending doom, abdominal pain, back pain, syncope, stroke symptoms, history of hypertension or collagen vascular disorders, history of cocaine or amphetamine use, history of cardiac surgery • Examination may reveal neurological or pulse deficits, aortic insufficiency murmur, hypertension, hypotension, shock • Imaging with CT with IV contrast is diagnostic evaluating for dissection and false lumen; chest x-ray may demonstrate pleural effusion, tracheal deviation, abnormal aortic contour, and/or widened mediastinum; point-of-care ultrasound may be used to demonstrate false lumen and evaluate for tamponade • Treatment includes resuscitation, consult surgical specialist, provide heart rate control and blood pressure control
Alcohol withdrawal	• History of chronic alcohol use with recent discontinuation or reduction, nausea, vomiting, headache, appetite loss • Examination may reveal tremor, agitation, tachycardia, hypertension, diaphoresis, insomnia, fever, anxiety, seizures, psychosis • Evaluate for metabolic derangement, toxic alcohol ingestion, drug ingestion, primary seizure disorder, intracranial hemorrhage, and/or infection • Treatment includes benzodiazepines, phenobarbital, seizure management
Neuromuscular disease	• History may reveal a hereditary component (i.e., hypokalemic periodic paralysis), malaise, weakness, cramps, paresthesias • Examination may reveal fasciculations, paralysis, tetany • Evaluation should include electrolytes and ECG • Treatment includes correction of metabolic derangements, intubation and mechanical ventilation as needed, neurology consultation
Pheochromocytoma	• History includes episodes of headache, flushing, diaphoresis • Examination may reveal severe hypertension, tachycardia • Testing includes 24-h urine assay, plasma fractionated metanephrines • Treatment includes IV phentolamine, resection
Serotonin syndrome	• History of serotonergic medication use • Examination may reveal altered mental status, agitation, dysautonomia, muscle rigidity, tremor, hyperreflexia, myoclonus, ataxia • Diagnosis is based on history and examination; electrolytes, creatine kinase, ECG, and evaluation for metabolic acidemia can assist • Treatment includes discontinuation of offending medication, benzodiazepines, supportive care, mechanical ventilation as needed
Salicylate toxicity	• History includes ingestion, either accidental or intentional • Examination may reveal altered mental status, tachypnea, fever, nausea, vomiting, tinnitus, hearing loss, diaphoresis, agitation, lethargy, confusion, seizure, coma • Evaluation includes serial salicylate levels, electrolytes, renal function, acetaminophen level, determination of acid-base status, ECG • Treatment includes volume repletion, metabolic derangement correction, GI contamination as indicated, reduction in total salicylate burden via urinary alkalinization with sodium bicarbonate infusion, and hemodialysis in refractory/severe cases
Septic shock	• History includes focal symptoms concerning for an infectious source with severe inflammatory response • Examination may reveal fever or hypothermia, tachycardia, hypotension, delirium, disorientation, confusion, pallor, diaphoresis, hypoperfusion, tachypnea, respiratory failure • Evaluation should be based on the underlying site of infection, CBC, lactic acid, evaluation for end organ injury, urinalysis, chest x-ray, ECG, blood and urine cultures; further testing (e.g., lumbar puncture and CT, determined by suspected site of infection) • Treatment includes antibiotics, volume repletion, vasopressors as needed
Sympathomimetic toxicity	• History includes cocaine, amphetamine, PCP, or LSD use • Examination includes tachycardia, diaphoresis, chest pain, mental status changes, mydriasis, hyperthermia • Evaluation includes ECG to evaluate for dysrhythmias, electrolytes, creatine kinase, coagulation studies, renal and liver function, troponin • Treatment includes benzodiazepines, aggressive cooling for hyperthermia, fluids
Psychiatric illness	• History includes a psychiatric disorder as primary presenting issue, typically occurs in the context of established related medical/psychiatric history • Examination may reveal response to internal stimuli, hallucinations, delusions, flight of ideas, grandiose thinking, magical thinking, disordered thoughts, pressured speech, no focal neurological deficits, anger, sadness, agitation, paranoia, no findings suggestive of organic disease • Evaluation should include electrolytes, TSH, pregnancy test, ECG, acetaminophen and aspirin levels, neuroimaging if indicated, lumbar puncture if indicated • Treatment includes de-escalation, behavior control if necessary, maintenance of a safe environment, psychiatry consultation

3.4. What are essential components of the evaluation, and where can emergency clinicians go wrong?

The first pitfall in the diagnosis of thyroid storm is failing to consider the diagnosis. The condition has a variety of nonspecific signs and symptoms and is rare, making diagnosis challenging. Laboratory thyroid assessment can assist. However, the results may be misinterpreted, and they may be similar to patients with uncomplicated hyperthyroidism. TSH specifically can be misleading, as some patients will have thyroid storm due to TRH release stimulating TSH production. TSH release can also be stimulated by pituitary tumors [4]. In both of these scenarios, TSH would be elevated. TSH can also be low in patients on levothyroxine, amiodarone, steroids, metformin, carbamazepine, or dopamine agonists [10].

As discussed, several clinical score systems (the Burch-Wartofsky scoring system and the Japan Thyroid Association diagnostic criteria) have been created to assist in the diagnosis of thyroid storm [4,13]. However, clinicians should not solely rely on these systems for diagnosis. The Burch-Wartofsky scoring system assigns points based on the degree of impairment in several systems, but this score is not a definitive means of diagnosis [12]. For example, a patient with a score > 45 points may have sepsis, rather than thyroid storm. A second scoring system published by the Japan Thyroid Association requires thyrotoxicosis as a prerequisite diagnosis prior to assessing for thyroid storm [6]. A retrospective cohort study found that the Burch-Wartofsky scoring system is more sensitive and less specific for the diagnosis of thyroid storm when compared with the Japan Thyroid Association criteria [21]. Neither diagnostic tool is thought to be superior, but the scores can provide a framework by which clinicians can consider the diagnosis of thyroid storm. Current recommendations are to apply both when considering a diagnosis of thyroid storm [4,19].

In conclusion, diagnosing thyroid storm is based on considering the disease using a combination of history and examination findings, with laboratory assessment providing supporting evidence for the diagnosis. The diagnosis should not be based on laboratory assessment alone, although a low TSH and elevated T3/T4 suggest the disease in the appropriate clinical setting [5]. Other laboratory findings that support the diagnosis include hyperglycemia, hypercalcemia, leukopenia, leukocytosis, or abnormal hepatic studies [5,10,27,29]. Lastly, the ECG is an integral component of the evaluation, as tachydysrhythmias such as atrial fibrillation are common findings in thyroid storm. Indeed, current literature suggests that atrial fibrillation occurs in 10–35% of patients with thyroid storm [10,53].

3.5. What are essential components of the management, and where can emergency clinicians go wrong?

By definition, thyroid storm is characterized by rapid deterioration of multiple organ systems. As such, treatment must be timely, aggressive, and involve a multidisciplinary and collaborative approach with critical care and endocrinology specialists, as well as clinical pharmacists when available. Resuscitation of patients in thyroid storm can be complex, with simultaneous attention paid to systemic symptoms and signs (high fever, dehydration, shock), organ-specific manifestations (cardiac, neurologic, psychiatric, GI/hepatic), identification and treatment of potential triggers, and reduction of thyroid hormone secretion and production [5,7,30]. The majority of these steps can occur concurrently, with several exceptions discussed in the following content. Given these complexities, there are a number of potential pitfalls for emergency clinicians. Firstly, any delay in considering an already difficult-to-make diagnosis with a multitude of potential mimics will delay treatment initiation. Secondly, emergency clinicians may fail to appreciate how rapidly these patients may decompensate, even with implementation of timely treatment. One retrospective study found that 15% of patients with diagnosed thyroid storm suffered cardiac arrest prior to ICU admission [40]. This may delay consultation of critical care specialists or transfer to a facility equipped with advanced therapies for refractory cases.

Cardiac stabilization and resuscitation are integral components of therapy. Beyond the insensible fluid losses from high fever, patients with thyroid storm often have copious vomiting and diarrhea resulting in severe dehydration [5,10]. The decision for resuscitation with IV fluids should be based on the clinical evaluation [5]. If the patient appears dehydrated, fluids should be administered [5]. However, IV fluids should be administered carefully, with frequent assessments of fluid responsiveness and with caution if concomitant signs of decompensated heart failure are present [5].

Cardiac dysfunction can be profound in thyroid storm. Beta blockers are typically considered a key component of therapy. Sinus tachycardia and atrial fibrillation are the most common tachyarrhythmias, with heart rates >150 and the presence of atrial fibrillation associated with higher mortality [4]. Propranolol is often considered the beta blocker of choice in thyroid storm due to its ability to decrease peripheral conversion of T4 to T3 and is recommended by the American Thyroid Association [14]. However, beta blockers may worsen shock in those with overt or severe heart failure, and the tachycardia is not the primary issue in thyroid storm but may serve as a compensatory response. Ultimately, just as fluid resuscitation should be performed with caution in patients with evidence of congestive heart failure, so should administration of beta blockers. With the risk of developing cardiogenic shock with beta blocker administration, especially in patients with low EF, the clinician should evaluate for evidence of severe heart failure and consider use of point of care ultrasound (POCUS) with echocardiogram to assess the patient's cardiac function prior to beta block administration. If the patient demonstrates evidence of severe heart failure on evaluation or depressed EF on POCUS, beta blockers may cause further hemodynamic decompensation. However, if the patient does not demonstrate evidence of severe or overt heart failure or a severely depressed EF, a beta blocker should be administered. Current literature advocates for the use of short acting intravenous beta blockers like esmolol [4,53]. The Japan Thyroid Association and Japan Endocrine Society Task Force cite increased mortality rates with propranolol versus esmolol or landiolol (super short-acting beta blocker used in Japan) in those with thyroid storm [4]. Esmolol has a significantly shorter half-life compared to propranolol, which may be beneficial in thyroid storm, as the infusion may be rapidly discontinued if decompensation occurs [4,30]. The elimination half-life (rate of decline in drug concentration related to metabolism) of propranolol is 2.3 h, compared to 9 min for esmolol. Once the infusion is stopped, the effect of esmolol will have completely disappeared by 18 minutes [4]. The goal heart rate once beta blockers are administered is less than or equal to 130 beats per minute [4]. Patients presenting with unstable dysrhythmias may require cardioversion, while those in cardiogenic shock may require vasopressors and inotropes. Severe hemodynamic instability and cardiogenic shock may require even more advanced therapies including therapeutic plasma exchange, intra-aortic balloon pump, or extracorporeal membrane oxygenation (ECMO) [4,7,40,53].

Steroids serve the dual purpose of preventing adrenal insufficiency in thyroid storm as well as reducing peripheral conversion of T4 to T3. Even though thyroid storm is often described as a state of hyperadrenergic stimulation, prolonged stimulation of the hypothalamus-pituitary-adrenal axis may ultimately lead to compromised adrenal functional reserve [31]. Hydrocortisone is the first line recommended steroid. If this is not available, dexamethasone may be administered [4].

Treatment aimed at reduction of thyroid hormone secretion and production may need to begin even before thyroid tests have resulted.

Thionamides such as PTU and methimazole reduce new thyroid hormone synthesis. While they both inhibit TPO, PTU also has the added benefit of inhibiting peripheral conversion of T4 to T3 and has been found to decrease thyroid hormone levels more rapidly than methimazole [19]. Use of methimazole has been associated with fewer adverse effects in Japanese populations, including reduced hepatotoxicity, and is recommended over PTU in non-pregnant patients by the Japan Thyroid Association [4]. Methimazole is recommended in pregnant patients with thyroid storm in the second and third trimester, though PTU is recommended in the first trimester [19,54]. Of note, literature has not found a mortality difference between PTU and methimazole in thyroid storm [4]. Both can be administered either orally or rectally, although the latter may require special formulation by a hospital pharmacist [5,10,55]. Options are limited when the patient is unable to tolerate oral intake. The rectal route may be utilized in this setting, or a nasogastric tube may be placed for administration. IV methimazole is not commercially available in the U.S., although it could theoretically be formulated through combination of methimazole powder and normal saline [5,56]. This may require close communication with ED or inpatient pharmacists when available to determine best available options.

Inorganic iodine inhibits new thyroid hormone production and blocks release of preformed T3 and T4 from thyroglobulin. It is typically recommended that iodine be given 1 h after the thionamide to avoid it being used as a substrate for new thyroid hormone production [14,30]. Of note, the Japan Thyroid Association states that iodine may be administered with the thionamide in the setting of Graves' disease complicated by thyroid storm, though this is controversial [4]. Iodine can also be administered orally or rectally. If anaphylactic to iodine, patients can be given lithium instead, which will impede T3 and T4 synthesis and potentially block release of preformed hormone from binding proteins as well [4,5,10,57]. However, use of lithium is limited by the potential for renal and neurologic toxicity.

Bile acid sequestrants reduce thyroid hormone levels and interfere with enterohepatic reabsorption and recycling of thyroid hormone. These may act as adjunctive therapies, particularly in those who do not tolerate thionamides. The most commonly utilized agent is cholestyramine [36-38].

For hyperthermia, acetaminophen can be administered, along with implementation of peripheral cooling techniques (ice packs in groin/axillae, cooling blankets) [4]. Salicylates and NSAIDs should be avoided, as they can increase circulating free T4 levels [5,39].

Neuropsychiatric manifestations of thyroid storm are potentially broad [10]. Restlessness, delirium, and psychosis can be treated with antipsychotics like risperidone or olanzapine, or benzodiazepines [4,58]. Haloperidol may precipitate thyroid storm, albeit by an unclear mechanism, so it should be avoided if possible [4]. For seizures and status epilepticus, benzodiazepines remain the first line treatment, followed by fosphenytoin and phenobarbital [4]. Although not mentioned specifically within thyroid storm literature, there do not appear to be any contraindications to the administration of levetiracetam, which may be an optimal second-line agent given its widespread availability in most EDs.

Recommended routes and doses of commonly used medications for management of thyroid storm in the ED are outlined in Table 6, and Table 7 lists pearls and considerations in the evaluation and management of thyroid storm.

Table 6
Medications used in thyroid storm.

Class	Medication	Mechanism of action	Oral route	Rectal route	Intravenous route	Considerations
Thionamides	Propylthiouracil	Decrease new thyroid hormone synthesis, inhibit peripheral conversion of T4 to T3	Loading dose of 500–1000 mg followed by 250 mg every 4 h	400–600 mg every 6 h[a]		Preferred agent in early pregnancy
	Methimazole	Decrease new thyroid hormone synthesis	Loading dose of 40 mg followed by 20 mg every 4 h	20–40 mg every 6 h[a]	10–30 mg every 6 h[a]	Fewer overall adverse effects, reduced hepatotoxicity
Iodine	Potassium iodide (SSKI)	Decrease new thyroid hormone synthesis, block release of preformed thyroid hormone from thyroglobulin	5 drops every 6 h	250–500 mg every 6 h		To be given 30 min to 1 h after administration of thionamides to prevent its use as a substrate for new thyroid hormone production
	Lugol's Solution	Decrease new thyroid hormone synthesis, block release of preformed thyroid hormone from thyroglobulin	8 drops every 6 h	80 drops per day/5–10 drops every 6 h		To be given 1 h after administration of thionamides to prevent its use as a substrate for new thyroid hormone production
	Lithium	Block release of preformed thyroid hormone from thyroglobulin	300 mg every 6–8 h			Alternative to SSKI or Lugol's solution in patients with anaphylaxis to iodine
Steroids	Hydrocortisone	Prevent adrenal insufficiency, inhibit peripheral conversion of T4 to T3			300 mg loading dose, followed by 100 mg every 8 h	
	Dexamethasone	Prevent adrenal insufficiency, inhibit peripheral conversion of T4 to T3			2 mg every 6 h up to 8 mg/day	
Beta blockers	Propranolol	Adrenergic blockade, inhibit peripheral conversion of T4 to T3	60–80 mg PO every 4 h or 80–120 mg every 6 h		0.5–1 mg slow IV push, then 1–2 mg at 15-min intervals	May lead to cardiogenic shock and should be avoided in patients with CHF
	Esmolol	Adrenergic blockade			Bolus 250–500 μg/kg followed by infusion rate of 50–100 μg/kg/min	
Bile acid sequestrants	Cholestyramine	Decrease reabsorption of thyroid hormone from enterohepatic circulation	4 mg every 6 h			Adjunctive therapy

[a] Rectal (retention enema or suppository) and IV formulations that are not readily available in the U.S. and would need to be specially prepared by a pharmacist.

Table 7
Thyroid storm pearls.

-Thyroid storm is a life-threatening condition characterized by exaggerated signs and symptoms of thyrotoxicosis along with evidence of multiorgan decompensation.
-A variety of underlying triggers may result in thyroid storm, including infection, medication noncompliance, thyroid/non-thyroid surgery, parturition, trauma, exposure to exogenous iodine, or use of amiodarone. However, up to 43% of cases have no identifiable trigger.
-Several conditions may mimic thyroid storm, including acute pulmonary edema, aortic dissection, alcohol withdrawal, neuromuscular disease, pheochromocytoma, serotonin syndrome, salicylate toxicity, septic shock, sympathomimetic toxicity, and psychiatric illness.
-Patients most commonly present with fever, diaphoresis, tachycardia, gastrointestinal signs and symptoms, and neurologic issues including alteration in mental status; heart failure may be present.
-Consider thyroid storm in any patient with new-onset atrial fibrillation or CHF, new-onset psychosis or delirium, sepsis without a focus of infection, or in any undifferentiated critically ill patient.
-Utilize the Burch-Wartofsky point scale and Japan Thyroid Association diagnostic criteria in conjunction with history and examination to assist in diagnosis.
-Laboratory analysis may demonstrate end organ injury, but do not rely on thyroid studies alone to establish a diagnosis.
-ED treatment includes diagnosing and managing the trigger; hemodynamic and end organ stabilization; administration of steroids, thionamides followed by iodine 1 h later, and cholestyramine; and treatment of hyperthermia and agitation. Beta blockers should also be administered if there is no evidence of severe heart failure.

4. Conclusion

Thyroid storm is an endocrinologic emergency associated with significant morbidity and mortality. The condition includes severe signs and symptoms of thyrotoxicosis and evidence of multiorgan decompensation. There is usually an underlying trigger, with infection one of the most common. Features include fever, tachycardia, signs of congestive heart failure, vomiting/diarrhea, hepatic dysfunction, and alterations in mental status. A variety of mimics may make the diagnosis challenging. The key to diagnosis is considering the disease. The Burch-Wartofsky point scale and Japan Thyroid Association diagnostic criteria may assist in diagnosis but should not be used in isolation. Laboratory assessment can also provide clues to the diagnosis, but there is no one laboratory value that definitely diagnoses thyroid storm. Management includes treating the underlying trigger; resuscitation; administration of steroids, thionamides followed by iodine, and cholestyramine; and treatment of hyperthermia and agitation. Beta blockers should be used in the absence of severe heart failure.

CRediT authorship contribution statement

Sonika Raj: Writing – review & editing, Writing – original draft, Visualization, Validation. **Samia Farooqi:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Alex Koyfman:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Conceptualization. **Brit Long:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Conceptualization.

Declaration of Competing Interest

None.

No author has completed a narrative review on orbital cellulitis.

The authors of this review will not be submitting a manuscript on thyroid storm to another journal until AJEM makes a decision to reject or actually publishes (not just accepts) this manuscript.

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