

# Predictive features associated with thyrotoxic storm and management

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**Abstract:** Thyroid storm (TS) is an endocrine emergency characterized by rapid deterioration, associated with high mortality rate therefore rapid diagnosis and emergent treatment is mandatory. In the past, thyroid surgery was the most common cause of TS, but recent preoperative medication creates a euthyroid state before performing surgery. An active approach during perioperative period could determine an effective clinical treatment of this life-threatening diseases. Recently, the Japan Thyroid Association and Japan Endocrine Society developed diagnostic criteria for TS focusing on premature and prompt diagnosis avoiding inopportune e useless drugs. This review analyses predictive features associated with thyrotoxic storm highlighting recent literature to optimize the patient quality of care.

**Keywords:** Thyroid storm (TS); thyroidectomy; management; thyrotoxic storm

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## Introduction

Thyroid storm (TS) is an endocrine emergency characterized by a rapid systemic deterioration, with a high mortality rate over 10% of hyperthyroid patients (1); therefore, a rapid diagnosis and emergent treatment prevents a catastrophic outcome (2,3). In a recent manuscript, the TS is estimated to be 0.2 persons/100,000 population/year, accounting for 0.22% of all thyrotoxic patients (3). Occurrence is main frequent into female gender with a ratio female:male of about 3:1 (3). Additionally, pregnancy and post-partum period are triggering factors to develop TS due to redefinition of autoimmunity state (4). Nowadays, thyroid surgery is the mainly endocrine procedures carried out in the world (5) and the hyperactivity of thyroid tissue after

sub-total thyroidectomy is the primarily aetiology of perioperative TS. It can also occur during the intra-op period as a result of uncontrolled follicular cells secretion. Otherwise, the onset rate correlated to endocrine surgery is decreasing according to recent preoperative indications that create an euthyroid state before performing surgery (6). Therefore, an unsuitable preoperative management is related to a disastrous outcome during preoperative, intraoperative and postoperative periods. The classical features of TS such as abdominal pain, diarrhoea, nervousness and restlessness are masked during general anaesthesia and only hyperthermia and cardiovascular effects could be the life threatening signs (7). Several conditions could simulate an inappropriate thyroid function and differential diagnoses [anaphylactic reaction, malignant hyperthermia, brain insult, phaeochromocytoma, neuroleptic

malignant syndrome or untreated hypertension (8)] could determine an inappropriate management delay. This review analyses predictive features associated with thyrotoxic storm highlighting recent literature to optimize the patient quality of care.

### Predictive features

TS is due to triggering conditions associated to unknown thyroid pathology (usually untreated or uncontrolled Graves' disease). More rarely other thyrotoxic disorders, such as destructive thyroiditis, toxic multinodular goiter, TSH-secreting pituitary adenoma, hCG-secreting hydatidiform mole or metastatic thyroid cancer, cause TS (9-12). Triggering conditions could be drugs such as amiodarone, sorafenib, ipilimumab and inappropriate hormone ingestion (13-15) or medical settings as surgery, radioiodine therapy and exposure to excess iodine in patients with hyperthyroidism (2,5,16,17). For these reasons, in all patients with known or unknown abnormal thyroid function submitted to surgical procedures it is necessary to assess the compliance to the prescribed therapy and to optimize hormonal secretion, to settle the better endocrinal function at hospitalization. During preoperative period a complete physical exam, focusing on cardiovascular signs, could suggest a clinical suspicion for thyrotoxicosis permitting to prevent perioperative systemic organ failure related to inappropriate hormonal excretion. When TS occurs, its mortality is approximately 11% (3) due to multiple organ failure. Acute heart failure is the initial event, followed by respiratory failure, disseminated intravascular coagulation (DIC), gastrointestinal signs, neurological collapse and sepsis (3). To reduce mortality and to improve survival rate early suspicion, prompt diagnosis and intensive treatment on presentation of TS are essential (18).

The Japan Thyroid Association and Japan Endocrine Society taskforce committee conducted nationwide surveys and developed new diagnostic criteria for TS, in addition to Burch and Wartofsky scale (3,19). The Burch-Wartofsky Point Scale (BWPS) for diagnosis of TS, proposed in 1993, is an empirically derived scoring system, which considers the precipitating factors and the severities of symptoms of multiple organ decompensation (thermoregulatory dysfunction, tachycardia/atrial fibrillation, disturbances of consciousness, congestive heart failure and gastro-hepatic dysfunction) (Table 1) (19). Instead, according to the Japanese Thyroid Association (JTA) diagnostic criteria, the presence of thyrotoxicosis is a prerequisite condition

to confirm TS (Figure 1) (3). The 2016 guidelines for the management of TS in order to increase the accuracy of clinical diagnosis recommend use of both diagnostic systems to evaluate patients (18).

The presentation of TS includes fever, profuse sweating, signs of encephalopathy (anxiety, emotional lability, restlessness, agitation, confusion, delirium, frank psychosis, coma), various cardiac manifestations (sinus tachycardia, atrial arrhythmias, congestive heart failure), systolic hypertension, and gastrointestinal symptoms (diffuse abdominal pain with abnormal liver enzymes levels) (17). The major challenges of an intraoperative TS onset are due to several conditions that could mimic a cardiovascular collapse with thermoregulatory signs such as pain, electrolytes disturbances, malignant hyperthermia, heart failure and anaphylactic reactions (7).

### Thyrotoxic storm management

The pillar of TS management is to treat the hormonal excess excretion starting prematurely all supportive maneuvers. Admission into intensive care unit (ICU) is recommended for all patients, not only when heart failure, haemostatic disorders and multiple organ failure are occurred but also to optimize physiological conditions. The intraoperative approach recently published (18) appears the finest method to treat this disorder. After the confounding diagnostic criteria are excluded, the intraoperative treatment of haemodynamic instability includes use of antithyroid drugs (ATDs), inorganic iodide,  $\beta$ -blockers, antipyretics, steroids and vasoactive medication.

#### ATDs

Thionamides, propylthiouracil (PTU) and methimazole (MMI), are the mainstays to control the activity of increased thyroid hormone levels. The main action of ATDs is the direct inhibition of thyroid peroxidase in the thyroid gland, with reduction of synthesis of new hormone.

The American Thyroid Association (ATA) recommends the PTU, probably due to inhibition of type I deiodinase activity in the thyroid gland and in peripheral tissues (20). The Japan nationwide surveys shows there were no significant differences in mortality between TS patients treated with MMI or PTU (3).

However, ATDs should be administered as soon as possible when TS in Graves' disease is diagnosed, but not in cases of TS by destructive thyroiditis, because ATDs are not

Prerequisite	The Japan thyroid association diagnostic criteria for thyroid storm (3)		
Presence of thyrotoxicosis with elevated levels of free triiodothyronine (FT3) or free thyroxine (FT4)	Symptoms Central nervous system manifestation Fever $\geq 38$ °C		
Prognosis and severity could be affected by:	Tachycardia $\geq 130$ beats per minute or heart rate major 130 in atrial fibrillation Congestive heart failure: pulmonary edema, cardiogenic shock or class IV by New York Heart Association or class $\geq$ II in the Killip classification		
<ul style="list-style-type: none"> <li>• Age</li> <li>• Glasgow Coma Scale (GCS)</li> <li>• Creatinine value</li> <li>• Albumin value</li> <li>• Base excess</li> <li>• Shock</li> <li>• PaCO<sub>2</sub></li> <li>• Disseminated intravascular coagulation (DIC)</li> <li>• Multiple organ failure (MOF)</li> </ul>	Gastrointestinal hepatic manifestation		
	Diagnosis		
	Grade of thyrotoxicosis	Combination of features	Requirements for diagnosis
	TS1	First combination	Thyrotoxicosis and at least on CNS manifestation and fever, tachycardia, congestive heart failure or gastro-intestinal hepatic manifestation
	TS1	Alternate combination	Thyrotoxicosis and at least three combinations of fever, tachycardia, congestive heart failure or gastro intestinal hepatic manifestation
	TS2	First combination	Thyrotoxicosis and a combination of two of the following: fever, tachycardia, congestive heart failure or gastro intestinal hepatic manifestations
	TS2	Alternate combination	Patients who met the diagnosis of TS! Except that serum FT $\epsilon$ or FT $\$$ level are not available
	Exclusion and provisions		
	Cases are excluded if other underlying diseases clearly causing any of the following symptoms: fever, impaired consciousness, heart failure and liver disorders. Therefore, it is difficult to determine whether the symptom is caused by thyrotoxicosis or is simply a manifestation of an underlying disease, the symptom should be regarded as being due to a thyrotoxicosis that is caused by the precipitating factors. Clinical judgment in this matter required		
	TS1: thyrotoxicosis DEFINITE; TS2: thyrotoxicosis SUSPECTED		

**Figure 1** Diagnostic criteria for thyroid storm (3).

effective against the destructive release of thyroid hormones stored in the gland and the recommended dose of PTU is 600 mg/die.

The MMI dose differ between oral intake and intravenous administration; it is 60 mg/day and 30 mg/die respectively.

### *Inorganic iodide*

Inorganic iodide inhibiting iodide oxidation and organification (the Wolff-Chaikoff effect). It is widely used

as pre-operative treatment for thyroid surgery in order to decrease intraoperative bleeding, because inorganic iodide can reduce blood flow to the thyroid gland (21). Inorganic iodide should be administered simultaneously with ATDs in patients with TS with hyperthyroidism condition.

### *Corticosteroids*

The hypermetabolic state related to TS could generate a depletion of stress hormones and corticosteroids should be administered as prophylaxis for related adrenal insufficiency.

**Table 1** Criteria Burch-Wartofsky point scale (monitoring: cardiovascular state, body temperature, gastrointestinal signs, neurological status and presence of triggering events)

Variables	Score
Thermoregulatory dysfunction (°C)	
37.2–37.7	5
37.8–38.3	10
38.4–38.8	15
38.9–39.3	20
39.4–39.9	25
≥40	30
Cardiovascular tachycardia (bpm)	
90–109	5
110–119	10
120–129	15
130–139	20
≥140	25
Atrial fibrillation	
Absent	0
Present	10
Congestive heart failure	
Absent	0
Mild	5
Moderate	10
Severe	15
Gastrointestinal-hepatic dysfunction	
Absent	0
Moderate	10
Severe	20
Central nervous system disturbance	
Absent	0
Mild	10
Moderate	20
Severe	30
Precipitating event	
Absent	0
Present	10

Criteria Burch-Wartofsky point scale (19): ≥45, thyroid storm; 25–44, impending storm; <25, storm unlikely.

Additionally, Bianco *et al.* (22) highlighted that large doses of corticosteroids inhibit thyroid hormone synthesis and peripheral conversion of T4 to T3. The recommended doses of corticosteroids are 300 mg/day hydrocortisone or 8 mg/day dexamethasone.

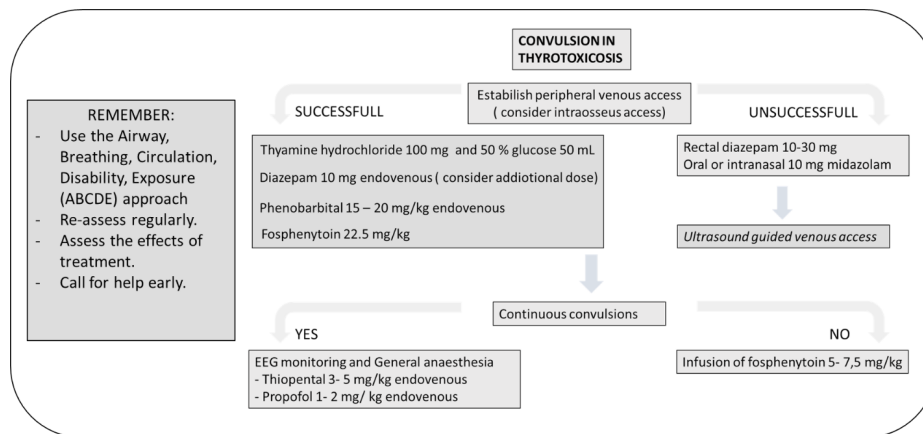
### *Antipyretics*

The restoration of thermoregulation is mandatory to reduce all deleterious effects on coagulation, electrolytes balance and pH. Acetaminophen is the first choice and all mechanical refrigeration techniques such as cooling blankets or ice packs should be used in TS patients with resistant fever. Larsen *et al.* showed that salicylate could worsen the status increasing free thyroid hormone levels due to alterations of thyroxine binding proteins (23). Infections, with fever onset, could manifest TS (2) and a precocious antibiotic therapy has to be applied on patients with suspected thyroid disease before sepsis signs are evident (24).

### *Beta-adrenergic receptor antagonists (beta-AAS)*

The treatment of hyperdynamic state related to inappropriate hormonal excretion is through beta-adrenergic receptor antagonist drugs. The principal drugs to treat supraventricular arrhythmias are endovenous landiolol and esmolol. The administration when heart rate is <80 bpm, systolic blood pressure <80 mmHg or cardiac index is ≤2.2 L/min/m<sup>2</sup> is not indicated. In patients with severe pulmonary disease, such as asthma and COPD, verapamil or diltiazem are the better choice. The incidence of atrial fibrillation in TS is reported between 12% and 28% (25), with an increased mortality rate (3), probably due to an accelerated systemic hemodynamic deterioration status (18). When supraventricular tachycardia occurred with impaired hemodynamic status is necessary to proceed to cardioversion. Indeed, digitalis is useful in patients with normal renal function without hemodynamic failure.

TS can lead to acute congestive heart failure (CHF). In this case, invasive hemodynamic monitoring such as Swan-Ganz catheter is recommended for patients with symptoms and signs of pulmonary edema (Killip class ≥ III) (18,26). In this setting, respiratory management should include non-invasive positive pressure ventilation (NIPPV), or tracheal intubation according to neurologic, pulmonary and cardiac functional status. Administration of endovenous vasoactive drugs and diuretics should be considered in order to maintain cardiovascular tone, to reduce venous return. The



**Figure 2** Algorithm for the treatment of convulsion in patients with thyrotoxic storm.

use of extracorporeal supportive maneuvers is rare.

Additionally, neurologic manifestation is common (3); to treat disturbances of consciousness and psychosis the psychiatrist or neurologist consultation to select doses of psychotropic medications should be considered (17). When convulsions are present, benzodiazepines are first-line agents. Alternative drugs for resistant convulsions are fosphenytoin, phenobarbital and sodium thiopental (Figure 2) (27). Nowadays, the patients with central nervous manifestations and age major to 60 years have a higher mortality.

There is an increased risk of gastrointestinal haemorrhage, due to corticosteroids administration, coagulopathy and mechanical ventilation (3). Acid-suppressive drugs, such as proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2As), are recommended (18).

Hepatic failure is not a rare complication. Actually, is recommended a carefully monitoring in patients with bilirubin levels >3.0 mg/dL. The emergency thyroidectomy could be the only solution to treat such complications and appropriate life support is suggested (19) including therapeutic plasmapheresis and haemodialysis (18).

## Conclusions

The above-mentioned literature shows that TS is a life threatening medical conditions due to excessive hormonal activity. Actually, TS is a dangerous expression of thyrotoxicosis precipitated by several events. The presence of heart collapse, coagulation abnormalities and organ failure determines a poor outcome and all the therapeutic

strategies are involved to reduce hormonal activity, to prevent organ damage and to sustain vital capacity. All the supportive measures employed during preoperative, intraoperative and postoperative periods are directed to avoid complications. Therefore, a thyroid function investigation should be performed in every patient with abnormal findings, such as tachycardia, weight loss, and tremors. The physicians have not to delay all the necessary treatment when there is a clinical suspicion to increase quality care of TS patients, in order to improve the outcome.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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