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OPINION

2016 Guidelines for the management of thyroid storm from The Japan Thyroid Association and Japan Endocrine Society (First edition)

The Japan Thyroid Association and Japan Endocrine Society Taskforce Committee for the establishment of diagnostic criteria and nationwide surveys for thyroid storm

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Abstract. Thyroid storm is an endocrine emergency which is characterized by multiple organ failure due to severe thyrotoxicosis, often associated with triggering illnesses. Early suspicion, prompt diagnosis and intensive treatment will improve survival in thyroid storm patients. Because of its rarity and high mortality, prospective intervention studies for the treatment of thyroid storm are difficult to carry out. We, the Japan Thyroid Association and Japan Endocrine Society taskforce committee, previously developed new diagnostic criteria and conducted nationwide surveys for thyroid storm in Japan. Detailed analyses of clinical data from 356 patients revealed that the mortality in Japan was still high (~11%) and that multiple organ failure and acute heart failure were common causes of death. In addition, multimodal treatment with antithyroid drugs, inorganic iodide, corticosteroids and beta-adrenergic antagonists has been suggested to improve mortality of these patients. Based on the evidence obtained by nationwide surveys and additional literature searches, we herein established clinical guidelines for the management of thyroid storm. The present guideline includes 15 recommendations for the treatment of thyrotoxicosis and organ failure in the central nervous system, cardiovascular system, and hepato-gastrointestinal tract, admission criteria for the intensive care unit, and prognostic evaluation. We also proposed preventive approaches to thyroid storm, roles of definitive therapy, and future prospective trial plans for the treatment of thyroid storm. We hope that this guideline will be useful for many physicians all over the world as well as in Japan in the management of thyroid storm and the improvement of its outcome.

Key words: Thyroid crisis, Diagnostic criteria, Prognosis assessment, Prevention, Thyrotoxicosis

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Introduction/Background

Thyroid storm is a life-threatening condition that requires rapid diagnosis and emergent treatment [1-3]. The condition manifests as decompensation of multiple organs with loss of consciousness, high fever, heart failure, diarrhea, and jaundice. Recent nationwide surveys in Japan have revealed that mortality remains over 10% [4]. Multiple organ failure was the most common cause of death, followed by congestive heart failure, respiratory failure, arrhythmia, disseminated intravascular coagulation (DIC), gastrointestinal perforation, hypoxic brain syndrome, and sepsis. Even when patients survive, some have irreversible damage including brain damage, disuse atrophy, cerebrovascular disease, renal insufficiency, and psychosis. Therefore, the prognosis of patients with thyroid storm needs to be improved.

Since multiple organ failure is characteristic of thyroid storm, multidisciplinary expertise and care involving endocrinologists, cardiologists, neurologists, and hepatologists are necessary for management. Furthermore, the decompensated state associated with thyroid storm often requires comprehensive and highly advanced medical treatment. Although several textbooks and guidelines have described the treatment of thyroid storm [3, 5-7], nationwide surveys in Japan revealed that methimazole (MMI) was preferentially used in thyroid storm despite recommendations for the use of propylthiouracil (PTU) [8]. Therefore, the establishment of more detailed guidelines for the management of thyroid storm is needed in Japan and other countries. Such guidelines should be helpful to many practitioners.

New diagnostic criteria for thyroid storm, in addition to those of Burch and Wartofsky [3, 4, 9], have been established. The next obvious step is to identify therapeutic procedures that improve prognosis [10, 11]. Five areas are important in the treatment of thyroid storm: 1) thyrotoxicosis (reduction of thyroid hormone secretion and production); 2) systemic symptoms and signs (including high fever, dehydration, shock, and DIC); 3) organ-specific manifestations, such as cardiovascular, neurological, and hepato-gastrointestinal; 4) triggers; and 5) definitive therapy. Although the appropriate responses to these problems have been described in endocrinology textbooks and reviews, several clinical questions remain, for example: 1) the choice and route of administration for antithyroid drugs (ATDs), 2) timing of iodide therapy, 3) criteria to judge thyroid storm severity, and 4) choice and fine-tuning of treatment based on severity and pathophysiological state. Although beta-adrenergic receptor antagonists (beta-AAs) are often used to treat thyroid storm, inappropriate choice or dose may lead to worse outcomes in patients with severe heart failure [8]. Furthermore, thyroid storm is characterized by multiple organ failure, decompensation, and highly variable clinical presentation, a clinical pic-

ture that requires comprehensive treatment. Thyroid storm is an emergent disorder characterized by rapid deterioration in its clinical course. Therefore, an algorithm-based approach is useful for the management of thyroid storm.

Given this context, we attempted to create recommendations for the management of thyroid storm based on the following principles. These recommendations should 1) contain information on both the diagnosis and treatment of thyroid storm; 2) illustrate algorithms; 3) consider the severity and pathophysiology of thyroid storm; 4) be detailed, concrete, and useful for clinical practice; 5) be evidence-based; and 6) possibly be internationally applicable. Based on the analysis of data concerning the treatment of thyroid storm collected in nationwide surveys in Japan [8], the treatment of not only thyrotoxicosis, but also the characteristic manifestations and complications of thyroid storm, are explained in detail. We also describe how to evaluate the severity of thyroid storm from the viewpoint of prognosis. In Section 11, the entire algorithm for the management of thyroid storm is illustrated in a summary schema. The last section of this chapter refers to a prospective prognostic study using these recommendations. We hope to achieve successful outcomes in the management of thyroid storm through effective implementation of these recommendations.

Basic Policy

In these recommendations, which use the Guideline Grading System developed by the American College of Physicians (ACP) [12], both **strength of recommendation** and **quality of evidence** were evaluated based on the criteria shown in Table 1.

The interpretation of each combination of "Strength of recommendation" and "Quality of evidence" is as follows: if the **strength of recommendation** is **strong** and **quality of evidence** is **high or moderate**, the clinical practice can be applicable to most patients in most circumstances without reservation. If the **strength of recommendation** is **strong** and **quality of evidence** is **low**, the recommendation may change when higher-quality evidence becomes available. If the **strength of recommendation** is **weak** and **quality of evidence** is **high or moderate**, the best course of action may differ depending on circumstances and patient or social values. If the **strength of recommendation** is **weak** and **quality of evidence** is **low**, the recommendation is very weak and other alternatives may be equally reasonable. **Quality of evidence: insufficient for grading** means that there is insufficient evidence to recommend for or against routinely providing the service.

Diagnostic and Therapeutic Recommendations for Thyroid Storm

1. Diagnostic challenges for thyroid storm

Thyroid storm is an endocrine emergency that is characterized by rapid deterioration within days or hours of presentation and is associated with high mortality [1-4]. Most cases of thyroid storm are caused by the presence of some triggering condition in conjunction with an underlying thyroid condition, usually untreated or uncontrolled Graves' disease, but very rarely other thyrotoxic disorders such as destructive thyroiditis, toxic multinodular goiter, TSH-secreting pituitary adenoma, hCG-secreting hydatidiform mole, or metastatic thyroid cancer [13-17]. Thyroid storm can also be caused by medical precipitants such as thyroidectomy, nonthyroid surgery, radioiodine therapy, exposure to excess iodine in patients with hyperthyroidism, or excess thyroid hormone ingestion [1-4]. In addition, several drugs that cause thyrotoxicosis as an

Table 1 Strength of recommendation and quality of evidence

Strength of recommendation	
Strong	Benefits clearly outweigh risks and burdens, or risks and burdens clearly outweigh benefits
Weak	Benefits closely balanced with risks and burdens
None	Balance of benefits and risks cannot be determined
Quality of evidence	
High	Randomized controlled trials without important limitations, or overwhelming evidence from observational studies
Moderate	Randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies
Low	Observation studies or case series
Insufficient for grading	Evidence is conflicting, of poor quality, or lacking

See ref. [12].

adverse event, including amiodarone, sorafenib, and ipilimumab, have been reported to precipitate thyroid storm [18-20]. Early awareness/suspicion, prompt diagnosis, and intensive treatment will improve survival in patients with thyroid storm. However, because biological markers useful for the diagnosis of thyroid storm are not established, and symptoms derived from the triggering condition are sometimes indistinguishable from those originating from thyroid storm, the diagnosis of thyroid storm has not always been straightforward. To address these diagnostic challenges, the Burch-Wartofsky Point Scale (BWPS) for diagnosis of thyroid storm and impending thyroid storm was proposed in 1993 [9]. The BWPS is an empirically derived scoring system that takes into account the severities of symptoms of multiple organ decompensation, including thermoregulatory dysfunction, tachycardia/atrial fibrillation, disturbances of consciousness, congestive heart failure, and gastro-hepatic dysfunction, as well as the role of precipitating factors (Table 2). The BWPS has been widely applied for the diagnosis of thyroid storm for more than 2 decades.

In 2012, the Japanese Thyroid Association (JTA) proposed new diagnostic criteria for thyroid storm that were initially established based on detailed analyses of 99 published cases and 7 taskforce committee's cases and finally revised according to the results of nationwide surveys [4]. In these JTA criteria, the presence of thyrotoxicosis is required as a prerequisite condition, and definite and possible thyroid storm can be diagnosed based on specific combinations of symptoms due to multiple organ decompensation, similarly to those listed in the BWPS (Table 3). One of the specific features in the JTA criteria is that disturbances of consciousness contribute to the diagnosis of thyroid storm much more than other organ symptoms [4].

The usefulness of the BWPS and JTA criteria has been compared by analyses of JTA nationwide surveys [4], and recently by 2 institutions that showed overall agreement between the 2 systems [21, 22]. However, a report from the United States suggested that the BWPS ≥ 45 appeared to select a higher percentage of patients for aggressive therapy than the JTA criteria [21]. Using both diagnostic systems to evaluate a patient's condition is recommended to increase the accuracy of clinical diagnosis and further validate the usefulness of these 2 sets of criteria. Most importantly, inappropriate application of either system can lead to misdiagnosis of thyroid storm, emphasizing the importance of carefully evaluating the clinical condition of each patient suspected of having thyroid storm. In cases where physicians are having difficulty judging whether the symptoms listed in the JTA criteria have arisen from precipitating events or from thyroid storm, the symptoms should be judged as having been caused by thyroid storm, as described in the JTA criteria [4].

Table 2 The Burch-Wartofsky Point Scale for diagnosis of thyroid storm

Criteria	Points
Thermoregulatory dysfunction	
Temperature (˚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
≥ 40.0	30
Cardiovascular	
Tachycardia (beats per minute)	
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	
Manifestation	
Absent	0
Moderate (diarrhea, abdominal pain, nausea/vomiting)	10
Severe (jaundice)	20
Central nervous system disturbance	
Manifestation	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, come)	30
Precipitating event	
Status	
Absent	0
Present	10
Total score	
≥ 45	Thyroid storm
25–44	Impending storm
< 25	Storm unlikely

Modified from ref. [9].

Table 3 The diagnostic criteria for thyroid storm (TS) of the Japan Thyroid Association

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, coma (≥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 Asscіation or ≥ Class III in the Killip classification		
5. Gastrointestinal (GI)/hepatic manifestations : nausea , vomiting, diarrhea, or a total bilirubin level ≥ 3.0 mg/dL		
Diagnosis		
Grade of TS	Combinations of features	Requirements for diagnosis
TS1	First combination	Thyrotoxicosis and at least one CNS manifestation and fever, tachycardia, CHF, or GI/ hapatic manifestations
TS1	Alternate combination	Thyrotoxicosis and at least three combinations of fever, tachycardia, CHF, or GI/ hapatic manifestations
TS2	First combination	Thyrotoxicosis and a combination of two of the following: fever, tachycardia, CHF, or GI/hepatic manifastations
TS2	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 (*e.g.*, pneumonia and malignant hyperthermia), impaired consciousness (*e.g.*, psychiatric disorders and cerebrovascular disease), heart failure (*e.g.*, acute myocardial infarction), and liver disorders (*e.g.*, viral hepatitis and acute liver failure). Therefore, it is difficult to determine whether the symptom is caused by TS or is simply a manifestation of an undelying disease; the symptom should be regarded as being due to a TS that is caused by these precipitating factors. Clinical judgment in this matter is required.		

TS1, "Definite" TS; TS2, "Suspected" TS.

2. Management of thyroid storm with antithyroid drugs, inorganic iodide, corticosteroids and antipyretics

■ RECOMMENDATION 1

A multimodality approach with ATDs, inorganic iodide, corticosteroids, beta-AAs, and antipyretic agents should be used to ameliorate thyrotoxicosis and its adverse effects on multiple organ systems.

Strength of recommendation: high
Quality of evidence: moderate

A. Antithyroid agents

■ RECOMMENDATION 2

1. ATDs, either MMI or PTU, should be administered for the treatment of hyperthyroidism in thyroid storm.

Strength of recommendation: high
Quality of evidence: low

2. Intravenous administration of MMI is recommended in severely ill patients with consciousness disturbances or impaired gastrointestinal tract function.

Strength of recommendation: high
Quality of evidence: low

● Evidence supporting the recommendations

The main action of ATDs is to directly inhibit thyroid peroxidase through the coupling of iodotyrosine in thyroglobulin molecules, resulting in reduced synthesis of new thyroid hormone molecules. The major functional difference between MMI and PTU is that large doses of PTU (at least 400 mg/day) inhibit type I deiodinase activity in the thyroid gland and other peripheral organs, and may therefore acutely decrease triiodothyronine (T3) levels more than MMI [23, 24]. These are the reasons that PTU, rather than MMI, is recommended in the guideline issued by the American Thyroid Association (ATA) [7].

A nationwide survey performed by the JTA revealed that both free T3 (FT3) levels and the FT3/free thyroxine (FT4) ratio, but not FT4 levels, were inversely correlated with disease severity assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment scores in patients with thyroid storm [8]. These findings strongly suggest that the conversion of T4 to T3 could already be suppressed in severe thyroid storm. In addition, there were no significant differences in disease severity or mortality between patients with thyroid storm treated with MMI or PTU [8]. Therefore, like PTU, MMI may be useful in severe thyroid storm in which there is reduced T4-to-T3 conversion. Doses of MMI, but not of PTU, were significantly correlated with both disease severity and FT4 levels in the nationwide surveys [8]. The median dose of MMI administered was 30 mg (range, 5–120 mg), whereas the median dose of PTU was 450 mg (range, 150–1,500 mg) (unpublished data).

Regarding the long-term efficacy of ATDs in thyrotoxicosis in compensated Graves' patients, a randomized prospective study performed in Japan revealed that MMI (30 mg/day) normalized thyroid hormone levels more rapidly than PTU (300 mg/day). This study also showed that the incidence of adverse effects in patients treated with MMI was significantly lower than in those treated with PTU [25]. Based on these findings, the JTA guidelines recommend MMI as the first-choice ATD for the treatment of compensated Graves' disease, except during early pregnancy [26]. Therefore, MMI has been favored by physicians in Japan for the treatment of compensated Graves' disease and more frequently used to treat uncompensated thyrotoxicosis in thyroid storm in the nationwide surveys (278 out of 356 cases, 78%) [8]. In addition to the nationwide surveys in Japan, a recent study from the United States also reported no significant difference in outcomes of patients with thyroid storm treated with MMI or PTU [27]. These observations together provide supporting evidence that MMI may not be disadvantageous compared to PTU for the treatment of thyrotoxicosis in thyroid storm.

Intravenous preparations of MMI are commercially available in some countries, including Japan and some European countries, but not in the United States or the United Kingdom. In the nationwide surveys, disease severity of patients with thyroid storm treated with intravenous MMI (47 out of 278 cases, 17%) was significantly higher than that of patients treated with oral preparations [8], suggesting that the patients with severe thyroid storm were more likely to be treated with intravenous MMI, as expected.

● Comments

When patients are diagnosed with thyroid storm caused by Graves' disease, ATDs should be administered as soon as possible. The recommended dose of oral MMI is 60 mg/day, while that of PTU is 600 mg/day. These are the maximum doses for the treatment of Graves' disease approved by the Ministry of Health, Labor and Welfare of Japan. In Western countries, the approved maximal doses of MMI and PTU are 100 and 1,600 mg, respectively. In thyroid storm caused by toxic nodular goiter, TSH-secreting pituitary adenoma, or hydatidiform mole, doses of ATDs may be adjusted on an individual basis. In cases of thyroid storm caused by destructive thyroiditis, such as subacute thyroiditis or drug-induced thyroiditis, administration of ATDs is contraindicated because the patient is unnecessarily exposed to the risk of the adverse effects of ATDs, which are not effective against the destructive release of thyroid hormones stored before the onset of thyroiditis.

In severely ill patients, especially those with disturbed consciousness or impaired gastrointestinal tract function with vomiting, severe diarrhea, active gastrointestinal bleeding, or intestinal edema secondary to congestive heart failure, hypoalbuminemia, or renal insufficiency, intravenous administration of MMI (30 mg/day) is recommended. However, even in countries where commercially available, intravenous MMI preparations may not always be in stock in all hospital pharmacies because of the rarity of their use. By the time that an intravenous MMI preparation is available, ATDs should have been administered *via* a non-parenteral route in severely ill patients.

In settings in the United States where intravenous MMI preparations have not been available, there have been reports of preparing MMI injections in hospital pharmacies and cases of successful treatment with MMI injections in patients refractory to oral MMI [28]. Rectal administration of ATDs in thyroid storm has also been previously reported, given either as enemas or as suppositories [29, 30]. Detailed methods for preparation of ATD enemas or suppositories are described elsewhere [29, 30].

When large doses of ATDs are administered, there should be careful monitoring for potential side effects such as pruritus/rashes, agranulocytosis, and liver dysfunction. When ATDs can no longer be used because of severe adverse effects, binding resins such as cholestyramine, which binds iodothyronine, are an adjunctive measure to physically remove thyroid hormones from the enterohepatic circulation, which is increased in hyperthyroidism [31, 32]. The dose of cholestyramine for effectively reducing thyroid hormone levels has been recommended to be 4 g three or four times daily [6]. Cholestyramine is also useful for the treatment of thyroid storm induced by ingestion of large doses of thyroid hormone preparations (thyrotoxicosis factitia).

When severe thyrotoxicosis is successfully managed during the early stage of thyroid storm, doses of ATDs can be tapered with close monitoring of thyroid hormone levels, but not of TSH levels, in a manner similar to that used in compensated Graves' disease.

B. Therapy with inorganic iodide

■ RECOMMENDATION 3

Inorganic iodide should be administered simultaneously with ATDs to patients with thyroid storm caused by thyrotoxic diseases associated with hyperthyroidism.

Strength of recommendation: high

Quality of evidence: moderate

● Evidence supporting the recommendation

The administration of inorganic iodide in large doses decreases thyroid hormone synthesis by inhibiting iodide oxidation and organification (the Wolff-Chaikoff effect), and also rapidly inhibits the release of thyroid hormones from the follicular lumen of the thyroid gland [33–36]. Therefore, inorganic iodide can decrease thyroid hormone levels more rapidly than other agents, including ATDs and corticosteroids [3, 5, 37]. Since there is some evidence that inorganic iodide can reduce blood flow to the thyroid gland, it is widely used as an essential treatment prior to thyroid surgery in order to decrease intraoperative bleeding [38, 39]. The inhibitory effect of inorganic iodide can continue for 1 to 2 weeks, but may disappear thereafter in some patients [33].

In a nationwide survey, the severity of thyroid storm was significantly greater in patients treated with inorganic iodide than in those who were not; however, no significant differences in mortality were observed between the 2 groups [8]. These findings suggest that inorganic iodide treatment may improve the outcome of thyroid storm patients.

The ATA guidelines [7] recommend that inorganic iodide be administered at least 1 hour after the administration of ATDs to prevent the organification of iodide. A recent prospective study comparing MMI treatment with MMI + potassium iodide (KI) treatment in terms of rapid normalization of thyroid hormones in compensated Graves' disease (134 cases) reported that FT3 levels in the combined treatment group decreased significantly faster than those in the MMI group, and none of the patients showed an increase in thyroid hormone levels or aggravation of disease during the combined treatment [40]. Another prospective study evaluating the efficacy of MMI 15 mg/day plus inorganic iodide 38.2 mg/day (equivalent to 50 mg KI) (M15 + KI) *vs*. MMI 30 mg/day (M30) for the treatment of moderate to severe uncomplicated Graves' disease (310 cases) also demonstrated that combined treatment with M15 + KI improved FT4 levels significantly faster than treatment with M30, with no exacerbation of thyrotoxicosis in patients treated with M15 + KI [41]. Based on these findings in 2 large prospective trials performed in Japan, we recommend that large doses of inorganic iodide be administered simultaneously with ATDs to Graves' patients complicated with thyroid storm. However, patients who are known to be allergic to inorganic iodide-containing drugs should not be given KI, though if they are they should be monitored carefully.

● Comments

Only KI in powder or tablet form is approved for oral use in Japan. On the other hand, Lugol's solution is only approved for topical administration, but can be administered orally and is effective for the treatment of thyrotoxicosis. Lugol's solution, as well as saturated solution of KI (SSKI), should be prepared in hospital pharmacies. Since the amount of iodide in these solutions may differ between hospitals, the concentration of iodide in these solutions should be confirmed prior to administration.

Despite the relatively high doses of iodide empirically used to treat thyrotoxicosis, the minimal effective dose of iodide was previously estimated to be between 5 and 10 mg/day [35]. Since the absorption of iodide may be impaired by many factors in patients

with critical conditions such as thyroid storm, larger doses of KI should be administered; the recommended dose is approximately 200 mg/day, taking consideration of the reported doses in our nationwide surveys [8]. The route of administration for inorganic iodide (oral, sublingual, rectal, or *via* a nasogastric tube) may be selected based on the patient's clinical condition [42]. The dose of inorganic iodide may be increased when administered rectally.

Apart from inorganic iodide, lithium carbonate is also known to inhibit the release of thyroid hormone from the thyroid gland by an unknown mechanism [43, 44]. Lithium may be used in patients allergic to ATDs or iodide to reduce circulating thyroid hormone levels, though serum lithium levels should be monitored to avoid toxicity.

After improvement of thyrotoxicosis by combination therapy with ATDs and inorganic iodide, the doses of inorganic iodide should be reduced before ATDs are tapered, and thyroid hormone levels, but not TSH levels, should be closely monitored.

C. Treatment with corticosteroids

■ RECOMMENDATION 4

Corticosteroids (300 mg/day hydrocortisone or 8 mg/day dexamethasone) should be administered to patients with thyroid storm regardless of its origin.

Strength of recommendation: high

Quality of evidence: moderate

● Evidence supporting the recommendations

Corticosteroids should be administered as prophylaxis for relative adrenal insufficiency caused by the hypermetabolic state in thyroid storm. Large doses of corticosteroids have been shown to inhibit both thyroid hormone synthesis and peripheral conversion of T4 to T3 [45]. Despite the predicted favorable effects of corticosteroids mentioned above, detailed analysis of nationwide surveys using multiple regression analysis showed that disease severity and mortality were significantly higher in patients who were treated with corticosteroids than in those who were not [8]. In multiple regression analyses, both the use of corticosteroids and their doses correlated with disease severity, but not with mortality [8]. The median dose and range of hydrocortisone, prednisolone, methylprednisolone, and dexamethasone were 300 mg (30–1,200 mg), 25 mg (5–60 mg), 375 mg (80–1,000 mg), and 6 mg (1.5–16 mg), respectively [8]. These findings suggest that the doses of corticosteroids administered might be insufficient in some patients. Alternatively, corticosteroids overdosing in some patients may cause unfavorable hyperglycemia and worsening of their general condition. Therefore, the type and dose of corticosteroids needs to be determined carefully on an individualized basis to improve the outcome of thyroid storm.

● Comments

Corticosteroids should be given to ameliorate relative adrenal insufficiency and thyrotoxicosis. The recommended dose of hydrocortisone is 300 mg/day (100 mg administered intravenously every 8 hours). Alternatively, dexamethasone (8 mg/day) can be administered, nearly equipotent to 300 mg/day hydrocortisone. There is no evidence that prednisolone or methylprednisolone is more beneficial than hydrocortisone or dexamethasone. Corticosteroid doses need to be altered on an individualized basis. There should be careful monitoring and prevention of potential side effects such as hyperglycemia, peptic ulcer, and infection.

After successful management of severe thyrotoxicosis during the early stage of thyroid storm, doses of corticosteroids should be tapered and discontinued following confirmation of adrenocortical recovery by measurement of fasting serum cortisol levels.

D. Treatment for fever

■ RECOMMENDATION 5

1. Aggressive cooling with acetaminophen and mechanical cooling with cooling blankets or ice packs should be performed for thyroid storm patients with high fever.

Strength of recommendation: high

Quality of evidence: low

2. The focus of infection should be investigated in patients with high fever and accompanying infection should be treated.

Strength of recommendation: high

Quality of evidence: moderate

● Evidence supporting the recommendations

As recommended in the ATA guidelines [7], acetaminophen is the first choice of antipyretic agents for the treatment of fever in thyroid storm because other antipyretics have been shown to increase free thyroid

hormone levels by interfering with binding to T4-binding proteins [46]. In a nationwide survey [4], the body temperature of thyroid storm patients treated with antipyretics was significantly higher than the body temperature of those who did not receive antipyretics. However, no significant differences were observed in disease severity and mortality between these patients [8]. This nationwide survey also found no significant difference in mortality between patients treated with acetaminophen *versus* other antipyretics [8]. Since patient outcomes are influenced by many factors, these data do not disprove the advantage of acetaminophen therapy suggested by *in vitro* data [46].

Infection is one of the causes of fever and is also a trigger for thyroid storm. Infection was shown to be the second most common triggering factor for thyroid storm (28%) in a nationwide survey [4]. The survey also revealed that the direct causes of death in patients with thyroid storm included sepsis, septic shock, DIC, and pneumonia [4]. These conditions are also closely related to infection. Therefore, the control of infection is important in order to improve prognosis in patients with thyroid storm. According to the guidelines for the treatment of sepsis by the Committee for Sepsis of the Japan Society of Intensive Care Medicine, appropriate antibiotic therapy needs to be started as soon as possible in patients exhibiting signs of infection [47].

● Comments

Since the control of fever may reduce adverse effects on the central nervous system (CNS) and cardiovascular function, extensive cooling with ice packs, cooling blanket or acetaminophen may be needed for thyroid storm patients with high fever. Acetaminophen may be administered orally or in the form of a suppository at a dose of 500 mg three times per day. Non-steroid anti-inflammatory agents as well as aspirin are not recommended because these drugs may increase free thyroid hormone levels [46].

Antibiotics should be administered to patients with fever or signs of infection based on symptoms and physical findings after appropriate sampling of blood, sputum, or urine to identify causative bacteria. According to Japan Society of Intensive Care Medicine guidelines, antibiotics should be administered in very severely ill patients [47]. These guidelines recommend that antibiotics with both Gram-positive and Gram-negative coverage should be used if the causative organism has not been identified. Pneumonia and urinary tract infections should be considered in severely ill patients that exhibit no signs of infection, and treatment should be initiated as soon as possible.

3. Use of therapeutic plasmapheresis to treat thyroid storm

■ RECOMMENDATION 6

Therapeutic plasmapheresis (TPE) should be considered if clinical improvement is not noted within 24–48 hours of initial treatment with appropriate doses of ATDs, inorganic iodine, corticosteroids, or beta-AAs, as well as specific treatment for the triggering disease and complications with thyroid storm.

Strength of recommendation: weak

Quality of evidence: low

● Evidence supporting the recommendation

The usefulness of TPE in treating thyroid storm was first described by Ashknar *et al*. in 1970 [48]. TPE efficiently improves thyrotoxicosis by rapidly removing and exchanging the serum proteins to which approximately 99% of thyroid hormones bind. To date, no prospective studies have verified the usefulness of TPE in treating thyroid storm. However, based on many case reports from Japan and other countries in which thyroid storm has been successfully treated using TPE, we recommend that TPE be considered if thyrotoxic symptoms such as tachycardia, high fever, and disturbances of consciousness have not improved within 24–48 hours of initial intensive treatment, because these symptoms in patients with thyroid storm typically improve within 12–24 hours of appropriate initial therapy [3].

● Comments

1. TPE exchanges the patient's plasma with fresh plasma from healthy donors and should be used to treat patients with thyroid storm complicated with acute liver failure with disturbances of consciousness. A more precise indication for TPE in acute liver failure is described in the "Treatment of gastrointestinal symptoms and hepatic injury in thyroid storm" section.

2. a) A relative indication for TPE in thyroid storm

Charcoal absorbance and blood exchange have previously been performed to remove excess serum thyroid hormone in patients with thyroid storm. TPE is considered to efficiently improve thyrotoxicosis by rapidly removing and exchanging the serum proteins to

which approximately 99% of thyroid hormones bind. The usefulness of TPE as a preoperative treatment for thyrotoxic patients complicated with agranulocytosis associated with ATD use has also been reported [49]. Theoretically, TPE could remove excess catecholamines, cytokines, and anti-thyroid stimulating hormone receptor antibodies (TRAb) [50]; however, these findings have not yet been confirmed in large case series. To date, no randomized study has evaluated the usefulness of TPE in the treatment of thyroid storm because thyroid storm is a rare endocrine emergency. However, based on many case reports in which the efficacy and safety of TPE have been demonstrated, we recommend that TPE be considered if thyrotoxicosis has not improved within 24–48 hours after the start of initial treatment because thyrotoxic symptoms in patients with thyroid storm generally improve within 12–24 hours after appropriate initial treatment [3, 51]. If the patient's condition has not improved after 24–48 hours, the condition is suspected to be highly resistant to conventional therapies due to an unknown mechanism. Rate control with beta-AAs may be necessary before starting TPE. Although TPE has been shown to be useful for the treatment of conventional therapy–resistant thyroid storm in many case reports, TPE is not approved for thyroid storm by the health insurance system in Japan.

b) Replacement fluids and the combination of TPE with continuous hemodiafiltration (CHDF)

Two types of replacement fluids exist for TPE: fresh frozen plasma (FFP) and albumin solution. FFP contains thyroxine-binding globulin (TBG) and is thought to be useful for the removal of TBG-bound thyroid hormones. In contrast, limitations of FFP include its high cost, risk of infection, and presence of thyroid hormones. In contrast, albumin solution is less expensive, associated with a lower risk of infection, and contains lower levels of thyroid hormones. Since albumin solution contains less TBG, it may cause worsening of thyroid storm. However, one previous study showed that the level of TBG rapidly increases after TPE with albumin solution [52]. Although no randomized study has yet evaluated the usefulness of FFP *versus* albumin solution in TPE to treat thyroid storm, FFP has been preferentially used in many case reports. Therefore, it is recommended that FFP be used as the replacement solution in TPE to treat thyroid storm because FFP is expected to reduce thyroid hormones more efficiently than albumin solution.

CHDF is sometimes performed in parallel with TPE because cardiohemodynamic conditions are often unstable in thyroid storm patients [53]. Several case reports have recently demonstrated the usefulness of using both methods to treat patients with thyroid storm resistant to conventional therapy [54–57]. Since CHDF is performed not only for the treatment of acute hepatic and renal failure, but also for the removal of excess cytokines in systemic inflammatory response syndrome (SIRS) [58], the combined use of TPE with CHDF is recommended for patients with severe complications such as multiple organ failure. The perfusate is basically maintained at body temperature, but when the solution are maintained a little cooler, the body temperature may decrease effectively. However, there is no significant evidence in mortality or effectiveness of cooling with TPE.

c) Evaluation of the role of TPE in the treatment of thyroid storm in other countries

In the guidelines on the use of TPE in clinical practice by the American Society for Apheresis, the evidence level of TPE for thyroid storm was categorized as type II-3 (obtained from multiple time series with or without the intervention). Dramatic results in uncontrolled experiments could also be regarded as this level of evidence and the usefulness of TPE was classified as Category III (the optimum role of apheresis therapy is not established, decision-making should be individualized). FFP is recommended as a replacement fluid to increase TBG levels and the replacement volume should be 1 to 1.5 times the total plasma volume. TPE daily or every 2 to 3 days is also recommended and should be continued until clinical improvement has been observed [59].

In a recent systemic review summarizing 126 case reports of thyroid storm treated with TPE, the recommended indications for TPE in thyroid storm were described as 1) severe symptoms (cardiothyrotoxicosis, neurological manifestations, disturbances in consciousness, and severe myopathy), 2) rapid clinical worsening, 3) contraindication to other therapies (including agranulocytosis, renal insufficiency, asthma, and heart failure), and 4) failure of conventional therapy [60]. This study recommended that TPE should be performed daily with 40–50 mL/kg of replacement solution until clinical improvements are noted, and FT3 and FT4 levels should be sampled before and after each session. TPE should not be discontinued if there is no reduction in FT3 or FT4 levels

because of biologico-clinical dissociation. The side effects of TPE are mostly reversible, with an incidence of approximately 5%. They include transfusion reaction, citrate-related nausea and vomiting, vasovagal or hypotensive reactions, respiratory distress, tetany, and convulsions. Death was also rarely observed and was commonly attributed to the underlying disease.

d) Outcome of thyroid storm patients treated with TPE in Japan

To evaluate the efficiency of TPE for thyroid storm in Japan, the Ichushi database (Japanese literature) was searched using the terms 'thyroid storm' and 'plasmapheresis' between 1983 and 2015. Analysis of the literature search results showed that the mortality rate of patients with thyroid storm that received TPE was 17.4% (11/63) and the clinical symptoms of many patients improved after a single course of TPE [61-110]. Thyroid hormone levels before and after TPE were significantly decreased in cases described in the literature (Fig. 1). TPE was performed on hospitalized day1 (3 patients), day 2 (2 patients), day 3 (2 patients), or day 9 (1 patient) in the 11 cases that died, and 2 patients died on hospitalized day 26 and day 36 from sepsis, respectively. Therefore, although TPE initially improved severe thyrotoxicosis in these patients, they died from a late-onset complication.

In nationwide surveys conducted in Japan [4], TPE was performed in 16 of 356 thyroid storm patients, and the mortality rate of patients who received TPE was 37.5% (6/16) [8], which is apparently higher than that in the literature (17.4%). This may have been due to publication bias because TPE-unresponsive patients may not have been reported in the literature. Six patients died between days 6 and 37. Four cases were complicated with multiple organ failure and 1 patient died from DIC. Thus, based on the literature and nationwide surveys conducted in Japan, some thyroid storm patients did not survive even with TPE. The usefulness of TPE as an alternative treatment for thyroid storm needs to be verified in a future prospective study.

4. Treatment of central nervous system manifestations of thyroid storm

■ **RECOMMENDATION 7**

1. In addition to prompt treatment of thyrotoxicosis, differential diagnosis and treatment of acute disturbances of consciousness, psychosis, and convulsion in thyroid storm should be performed based on established guidelines in consultation with a psychiatrist or neurologist.

Strength of recommendation: strong

Quality of evidence: low

2. Since thyrotoxicosis and dysfunction of multiple organs such as the liver and kidney can affect pharmacokinetics in thyroid storm patients, the condition of each patient should be considered individually when selecting and adjusting doses of psychotropic medications.

Strength of recommendation: strong

Quality of evidence: low

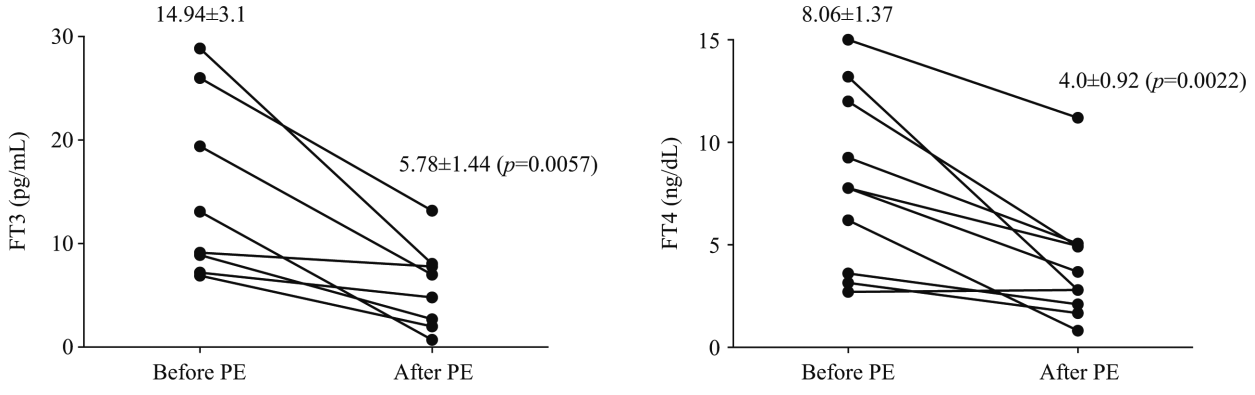


Fig. 1 Significant reduction in thyroid hormone levels before and after plasma exchange (PE) in patients with thyroid storm in the Ichushi database

Changes in free triiodothyronine (FT3) (pg/mL) (n = 8) and free thyroxine (FT4) (ng/dL) (n = 10) levels in patients with thyroid storm after a single session of PE described in case reports between 1983 and 2011 in the Ichushi database were analyzed using the paired *t*-test.

• Evidence supporting the recommendations

1. Thyroid storm often presents with CNS manifestations such as restlessness, delirium, psychosis, somnolence, convulsion, and coma. These CNS manifestations may be caused by overactivity of the adrenergic nervous system [111, 112], autoimmune processes [113], direct effects of excess thyroid hormone levels on brain function [114], or neurotransmitters such as serotonin [115]. However, the precise mechanisms responsible remain unknown. The amelioration of thyrotoxicosis has been shown to be most effective in treating CNS manifestations [116, 117]; however, there is insufficient evidence to support other specific treatments. In a small clinical study, mental symptoms such as anxiety and depression in thyrotoxicosis were significantly improved by beta-AAs [116]. In contrast, another study reported that beta-AAs and placebo had similar effects on anxiety [118]. Moreover, no association was observed between the choice of medication to treat CNS manifestations and prognosis in nationwide surveys in Japan [4]. The 2010 Japan Resuscitation Council (JRC) guidelines [119], Guidelines for Psychiatric Emergency Treatment [120], and 2010 Guidelines for Epilepsy Treatment [121] have been established in Japan for the general management of CNS symptoms. We base our recommendations for the management of CNS manifestations secondary to thyroid storm on these guidelines.

2. Thyrotoxicosis can affect pharmacokinetics by altering the absorption, distribution, metabolism, and excretion of drugs [122]; these effects may change dynamically during the treatment of thyroid storm. Patients with thyroid storm often have dysfunction of multiple organs such as the liver and kidney, which can also affect pharmacokinetics. Therefore, the selection of drugs to treat CNS symptoms and dose adjustment should be individually determined.

• Comments

1. Initial care and differential diagnosis

According to the 2010 JRC guidelines [119], glucose should be administered when hypoglycemia is confirmed in the initial care of acute disturbances in consciousness. The administration of vitamin B1 prior to or at the same time as glucose injection is recommended when malnutrition is suspected based on medical history and physical examination. A differential diagnosis for cerebrovascular disease, meningitis, metabolic disorders, or poisoning should be constructed based on the history of present illness, physical examination for focal and meningeal signs, and urine and blood tests, as well as various imaging studies when altered consciousness has not improved with these treatments. If diseases presenting with CNS symptoms are present, treatments for these illnesses should be performed in parallel with therapy for thyroid storm.

2. Restlessness, delirium, and psychosis

First-line drugs for restlessness, delirium, and psychosis for patients who can tolerate oral medications are second-generation antipsychotics such as risperidone and olanzapine. For patients who cannot tolerate oral medication, first-generation antipsychotic drugs such as haloperidol and olanzapine [120] by intramuscular or intravenous injection are the first-line choices. Although the precise mechanism is unknown, previous case reports have shown that haloperidol can lead to the onset of thyroid storm [123], which can result in neurotoxic effects [124]. Therefore, haloperidol should be carefully administered to patients with thyroid storm.

a) Convulsion, somnolence, and coma

The initial management of patients with convulsions should focus on securing an airway, breathing, and peripheral venous access (Fig. 2). Benzodiazepines are first-line agents for the acute management of convulsions. Fosphenytoin or phenobarbital is recommended if convulsions continue after repeated doses of benzodiazepines [121].

Somnolence and coma can be caused by a variety of conditions, such as hypoxemia due to heart failure or shock, liver failure, renal failure, severe infection, cerebrovascular disease, electrolyte abnormalities, and glucose metabolism. Thyroid storm is often complicated by these conditions; therefore, a differential diagnosis is important in thyroid storm patients in a coma (Fig. 3). Because the underlying cerebrovascular disease or encephalitis may become apparent during the treatment of thyroid storm in patients with CNS manifestations, physical findings should be carefully monitored and an examination of the cerebrospinal fluid examination, brain magnetic resonance imaging (MRI), or electroencephalography should be performed as needed. Early initiation of rehabilitation is recommended to prevent disuse muscle atrophy, especially in patients receiving mechanical ventilation [125].

b) The influence of thyrotoxicosis on pharmacokinetics

Thyrotoxicosis does not have a pronounced effect on the pharmacokinetics of diazepam [126], phenytoin

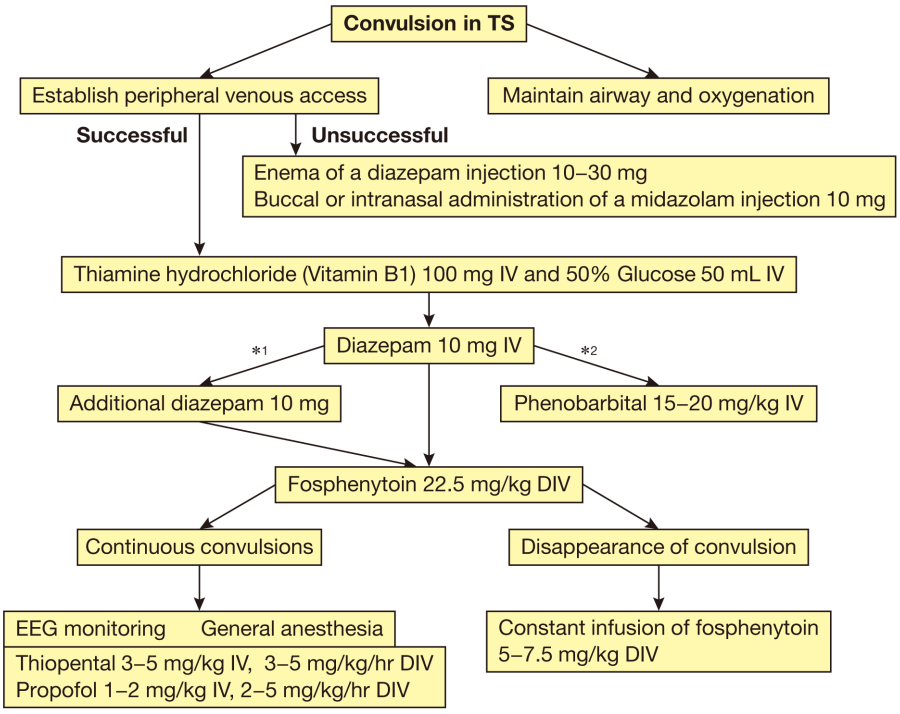


Fig. 2 Medical treatment for convulsions

A proposed algorithm for the treatment of convulsion in patients with thyroid storm, modified from ref. [121]. *1 Standard therapy, *2 alternative therapy. TS, thyroid storm; EEG, Electroencephalogram.

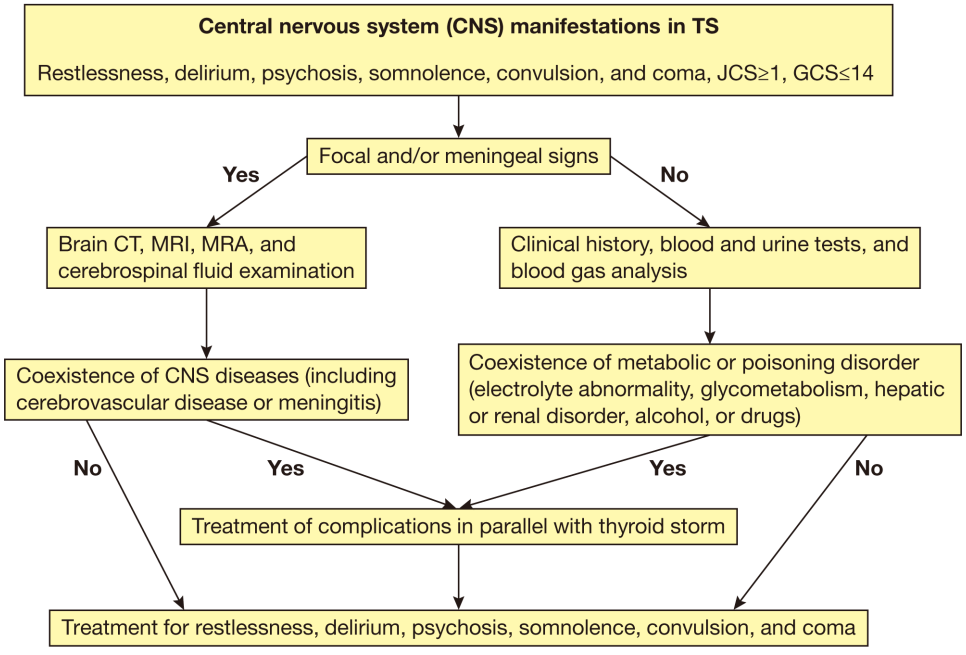


Fig. 3 Differential diagnosis of central nervous system (CNS) manifestations in thyroid storm patients

An algorithm for the differential diagnosis and treatment of CNS manifestations in thyroid storm patients is proposed. TS, thyroid storm; JCS, Japan Coma Scale; GCS, Glasgow Coma Scale; CT, computed tomography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography.

[127], or phenobarbital [128] *in vivo*. On the other hand, in thyrotoxic patients the effect of propofol is decreased due to increased clearance and distribution volume [129]. Since the influence of thyrotoxicosis on the pharmacokinetics of other antipsychotic drugs has not been studied in detail, dose adjustments should be carefully performed with monitoring of therapeutic effects.

5. Treatment of tachycardia and atrial fibrillation in thyroid storm

■ RECOMMENDATION 8

1. Beta1-selective AAs (landiolol, esmolol (intravenous), or bisoprolol (oral)) should be selected as the first choice of treatment for tachycardia in thyroid storm. Other beta1-selective oral drugs are also recommended. Although the non-selective beta-AA propranolol is not contraindicated, it is not recommended for the treatment of tachycardia in thyroid storm.

1) When the heart rate of patients classified as Killip class ≤ III is ≥150 bpm, landiolol or esmolol should be selected as the first choice treatment. If the heart rate is <150 bpm, landiolol or esmolol can be changed to an oral beta1-selective agent.

2) If the heart rate of patients classified as Killip class IV is ≥150 bpm, the use of landiolol or esmolol may be considered.

3) Landiolol should be initially administered intravenously at a dose of 1 μg/kg/min, and its dosage should be controlled appropriately while monitoring the heart rate (1–10 μg/kg/min). Esmolol should be initially administered intravenously at a dose of 1 mg/kg for 30 seconds, and its dosage should be controlled appropriately while monitoring the heart rate (~150 μg/kg/min). Bisoprolol should be administered orally at a dose of 2.5–5 mg/day.

4) Heart rate should be controlled to ≤130 bpm when beta-AAs are used. Discontinuation of beta-AAs should be considered when heart rate is <80 bpm, systolic blood pressure is <80 mmHg, or the cardiac index is ≤2.2 L/min/m^2.

5) Landiolol or esmolol should be used carefully in patients with bronchial asthma and chronic obstructive pulmonary disease (COPD) and may be switched to verapamil or diltiazem if an asthma attack occurs.

Strength of recommendation: high

Quality of evidence: low

2. When atrial fibrillation occurs,

1) Digitalis is used in patients without severe renal dysfunction. It is given intravenously at an initial dose of 0.125 to 0.25 mg, followed by an appropriate maintenance dose with careful monitoring for signs and symptoms of digitalis toxicity.

2) When hemodynamics is impaired rapidly because of atrial fibrillation, cardioversion is recommended when left atrial thrombus has been ruled out.

3) Class Ia and Ic antiarrhythmics are recommended to maintain sinus rhythm after cardioversion. Amiodarone may be considered for patients with impaired left ventricular systolic function.

Strength of recommendation: high

Quality of evidence: low

3. Anticoagulation should be used for persistent atrial fibrillation based on the $CHADS_2$ score, which has been used to evaluate the risk of stroke onset.

Strength of recommendation: high

Quality of evidence: low

● Evidence supporting the recommendations

1. Tachycardia should be treated aggressively because the results of our nationwide survey revealed that tachycardia ≥150 bpm was associated with increased mortality in patients with thyroid storm [4]. All patients with Killip class ≥ III disease treated with beta-AAs who died were treated with non-selective beta-AAs, although there were some patients whose details were unknown and some who were not treated with beta-adrenergic antagonists. In contrast, all patients with Killip class ≥ III disease who survived were treated with beta1-selective AAs.

2. The results of our nationwide survey showed that atrial fibrillation in the presence of thyroid storm is associated with significantly increased mortality (p=0.0024). This finding suggests that systemic hemodynamic deterioration is accelerated by atrial fibrillation in thyroid storm; therefore, cardioversion should be considered when hemodynamics is impaired rapidly because of atrial fibrillation.

3. Anticoagulation is recommended for non-valvular atrial fibrillation when the $CHADS_2$ score, used to evaluate the risk of stroke onset, is ≥2 points. In addition, dabigatran and apixaban are recommended when the $CHADS_2$ score is 1 point. Because hyperthyroidism increases the risk of thrombosis by modifying the coagulation-fibrinolysis balance [130], anticoagulation should be initiated based on the Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013) [131].

● Comments

1. Heart rate needs to be controlled during the treatment of thyroid storm; our nationwide survey revealed that heart rate ≥150 bpm is associated with increased mortality in patients with thyroid storm [4]. Thyroid hormones have been shown to increase the density of beta-adrenergic receptors and cyclic adenosine monophosphate, and decrease the density of alpha-adrenergic receptors [132]; therefore, the usefulness of beta-AAs for tachycardia associated with thyrotoxicosis has been advocated. Beta-AAs were used in 286 patients (80.3%) in our nationwide survey, non-selective beta-AAs in 190 patients, beta1-selective AAs in 66 patients, beta1-selective and non-selective beta-AAs in 3 patients, alpha-, beta-adrenergic antagonists in 18 patients, and unknown in 9 patients. All deaths in patients with Killip class ≥3 disease who met our diagnostic criteria for thyroid storm were treated with non-selective beta-AAs (except for those whose details were unknown or were not treated with beta-AAs), while all patients who survived were treated with beta1-selective AAs.

The effects of beta-AAs with respect to differences in selectivity for beta-adrenergic receptors or the duration of action as treatment for hyperthyroidism have not yet been investigated. Since the 1970s, many studies suggested the usefulness of propranolol. However, most of these studies proposed the usefulness of beta-AAs in general, rather than propranolol specifically [133]. The number of studies that suggest the risks associated with propranolol and the usefulness of esmolol increased after the 1990s [134-139]. Esmolol has several potential advantages over propranolol in thyroid storm. One is its short elimination half-life (t1/2) and duration of action. Another advantage is its relatively higher beta1-selectivity [139]. Although the onset of action of intravenous propranolol and esmolol are similar, their t1/2 and duration of action are markedly different. The t1/2 alpha and beta for propranolol are 10 minutes and 2.3 hours, respectively, while the t1/2 alpha and beta for esmolol are 2 minutes and 9 minutes, respectively [140]. A human volunteer study demonstrated that the effects of beta-blockade completely disappeared 18 minutes after the infusion of esmolol (300 μg/kg/min) had been stopped, while no significant differences were observed in the effects of beta-blockade 30 minutes after stopping the infusion of propranolol (55 μg/min) [141]. Beta1-selectivity raises the possibility that esmolol can be used more safely for patients with asthma. Previous studies have demonstrated that beta1-selective AAs do not exacerbate bronchoconstriction or wheezing induced by tracheal intubation in patients with asthma [142, 143]. Furthermore, a patient with thyroid storm and bronchial asthma was successfully managed with esmolol [144]. Landiolol, an ultra–short-acting beta1-selective AA with a t1/2 of 3–4 minutes and approximately 8-fold greater beta1-selectivity than esmolol, has been approved in Japan for the treatment of intraoperative and postoperative tachyarrhythmias [145]. Landiol was recently approved for the treatment of tachyarrhythmias in other situations, which strongly suggests that it is useful for the treatment of tachyarrhythmias in thyroid storm.

The effect of calcium channel blockers on tachycardia in thyroid storm could not be analyzed in our nationwide surveys because they were used only in a small number of patients. Verapamil is a cardioselective calcium channel blocker that is widely used to slow heart rate, especially in rapid atrial fibrillation. However, verapamil was not efficacious in treating thyroid storm-related cardiac failure in one study [146]. Calcium channel blockers may not be recommended as first-line treatment for tachycardia in thyroid storm due to the pathophysiology of thyroid storm, which is characterized by peripheral vasodilation associated with increased beta-adrenergic action. Landiolol or esmolol should be used carefully in patients with respiratory diseases such as bronchial asthma and COPD. Verapamil can be considered a potential alternative for rate control in patients with bronchial asthma or COPD.

2. In our nationwide surveys, 136 patients with thyroid storm had atrial fibrillation and 130 did not have atrial fibrillation. There were 20 and 5 deaths, respectively. Atrial fibrillation status was unknown in 90 patients, of whom 13 died. The presence of atrial fibrillation in thyroid storm was associated with significantly increased mortality in our nationwide surveys (p=0.0024), as assessed by the Fisher's exact test. The reported incidence of atrial fibrillation in thyrotoxicosis ranges between 12% and 28% [147]. Atrial fibrillation further accelerates systemic hemodynamic disturbances and increases mortality in thyroid storm; therefore, cardioversion should be considered if hemodynamics is impaired rapidly because of atrial fibrillation.

The treatment of atrial fibrillation includes both rate and rhythm control. Beta-AAs are recommended as first-line treatment for rate control due to the patho-

physiology of thyroid storm. However, a treatment protocol has not yet been established for rhythm control in thyroid storm. Digitalis was used in 30 patients (8.4%) in our nationwide surveys, of whom 4 died. Since digitalis was only sometimes used as a cardiotonic agent under critical conditions, this result does not necessarily indicate the inferiority of digitalis in the treatment of atrial fibrillation associated with thyroid storm. Digitalis is recommended for tachycardia-induced heart failure due to atrial fibrillation by the Guidelines for the Treatment of Acute Heart Failure (JCS 2011); [148] however, it should be used with caution because of the possibility of digitalis intoxication, especially in patients with renal dysfunction. In addition, because thyrotoxicosis accelerates the clearance of digoxin [149], digoxin levels should be monitored and the dose adjusted appropriately as the patient becomes euthyroid. To prevent relapse of atrial fibrillation, class Ia and Ic antiarrhythmics are recommended for patients without impaired left ventricular systolic function according to the Guidelines for Pharmacotherapy for Atrial Fibrillation (JCS 2013) [150]. In patients with impaired left ventricular systolic function, amiodarone is a first choice of treatment for atrial fibrillation in Europe and United States [151] and recommended by the Guidelines for Pharmacotherapy for Atrial Fibrillation (JCS 2013) [150].

3. Appropriate anticoagulation should be given based on an assessment of the risk of cerebral infarction in patients with non-valvular atrial fibrillation, as recommended by the Guidelines for Pharmacotherapy for Atrial Fibrillation (JCS 2013) [150]. The $CHADS_2$ score has been proposed to assess the risk of developing cerebral infarction [152]. CHADS is an acronym for Congestive heart failure, Hypertension, Age ≥ 75 years of age, Diabetes mellitus, and Stroke/Transient ischemic attack (TIA). The $CHADS_2$ score is calculated as the sum of the points for each risk factor (1 point for each of the first 4 factors and 2 points for history of stroke/TIA), with higher scores representing higher risk of cerebral infarction. Anticoagulation is recommended for patients with a $CHADS_2$ score ≥2 points. Since hyperthyroidism increases the risk of thrombosis by altering the coagulation-fibrinolytic balance [130], anticoagulation should be given based on the Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013). Dabigatran, a direct thrombin inhibitor, and apixaban, a direct factor Xa inhibitor, have recently been recommended for patients with a $CHADS_2$ score ≥1 point in the Guidelines for Pharmacotherapy of Atrial Fibrillation [150]. Other direct factor Xa inhibitors such as rivaroxaban and edoxaban may also be used in patients with atrial fibrillation. However, there have been to date no clinical trials assessing the usefulness of rivaroxaban and edoxaban in patients with a $CHADS_2$ score of 1 point. Recommendations regarding these novel oral anticoagulants may be reevaluated in the future based on new information.

6. Treatment of acute congestive heart failure in thyroid storm

■ RECOMMENDATION 9

1. Hemodynamic monitoring using a Swan-Ganz catheter is recommended for patients with acute congestive heart failure classified as Killip class ≥III.

Strength of recommendation: high

Quality of evidence: low

2. Acute congestive heart failure in thyroid storm should be treated according to the Guidelines for the Treatment of Acute Heart Failure (JCS 2011) [148], given the pathophysiology of thyroid storm.

1) In patients with acute congestive heart failure classified as Killip class III,

i) Respiratory management: Respiratory management should include noninvasive positive-pressure ventilation (NIPPV) or artificial respiration by intratracheal intubation if the patient's respiratory status has not improved with oxygen administration.

ii) Drug therapy: Furosemide (intravenous), nitrate (sublingual or intravenous), and/or carperitide (intravenous) should be administered. Beta-AAs are used for the treatment of tachycardia. When atrial fibrillation is present, digitalis is used simultaneously. Calcium channel blockers (intravenous) should be considered if hypertension is present. If the patient's hemodynamic status does not improve with these treatments, treatments recommended for patients classified as Killip class IV should be started, as described below.

2) In patients with acute congestive heart failure classified as Killip class IV,

i) Respiratory management: Respiratory management should be the same as for patients with acute congestive heart failure classified as Killip class III.

ii) Drug therapy: Adrenergic agonists should be used. Dopamine should be administered intravenously at a dose of 5–20 μg/kg/min when systolic blood pressure is between 70 to 90 mmHg. Dobutamine at a dose of ~10 μg/kg/min should be considered when the patient is in cardiac shock and systolic blood pressure is ≤70 mmHg. Norepinephrine at a dose of 0.03–0.3 μg/kg/min is also used when the patient's hemodynamic condition does not improve with these agents or systolic blood pressure is ≤70 mmHg. The short-acting beta1-selective adrenergic antagonists landiolol or esmolol may be considered when heart rate is ≥150 bpm. When atrial fibrillation is present, digitalis should be used simultaneously.

Strength of recommendation: high
Quality of evidence: low

3. An artificial heart–lung machine should be used before the development of irreversible multiple organ failure when hemodynamic status has not improved with the maximum dose of adrenergic agonists.

Strength of recommendation: high
Quality of evidence: low

● Evidence supporting the recommendations

1. Hemodynamic monitoring using a Swan-Ganz catheter should be considered on an individualized basis, as described in the Guidelines for the Treatment of Acute Heart Failure (JCS 2011) [148, 150]. Hemodynamic monitoring using a Swan-Ganz catheter is recommended for assessing the severity of acute congestive heart failure in patients classified as Killip class ≥ III.

2. The treatment of acute congestive heart failure in patients with thyroid storm has not been studied in detail. Acute congestive heart failure in thyroid storm should be treated according to the Guidelines for the Treatment of Acute Heart Failure (JCS 2011) [148] on an individualized basis, with consideration of the pathophysiology of thyroid storm.

3. Our nationwide surveys revealed that 5 of 9 patients treated with an artificial heart–lung machine survived [4]. An artificial heart–lung machine should be used before the development of irreversible multiple organ failure.

● Comments

1. Hemodynamic monitoring with a Swan-Ganz catheter should be considered on an individualized basis [153]. Hemodynamic monitoring using a Swan-Ganz catheter is recommended for assessing the severity of acute congestive heart failure in patients classified as Killip class ≥III. If it is not possible to monitor hemodynamic status using a Swan-Ganz catheter, accurate assessment by physical examination, chest X-ray, or echocardiography is required.

2. Vasoconstrictor agents, cardiotonic agents, and/or diuretics were used in 100 patients in our nationwide surveys [4]: adrenergic agonists in 45 patients; digitalis in 30 patients; vasodilator agents (nitroglycerin and isosorbide dinitrate) in 4 patients; carperitide in 6 patients; furosemide in 5 patients; and unknown or other in 15 patients. None of these agents were used in 229 patients. Whether these agents were used was unknown in 27 patients. Although the use of these agents was associated with significantly increased mortality in our nationwide surveys ($p<0.0001$), as assessed with the Fisher's exact test, this result was attributed to these agents being used in patients in critical condition with a high likelihood of death. No definite trend was observed when the analysis was performed for each agent separately. The treatment of acute congestive heart failure in patients with thyroid storm has not been examined in detail. Therefore, the use of vasoconstrictor agents with or without diuretics should be considered on an individualized basis according to the Guidelines for the Treatment of Acute Heart Failure (JCS 2011) [148]. Digitalis along with beta-AAs may be considered for tachycardia in the presence of atrial fibrillation, as described in the Guidelines on the Treatment of Tachycardia and Atrial Fibrillation in thyroid storm (Section 4). However, phosphodiesterase III inhibitors are not recommended for thyroid storm because of the enhanced production of cyclic adenosine monophosphate with overstimulation of beta-adrenergic receptors.

3. Artificial heart–lung machines were used in 9 patients in our nationwide surveys [4]: 2 patients with Killip class 4 disease, 4 patients with class 3 disease, 2 patients with class 2 disease, and 1 patient with unknown status. Five patients survived: 2 patients with class 4 disease, and 1 patient each with class 3 disease, class 2 disease, and unknown status. Four patients died: 3 patients with class 3 disease and 1 patient with class 2 disease. It should be appreciated that artificial heart–lung machines should be used before the development of irreversible multiple organ failure.

7. Treatment of gastrointestinal disorders and hepatic damage in thyroid storm

■ **RECOMMENDATION 10**

1. Gastrointestinal symptoms, including diarrhea, nausea, and vomiting, are associated with thyrotoxicosis, heart failure, neurological disorders, and gastrointestinal infection. Treatment for gastrointestinal infection should be performed in parallel with that for thyrotoxicosis to improve gastrointestinal symptoms.

Strength of recommendation: strong

Quality of evidence: low

2. Administration of large doses of corticosteroids, coagulopathy associated with thyroid storm, and intensive care unit (ICU) stay with prolonged mechanical ventilation may be risk factors for gastrointestinal hemorrhage and mortality. Acid-suppressive drugs such as proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2As) are recommended for patients in these instances.

Strength of recommendation: strong

Quality of evidence: low

3. Hepatotoxicity with or without jaundice in thyroid storm can be caused by hepatocyte damage due to thyrotoxicosis, heart failure, precipitating hepatic-biliary infection, or drug-induced liver damage. The nationwide surveys showed that patient prognosis is worse when total bilirubin levels are ≥ 3.0 mg/dL. Differential diagnosis for the origin of hepatic dysfunction and appropriate treatment based on its origin should be performed, including TPE for acute hepatic failure.

Strength of recommendation: strong

Quality of evidence: low

● **Evidence supporting the recommendations**

1. Gastrointestinal disorders

Diarrhea is the most common gastrointestinal symptom in thyrotoxicosis, including thyroid storm. The incidence and severity of diarrhea have been associated with serum FT3 and FT4 levels [4]. Therefore, a reduction in serum thyroid hormone levels could stop diarrhea without the use of specific antidiarrheals. Antidiarrheals are not necessary for many cases of thyroid storm with coma. Thyroid storm causes muscle weakness in the diaphragm and esophagus, and gastric wall motility dysfunction, which results in nausea, vomiting, and abdominal pain. Gastrointestinal tract motility is also affected by CNS impairment. Therefore, gastrointestinal disorders could be treated primarily by improving thyrotoxicosis with limited use of anti-emetics.

2. Prevention of gastrointestinal bleeding

Acid-suppressive drugs are commonly used in the emergency room to prevent gastric ulcers and acute gastric mucosal lesions. Patients under mechanical ventilation and those with coagulopathy are at the highest risk of gastrointestinal hemorrhage in the ICU [154, 155]. ICU patients with gastrointestinal bleeding have 46% higher mortality [155]. The American Society of Health-System Pharmacists (ASHP) guidelines recommend prophylactic treatment with acid-suppressive drugs (antiulcer agents) such as PPIs and H2As [156]. H2As can reduce the risk of overt bleeding by 58% [157]. Although proven to be highly effective in raising gastric pH, recent studies, including a meta-analysis, revealed that acid-suppressive drugs alone do not decrease the overall mortality rate [158]. Guidelines issued by the Agency for Healthcare Research and Quality (AHRQ) recommend prophylactic treatment as level 1 for ICU patients with coagulopathy, head injury, severe burns, or mechanical ventilation [159]. PPIs and H2As cannot fully prevent stress-induced mucosal bleeding, and the risk of *Clostridium difficile* infection could be increased with the use of acid-suppressive drugs. Furthermore, acid-suppressive drugs can cause hypomagnesaemia, vitamin B12 deficiency, upper respiratory tract infection, pneumonia, and clinical fractures of the hip, spine, and wrist. Continuation of these medications should be reassessed once the patient is discharged from the ICU. The AHRQ guidelines state that the risk of gastrointestinal bleeding increases with the number of days on mechanical ventilation and ICU stay, respectively [159]. Mechanical ventilation and coagulopathy, especially DIC, also contribute to poorer prognosis in patients with thyroid storm.

3. Jaundice and hepatic damage

Congestive heart failure is one of the most common causes of hepatic damage and jaundice. Treating congestive heart failure could contribute to the recovery of normal liver function. Ursodeoxycholic acid, which relieves liver dysfunction, and Stronger Neo-Minophagen C, a glycyrrhizin-containing liver protector, can also be used; however, these drugs may induce further liver damage [160]. When an adequate reduction in thyroid hormone levels cannot be achieved, TPE and/or CHDF should be considered to remove excess thyroid hormone, autoantibodies, mol-

ecules that cause coma, and pro-inflammatory cytokines. Severe liver failure induces reduced protein synthesis, which results in coagulopathy, host defense disorders, and eventually multiple organ failure. TPE with FFP may effectively compensate for the loss of coagulation factors. In addition, hemodialysis could support detoxification in liver failure [161]. TPE and CHDF may contribute to the recovery of homeostasis in electrolytes, fluid volume, and acid-base balance in multiple organ failure, providing sufficient extracellular fluid space for treatment [162, 163]. Additional information regarding the indication for TPE in thyroid storm is described in the Section 2.

● Comments

a) Gastrointestinal disorders in thyroid storm

CNS manifestations weighted most heavily in our diagnostic criteria for thyroid storm, while gastrointestinal symptoms contributed less to the diagnosis of thyroid storm [4]. However, if we exclude gastrointestinal manifestations from the diagnostic criteria of thyroid storm, 38 of 55 patients (including 7 fatal cases) without CNS manifestations would not have been diagnosed with thyroid storm. Therefore, we cannot ignore gastrointestinal symptoms in the diagnosis of thyroid storm; however, the treatment of these disorders mainly depends on reducing serum thyroid hormone levels. The prognosis is affected by CNS manifestations and heart failure. Based on the results of our national survey in Japan [4], we could not identify any specific drugs that affected liver function or mortality in patients with thyroid storm.

b) Hepatic damage

Increased oxygen consumption in hepatocytes resulting in relative hypoxia in the perivenular region, may be responsible for inducing hepatocyte damage in thyrotoxicosis. One pathological study showed simple atrophy, sinusoid congestion, and fatty metamorphosis [164]. The presence of autoimmune diseases such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis may also exacerbate liver damage in thyrotoxicosis. Graves' disease is also categorized as an autoimmune disease. The principal treatment during the acute phase of thyroid storm should focus on thyrotoxicosis and heart failure.

c) TPE and hemodialysis

According to the guidelines of the Japan Society for Apheresis, indications for TPE in acute liver failure are as follows: altered consciousness, serum total bilirubin level >5.0 mg/dL or hepaplastin <30%, and arterial ketone body ratio (acetoacetate/3-hydoxybutyrate) <0.7 [165]. Three types of apheresis are used for acute liver failure: TPE, CHDF, and plasma adsorption. TPE can remove intermediate–molecular-weight proteins such as bilirubin, replace proteins such as coagulation factors, and provide sufficient extracellular space for treatment. CHDF is used to remove low–molecular-weight molecules that can induce hepatic coma and adjust balances in fluid, electrolyte, and acid-base levels. Like TPE, plasma adsorption can also remove bilirubin. In multiple organ failure, TPE and CHDF could contribute to the recovery of the homeostasis of electrolyte, fluid volume, and acid-base balance and provide sufficient extracellular fluid space for treatment. In Japan, TPE is reimbursed by the health insurance system when a patient is in acute liver failure.

8. Recommended admission criteria for the intensive care unit and therapeutic strategy for comorbidities

■ RECOMMENDATION 11

1. Intensive care unit (ICU) admission should be recommended for all thyroid storm patients. Patients with potentially fatal conditions such as shock, DIC, and multiple organ failure should immediately be admitted to the ICU.

Strength of recommendation: strong

Quality of evidence: low

2. Based on nationwide survey analyses, it is strongly recommended that patients with APACHE II scores above 9 be admitted to the ICU.

Strength of recommendation: strong

Quality of evidence: low

3. DIC, which is often complicated with thyroid storm, should be intensively treated, because DIC was shown to be associated with high mortality in the JTA nationwide surveys.

Strength of recommendation: strong

Quality of evidence: low

● Evidence supporting the recommendations

Thyroid storm constitutes an endocrine emergency that causes multiple organ failure with a mortality rate of approximately 10% [4]. In addition to rapid triage, prompt initiation of aggressive treatment is essential; however, there are no clinical studies that have investigated fatal comorbidities or prognostic factors

in a large cohort of thyroid storm patients. Although it was retrospective in nature, the nationwide survey performed in Japan is the largest cohort study conducted thus far worldwide, and it demonstrated that systemic comorbidities, including DIC, were associated with higher mortality [4]. The presence of shock, complications of DIC, and multiple organ failure were identified as the prognostic factors most strongly associated with mortality by multiple regression analyses [4]. Therefore, patients with these comorbidities should immediately be admitted to the ICU for intensive monitoring and treatment.

Although the APACHE II scoring system has frequently been used in critical care medicine to evaluate the mortality of ICU-admitted patients [166], the prognosis of thyroid storm has never been evaluated in a large cohort using this scoring system. In the nationwide survey, APACHE II score was significantly correlated with mortality (odds ratio, 1.10, 95% CI 1.05 to 1.15; p=0.0001). The average APACHE II scores of all patients, survivors, and non-survivors were 11.0, 10.5, and 15.0, respectively, and those of patients admitted to a general ward or ICU were 9.1 and 13.6, respectively. The APACHE II score was above 8.8 in 75% of the patients who died, while in the 8 patients who were admitted to general wards and subsequently died the scores were 5 (2 cases), 11, 12, 13 (2 cases), 24, and 32. A nationwide survey conducted by the Japan Society for Emergency Medicine at 178 hospitals in 2007 reported that the APACHE II scores were 11 or 12 in all ICU-admitted patients [167]. Based on these findings as well as our own, we strongly recommend that patients with an APACHE II score above 9 receive ICU care to ameliorate thyroid storm–mediated mortality.

A recent clinical study revealed a close relationship between hyperthyroidism and coagulation disorders [168]. In the nationwide surveys, 9.3% of patients had associated DIC and their mortality was 45% [4]. A case report also described the presence of multiple organ failure in thyroid storm with possible association with DIC [169]. Multiple organ failure is a characteristic feature of thyroid storm, and may be complicated with DIC, and vice versa; DIC often progresses to multiple organ failure. Therefore, DIC in thyroid storm should be treated aggressively.

• Comments

ICU admission criteria vary by country and hospital, which has been attributed to differences in the number of ICU beds in each country or hospital. A previous study reported that adult ICU beds ranged from 24/100,000 population in Germany to 3.3 beds/100,000 in the United Kingdom [170]. Japan has an estimated 4.3 ICU beds/100,000 [167]. The prognosis of patients also differs by disease category, and patients with certain diseases should be admitted to the ICU even if they have a low APACHE II score. In conclusion, specific criteria for ICU admission are needed for thyroid storm.

Since the most important objectives of ICU admission are to improve prognosis and reduce mortality, analyzing the cause of death is essential. Table 4 shows the final outcomes from a nationwide survey of patients with thyroid storm [4]. Of 356 patients, 38 died and 318 survived. Among the survivors, 289 did not have any sequelae, while 29 had some sequelae. Logistic regression analysis revealed that only the presence of fatal comorbidities was associated with mortality. We then evaluated each comorbidity (shock, rhabdomyolysis, DIC, or multiple organ failure) individually, and found that shock, DIC, and multiple organ failure were independent risk factors for mortality. There were 125 patients with these comorbidities (35.1%). Shock (53 cases) was the most common comorbidity [4]. Taken together, the presence of these comorbidities imply poor prognosis and require medical care in the ICU.

Multiple organ failure is another important comorbidity of thyroid storm. The incidence of multiple organ failure in thyroid storm was 9% in a nationwide survey and it is an independent risk factor for mortality [4]. Multiple organ failure is defined as a condition in which an uncontrolled systemic inflammatory response or increase in cytokine levels leads to progressive damage of 2 or more organs or organ systems

Table 4 Direct causes of death in thyroid storm

Causes	Number of patients
MOF	9
Heart failure	8
Respiratory failure	3
Arrhythmia	3
DIC	2
Gastointestinal perforation	2
Hypoxic brain damages	1
Sepsis	1
Unknown	9
Total	38

MOF, multiple organ failure; DIC, disseminated intravascular coagulation.

[171]. The pathogenesis of multiple organ failure has been divided into the following 2 mechanisms: 1) tissue hypoxia induced by tissue hypoperfusion in shock or hypotension and 2) decompensation or overcompensation for systemic inflammation induced by various pathogens, such as during infection, leading to overactivation of inflammatory responses. Causes of multiple organ failure include severe infection, trauma, major surgery, shock, pancreatitis, massive bleeding, DIC, heart failure, hypotension, hypoxia, and malignant tumors. Cardiogenic shock or DIC induced by a coagulation disorder can progress to multiple organ failure in patients with thyroid storm. A specific therapeutic strategy has not been established and the management of thyroid function is considered to be essential. Palliative therapy for each type of organ failure is also considered important. They include management with a respirator for respiratory failure, hemodialysis for renal failure, plasma exchange for hepatic insufficiency, cardioactive medications or assisted circulation for heart failure, intravenous hyperalimentation for nutritional support, insulin therapy for hyperglycemia, and plasmapheresis for various kinds of chemical mediators. Patients with thyroid storm and multiple organ failure should be admitted to the ICU, because multiple organ failure carries an especially high mortality in thyroid storm.

Guidelines for ICU admission or discharge needed to be established using objective criteria, such as the APACHE II score. The APACHE II score was proposed as a measure of disease severity by Knaus *et al*. in 1981 [166]. The score is calculated as the acute physiology score (APS) as the sum of the worst values for 12 clinical indexes including respiration, circulation, blood chemistry, and Glasgow Coma Scale in the 24 hours after ICU admission. APS is then added to scores based on age and chronicity, yielding the APACHE II score. This APACHE II score was then re-evaluated by disease and an estimated mortality rate was calculated. The final assessment of the APACHE II score was based on the probability of mortality (Table 5) [166]. The median APACHE II score was 10 and the mean was 10.9 in a nationwide survey [4]. The mortality of thyroid storm in this survey was 11% and the mean value of the APACHE II score was 10.97±0.35, indicating agreement between thyroid storm mortality and APACHE II score. The validity of APACHE II scores was established; the mortality of thyroid storm could be evaluated using the APACHE II score.

Sequential Organ Failure Assessment is another scoring system for systemic conditions. It is calculated based on 6 clinical indexes evaluating the respiratory, coagulation, liver, cardiovascular, central nervous, and renal systems. Each index has 5 grades, ranging from 0 to 4 [172]. A Sequential Organ Failure Assessment score above 5 corresponds to a mortality rate of 20%. In the nationwide survey, the mean Sequential Organ Failure Assessment score was 2.7±0.5. The mean value of patients who died was 3.1±0.5, and the mean value of patients who survived was 2.4±0.1 (p<0.0001). The odds ratio for death was 1.33 (95% CI, 1.20 to 1.50; p<0.0001). Although absolute values were as low as 2, sequential changes in this score can be useful for the assessment of the patient's prognosis since this value was associated with mortality.

A recent study reported the relationship between thyroid dysfunction and coagulation disorders [130]. The mechanisms underlying this relationship were considered to be the direct effects of thyroid hormones on the coagulation or immune system. One study showed increased serum levels of coagulation factors such as factor VIII and von Willebrand factor following systemic infusion of thyroid hormones in normal healthy volunteers [173, 174]. Several case reports also described patients with severe thyroid storm complicated with DIC. Controlling systemic thyroid hormone levels is important because the basic mechanism for DIC in thyroid storm is coagulation system disorder. Interventional clinical trials may be necessary to establish the appropriate management of DIC in thyroid storm.

9. Prognostic evaluation of thyroid storm

■ RECOMMENDATION 12

The APACHE II score or Sequential Organ Failure Assessment score can be used for the prognostic prediction of thyroid storm.

Strength of recommendation: weak

Quality of evidence: low

● Evidence supporting the recommendations

Although thyroid storm is often a fatal condition, prognostic information including the cause of death has not yet been fully elucidated. Few studies have evaluated the prognosis of thyroid storm. Although the fatality rate was estimated to be as high as 10% to 30% in previous studies conducted outside of Japan, these

findings may not be applicable to the current clinical setting due to significant advances in critical care medicine [6, 175, 176]. We used the results of a nationwide survey conducted in Japan to comment on current clinical practices in Japan [4].

The prognoses of patients with thyroid storm were as follows: 38 of 356 cases died, yielding a mortality rate of 10.7%. Among thyroid storm survivors, 318 patients did not have any sequelae, while 29 patients had some sequelae. Half of the deaths were caused directly by heart failure and or multiple organ failure (Table 4) [4]. Logistic regression analysis identified the presence of comorbidity (shock, rhabdomyolysis, DIC, or multiple organ failure) as an independent significant risk factor for mortality [4]. Most sequelae consisted of neurological disorders, either central or peripheral (Table 6). The Glasgow Coma Scale and BUN value at the time of hospital admission were listed as factors contributing to future development of neurological sequelae [4].

When analyzing data on patients who have died, we have to recognize the limitations of this survey. Since this was a retrospective survey, all patients were treated with some interventions, and some factors that were well managed could not be detected as important risk factors for mortality. Therefore, it is necessary to identify factors indicating serious conditions at the initial assessment before the treatment. We identified factors indicating a serious condition on the basis of some established indices that are associated with mortality. These factors include the APACHE II [166] and Sequential Organ Failure Assessment scores [177]. As described in the previous section, both factors are correlated with mortality. These results indicated that either score can be used as an alternative index of mortality.

The parameters independently associated with the calculated APACHE II score include the Glasgow Coma Scale score, age, serum creatinine, serum albumin, and base excess. The parameters independently associated with the calculated Sequential Organ Failure Assessment score include the presence of ophthalmopathy, Glasgow Coma Scale score, shock, serum albumin, serum total bilirubin, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), and heart failure. In conclusion, age, Glasgow Coma Scale score, presence of ophthalmopathy, serum creatinine, albumin, base excess, shock, serum total bilirubin, $PaCO_2$, and heart failure were identified as independent risk factors for severe thyroid storm [4].

Table 5 Mortality evaluated by acute physiology and chronic health evaluation (APACHE) II score

Mortality evaluated by acute physiology and chronic health evaluation (APACHE) II score	
APACHE II score	Mortality
0–4	~4% death rate
5–9	~8% death rate
10–14	~15% death rate
15–19	~25% death rate
20–24	~40% death rate
25–29	~55% death rate
30–34	~75% death rate
>34	~85% death rate

Table 6 Sequelae of thyroid storm

Sequlae	Number of patients
Post-resuscitation encephalopathy	6
Disuse muscle atrophy	5
Cerebrovascular disease	4
Atrial fibrillation	4
Renal insufficiency	2
Psychosis	2
Hypothyroidism	2
Gastric ulcer	1
Others	3
Total	29

• Comments

No large-scale observational cohort studies have been conducted to date. Only single center analyses or long-term retrospective observational studies have been performed. These previous studies have drawbacks such as differences in treatments used or a small number of patients. The recent nationwide survey supported by the Japanese Ministry of Welfare, Labor and Health was a multi-center study with 356 registered cases between 2004 and 2008 [4]. Although the findings were considered to be reliable, limitations included the study being cross-sectional in design and that the clinical course of each patient was modified by treatment chosen based on the severity of thyroid storm. For example, any cardiac involvement was not selected as a risk factor for mortality in this analysis because these complications were controlled, so they did not have an effect on mortality. On the other hand, the identification of DIC, shock, and multiple organ failure as risk factors for mortality was plausible because these conditions are by themselves fatal. Since these factors may not have been detected or fully

treated, they could be identified as risk factors. These fatal complications must be considered in the management of thyroid storm.

The survey also provided pivotal information on the sequelae of thyroid storm. It revealed that thyroid storm frequently causes neurological sequelae and that Glasgow Coma Scale score and serum BUN are risk factors for the development of neurological sequelae. These results were consistent with diagnostic criteria of thyroid storm that stress the importance of neurological findings [4]. In this regard, the clinical course of neurological complications should be carefully followed. The mechanisms underlying this neurological involvement have not been fully elucidated. One possible mechanism may be that shock or hypoxia could lead to brain damage. A laboratory investigation to elucidate these mechanisms is warranted.

10. Prevention of thyroid storm and roles of definitive treatment

■ RECOMMENDATION 13

1. Care should be taken to prevent thyroid storm in patients with poor adherence who are undergoing ATD treatment.

Strength of recommendation: high

Quality of evidence: low

2. Definitive treatment of Graves' disease, either by radioiodine treatment or thyroidectomy, should be considered to prevent recurrent thyroid storm in patients successfully managed during the acute stage of thyroid storm.

Strength of recommendation: high

Quality of evidence: low

● Evidence supporting the recommendations with comments

In the nationwide surveys performed in Japan, the precipitating factor most frequently reported was poor adherence with or abrupt discontinuation of ATDs [4]. Therefore, at the time ATDs are initiated, every patient with Graves' disease should be given full information about life-threatening thyroid storm and its triggering conditions. Patients with continuously poor adherence even after repeated education should be treated by radioiodine treatment or thyroidectomy. In thyrotoxic patients with potential triggering conditions for thyroid storm, these triggering factors should be simultaneously treated.

The nationwide surveys provided the novel finding that in about 20% of cases, thyroid storm originated from undiagnosed Graves' disease [8]. In order to prevent the onset of thyroid storm in such cases, providing information to the general population about life-threatening thyroid storm may be important. In addition, providing knowledge about thyroid storm and its diagnostic criteria to acute care physicians and cardiologists who may be more likely to encounter thyroid storm patients will lead to timely diagnosis and treatment.

Thyroid storm can be caused by several medical triggers such as radioiodine therapy, thyroidectomy, and nonthyroid surgery in patients with uncontrolled Graves' disease. The JTA nationwide surveys identified 6 cases of thyroid storm in relation to radioiodine therapy, but no patients who developed thyroid storm after thyroidectomy [4]. Therefore, it is important to carefully monitor general patient condition and thyroid hormone levels prior to and after radioiodine therapy. In patients treated with ATDs prior to radioiodine therapy, discontinuation of ATD for radioiodine therapy should be minimized, and treatment for tachycardia with beta-AAs is recommended. Elective surgical procedures should be postponed until euthyroidism has been achieved using ATDs and inorganic iodide. Patients who cannot tolerate these treatments or respond poorly to them require preparation for surgery using all available means to normalize thyroid hormone levels preoperatively, as mentioned above.

Several drugs have been reported to cause thyroid storm in rare instances, such as iodine contrast agent in patients with uncontrolled Graves' disease [1-4] as well as amiodarone [18], sorafenib [19], and ipilimumab [20] in patients without Graves' disease, all these drugs can develop thyrotoxicosis as an adverse event. Administration of iodine contrast agent to patients with uncontrolled Graves' disease should be avoided, and scheduled monitoring of thyroid hormone levels during treatment with these drugs is necessary.

A series of emergent thyroidectomy has been reported to treat thyroid storm patients who continued to deteriorate despite the use of standard medical therapy. Postoperative mortality in these patients was reported in 5 of 49 patients (10.2%) [178]. The authors advocated early thyroidectomy to treat thyroid storm, particularly in chronically ill older patients with concurrent cardio-pulmonary and renal failure who fail to respond to the standard intensive multifaceted therapy for thyroid storm [178]. However, the combined use

of TPE with CHDF should be considered before performing emergent thyroidectomy in such patients with Graves' disease in iodine-sufficient area.

11. An algorithm for the diagnosis and management of thyroid storm

■ RECOMMENDATION 14

When patients with high fever (≥38°C), marked tachycardia (≥130 bpm), and symptoms originating from multiple organ systems such as the CNS, cardiovascular system, and gastrointestinal tract present, it is important to consider the possibility of thyroid storm. When thyroid storm is suspected, physicians should refer to the diagnostic criteria for thyroid storm [4, 8] during initial evaluation of airway, breathing, circulation, dysfunction of CNS and exposure & environmental control (ABCDE) and treatment. Patients who are highly suspected of having thyroid storm based on these criteria should be transferred to a general hospital with an ICU and specialists in endocrinology and other subspecialties.

Strength of recommendation: high

Quality of evidence: low

● Comments

The first important step in making a prompt diagnosis of thyroid storm is to suspect the possibility of thyroid storm when a patient has high fever (≥38°C), marked tachycardia (≥130/min), atrial fibrillation, congestive heart failure, disturbance in consciousness (Glasgow Coma Scale ≤14), and gastrointestinal symptoms such as nausea, vomiting, diarrhea, and jaundice, especially when symptoms originating from multiple organ systems are observed at the same time (Fig. 4). If the patient has a history of treatment for Graves' disease, family history of thyroid disease, and body weight loss in a short period of time, and physiological findings such as goiter, an anterior neck bruit, and exophthalmos, the possibility of thyroid storm is much higher. During the initial evaluation of ABCDE and treatment, physicians need to refer to the diagnostic criteria for thyroid storm [4, 8]. The patient's condition should be evaluated by blood gas analyses, electrocardiogram monitoring, chest X-ray, urinalysis, and routine blood examination including complete blood count, coagulation tests, and blood chemistry. Appropriate sampling of blood, urine, and sputum is essential in patients with high fever. Magnetic reso-

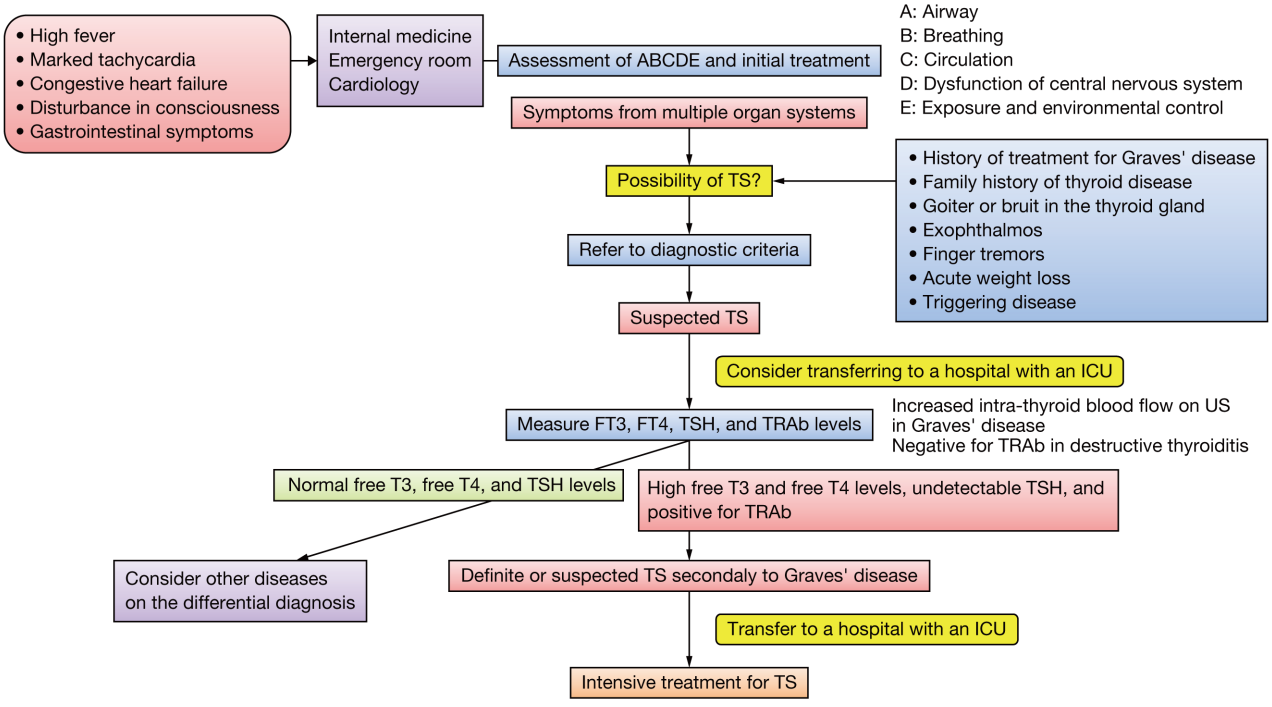


Fig. 4 An algorithm for diagnostic considerations in thyroid storm

TS, thyroid storm; ICU, intensive care unit; T3, triiodothyronine; T4, thyroxine; US, ultrasound examination; TRAb, anti-thyroid stimulating hormone receptor antibody.

nance imaging or brain computed tomography without intravenous contrast is required in patients with disturbances of consciousness. FT3, FT4 (but not total T4 as in Refs. 4, 7, or 26), TSH, and TRAb levels should be immediately measured if the patient's symptoms fulfill the criteria for thyroid storm [4, 8] and it is highly suspected. If these laboratory tests cannot be performed, the patient needs to be transferred to a hospital with an ICU. An increase in intra-thyroidal blood flow on bedside ultrasonography is highly suggestive of Graves' disease. TRAb is generally negative in destructive thyroiditis, which is a very rare cause of thyroid storm. However, the patient can be diagnosed with definite or suspected thyroid storm when thyroid hormone levels are elevated (note that FT3 levels may be normal in severely ill patients because of reduced conversion of T4 to T3), TSH is undetectable, and TRAb is positive; such patients should be immediately transferred to a hospital with an ICU.

A second ABCDE evaluation should be performed in patients with thyroid storm at the hospital with an ICU (Fig. 5). Thyroid storm patients with shock, DIC, or multiple organ failure should be admitted to the ICU. To assess the need for ICU admission, the APACHE II score should be assessed in combination with the Glasgow Coma Scale score, vital signs (body temperature, blood pressure, pulse rate, and respiratory rate), arterial blood gas analysis (pH, PaO_2, HCO_3^-, and alveolar oxygen tension ($A\text{-}aDO_2$), electrolytes (Na, K, and Cl), hematology results (hematocrit (Hct) and white blood cell count (WBC)), age, and history of chronic disease [166]. When the APACHE II score is 9 points or higher, admission to the ICU is recommended (for more details, see Section 8). In parallel with evaluating the APACHE II score, intense cooling with ice packs/cooling blanket and administration of acetaminophen, ATDs, corticosteroids, and inorganic iodide should be started (Figs. 6–8 and Fig. 9) (for more details, see Section 2).

In the ICU, intensivists need to consult with endocrinologists and other specialists and evaluate the function of multiple organ systems. The presence of factors that can precipitate thyroid storm should be evaluated and, if present, a treatment specific to the disease needs to be initiated. If disturbances of consciousness or convulsions are present, a differential diagnosis that includes cerebrovascular disease, meningitis, metabolic abnormalities, or drug overdose is required and, if present, a specific treatment for the underlying disease is required. Sedation may be required when neurological symptoms are attributed to severe thyrotoxicosis (Fig. 10) (For more details, see Section 4).

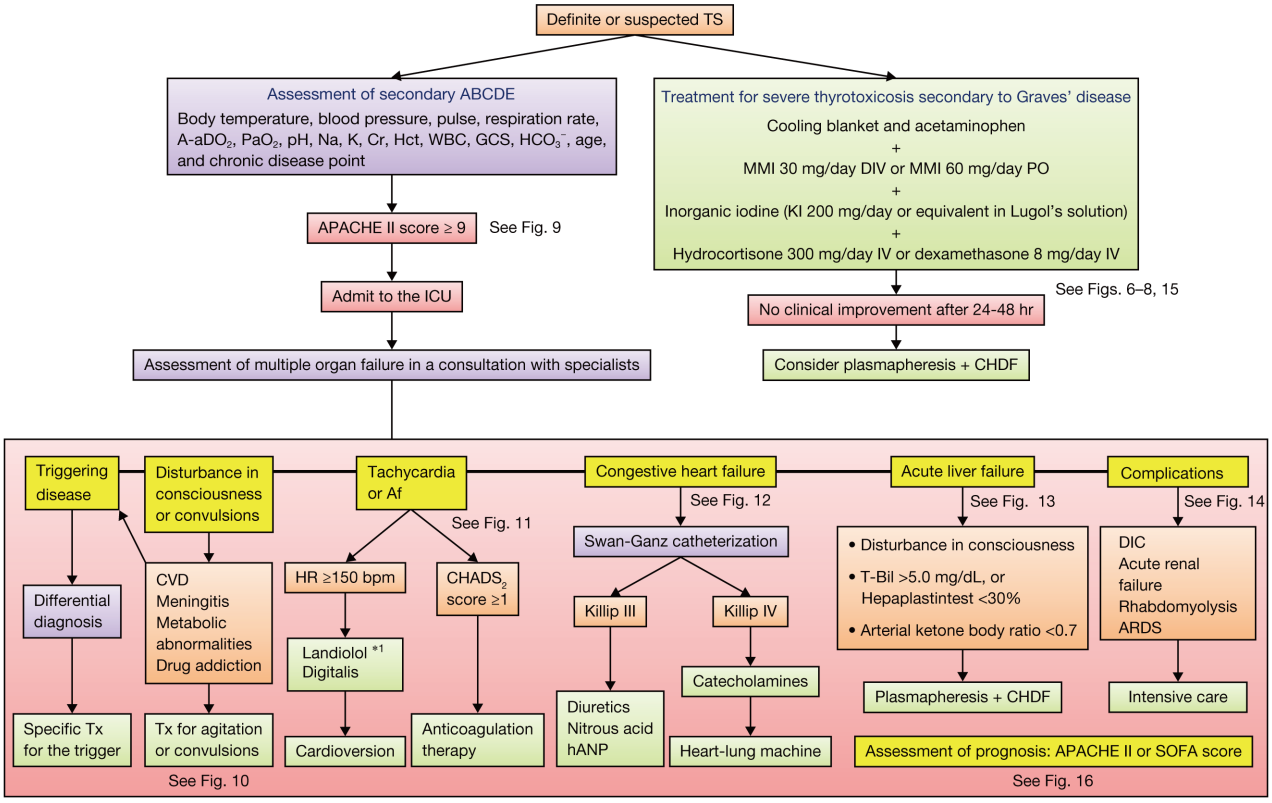
When sinus tachycardia or atrial fibrillation with pulse >150 bpm is present, beta1-selective AAs (administered with caution in patients with asthma and COPD) and/or digitalis should be administered to control tachycardia in patients with Killip ≤III heart failure. When persistent atrial fibrillation is present, cardioversion should be considered after ruling out left atrial thrombosis if hemodynamics is impaired rapidly. A $CHADS_2$ score ≥1 is required for anticoagulation therapy to be initiated [152]. In congestive heart failure, we recommend assessment of cardiac function with Swan-Ganz catheterization. In Killip III disease, anti-diuretics, nitrous acid products, and human atrial natriuretic peptide need to be administered. In Killip IV disease, catecholamine preparations need to be administered to maintain blood pressure; however, if no response is observed, a heart–lung machine should be used (Figs. 11 and 12). See Sections 5 and 6 for more details on the treatment of atrial fibrillation and congestive heart failure in thyroid storm.

According to the Guidelines from the Japan Society for Apheresis [161], acute liver failure is diagnosed based on 1) the presence of disturbances in consciousness; 2) total bilirubin >5.0 mg/dL, or hepaplastin <30%; and 3) arterial ketone body ratio <0.7. TPE should be performed in combination with CHDF (Fig. 13) (for more details, see Section 7).

When life-threatening complications associated with thyroid storm such as DIC (Fig. 14), acute renal failure, rhabdomyolysis, or adult respiratory distress syndrome occur, aggressive therapy for these conditions should be performed (for more details, see Section 8).

TPE should be considered if no clinical improvement is observed after 24–48 hours of multimodal therapy. The co-induction of CHDF is recommended when the cardiohemodynamic condition of a patient with thyroid storm is unstable (Fig. 15) (for more details, see Section 3).

Based on the findings in a nationwide survey in Japan [4], both the APACHE II and Sequential Organ Failure Assessment scores [166, 177] are useful for predicting the prognosis of patients with thyroid storm (Fig. 16) (for more details, see Section 9).



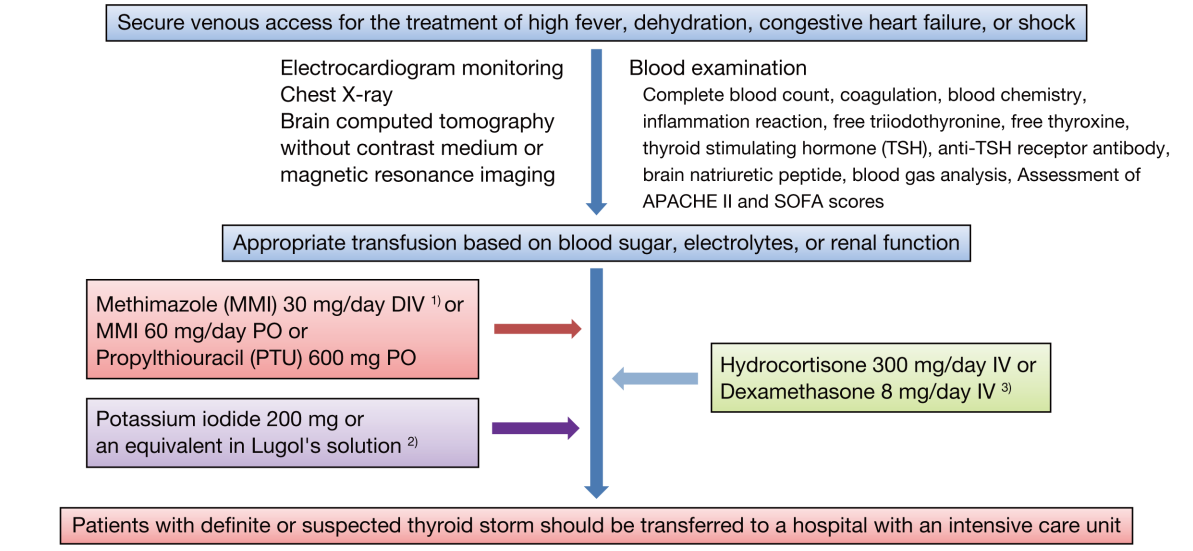
*1 When the pulse rate ≥150 bpm and Killip classification is III or lower, the infusion of a short-acting beta-blocker is the first choice. A beta-blocker can be administered orally when the pulse rate decreases to <150 bpm. In Killip IV disease, consider the infusion of a short-acting beta-blocker when pulse is ≥150 bpm.

Fig. 5 A treatment algorithm for thyroid storm

Brief comments on the treatment of severe thyrotoxicosis and manifestations in various organs are described in Figs. 6–16.
TS, thyroid storm; Hct, hematocrit; WBC, white blood cell count; A-aDO2, alveolar oxygen tension; PaO2, partial pressure of oxygen in arterial blood; Cr, creatinine; ICU, intensive care unit; GCS, Glasgow Coma Scale; APACHE II, acute physiology, and chronic health evaluation II; MMI, methimazole; KI, potassium iodide; HR, heart rate; CHDF, continuous hemodiafiltration; Tx, treatment; CVD, cerebrovascular disease; Af, atrial fibrillation; HR, heart rate; hANP, human atrial natriuretic polypeptide; T-Bil, total bilirubin; DIC, disseminated intravascular coagulation; ARDS, adult respiratory distress syndrome; SOFA, sequential organ failure assessment.

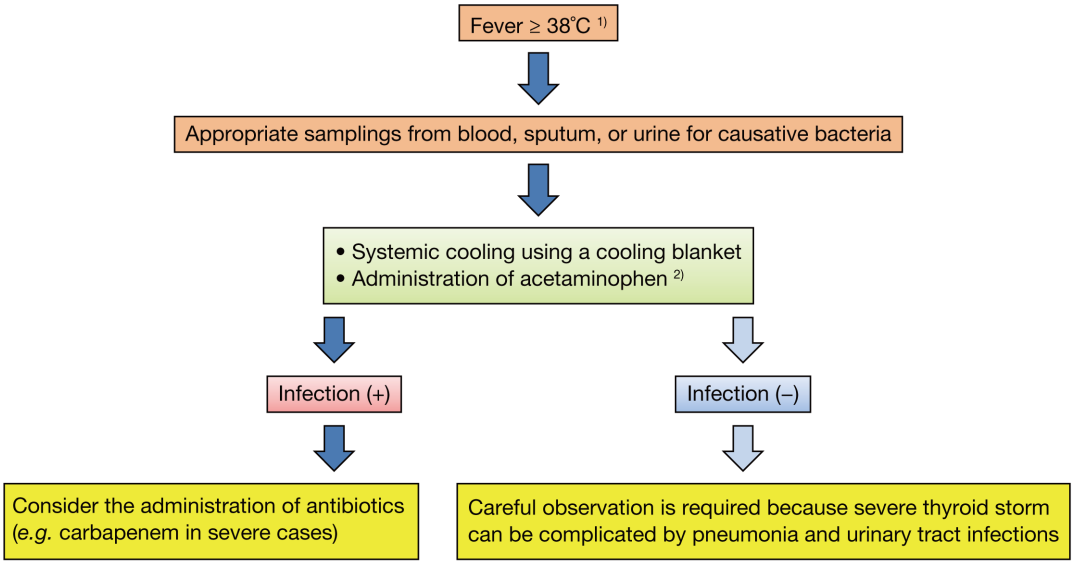
- There is no strong evidence concerning the appropriate doses of anti-thyroid drugs, inorganic iodine, or corticosteroids to treat severe thyrotoxicosis in thyroid storm.
- Based on data from a nationwide survey (8), methimazole (MMI) was equally useful as propylthiouracil (PTU). Intravenous administration of MMI, if available, is recommended in severe cases.
- Inorganic iodine should be administered because its use appears to improve prognosis in thyroid storm.
- Sufficient amounts of corticosteroids should be administered in severe cases.

Fig. 6 Comments on the use of antithyroid drugs, inorganic iodide and corticosteroids



1) Intravenous administration of MMI is recommended in patients with disturbances of consciousness or non-functioning gastrointestinal tract. If unavailable, MMI or PTU can be administered orally or *via* a nasogastric tube or rectally.
2) Although the amount of inorganic iodide necessary to suppress thyroid hormone secretion is assumed to be 20 mg, a sufficient amount, up to 200 mg/day, is recommended for thyroid storm. The textbook recommends that inorganic iodide be used 1 hour after the administration of antithyroid drug to prevent iodide organification, although large doses of inorganic iodide can inhibit iodide organification and thyroid hormone release.
3) Hydrocortisone 100 mg is recommended every 8 hours. Alternatively, 8 mg dexamethasone can be used.

Fig. 7 Schematic representation of recommended imaging studies and laboratory examination and the initial treatment of thyroid storm



1) Antipyresis could be important to reduce overload on central nervous system and cardiac function.
2) Non steroidal anti-inflammatory drugs and aspirin should be avoided because these drugs could interfere with thyroxine-binding proteins and increase free thyroid hormone levels. The careful use of antipyretic agents is required because these drugs could mask unidentified infections.

Fig. 8 Schematic representation of treatment of fever in thyroid storm

- Thyroid storm (TS) patients with life-threatening shock, disseminated intravascular coagulation (DIC), and multiple organ failure should be treated in the intensive care unit (ICU).
- Consider treating TS patients with an acute physiology and chronic health evaluation (APACHE) II score ≥ 9 in the ICU.
- DIC in TS needs to be treated because the mortality of TS complicated by DIC is high.
- Care must be taken because multiple organ failure often develops in patients with TS.

Fig. 9 Recommended criteria for intensive care unit admission and treatment of disseminated vascular coagulation and multiple organ failure

- There is currently no established specific treatment for central nervous system (CNS) symptoms caused by thyroid storm (TS).
- No significant differences were observed in the prognosis of patients with TS treated with various psychotropic medicine in a nationwide survey.
- The treatment of CNS symptoms in TS is recommended according to the Guidelines. *

* 2009 Guidelines for Psychiatric Emergency Treatment (Japanese Association for Emergency Psychiatry) (Ref. [120])
Guidelines for Epilepsy Treatment 2010 (Societas Neurologica Japonica) (Ref. [121])

Drugs to treat CNS symptoms in TS

- **Agitation, delirium, psychosis**
  Oral administration possible: risperidone, olanzapine
  Oral administration not possible: haloperidol IV or DIV
- **Somnolence, Coma**
  Differential diagnosis and treatment of the underlying disease needed
- **Seizure**
  Diazepam IV
  Status epilepticus: fosphenytoin IV

Fig. 10 Management of central nervous system symptoms in thyroid storm

• Pulse ≥ 150 bpm was correlated with severity and mortality of thyroid storm (TS) in the nationwide survey.

	Pulse rate <150 bpm		Pulse rate ≥150 bpm	
	Killip ≤III	Killip IV	Killip ≤III	Killip IV
Atrial fibrillation (Af) (–)	Landiolol, or Beta1-blocker PO Bisoprolol has indications for heart failure	Not necessary	Landiolol	Consider landiolol
Af (+)	In addition to the above treatments, digitalization is required. Monitor renal function.			

- Short-acting beta1-selective landiolol or esmolol is recommended to control the pulse rate. Among the oral beta-blockers, bisoprolol is highly recommended; however, other beta1-selective drugs can be used. Propranolol is not recommended, although it is not contraindicated.
- Landiolol should be carefully administered to TS patients with a history of asthma or obstructive pulmonary disease when an asthma attack is not present. Change landiolol to verapamil or diltiazem if an asthma attack is induced.
- The pulse rate needs to be controlled to <130 bpm, and beta-blockers should be discontinued when pulse <80 bpm, blood pressure <80 mmHg, or cardiac index <2.2 L/min/m^2 with Swan-Ganz catheterization.
- Cardioversion for Af is considered when a left atrial thrombus has been excluded and hemodynamics is impaired rapidly.
- Class Ia and Ic antiarrhythmics are administered to maintain sinus rhythm after cardioversion, and amiodarone is recommended in patients with cardiac failure.
- Anticoagulation is recommended when the Congestive heart failure / Hypertension / Age over 75 / Diabetes mellitus / Stroke / TIA ($CHADS_2$) score is ≥1. Heparin and warfarin are initially administered. When prothrombin time-international normalized ratio is in appropriate range, stop heparin.

Fig. 11 Management of tachycardia and atrial fibrillation in thyroid storm

• Swan-Ganz (SG) catheterization is recommended to monitor cardiac function in patients with Killip III or IV heart failure. When SG catheterization cannot be performed, the decision to initiate treatment is based on cardiohemodynamics evaluated with physical examination, chest X-ray, and echocardiography.

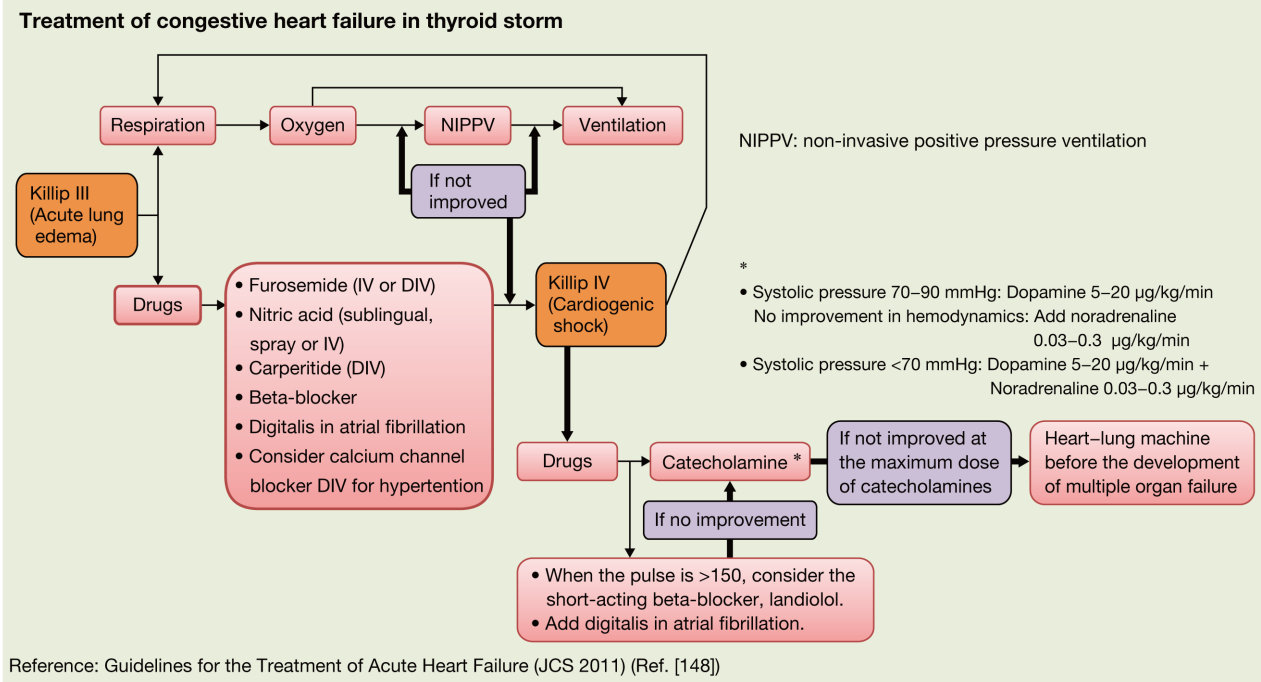
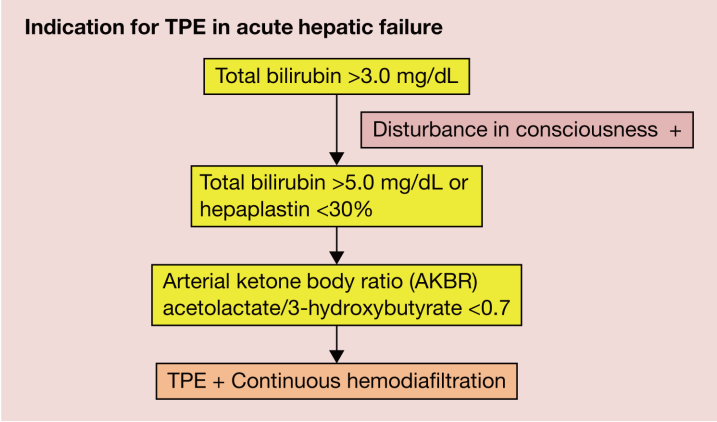


Fig. 12 An algorithm for management of congestive heart failure in thyroid storm

- No significant differences were observed in the incidence of liver injury among the drugs used to treat thyroid storm (TS) in the nationwide survey.
- Patients with total bilirubin >3.0 mg/dL had slightly more severe clinical manifestations in the nationwide survey. Bilirubin levels could also be elevated due to multiple organ failure; therefore, the indication of therapeutic plasmapheresis (TPE) cannot be determined only by total bilirubin concentrations.
- Indications for TPE in TS complicated by acute liver failure can be found in the Guidelines from the Japan Society for Apheresis (Apheresis Manual, third edition).



See ref. [165].

Fig. 13 Indication for plasamapheresis in acute hepatic failure in thyroid storm

- The mortality rate in patients with disseminated intravascular coagulation (DIC) diagnosed according to guidelines from the Ministry of Welfare of Japan was approximately 60%.
- DIC was comprised 9.27% of patients with thyroid storm (TS) in the nationwide survey, and the mortality rate in these patients was 45.5%. The presence of DIC was correlated with mortality (p<0.0001).
- The diagnostic criteria from the Japan Association for Acute Medicine are recommended for rapid diagnosis of DIC in TS. Since TS often fulfills two of the diagnostic criteria (body temperature and heart rate) for systemic inflammatory response syndrome (SIRS), DIC may easily develop in patients with TS.

Diagnostic criteria for DIC (Japanese Association of Acute Medicine) (Ref. [129])

Score	SIRS item *	Platelets (/mm^3)	Prothrombin time ratio	Fibrinogen degradation product (μg/mL)
1 point	Positive for more than 3 items	≥80,000 and <120,000 or more than a 30% decrease within 24 hours	≥1.2	≥10 and <25
2 points				
3 points		<80,000 or more than a 50% decrease within 24 hours		≥25

DIC can be diagnosed with a total score ≥ 4 points.

* **Diagnostic criteria for SIRS** (SIRS can be diagnosed when more than 3 items are positive.)

Body temperature >38°C or <36°C
Heart rate >90 bpm
Respiration rate >20/min or $PaCO_2$ <32 mmHg
WBC >12,000/mm^3 or <4,000/mm^3 or blasts >10%

Fig. 14 Comments on the treatment and diagnostic criteria for disseminated intravascular coagulation

- Excess thyroid hormone can be rapidly removed, thyroid hormone binding proteins can be replaced, and catecholamines, cytokines, and anti-thyroid stimulating hormone receptor antibody may also be removed by therapeutic plasmapheresis (TPE).
- The efficacy of TPE has been reported in a recent review that summarized many cases of TS (Ref. [60]); however, a few cases of death were also reported.
- The mortality rate of TPE-treated TS reported in Japan between 1983 and 2015 was 17.4% (11/63).
- The mortality rate of TPE-treated TS in the nationwide survey in Japan was 37.5% (6/16).
- The strength of the recommendation for TPE in TS in the 2010 Guidelines from the American Society for Apheresis is
  Grade 2C: Weak recommendation, low-quality or very low-quality evidence
  Category III: Optimum role of apheresis therapy is not established. Decision-making should be individualized.

1) **Absolute indication for TPE**: TS complicated by acute liver failure (for more details, see Section 7)
2) **Relative indication for TPE**: Uncontrolled thyrotoxicosis 24–48 hours after the initiation of intensive treatment (for more details, see Section 3)

Fig. 15 Comments on the usefulness of and indication for plasmapheresis in thyroid storm

- Factors associated with severity, mortality, and irreversible damage were determined by the analysis of nationwide surveys, as shown in the figure below.
- Attention must be paid to central nervous system symptoms, thyroid function, cardiac function (shock), renal function, and disseminated intravascular coagulation (DIC) in thyroid storm.
- Serum creatinine levels were similar between survivors and non-survivors (0.54 ± 0.02 mg/dL *vs*. 0.81 ± 0.09 mg/dL), which may have been due to the abnormal creatinine metabolism in thyrotoxicosis. Therefore, even if serum creatinine is within the normal ranges, it should be carefully monitored during the treatment of TS.

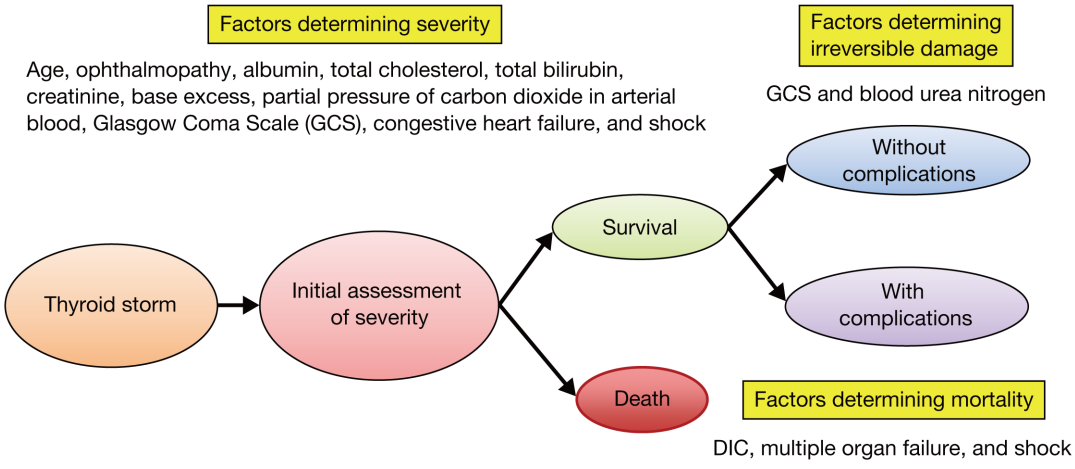


Fig. 16 Comments on the prognosis of thyroid storm in the nationwide surveys

12. Future directions for clinical trials in the management of thyroid storm

■ **RECOMMENDATION 15**

1. Designing an interventional clinical trial for testing treatments for shock, DIC, and multiple organ failure is recommended.

Strength of recommendation: strong

Quality of evidence: low

2. Testing the safety and clinical effectiveness of TPE treatment for thyroid storm is recommended.

Strength of recommendation: strong

Quality of evidence: low

● **Evidence supporting the recommendations**

Thyroid storm is a severe form of hyperthyroidism with high mortality and serious sequelae. This condition is characterized by multiple organ failure, decompensation, and death. Therefore, although it is rare, thyroid storm requires prompt diagnosis and multidisciplinary intensive medical care.

Medical support and advanced techniques are needed from experienced doctors in various medical fields besides endocrinology, such as emergency medicine, cardiology, gastroenterology, and neurology. Therefore, the establishment of appropriate diagnostic and therapeutic guidelines has been eagerly awaited from these medical fields. Nationwide surveys conducted by the JTA and Japan Endocrine Society (JES) were the first studies worldwide to describe the clinical realities of thyroid storm, and new diagnostic criteria were established [4]. Detailed clinical data from 356 patients with thyroid storm were obtained by this process, which revealed that the incidence of thyroid storm was estimated as 150 cases/year (0.13/100,000 persons). The mortality rate of cases admitted to the ICU is over 17%, and many patients were found to have irreversible sequelae. Based on these findings, the JTA and JES started to issue therapeutic recommendations and standardize therapeutic decision-making in 2013. However, there have been difficulties in making a generalized treatment plan because of the rarity of thyroid storm, its acute clinical course, and the need for prompt decision-making. In addition, a randomized clinical trial may not be allowed from an ethical point of view because of the poor prognosis of thyroid storm. Therefore, a randomized controlled intervention trial to determine the optimal therapy has not yet been performed.

We obtained a detailed clinical database of 356 thyroid storm cases between 2004 and 2008 after a nationwide large-scale survey. One of the important findings from this database was the cause of death in patients with thyroid storm. The most frequent cause of death was multiple organ failure, followed by heart failure, respiratory failure, arrhythmia, DIC, gastrointestinal perforation, hypoxic brain damage, and sepsis. Multiple regression analysis demonstrated that independent risk factors for death by thyroid storm included comorbid multiple organ failure, shock, and DIC. Therefore, in order to improve the prognosis of patients with thyroid storm, clinical trials are needed to determine the effectiveness of treatments for these comorbidities.

Another important finding from the nationwide survey regarding therapy was based on the medical records documenting various actual treatment practices in each patient with thyroid storm. For example, plasma exchange should theoretically be an effective treatment for eliminating excess thyroid hormone [179]. A large prospective randomized interventional study is needed to prove the efficacy of TPE. A clinical trial plan composed of a one-arm treatment group can be designed with thyroid storm cases in which TPE was used and historical control cases.

● **Comments**

Various prospective clinical trials aimed at examining treatments for thyroid storm have been proposed because different kinds of therapeutic measures are needed to control thyroid function and the complications associated with the cardiovascular and nervous system. On the other hand, large clinical trials that have been designed but not yet been performed actually because of the poor prognosis of thyroid storm. Various clinical questions have been proposed regarding thyroid storm treatments. For example, which is the more preferable ATD for thyroid storm, PTU or MMI? Can CS therapy affect the prognosis of patients with thyroid storm patients? Is psychotropic therapy necessary for mild disturbances in consciousness in thyroid storm? Is rehabilitation in early thyroid storm effective for preventing the neurological complications associated with thyroid storm? We here listed two kinds of treatments worth testing in clinical trials, treatment for coagulation disorder and TPE.

The relationship between thyroid function and coagulation disorder has been previously described [130, 168, 169]. One suggested mechanism is the increase in

factor VIII in the coagulation cascade [173, 174]. The fibrinolysis type of DIC is the dominant form of thyroid storm-associated DIC [180]. In 2009, the DIC section of the Guideline Committee of the Japanese Society of Thrombosis and Hemostasis published an "Expert consensus on therapeutic guidelines for infection-associated DIC based on scientific evidence" [181]. These guidelines recommended that treatment should be individualized according to the subtype of DIC, for example, asymptomatic, bleeding, organ failure, and other. Therapeutic choices include low–molecular-weight heparin, gabexate mesilate, nafamostat mesilate, and anti-thrombin agents.

TPE facilitates the removal of excess thyroid hormones, TRAb, catecholamines, and cytokines. The half-life of thyroid hormones is as long as 6.7 ± 0.7 days in normal subjects and 4.4 ± 1.1 days in patients with hyperthyroidism [182]. Therefore, thyroid function takes a long time to recover from thyroid storm after thyroid hormone production has been suppressed by anti-thyroid medications. Compensatory mechanisms in each affected organ fail before achieving euthyroidism, resulting in multiple organ failure. Based on these findings, TPE has been considered to be a more essential therapeutic option than originally thought [31, 41]. On the other hand, case reports from around the world, including Japan, have described TPE as ineffective in several cases. Some patients have died despite TPE [183, 184]. In thyroid storm case reports published in Japan between 1983 and 2015, the time period during which TPE was being used, 11 out of 63 patients died, representing a mortality rate of 17.4%, which was similar to the overall mortality rate for thyroid storm (11%). In the nationwide survey, 6 of 16 patients treated with TPE died, representing a mortality rate of 37.5%. These results do not necessarily indicate the ineffectiveness of TPE because the survey was conducted retrospectively. TPE was also used in patients with the most severed disease, for which the initiation of TPE may have been too late. These factors may have affected the unfavorable results for TPE. Therefore, a prospective intervention trial to test the effectiveness of TPE in thyroid storm is warranted. Due to the lack of clinical trials, TPE has a grade IIc (weak recommendation, low-quality or very low–quality evidence) and category III recommendation (optimum role of apheresis therapy is not established, decision-making should be individualized) in the latest American Society for Apheresis Guidelines [59]. TPE should be performed for the following indications: severe symptoms such as cardiothyrotoxicosis, neurological manifestations, impairment of consciousness, and severe myopathy; rapid clinical degradation; contraindication to other therapies such as agranulocytosis, renal insufficiency, asthma, and heart failure; and prior to emergency surgery [49, 60]. TPE may be performed under extremely specific conditions in thyroid storm. Therefore, the safety and effectiveness of TPE needs to be verified in clinical practice.

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Disclosure Statement

The authors declare that they have no conflict of interest to disclose.

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