日本甲状腺学会　会員各位

臨床重要課題「甲状腺クリーゼの診療指針作成」の最終成果物に関する
public comment の募集

「甲状腺クリーゼの診療指針作成」の最終成果物（Thyroid 誌に投稿）が出来上がりました。この成果物に関して甲状腺学会会員と内分泌学会会員それぞれにパブリックコメントを募りたいと思います。

つきましては、その PDF ファイルを添付しますので、お取り計らいのほど宜しくお願い致します。

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「甲状腺クリーゼの診療指針」へのご意見・ご提案

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Practice Patterns and Recommendations for the Management of Thyroid Storm in Japan

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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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 for the

88 treatment of thyroid storm: 1) thyrotoxicosis (reduction of thyroid hormone secretion
89 and production); 2) systemic symptoms and signs (including high fever, dehydration,
90 shock, and DIC); 3) organ-specific manifestations, such as cardiovascular, neurological,
91 and hepato-gastrointestinal; 4) triggers; 5) definitive therapy. Although the appropriate
92 responses to these problems have been described in endocrinology textbooks and
93 reviews, several clinical questions remain, for example: 1) the choice and route of
94 administration for antithyroid drugs (ATDs), 2) timing of iodide therapy, 3) criteria to
95 judge thyroid storm severity, and 4) choice and fine-tuning of treatment based on
96 severity and pathophysiological state. Although beta-adrenergic receptor antagonists
97 (beta-AAs) are often used to treat thyroid storm, inappropriate choice or dose may lead
98 to worse outcomes in patients with severe heart failure (8). Furthermore, thyroid storm
99 is characterized by multiple organ failure, decompensation, and highly variable clinical
100 presentation, which require comprehensive treatment. Thyroid storm is an emergent
101 disorder characterized with rapid deterioration in its clinical course. Therefore, an
102 algorithm-based approach is useful for the management of thyroid storm.

103 Given this context, we attempted to create recommendations for the
104 management of thyroid storm based on the following principles. These
105 recommendations should 1) contain information on both the diagnosis and treatment of
106 thyroid storm; 2) illustrate algorithms; 3) consider the severity and pathophysiology of
107 thyroid storm; 4) be detailed, concrete, and useful for clinical practice; 5) be
108 evidence-based; and 6) possibly be internationally applicable. Based on the analysis of
109 data concerning the treatment of thyroid storm collected in nationwide surveys in Japan
110 (8), the treatment of not only thyrotoxicosis, but also the characteristic manifestations
111 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 the following table (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 hours and days of presentation and associated with high mortality (1-4). In the presence of some triggering condition, a majority of thyroid storm originates from untreated or uncontrolled Graves' disease, and very rarely from 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 be caused also by medical precipitants such as thyroidectomy, nonthyroid surgery, radioiodine therapy, exposure to excess iodine in a patient with hyperthyroidism, or excess thyroid hormone ingestion (1-4). In addition, several drugs, which cause thyrotoxicosis as an adverse event, have been reported to precipitate into thyroid storm such as amiodarone, sorafenib and ipilimumab (18-20). Early awareness/suspicion, prompt diagnosis and intensive treatment will lead to the improved 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, 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 has been proposed in 1993 (9). The BWPS was an empirically derived scoring system, which is taking account for the

157 severities of symptoms derived from multiple organ decompensation including
158 thermoregulatory dysfunction, tachycardia/atrial fibrillation, disturbances of
159 consciousness, congestive heart failure, and gastro-hepatic dysfunction and the role of
160 precipitating factors (Table 2). The BWPS has widely been applied for diagnosis of
161 thyroid storm for more than two decades.

162 In 2012, the Japanese Thyroid Association (JTA) proposed new diagnostic
163 criteria for thyroid storm, which has been initially designed based on detailed analyses
164 of 99 literature and 7 own cases and finally revised according to the results of
165 nationwide surveys (4). In this JTA criteria, the presence of thyrotoxicosis is required as
166 a prerequisite condition, and definite and possible thyroid storm can be diagnosed in
167 specific combination of symptoms derived from multiple organ decompensation
168 similarly to those listed in the BWPS (Table 3). One of the specific features in the JTA
169 criteria is that the presence of consciousness disturbances contributes to the diagnosis of
170 thyroid storm much more than other organ symptoms (4). In addition to the analyses in
171 JTA nationwide surveys (4), comparison of the usefulness of these two diagnostic
172 criteria has recently been reported from two institutions and the results showed that
173 there is an overall agreement between these two diagnostic systems (21, 22). However,
174 a report from the United States suggested that the BWPS appeared to select a higher
175 percentage of patients for aggressive therapy than the JTA criteria (21).
176 Double-checking using these two diagnostic criteria for the patient condition would be
177 recommended in individual case to make accurate clinical diagnosis and further validate
178 the usefulness of these two diagnostic systems. Most importantly, inappropriate

179 application of either system can lead to misdiagnosis of thyroid storm, emphasizing the
180 importance of careful evaluation for the clinical condition in each patient suspicious of
181 having thyroid storm. When physicians feel difficult to judge whether the symptoms
182 listed in the JTA criteria develop from precipitating events or thyroid storm in
183 individual case, the symptoms should be judged as those developing from thyroid storm,
184 as described in the JTA criteria (4).
185
186

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

■ **RECOMMENDATION 1**

A multimodality approach with ATDs, inorganic iodide, corticosteroids (CSs), 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: moderate

2. Intravenous administration of MMI is recommended in severely ill patients with consciousness disturbances or non-functioning gastrointestinal tract.

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 a large dose of PTU (at least 400 mg) inhibits type I deiodinase activity in thyroid gland and other peripheral organs and therefore may acutely decrease triiodothyronine (T3) levels more than MMI (23, 24). These are the reasons that PTU, rather than MMI, is recommended in the guideline jointly issued by the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) (7).

A nationwide survey performed by the JTA revealed that both free T3 (FT3) levels and 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 be already 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 with less T4-to-T3 conversion. Doses of MMI, but not of PTU, were significantly correlated with 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, 150–1500 mg) (unpublished data).

Regarding the long-term efficiency of ATDs on thyrotoxicosis in compensated

Graves' patients, a randomized prospective study previously 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 has also been 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 or PTU is recommended to administer at a dose of 600 mg/day. These are the maximum doses for the treatment of Graves' disease approved by the Ministry, Labor and Welfare in Japan. In thyroid storm caused by toxic nodular goiter, TSH-secreting pituitary adenoma, or hydatidiform mole, doses of ATDs may be adjusted on the individual basis. In the case of thyroid storm caused by destructive thyroiditis such as subacute thyroiditis or drug-induced thyroiditis, administration of ATDs is contraindicative because the patient is unnecessarily exposed to the risk of adverse effect of ATDs, which are not effective against the destructive release of thyroid hormones stored before the onset of thyroiditis.

In severely ill patients especially with disturbed consciousness or impaired gastrointestinal tract function by vomiting, severe diarrhea, active gastrointestinal bleeding, or intestinal edema secondly 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 preparation may not always be in stock in all hospital pharmacies because of the rarity of its use. By the time that the intravenous MMI preparation is available, ATDs should be administered via a non-parenteral route in severely ill patients.

When an intravenous MMI preparation is not available, methods for preparing MMI injections in the hospital pharmacies and cases of successful treatment with MMI injections in patients refractory to oral MMI have been previously reported from the

United States (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 were 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 be no longer used because of severe adverse effects, binding resins such as cholestyramine, which binds iodothyronine is another adjunctive measure to physically remove thyroid hormone from the enterohepatic circulation, which is increased in hyperthyroidism (31, 32). The dose of cholestyramine effectively reducing thyroid hormone levels has been recommended to be 4 g three or four times daily (6).

When severe thyrotoxicosis is successfully managed during the early stage of thyroid storm, dose of ATDs can be tapered with close monitoring for thyroid hormone levels, but not for TSH levels in a manner similarly 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 CSs (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 be escaped thereafter in some patients (33).

In a nationwide survey, the severity of thyroid storm in patients treated with inorganic iodide was significantly higher than in patients treated without inorganic iodide; however, no significant differences in mortality were observed between the two groups (8). These findings suggest that inorganic iodide treatment may improve the outcome of thyroid storm patients.

In the ATA and AACE guidelines (7), it is recommended that inorganic iodide should be administered at least one 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 included) reported that FT3 levels in combined treatment groups were decreased significantly faster than those in MMI

groups, and none of the patients showed an increase in thyroid hormone levels or aggravation of disease during combined treatment with MMI and KI (40). Another prospective study evaluating efficacy of MMI 15 mg plus KI 38.2 mg (M15 + KI) vs. MMI 30 mg (M30) for the treatment of moderate to severe uncomplicated Graves' disease (310 cases included) also demonstrated that combined treatment with M15 + KI improved FT4 levels significantly faster than treatment with M30, and no exacerbation of thyrotoxicosis in patients treated with M15 + KI was observed (41). Based on these findings in two large prospective trials performed in Japan, we recommend that a large doses of inorganic iodide can be administered simultaneously with ATDs to Graves' patients complicated with thyroid storm. However, patients who are known to be allergic to iodine should not be given it or at least be monitored carefully.

● **Comments**

Only potassium iodide (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 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 under critical conditions as in thyroid storm, larger doses of KI should be provided; the recommended dose is 200 mg/day. 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 thyroid gland by unknown mechanism (43, 44). Lithium may be used in patients allergic to ATDs or iodide to reduce circulating thyroid hormone levels with monitoring serum lithium levels to avoid its toxicity.

After improvement of thyrotoxicosis by the combination therapies with ATDs and inorganic iodide, the doses of inorganic iodide should be reduced before the tapering of ATDs with close monitoring of thyroid hormone levels, but not TSH levels.

D. Treatment with CSs

■ **RECOMMENDATION 4**

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

Strength of recommendation: high

Quality of evidence: moderate

● **Evidence supporting the recommendations**

CSs should be administered as prophylaxis for relative adrenal insufficiency caused by the hypermetabolic state in thyroid storm. Large doses of CSs have been shown to inhibit both thyroid hormone synthesis and peripheral conversion of T4 to T3 (45). Despite the predicted favorable effects of CSs mentioned above, detailed analysis of nationwide surveys using multiple regression analysis showed that disease severity and mortality of patients treated with CSs were significantly higher than not treated with CSs (8). The use of CS as well as the doses of CSs correlated with severities of the patients, but not with the mortality in multiple regression analyses (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 CSs administered might be insufficient in some patients. Alternatively, CS overdosing in some patients may cause unfavorable hyperglycemia and worsening of their general condition. Therefore, the type and dose of CSs needs to be determined carefully on an individualized basis to improve the outcome of thyroid storm.

● **Comments**

CSs 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. CS dose needs to be altered on an individualized basis. There

should be careful monitoring and prevention for 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 CSs should be tapered and discontinued after confirmation of the adrenocortical reserve by measuring fasting serum cortisol levels.

D. Treatment for fever

■ **RECOMMENDATION 5**

1. Aggressive cooling with acetaminophen and mechanical cooling using 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 and AACE 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 and signs of infection based on symptoms and physical findings after appropriate sampling from 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, CSs, 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 should be considered if thyrotoxic symptoms such as tachycardia, high fever, and disturbances of consciousness has not improved within 24–48 hours of initial intensive treatment because these thyrotoxic symptoms in patients with thyroid storm can typically be improved with 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. The usefulness of TPE for the treatment of thyroid storm was first reported by Ashknar et al. in 1970 (48). 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). If the patient's condition has not

488 improved after 24–48 hours, the condition is suspected to be highly resistant to
489 conventional therapies due to an unknown mechanism. Rate control with beta-AAs may
490 be necessary before starting TPE. Although TPE has been shown to be useful for the
491 treatment of conventional therapy–resistant thyroid storm in many case reports, TPE is
492 not approved for thyroid storm by the health insurance system in Japan.

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

495 Two types of replacement fluids exist for TPE: fresh frozen plasma (FFP) and
496 albumin solution. FFP contains thyroxine-binding globulin (TBG) and is thought to be
497 useful for the removal of TBG-bound thyroid hormones. In contrast, limitations of FFP
498 include its high cost, risk of infection, and presence of thyroid hormones. In contrast,
499 albumin solution is less expensive, associated with a lower risk of infection, and
500 contains lower levels of thyroid hormones. Since albumin solution contains less TBG, it
501 may cause worsening of thyroid storm. However, one previous study showed that the
502 level of TBG rapidly increases after TPE with albumin solution (51). Although no
503 randomized study has yet evaluated the usefulness of FFP versus albumin solution in
504 TPE to treatthyroid storm, FFP has been preferentially used in many case reports.
505 Therefore, it is recommended that FFP be used as the replacement solution in TPE to
506 treat thyroid storm because FFP is expected to reduce thyroid hormones more
507 efficiently than albumin solution.

508 CHDF is sometimes performed in parallel with TPE because
509 cardiohemodynamic conditions are often unstable in thyroid storm patients (52).

Several case reports have recently demonstrated the usefulness of using both methods to treat patients with thyroid storm resistant to conventional therapy (53–56). 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) (57), the combined use of TPE with CHDF is recommended for patients with severe complications such as multiple organ failure.

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 (58).

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 (59). 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 2011. Analysis of the literature search results showed that the mortality rate of patients with thyroid storm that received TPE was 13.2% (5/38) and the clinical symptoms of many patients improved after a single course of TPE (Supplementary refs. 1–30). Thyroid hormone levels before and after TPE were significantly decreased in cases described in the literature (Fig. 1). TPE was performed on hospitalized day 2 (2 patients), day 3 (1 patient), or day 9 (1 patient) in the 5 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

554 thyroid storm patients, and the mortality rate of patients who received TPE was 37.5%
555 (6/16) (8), which is apparently higher than that in the literature (13.2%). This may have
556 been due to publication bias because TPE-unresponsive patients may not have been
557 reported in the literature. Six patients died between days 6 and 37. Four cases were
558 complicated with multiple organ failure and 1 patient died from DIC. Thus, based on
559 the literature and nationwide surveys conducted in Japan, some thyroid storm patients
560 did not survive even with TPE. The usefulness of TPE as an alternative treatment for
561 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 for thyrotoxicosis, differential diagnosis and treatment for 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 could affect pharmacokinetics in thyroid storm patients, each patient's condition should be considered when selecting and adjusting doses of psychotropic medications.

Strength of recommendation: strong

Quality of evidence: low

● 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 (60, 61), autoimmune processes (62), direct effects of excess thyroid hormone levels on brain function (63), or neurotransmitters such as serotonin (64). However, the precise mechanisms responsible

584 remain unknown. The amelioration of thyrotoxicosis has been shown to be most
585 effective in treating CNS manifestations (65, 66); however, there is insufficient
586 evidence to support other specific treatments. In a small clinical study, mental
587 symptoms such as anxiety and depression in thyrotoxicosis were significantly improved
588 by beta-AAs (65). In contrast, another study reported that beta-AAs and placebo had
589 similar effects on anxiety (67). Moreover, no association was observed between the
590 choice of medication to treat CNS manifestations and prognosis in nationwide surveys
591 in Japan (4). The 2010 Japan Resuscitation Council (JRC) guidelines (68), Guidelines
592 for Psychiatric Emergency Treatment (69), and 2010 Guidelines for Epilepsy Treatment
593 (70) have been established in Japan for the general management of CNS symptoms. We
594 base our recommendations for the management of CNS manifestations secondary to
595 thyroid storm on these guidelines.
596 2. Thyrotoxicosis can affect pharmacokinetics by altering the absorption, distribution,
597 metabolism, and excretion of drugs (71); these effects may change dynamically during
598 the treatment of thyroid storm. Patients with often have dysfunction of multiple organs
599 such as the liver and kidney, which can also affect pharmacokinetics. Therefore, the
600 selection of drugs to treat CNS symptoms and dose adjustment should be individually
601 determined.
602
603 ● **Comments**
604 **1. Initial care and differential diagnosis**

According to the 2010 JRC guidelines (68), 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 (69) by intramuscular or intravenous injection are the first-line choices. Although precise mechanism is unknown, previous case reports have shown that haloperidol can lead to the onset of thyroid storm (72), which can result in neurotoxic effects (73). Therefore, haloperidol would be carefully administrated 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

627 agents for the acute management of convulsions. Fosphenytoin or phenobarbital is
628 recommended if convulsions continue after repeated doses of benzodiazepines (70).
629 Somnolence and coma can be caused by a variety of conditions, such as hypoxemia due
630 to heart failure or shock, liver failure, renal failure, severe infection, cerebrovascular
631 disease, electrolyte abnormalities, and glucose metabolism. Thyroid storm often
632 complicated by these conditions; therefore, a differential diagnosis is important in
633 thyroid storm patients in a coma (Fig. 3). Because the underlying cerebrovascular
634 disease or encephalitis may become apparent during the treatment of thyroid storm in
635 patients with CNS manifestations, physical findings should be carefully monitored and
636 an examination of the cerebrospinal fluid examination, brain magnetic resonance
637 imaging (MRI), or electroencephalography should be performed as needed. Early
638 initiation of rehabilitation is recommended to prevent disuse muscle atrophy, especially
639 in patients receiving mechanical ventilation (74).

640 **b) The influence of thyrotoxicosis on pharmacokinetics**

641 Thyrotoxicosis does not have a pronounced effect on the pharmacokinetics of diazepam
642 (75), phenytoin (76), or phenobarbital (77) *in vivo*. On the other hand, in thyrotoxic
643 patients the effect of propofol is decreased due to increased clearance and distribution
644 volume (78). Since the influence of thyrotoxicosis on the pharmacokinetics of other
645 antipsychotic drugs has not been studied in detail, dose adjustments should be carefully
646 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) 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.
    4) 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 hemodynamic stability cannot be achieved because of atrial fibrillation, cardioversion should be considered if a left atrial thrombus has been ruled out.

   3) Disopyramide is 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 if hemodynamic stability cannot be achieved 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 (79), anticoagulation should be initiated based on the Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013) (80).

● **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 (81);

713 therefore, the usefulness of beta-AAs for tachycardia associated with
714 thyrotoxicosis has been advocated. Beta-AAs were used in 286 patients (80.3%) in
715 our nationwide survey, non-selective beta-AAs in 190 patients, beta1-selective
716 AAs in 66 patients, beta1-selective and non-selective beta-AAs in 3 patients,
717 alpha-, beta-adrenergic antagonists in 18 patients, and unknown in 9 patients. All
718 deaths in patients with Killip class ≥3 disease who met our diagnostic criteria for
719 thyroid storm were treated with non-selective beta-AAs (except for those whose
720 details were unknown or were not treated with beta-AAs), while all patients who
721 survived were treated with beta1-selective AAs.

722 The effects of beta-AAs with respect to differences in selectivity for
723 beta-adrenergic receptors or the duration of action as treatment for
724 hyperthyroidism have not yet been investigated. Since the 1970s, many studies
725 suggested the usefulness of propranolol. However, most of these studies proposed
726 the usefulness of beta-AAs in general, rather than propranolol specifically (82).
727 The number of studies that suggest the risks associated with propranolol and the
728 usefulness of esmolol increased after the 1990s (83-88). Esmolol has several
729 potential advantages over propranolol in thyroid storm. One is its short elimination
730 half-life (t1/2) and duration of action. Another advantage is its relatively higher
731 beta1-selectivity (88). Although the onset of action of intravenous propranolol and
732 esmolol are similar, their t1/2 and duration of action are markedly different. The
733 t1/2 alpha and beta for propranolol are 10 minutes and 2.3 hours, respectively,
734 while the t1/2 alpha and beta for esmolol are 2 minutes and 9 minutes, respectively

735 (89). A human volunteer study demonstrated that the effects of beta-blockade
736 completely disappeared 18 minutes after the infusion of esmolol (300 μg/kg/min)
737 had been stopped, while no significant differences were observed in the effects of
738 beta-blockade 30 minutes after stopping the infusion of propranolol (55 μg/min)
739 (90). Beta1-selectivity raises the possibility that esmolol can be used more safely
740 for patients with asthma. Previous studies have demonstrated that beta1-selective
741 AAs do not exacerbate bronchoconstriction or wheezing induced by tracheal
742 intubation in patients with asthma (91, 92). Furthermore, a patient with thyroid
743 storm and bronchial asthma was successfully managed with esmolol (93).
744 Landiolol, an ultra–short-acting beta1-selective AA with a t1/2 of 3–4 minutes and
745 approximately 8-fold greater beta1-selectivity than esmolol, has been approved in
746 Japan for the treatment of intraoperative and postoperative tachyarrhythmias (94).
747 Landiol was recently approved for the treatment of tachyarrhythmias in other
748 situations, which strongly suggests that it is useful for the treatment of
749 tachyarrhythmias in thyroid storm.

750 The effect of calcium channel blockers on tachycardia in thyroid storm could
751 not be analyzed in our nationwide surveys because they were used only in a small
752 number of patients. Verapamil is a cardioselective calcium channel blocker that is
753 widely used to slow heart rate, especially in rapid atrial fibrillation. However,
754 verapamil was not efficacious in treating TS-related cardiac failure in one study
755 (95). Calcium channel blockers may not be recommended as first-line treatment for
756 tachycardia in TS due to the pathophysiology of thyroid storm, which is

757 characterized by peripheral vasodilation associated with increased beta-adrenergic
758 action. Landiolol or esmolol should be used carefully in patients with respiratory
759 diseases such as bronchial asthma and COPD. Verapamil can be considered a
760 potential alternative for rate control in patients with bronchial asthma or COPD.
761 2. In our nationwide surveys, 136 patients with thyroid storm had atrial fibrillation
762 and 130 did not have atrial fibrillation. There were 20 and 5 deaths, respectively.
763 Atrial fibrillation status was unknown in 90 patients, of whom 13 died. The
764 presence of atrial fibrillation in TS was associated with significantly increased
765 mortality in our nationwide surveys (p=0.0024), as assessed by the Fisher's exact
766 test. The reported incidence of atrial fibrillation in thyrotoxicosis ranges between
767 12% and 28% (96). Atrial fibrillation further accelerates systemic hemodynamic
768 disturbances and increases mortality in TS; therefore, cardioversion should be
769 considered if hemodynamic stability cannot be achieved because of atrial
770 fibrillation.

771 The treatment of atrial fibrillation includes both rate and rhythm control.
772 Beta-AAs are recommended as first-line treatment for rate control due to the
773 pathophysiology of thyroid storm. However, a treatment protocol has not yet been
774 established for rhythm control in thyroid storm. Digitalis was used in 30 patients
775 (8.4%) in our nationwide surveys, of whom 4 died. Since digitalis was only
776 sometimes used as a cardiotonic agent under critical conditions, this result does not
777 necessarily indicate the inferiority of digitalis in the treatment of atrial fibrillation
778 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); (97) 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 clearance of digoxin (98), digoxin levels should be monitored as the patient becomes euthyroid and the dose adjusted appropriately.

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) (99). The $CHADS_2$ score has been proposed to assess the risk of developing cerebral infarction (100). 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 (94), 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 (99). 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) (94), given the pathophysiology of thyroid storm.

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

① Respiratory management: Respiratory management should include non-invasive positive pressure ventilation (NIPPV) or artificial respiration by intratracheal intubation if the patient's respiratory status has not improved with oxygen administration.

② 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,

① Respiratory management: Respiratory management should be the same as for patients with acute congestive heart failure classified as Killip class III.

② Drug therapy: Adrenergic agonists should be used. Dobutamine or dopamine should be administered intravenously at a dose of 5–20 μg/kg/min when systolic blood pressure is between 70 to 90 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) (97, 99). 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) (97) on an individualized basis, with consideration of the pathophysiology of TS.
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.
4.

● **Comments**

1. Hemodynamic monitoring with a Swan-Ganz catheter should be considered on an individualized basis (101). 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) (97). 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 5 of 9 patients treated with an artificial heart–lung machine survived. 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 precipitating gastrointestinal infection. Treatment for precipitating gastrointestinal infection in parallel with that for thyrotoxicosis should be performed to improve gastrointestinal symptoms.

Strength of recommendation: strong

Quality of evidence level: low

2. Administration of large doses of CSs, coagulopathy associated with thyroid storm, and intensive care unit (ICU) stay with prolonged mechanical ventilation may be the 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 level: 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 prognosis of patients has been shown to be worse when total bilirubin levels are ≥ 3.0 mg/dL in the nationwide surveys. 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 level: 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 (102, 103). ICU patients with gastrointestinal bleeding have 46% higher mortality (103). The American Society of Health-System Pharmacists (ASHP) guidelines

945 recommend prophylactic treatment with acid-suppressive drugs (antiulcer agents) such
946 as PPIs and H2As (104). H2As can reduce the risk of overt bleeding by 58% (105).
947 Although proven to be highly effective in raising gastric pH, recent studies, including a
948 meta-analysis, revealed that acid-suppressive drugs alone do not decrease the overall
949 mortality rate (106). Guidelines issued by the Agency for Healthcare Research and
950 Quality (AHRQ) recommend prophylactic treatment as level 1 for ICU patients with
951 coagulopathy, head injury, severe burns, or mechanical ventilation (107). PPIs and
952 H2As cannot fully prevent stress-induced mucosal bleeding, and the risk of *Clostridium*
953 *difficile* infection could be increased with the use of acid-suppressive drugs.
954 Furthermore, acid-suppressive drugs can cause hypomagnesaemia, vitamin B12
955 deficiency, upper respiratory tract infection, pneumonia, and clinical fractures of the hip,
956 spine, and wrist. Continuation of these medications should be reassessed once the
957 patient is discharged from the ICU. The AHRQ guidelines state that the risk of
958 gastrointestinal bleeding increases with the number of days on mechanical ventilation
959 and ICU stay, respectively (107). Mechanical ventilation and coagulopathy, especially
960 DIC, also contribute to poorer prognosis in patients with TS.

961 **3. Jaundice and hepatic damage**

962 Congestive heart failure is one of the most common causes of hepatic damage and
963 jaundice. Treating congestive heart failure could contribute to the recovery of normal
964 liver function. Ursodeoxycholic acid, which relieves liver dysfunction, and Stronger
965 Neo-Minophagen C, a glycyrrhizin-containing liver protector, can also be used;
966 however, these drugs may induce further liver damage (108). When an adequate

967 reduction in thyroid hormone levels cannot be achieved, TPE and/or CHDF should be
968 considered to remove excess thyroid hormone, autoantibodies, molecules that cause
969 coma, and pro-inflammatory cytokines. Severe liver failure induces reduced protein
970 synthesis, which results in coagulopathy, host defense disorders, and eventually
971 multiple organ failure. TPE with FFP may effectively compensate for the loss of
972 coagulation factors. In addition, hemodialysis could support detoxification in liver
973 failure (109). TPE and CHDF may contribute to the recovery of homeostasis in
974 electrolytes, fluid volume, and acid-base balance in multiple organ failure, providing
975 sufficient extracellular fluid space for treatment (110, 111). Additional information
976 regarding the indication for TPE in thyroid storm is described in the Section 2.
977
978 ● **Comments**
979 **a) Gastrointestinal disorders in thyroid crisis**
980 CNS manifestations weighted most heavily in our diagnostic criteria for thyroid
981 storm, while gastrointestinal symptoms contributed less to the diagnosis of thyroid
982 storm (4). However, if we exclude gastrointestinal manifestations from the diagnostic
983 criteria ofthyroid storm, 38 of 55 patients (including 7 fatal cases) without CNS
984 manifestations would not have been diagnosed with thyroid storm. Therefore, we cannot
985 ignore gastrointestinal symptoms in the diagnosis of thyroid storm; however, the
986 treatment of these disorders mainly depends on reducing serum thyroid hormone levels.
987 The prognosis is affected by CNS manifestations and heart failure. Based on the results
988 of our national survey in Japan (4), we could not identify any specific drugs that

989 affected liver function or mortality in patients with thyroid storm.

990 **b) Hepatic damage**

991 Increased oxygen consumption in hepatocytes resulting in relative hypoxia in
992 the perivenular region, may be responsible for inducing hepatocyte damage in
993 thyrotoxicosis. One pathological study showed simple atrophy, sinusoid congestion, and
994 fatty metamorphosis (112). The presence of autoimmune diseases such as autoimmune
995 hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis may also
996 exacerbate liver damage in thyrotoxicosis. Graves' disease is also categorized as an
997 autoimmune disease. The principal treatment during the acute phase of thyroid storm
998 should focus on thyrotoxicosis and heart failure.

999 **c) TPE and hemodialysis**

1000 According to the guidelines of the Japan Society for Apheresis, indications for
1001 TPE in acute liver failure are as follows: altered consciousness, serum total bilirubin
1002 level >5.0 mg/dL or hepaplastin <30%, and arterial ketone body ratio
1003 (acetoacetate/3-hydoxybutyrate) <0.7 (113). Three types of apheresis are used for acute
1004 liver failure: TPE, CHDF, and plasma adsorption. TPE can remove
1005 intermediate–molecular-weight proteins such as bilirubin, replace proteins such as
1006 coagulation factors, and provide sufficient extracellular space for treatment. CHDF is
1007 used to remove low–molecular-weight molecules that can induce hepatic coma and
1008 adjust balances in fluid, electrolyte, and acid-base levels. Like TPE, plasma adsorption
1009 can also remove bilirubin. In multiple organ failure, TPE and CHDF could contribute to
1010 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 in all thyroid storm patients. Patients with potentially fatal conditions such as shock, DIC, and multiple organ failure should immediately be admitted to ICU.

   Strength of recommendation: strong

   Quality of evidence: low

2. Based on nationwide survey analyses, patients with APACHE II scores above 9 is strongly recommended to admit to ICU.

   Strength of recommendation: strong

   Quality of evidence: low

3. DIC, which is often complicated with thyroid storm should be intensively treated, because DIC has been shown to associate 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 is no clinical study

to identify fatal comorbidities or prognostic factors in a large cohort of thyroid storm patients. Although it was a retrospective, but the largest cohort study ever been conducted worldwide, the nationwide survey performed in Japan identified that systemic comorbidities, including DIC are associated with higher mortality (4). In this survey, 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 complicated 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 (114), the prognosis of thyroid storm in a large cohort has ever been evaluated 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 scores in 75% of patients who died was above 8.8 and those of the 8 patients who were admitted to general wards and subsequently died were 5 in two cases, 11, 12, 13 in two 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 in ICU-admitted patients were 11 or 12 (115). Taken together with our findings, we strongly recommend that patients with an APACHE II score above 9 should receive ICU care to ameliorate thyroid storm-mediated mortality.

A recent clinical study revealed a close relationship between hyperthyroidism and coagulation disorders (116). In the nationwide surveys, DIC was associated in 9.3% and the mortality of patients with DIC was 45% (4). A case report also described the presence of multiple organ failure in thyroid storm with possible association with DIC (117). The multiple organ failure is the characteristic feature in thyroid storm, which 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 (118). Japan has an estimated 4.3 ICU beds/100,000 (115). 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, and multiple organ failure) individually, and found that shock, DIC, and multiple organ failure are 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 has been defined as a condition in which an uncontrolled systemic inflammatory response or increase in cytokine levels leads to progressive damage of two or more organs or organ systems (119). The pathogenesis of multiple organ failure has been divided into the two following 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

1103 respiratory failure, hemodialysis for renal failure, plasma exchange for hepatic
1104 insufficiency, cardiomimetic medications or assisted circulation for heart failure,
1105 intravenous hyperalimentation for nutritional support, insulin therapy for hyperglycemia,
1106 and plasmapheresis for various kinds of chemical mediators. Patients with thyroid storm
1107 and multiple organ failure should be admitted to the ICU because multiple organ failure
1108 is fatal in thyroid storm.

1109 Guidelines for ICU admission or discharge needed to be established using
1110 objective criteria, such as the APACHE II score. The APACHE II score was proposed
1111 as a measure of disease severity by Knaus et al. in 1981 (114). The score is calculated as
1112 the acute physiology score (APS) as the sum of the worst values for 12 clinical indexes
1113 including respiration, circulation, blood chemistry, and Glasgow Coma Scale in the 24
1114 hours after ICU admission. APS is then added to scores based on age and chronicity,
1115 yielding the APACHE II score. This APACHE II score was then re-evaluated by
1116 disease and an estimated mortality rate was calculated. The final assessment of the
1117 APACHE II score was based on the probability of mortality (Supplementary Table)
1118 (114). The median APACHE II score was 10 and the mean was 10.9 in a nationwide
1119 survey (4). The mortality of thyroid storm in this survey was 11% and the mean value
1120 of the APACHE II score was 10.97±0.35, indicating agreement between thyroid storm
1121 mortality and APACHE II score. The validity of APACHE II scores was established;
1122 the mortality of thyroid storm could be evaluated using the APACHE II score.

1123 Sequential Organ Failure Assessment is another scoring system for systemic
1124 conditions. Six clinical indexes evaluating the respiratory, coagulation, liver,

1125 cardiovascular, central nervous, and renal systems are used to calculate the Sequential
1126 Organ Failure Assessment score. Each index has five grades, 0 to 4 (120). A Sequential
1127 Organ Failure Assessment score above 5 corresponds to a mortality rate of 20%. In the
1128 nationwide survey, the mean Sequential Organ Failure Assessment score was 2.7±0.5.
1129 The mean value of patients who died was 3.1±0.5, and the mean value of patients who
1130 survived was 2.4±0.1 (p<0.0001). The odds ratio for death was 1.33 (95% CI, 1.20 to
1131 1.50; p<0.0001). However, absolute values were as low as 2, which implied the
1132 possibility that Sequential Organ Failure Assessment does not precisely estimate patient
1133 mortality. Since this score was originally designed to assess patients with sepsis, the
1134 Sequential Organ Failure Assessment score was not included in these recommendations.
1135 A recent study reported the relationship between thyroid dysfunction and
1136 coagulation disorders (79). The mechanisms underlying this relationship were
1137 considered to be the direct effects of thyroid hormones on the coagulation or immune
1138 system. One study showed increased serum levels of coagulation factors such as factor
1139 VIII and von Willebrand factor following systemic infusion of thyroid hormones in
1140 normal healthy volunteers (121, 122). Several case reports also described patients with
1141 severe thyroid storm complicated with DIC. Controlling systemic thyroid hormone
1142 levels is important because the basic mechanism for DIC in thyroid storm is coagulation
1143 system disorder. Interventional clinical trials may be necessary to establish the
1144 appropriate management of DIC in thyroid storm.
1145

9. Prognostic evaluation of thyroid storm

■ **RECOMMENDATION 12**

The APACHE II score or Sequential Organ Failure Assessment score can be used for the prognosis 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, 123, 124). 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 direct causes of death were attributed to heart failure and multiple organ failure (Table 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 5). 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 when left untreated. 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 (114) and Sequential Organ Failure Assessment scores (125). 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 calculated APACHE II score include Glasgow Coma Scale, age, serum creatinine, serum albumin, and base excess. The parameters independently associated with calculated Sequential Organ Failure Assessment score also include the presence of ophthalmopathy, Glasgow Coma Scale, 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).

● **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, Labour 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 provides 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 for prevention of thyroid storm in patients undergoing ATD treatment with poor adherence.

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 a recurrent thyroid storm for the 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/abrupt discontinuation of ATDs (4). Therefore, each patient with Graves' disease should be given full information about life-threatening thyroid storm and its triggering condition when treatment with ATDs is initiated. The patients with continuously poor adherence even after repeated education should be treated with definitive therapy. In thyrotoxic patients with potential triggering conditions for thyroid storm, these triggering factors should be simultaneously treated.

The nationwide surveys provided a novel finding that about 10% of thyroid

storm was originated from undiagnosed Graves' disease with some triggers (8). In order to prevent the onset of thyroid storm in such cases, providing information to general population about life-threatening thyroid storm may be important. In addition, providing knowledge about thyroid storm and its diagnostic criteria to acute physicians and cardiologists who may have higher chance 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. Six cases of thyroid storm in relation to radioiodone therapy, but no patients with thyroid storm after thyroidectomy have been reported in the nationwide surveys (4). Therefore, it is important to carefully monitor for general condition and thyroid hormone levels prior to and after radioiodine therapy. In patients treated with ATDs prior to radioiodine ablation, ATD discontinuance 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 by using ATDs and inorganic iodide. Patients unable to use or responding poorly to these treatment require preparation for surgery using all available means, as mentioned above to normalize thyroid hormone levels preoperatively.

Several drugs has been reported to rarely cause thyroid storm 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 of which 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.

Emergent thyroidectomy has previously been performed to treat thyroid storm patients who continued to deteriorate despite the use of standard medical therapy. Early or late postoperative mortality in patients performed with emergent thyroidectomy was reported in 5 of 49 patients (10.2%) (126). 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 (126).

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, heart, 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 condition should be evaluated by blood gas analyses, electrocardiogram monitoring, routine blood examination including complete blood count, coagulation test and blood chemistry, urinalysis, and chest X-ray. Appropriate sampling for blood, urine and sputum is essential for patient with high fever. A brain computed tomography without intravenous contrast or magnetic resonance imaging is required for patients with disturbances of consciousness. FT3, FT4 but not total T4, TSH, and TRAb levels should be immediately measured if the patient's symptoms fulfill the criteria (4, 8) and thyroid storm 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 cases 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. The APACHE II score should be assessed in combination with Glasgow Coma Scale, 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 to assess the need for ICU admission (114). When the APACHE II score is 9 points or higher, admission to the ICU is recommended (for more details, see Section 7). In parallel with evaluating the APACHE II score, intense cooling with ice packs/cooling blanket and administration of acetaminophen, ATDs, CSs, and inorganic iodide should be started (Supplementary Figs. 1-1~3 and Supplementary Fig. 2) (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 disturbance 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 (Supplementary Fig. 3) (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, pulse rate is >150 bpm, and Killip ≥III disease has been detected, cardioversion should be considered after ruling out left atrial thrombosis if hemodynamic parameters cannot be stabilized. A $CHADS_2$ score ≥1 is required for anticoagulation therapy to be initiated (100). 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 (Supplementary Figs. 4-1 and 4-2). See Sections 5 and 6 for more details on the treatment of atrial fibrillation and congestive heart failure in TS.

According to the Guidelines from the Japan Society for Apheresis (109), 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 (Supplementary Fig. 5) (for more details, see Section 7).

When life-threatening complications associated with thyroid storm such as DIC (Supplementary Fig. 6), 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 (Supplementary Fig. 1–4) (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 (119, 120) are useful for predicting the prognosis of patients with thyroid storm (Supplementary Fig. 7) (for more details, see Section 9).

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 JES described the clinical realities of thyroid storm for the first time in the world 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 (127). 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 have not yet been performed 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 (79, 116, 125). One suggested mechanism is the increase in factor VIII in the coagulation cascade (121, 122). The fibrinolysis type of DIC is the dominant form of thyroid storm-associated DIC. 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" (129). 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 7.2 days in normal subjects and 6.2 days in patients with hyperthyroidism. 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 during these periods, 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 (130, 131). In thyroid storm case reports published in Japan between 1983 and 2011, the time period during which TPE was being used, 5 out of 38 patients died, representing a mortality rate of 13.2%, 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 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 (58). 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, 59). 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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The authors declare that they have no conflict of interest to disclose.

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Figure Legends

Figure 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) (pmol/dL) (n = 8) and free thyroxine (FT4) (nmol/L) (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.

Figure 2. Medical treatment for convulsions

A proposed algorithm for the treatment of convulsion in patients with thyroid storm, modified from the 2010 Guideline for Epilepsy Treatment by the Japanese Society of Neurology (52). *1, standard therapy, *2, alternative therapy, EEG, Electroencephalogram.

Figure 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. JCS, Japan Coma Scale; GCS, Glasgow Coma Scale; CT, computed tomography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography

Figure 4. An algorithm for diagnostic considerations in thyroid storm

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

Figure 5. A treatment algorithm for thyroid storm

Brief comments on the treatment of severe thyrotoxicosis and manifestations in various organs are described in Supplementary Figures 1–7 (Suppl).

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, thiamazole; 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

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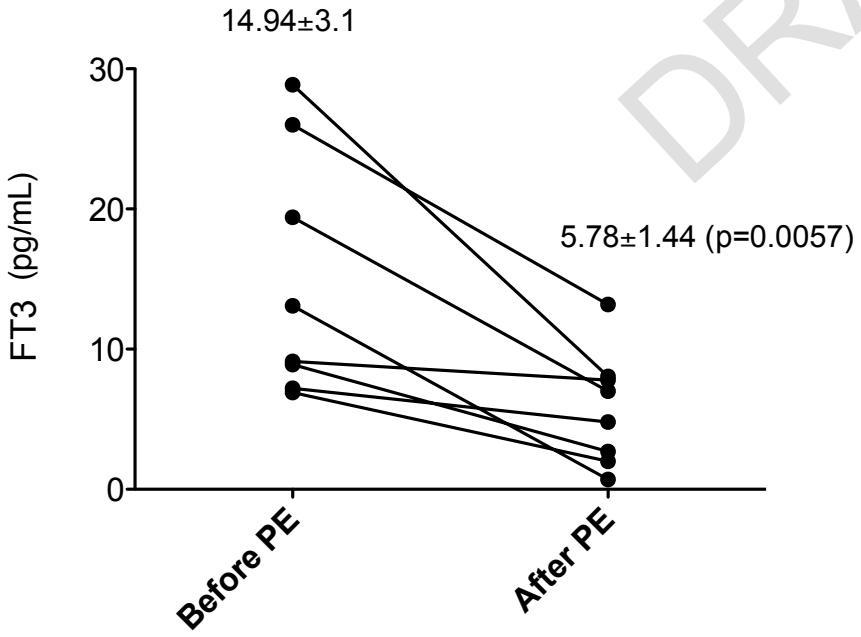
Figure 1



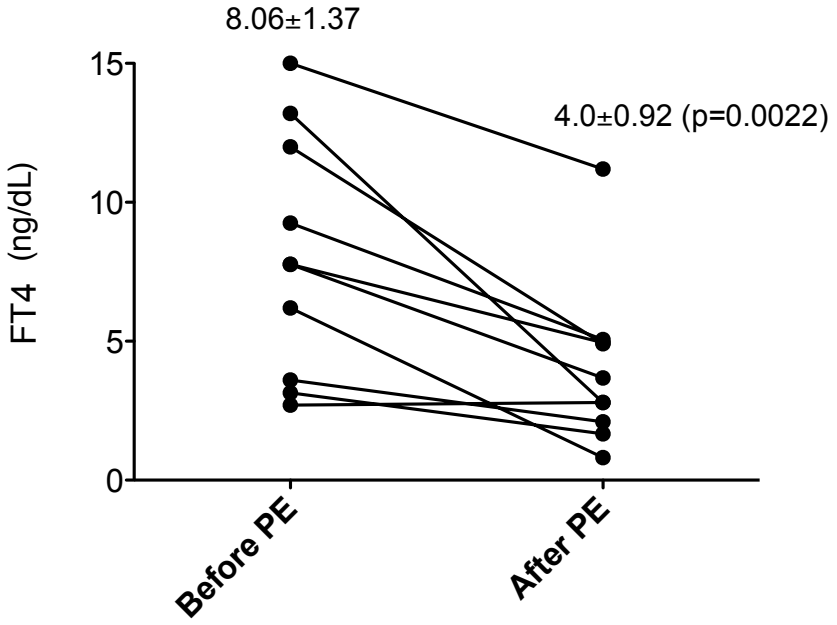
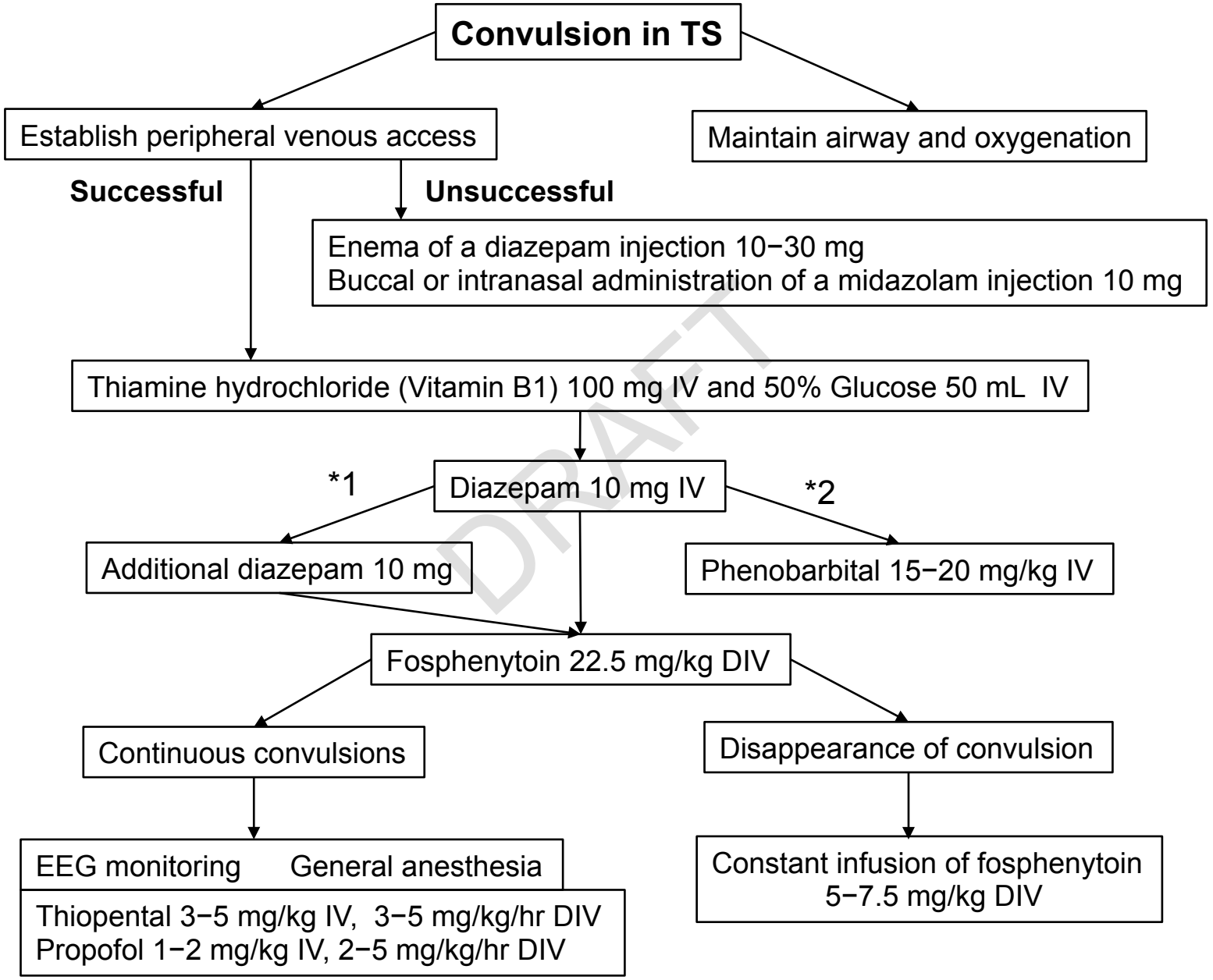


Figure 2



(modified Epilepsy Treatment Guidelines 2010 (52))

Figure 3

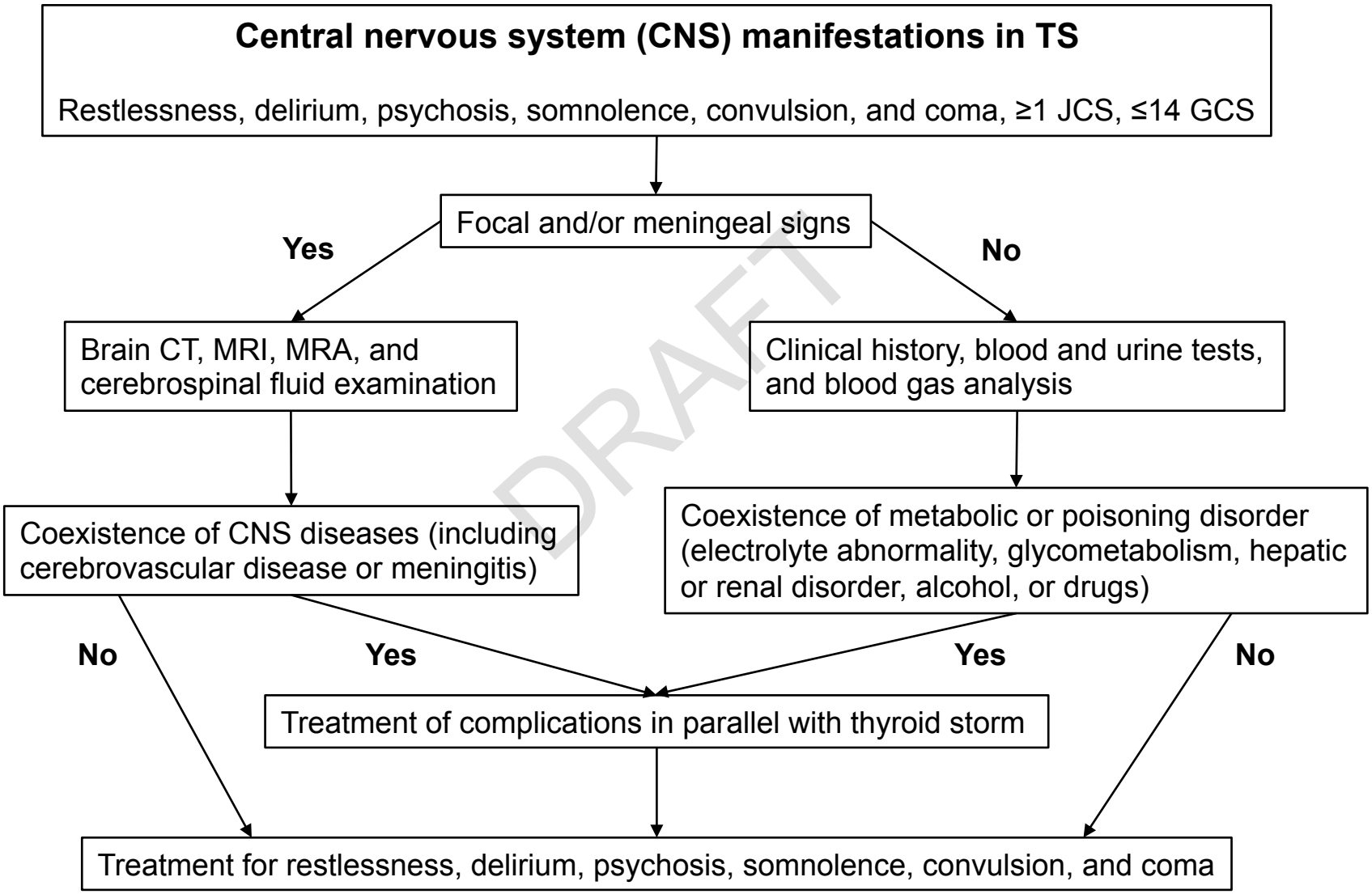


Figure 4

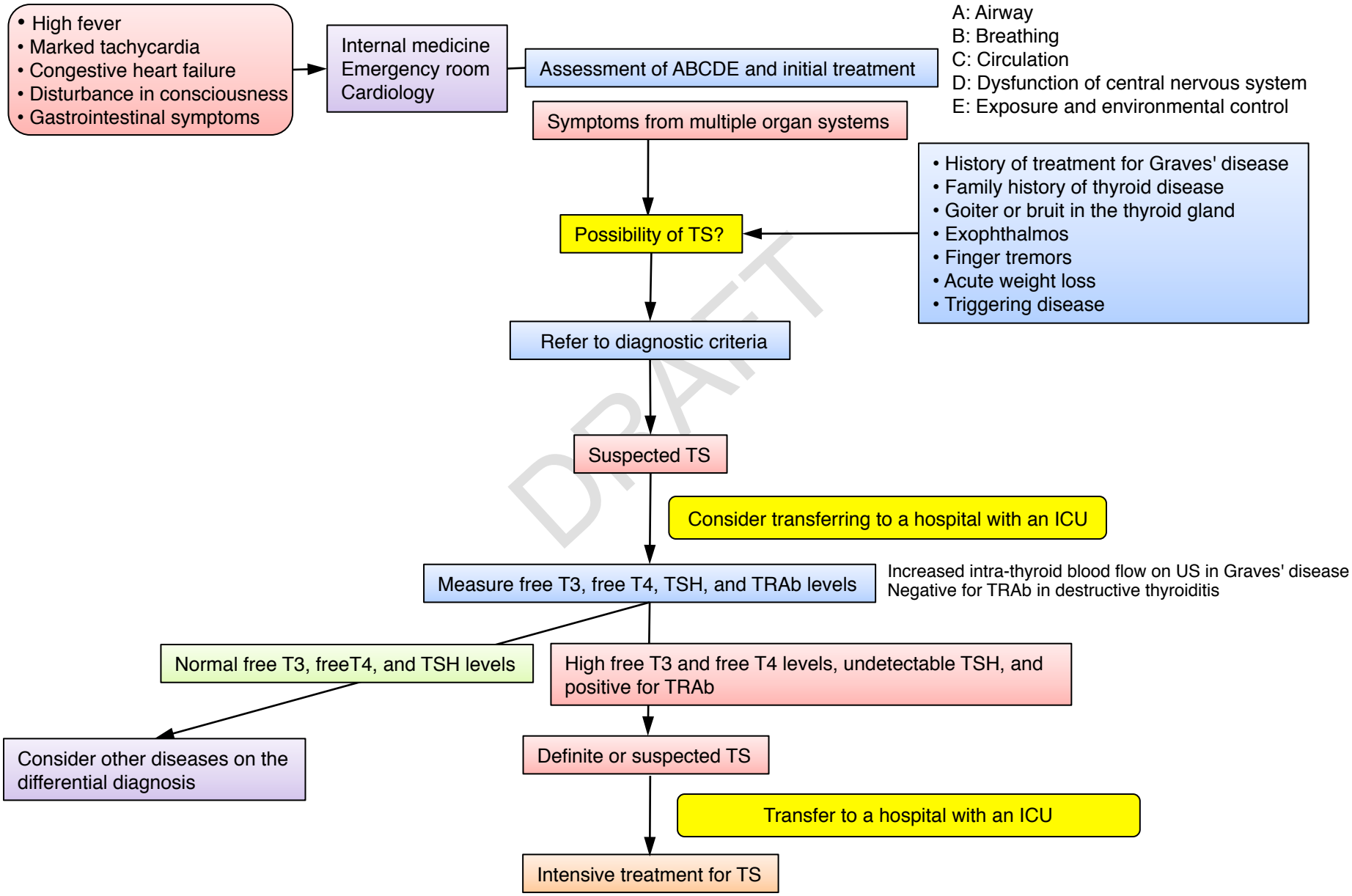
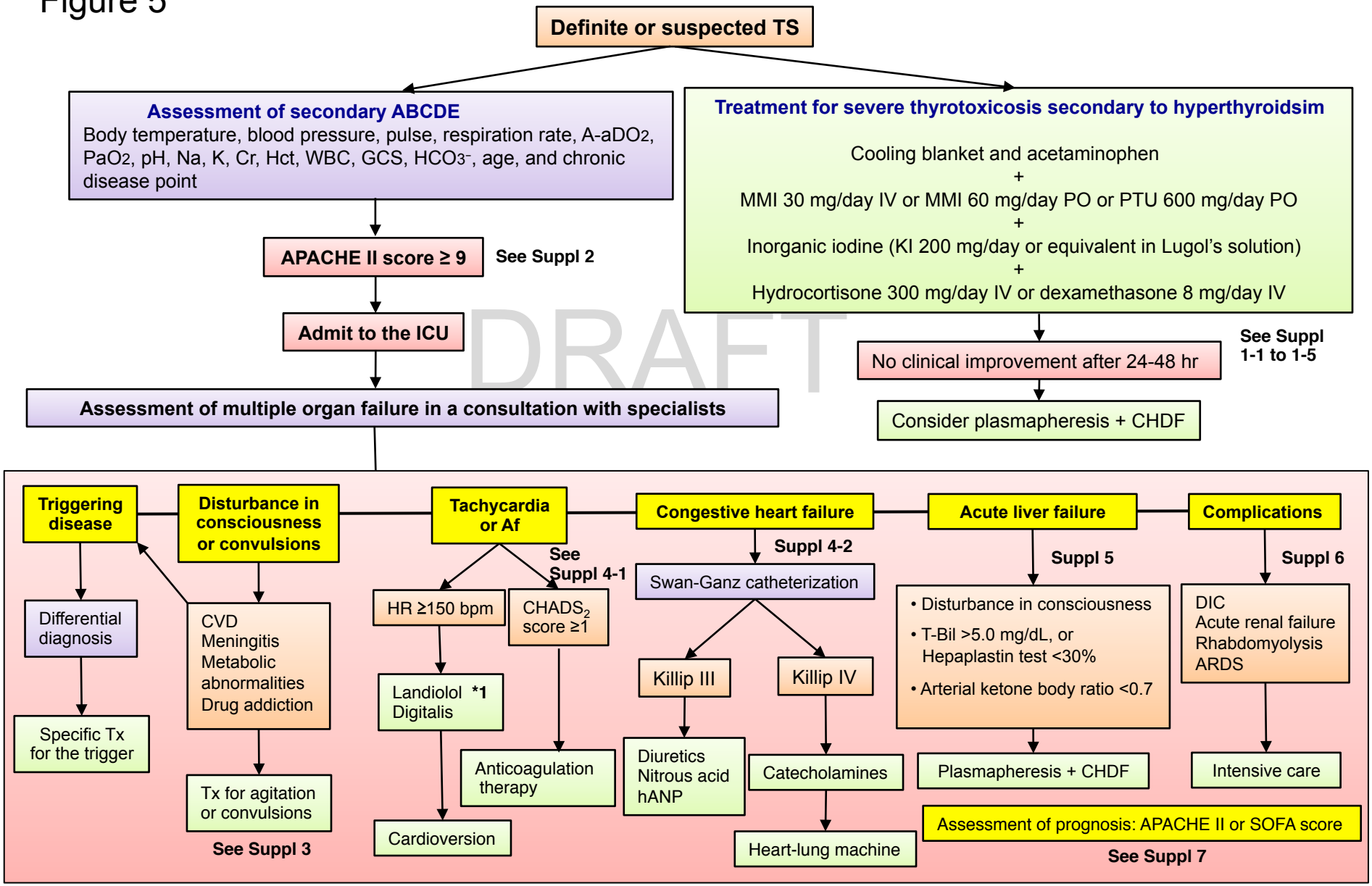

• High fever
• Marked tachycardia
• Congestive heart failure
• Disturbance in consciousness
• Gastrointestinal symptoms
Internal medicine
Emergency room
Cardiology
Assessment of ABCDE and initial treatment
A: Airway
B: Breathing
C: Circulation
D: Dysfunction of central nervous system
E: Exposure and environmental control
Symptoms from multiple organ systems
• History of treatment for Graves' disease
• Family history of thyroid disease
• Goiter or bruit in the thyroid gland
• Exophthalmos
• Finger tremors
• Acute weight loss
• Triggering disease
Possibility of TS?
Refer to diagnostic criteria
Suspected TS
Consider transferring to a hospital with an ICU
Measure free T3, free T4, TSH, and TRAb levels
Increased intra-thyroid blood flow on US in Graves' disease
Negative for TRAb in destructive thyroiditis
Normal free T3, freeT4, and TSH levels
High free T3 and free T4 levels, undetectable TSH, and positive for TRAb
Consider other diseases on the differential diagnosis
Definite or suspected TS
Transfer to a hospital with an ICU
Intensive treatment for TS
DRAFT

Figure 5



*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.

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

Ref: Qaseem A, et al. 2010 Ann Intern Med 153:194-199

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
38.9–39.4	20
39.4–39.9	25
≥ 40.0	30
Cardiovascular	
Tachycardia (beats per minute)	
100–109	5
110–119	10
120–129	15
13–139	20
≥ 140	25
Atrial fibrillation	
Absent	0
Present	10
Congestive heart failure	
Absent	0
Mild	5
Moderate	10
Severe	20

Criteria	*Points*
Gastrointestinal-hepatic dysfunction	
Manifestation	
Absent	0
Moderate (diarrhea, abdominal pain, nausea/vomiting)	10
Severe (jaundice)	15
Central nervous system disturbance	
Manifestation	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, come)	30
Precipitant history	
Status	
Absent	0
Present	10

Score totaled	
> 45	Thyroid storm
	Impending storm
< 25	Storm unlikely

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

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

Symptoms
1. Central nervous system (CNS) manifestations: Restlessness, delirium, mental aberration/psychosis, somnolence/lethargy, coma including ≥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 for more than half of the lung field, cardiogenic shock or Class IV by the New York Heart Assciation or ≥ Class III in the Killip classification
5. Gastrointestinal (GI)/hepatic manifestations : nausea , vomiting, diarrhea, or a total bilirubin ≥ 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 or tachycardia or CHF or GI/hapatic manifestations
TS1	Alternate combination	Thyrotoxicosis and at least three combinations of fever or tachycardia or CHF or GI/hapatic manifestations
TS2	First combination	Thyrotoxicosis and a combination of two of the following: fever or tachycardia or 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). However, some of these disorders trigger thyroid storm. Therefore, it is difficult to determine whether the symptom is caused by TS or is simply a symptom of underlying disease that is possibly triggered by TS; 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.

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

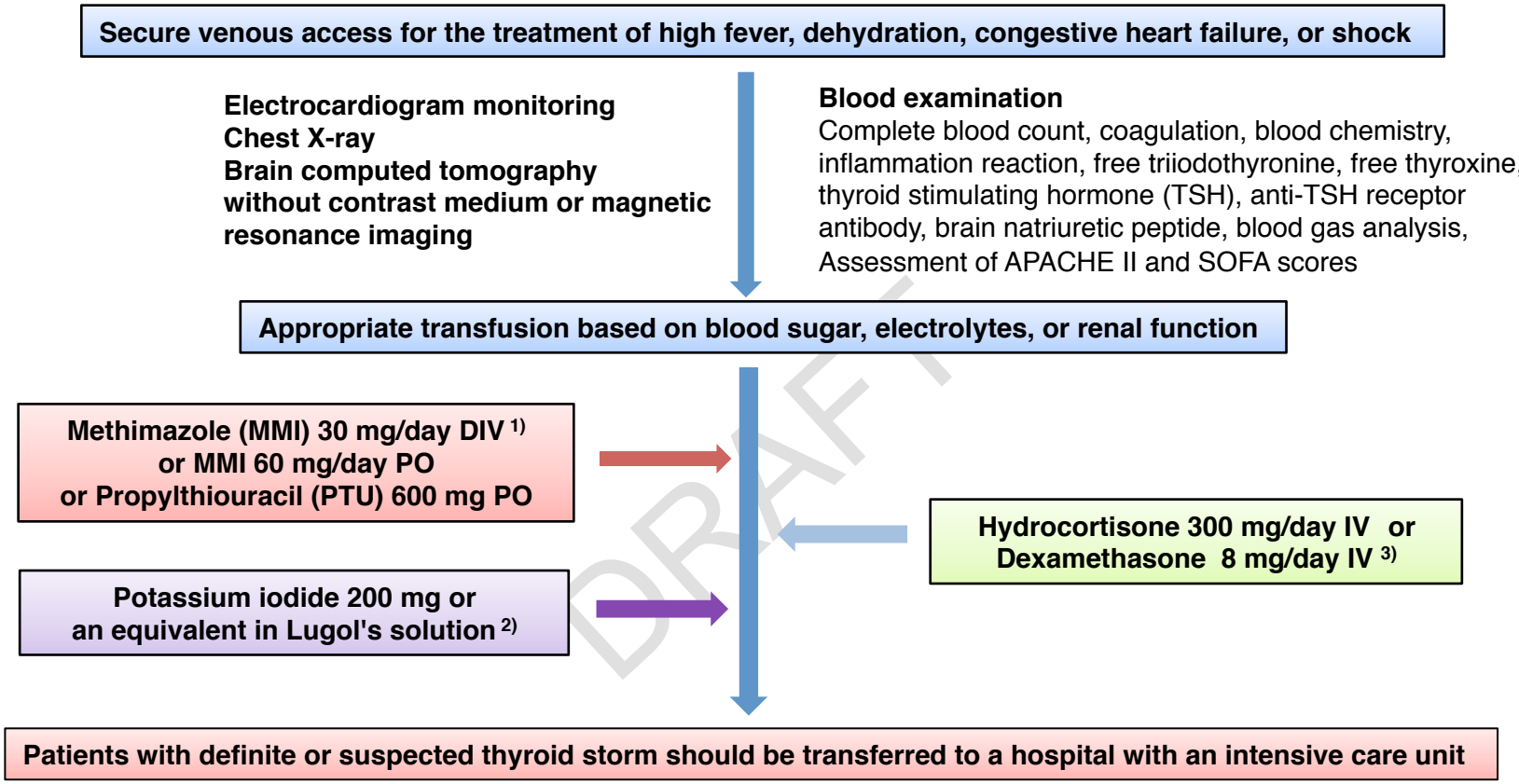
Table 5. Sequelae of thyroid storm

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
Gasric ulcer	1
Others	3
Total	29

Supplementary Figure 1-1

- 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.

Supplementary Figure 1-2

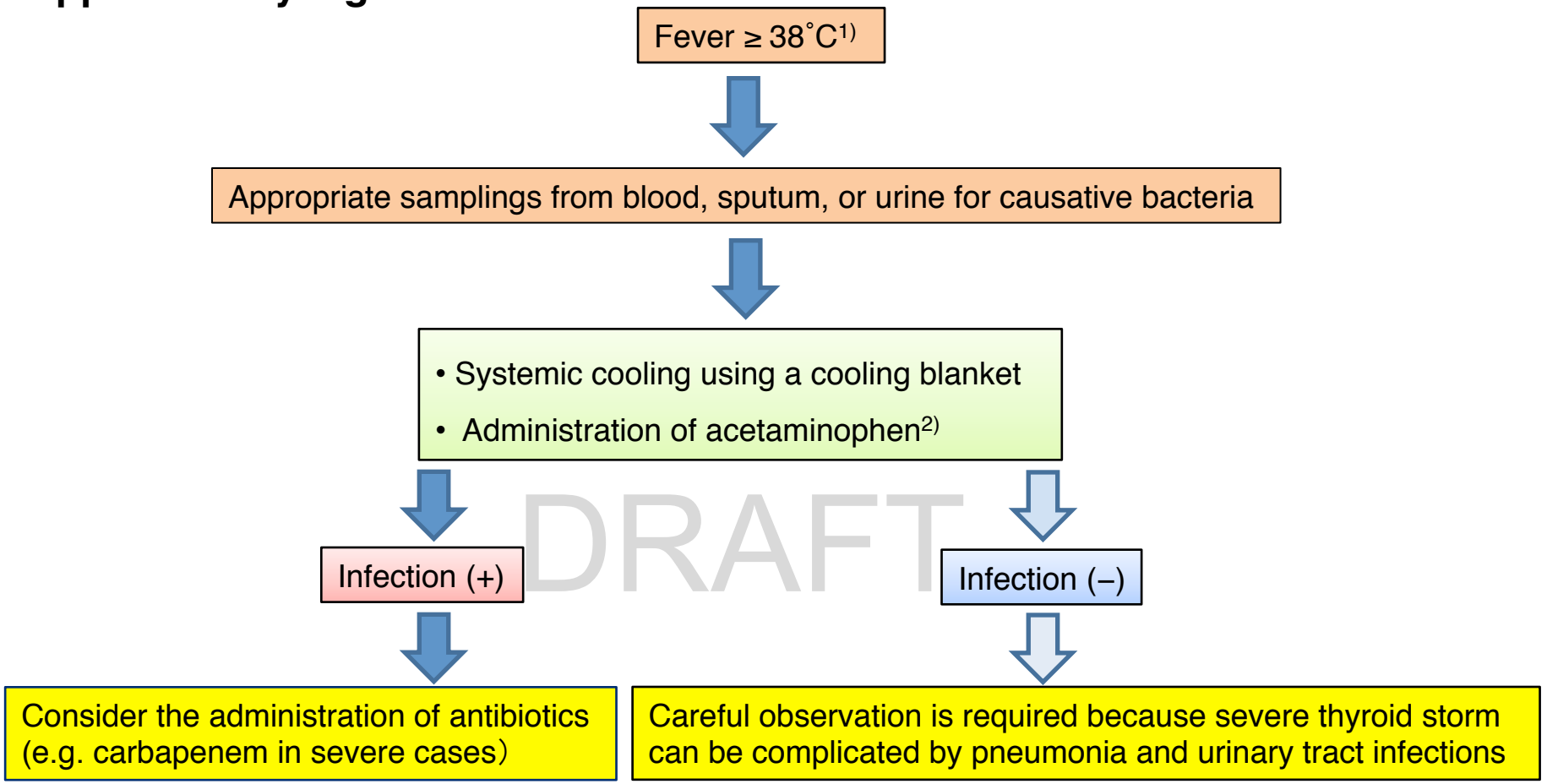


1) Intravenous administration of MMI is recommended in patients with disturbances of consciousness or non-functioning gastrointestinal tract. If unavailable, MMI or PTU can be administered orally or via a nasogastric tube or rectally.

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.

Supplementary Figure 1-3



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.

Supplementary Figure 1-4

• 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 (*Therapeutic Apheresis and Dialysis* 2011; 15: 522-531); however, a few cases of death were also reported.

• The mortality rate of TPE-treated TS reported in Japan between 1983 and 2011 was 13.4% (5/38).

• 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 2-6)

2**) Relative indication for TPE**: Uncontrolled thyrotoxicosis 24–48 hours after the initiation of intensive treatment (for more details, see Section 2-2)

Supplementary Figure 2

- 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 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.

Supplementary Figure 3

- 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)
Guidelines for the Treatment of Epilepsy 2010 (Societas Neurologica Japonica)

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

Supplementary Figure 4-1

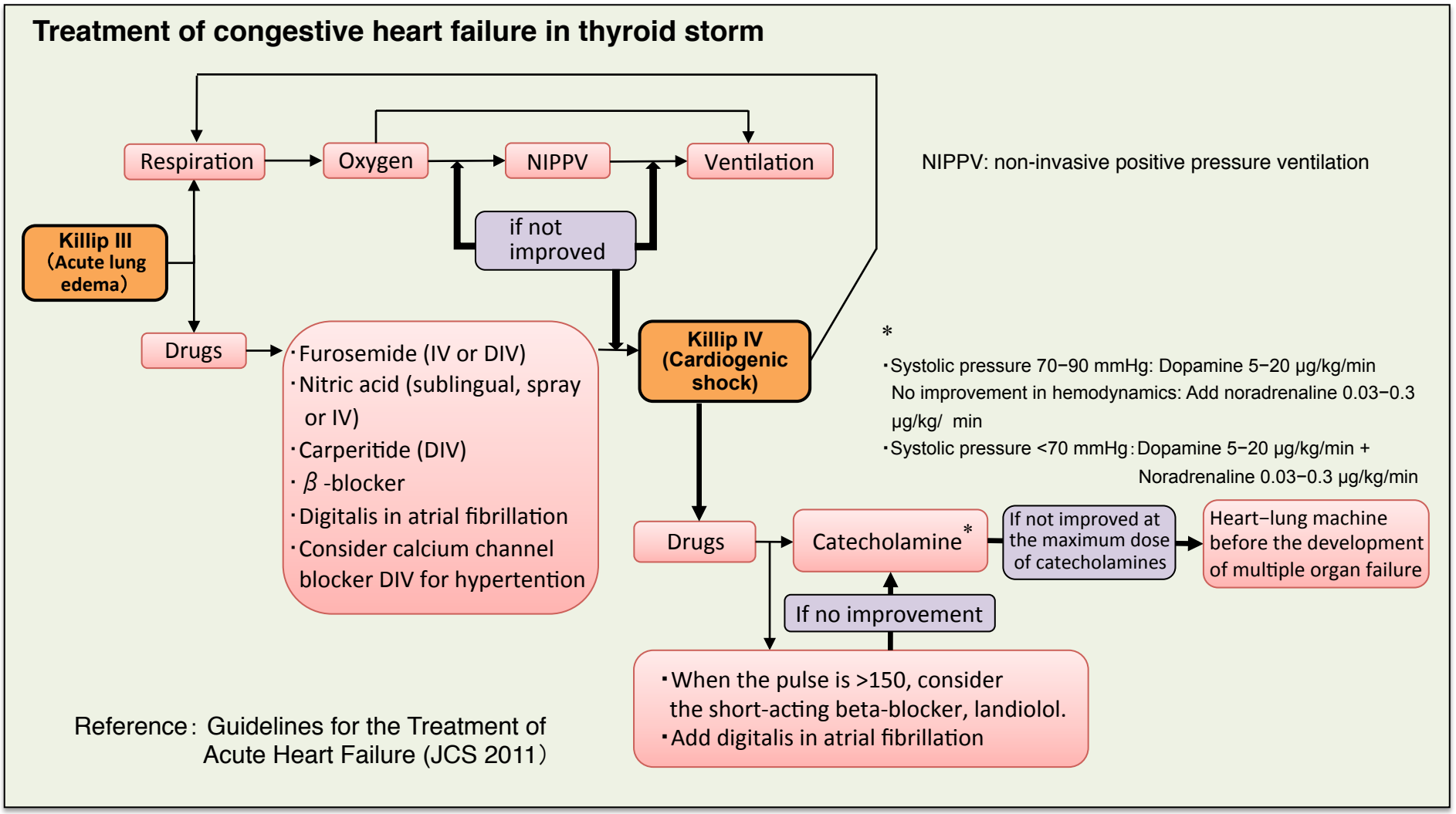
- Pulse ≥ 150 bpm was correlated with severity and mortality of thyroid storm (TS) in the nationwide survey.

	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 hemodynamic status cannot be stabilized.
- Digitalis and disopyramide 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.

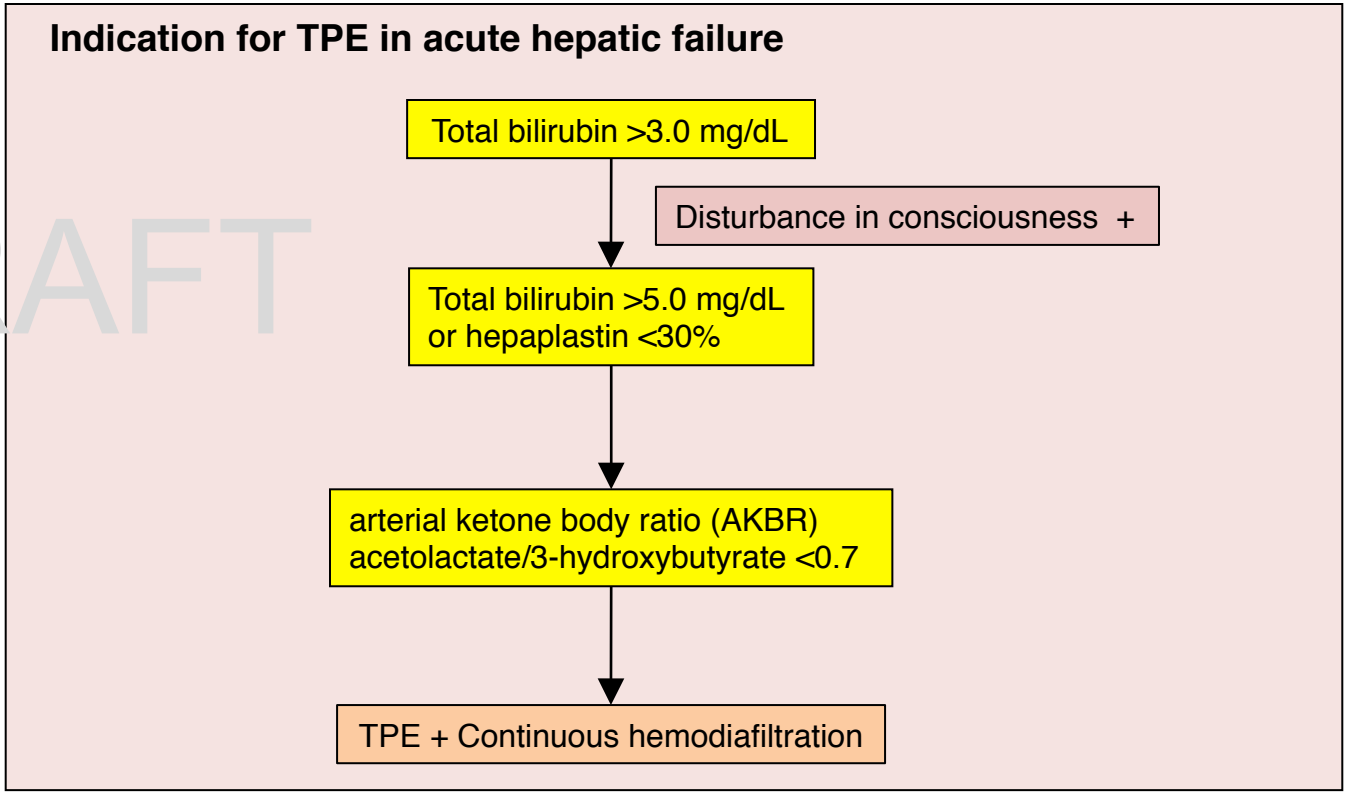
Supplementary Figure 4-2

• 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.



Supplementary Figure 5

- 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).



Reference: Apheresis Manual (third edition) (Japan Society for Apheresis)

Supplementary Figure 6

- 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

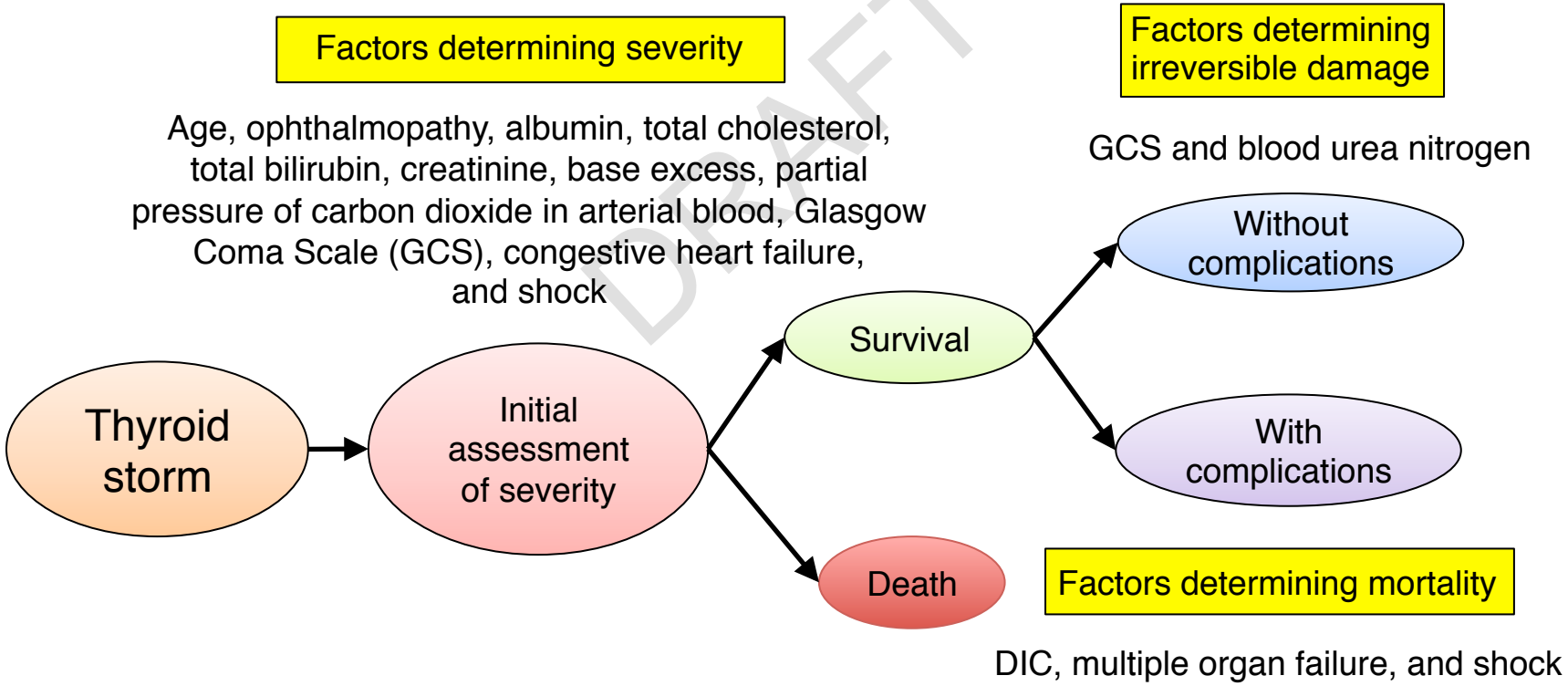
DIC can be diagnosed with a total score ≥ 4 points.

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

Body temperature >38℃ 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%

Supplementary Figure 7

- 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 (TS).
- 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.



Supplementary Table

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