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THYROID MANAGEMENT IN THE ICU

SUMMARY

Patients may present with severe endocrine derangements as a result of their critical illness. It is imperative to identify those patients with known thyroid disease and those who present with acute alterations in thyroid function tests or display signs of non-thyroidal illness. This guideline provides an overview of testing for thyroid disease in critically ill patients as well as recommendations for management of patients with thyroid hormone abnormalities.

RECOMMENDATIONS

- **Level 1**
 - None
- **Level 2**
 - The half-life of levothyroxine is one week and peri-operative thyroid hormone replacement is unnecessary in most patients.
 - Thyroid hormone replacement should continue for patients with hypothyroidism.
 - Patients on antithyroid medication should receive their medication prior to surgery and during their hospital course.
 - Thyroid hormone replacement therapy testing should be performed every 6-8 weeks for patients without a stable TSH (thyroid stimulating hormone) or earlier if there is question of medication compliance.
- **Level 3**
 - The effectiveness of thyroid hormone replacement in ICU patients with non-thyroidal illness syndrome (NTIS) is unclear.
 - Patients with ongoing critical illness including hypotension should be evaluated for thyroid hormone deficiency.

INTRODUCTION

Critically ill patients can present with profound endocrine and metabolic issues. Many conditions seen in the ICU have been shown to correlate with thyroid dysfunction including sepsis, starvation, and myocardial infarction (1). The endocrine feedback loop controls the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) is released from the hypothalamus and stimulates the anterior pituitary to release thyroid stimulating hormone (TSH). TSH then stimulates release of thyroxine (T4) and triiodothyronine (T3). T3 and T4 are the active thyroid hormones and regulators of cellular metabolic activity (2). T4 is made almost entirely by the thyroid gland. T4 is converted to the active hormone T3 in the peripheral tissues. Studies have shown that thyroid hormone serum concentrations can vary and respond to environmental factors such as nutrient availability and inflammation (3,4).

Hyperthyroidism is diagnosed clinically by low TSH and high T4 levels. Symptoms include palpitations, nervousness, insomnia, diarrhea, heat intolerance, exophthalmos, hair loss and itching. Hypothyroidism is diagnosed clinically by high TSH and low T4 levels. Symptoms include lethargy, memory loss, weight

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

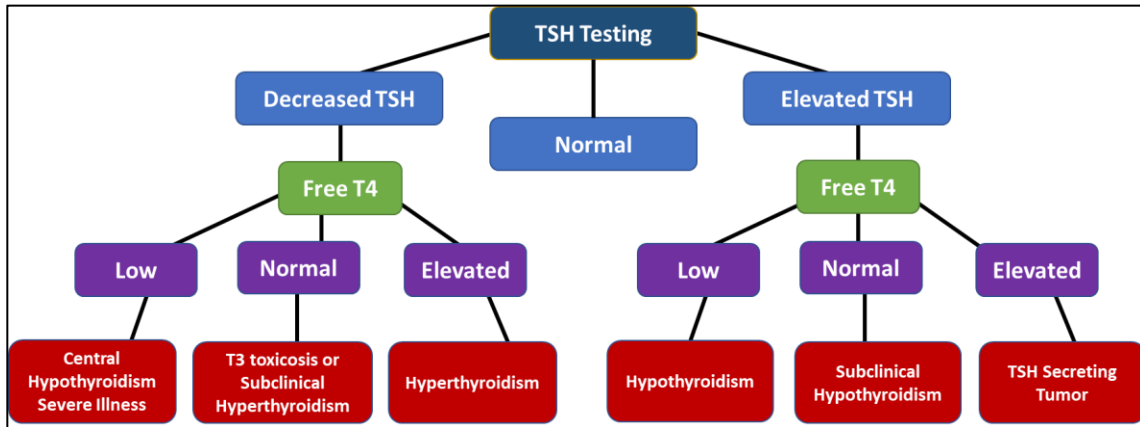
gain, constipation, cold intolerance and depression. In the acute phase of critical illness or major surgery, changes in T3 and T4 can occur in the first 30-120 minutes. The decrease in T3 level is a result of decreased peripheral conversion and is a staple of critical illness (2).

Non-thyroidal illness syndrome (NTIS) is seen in patients with decreased T3 and T4 while TSH is maintained within a normal to slightly decreased range. Other names for these findings include euthyroid syndrome or low T3 syndrome. Identifying NTIS and distinguishing this condition from other thyroid disorders can be difficult in critically ill ICU patients.

DIAGNOSIS OF THYROID HORMONE ABNORMALITIES

The first step in thyroid hormone abnormality testing is checking for derangements in TSH. Depending upon whether the TSH is high, low or normal will determine if a patient is hyper, hypo, or euthyroid. After checking the patient’s TSH level, free T4 and occasionally T3 levels should be evaluated. Figure 1 details a schematic on testing for thyroid abnormalities.

Figure 1: Evaluation of Thyroid Abnormalities



When testing for thyroid abnormalities, clinicians should evaluate TSH, free T4, free T3, and possibly reverse T3 levels. Normal values are laboratory dependent, so one must know reference ranges for the lab performing the analysis. The most common ranges and possible associated clinical abnormalities are listed in Table 2.

Figure 2: Common Thyroid Laboratory Values with Ranges

Thyroid Function Tested	Adult Range	Comments
TSH	0.45-5.33 uIU/mL	Elevated in Hypothyroidism Decreased in Hyperthyroidism
Free T4	0.61 – 1.12 ng/dL	Elevated in Hyperthyroidism Decreased in Hypothyroidism
Free T3	2.5 – 3.9 pg/dL	Elevated in Hyperthyroidism Decreased in Hypothyroidism
Reverse T3	13.5 – 34.2 ng/dL	Elevated rT3 can result in suboptimal free T3 levels which can contribute to hypothyroid
T3 Uptake	32-48%	
Total T3	87.0 – 178.0 ng/dL	
TBG	15.0 – 30.0 ug/dL	
TPO and TBG Antibodies	<32 IU/mL	Seen in Hashimoto’s (Hypothyroidism)
TSI and TR Antibodies	0.0-0.9 IU/mL	Seen in Graves Disease (Hyperthyroidism)

Ranges are based upon laboratory references at Orlando Regional Medical Center in Orlando, FL.

MANAGEMENT OF THYROID HORMONE LEVELS

Patients on maintenance thyroid hormone supplementation who do not have derangements in their hypothalamic pituitary function axis should have TSH levels measured annually. Patients being started on thyroid hormone supplementation or who have had thyroid medication adjustments should have their thyroid function tested (primarily TSH) every 6-8 weeks. TSH testing should be performed in those patients for whom there is a question of compliance to therapy (5,6).

NON-THYROIDAL ILLNESS SYNDROME (NTIS)

Patients with NTIS do not have normal negative feedback regulation in the hypothalamic-pituitary-thyroid axis. When T3 and T4 levels decrease, TSH levels should increase. In NTIS, however, decreased T3 and T4 are seen with normal or decreased TSH. The liver is an important metabolizer of thyroid hormone as it expresses thyroid hormone transporters and several thyroid hormone metabolism enzymes. During critical illness, thyroid hormone levels are decreased as result of decreased D1 enzyme production or increased D3 enzyme production (2). Cytokines, including IL-1, IL-6 and TNF-alpha which are part of the acute phase response, also affect thyroid hormone levels (7). Decreased nutritional intake is also suggested to have an association with decreased thyroid hormone and NTIS. The EPaNIC trial suggested that T3 to rT3 inactivation is an adaption in the fasting or starvation response to conserve energy, but the long-term lowering of T3 and T4 could be dangerous (8).

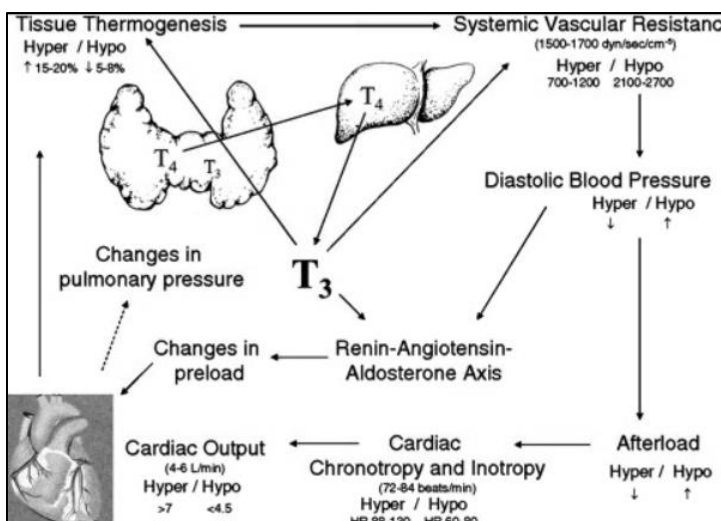
Several studies have demonstrated that acute stress can cause T3 to decrease (2). These acute stresses include, but are not limited to, myocardial infarction, recent surgery, trauma, burns and acute illness. Patients with chronic illnesses and cancer can also develop NTIS. It has been noted that the decrease in T3 is inversely correlated with myocardial infarction size and/or rise in serum creatine in renal injury (9). Gerdes et al. demonstrated that low T3 was a strong predictor for mortality in patients with cardiac disease (10). There have been few clinical studies or randomized controlled trials that have examined NTIS. Clinical studies describing NTIS interventions have focused upon patients with acute renal failure, burn injury, cardiac surgery and those patients with low T4 concentrations (2,11,12).

PERIOPERATIVE MANAGEMENT OF THYROID DISEASE

Hyperthyroidism

Hyperthyroidism is most commonly caused by the autoimmune illness, Graves' disease. Laboratory studies demonstrate elevated thyroid hormone (T3 or T4) and normal or mildly decreased TSH. Rarely, T3 or T4 become extremely elevated resulting in thyrotoxicosis. Elevated thyroid hormone levels can result in increased systemic vascular resistance secondary to activation of the renin-angiotensin syndrome. When thyroid hormone levels are chronically elevated, this can lead to cardiovascular collapse during surgery and critical illness (13).

Figure 3: Thyroid hormone effects on body systems



*Image from *How to Manage Perioperative Endocrine Insufficiency* by Drs. Kohl and Schwartz.

Patients who take anti-thyroid medications with controlled hyperthyroidism should take their medications the morning of surgery. Those patients with uncontrolled hyperthyroidism should have surgery postponed until they are appropriately optimized. Patients who present for urgent or emergent surgery should be managed with beta-blockers, anti-thyroid medications, or iodine prior to undergoing surgical intervention. The most feared complication of uncontrolled hyperthyroidism is thyroid storm which is discussed below.

Hypothyroidism

Hypothyroidism affects approximately 1% of patients and is more common in females. It is identified by elevated TSH and low thyroid hormones (T3 or T4). Common causes of hypothyroidism include autoimmune disease (Hashimoto's), surgical resection, radiation, or medication-induced (including amiodarone, lithium, iron and cholestyramine). Deficiencies in thyroid hormone can decrease cardiovascular response (including inotropy and chronotropic) and increase vascular resistance. Sodium excretion is increased due to malfunction of the renin angiotensin syndrome potentially resulting in hyponatremia.

T4 (levothyroxine) is preferred over T3 for thyroid hormone replacement. The half-life of levothyroxine (T4) is one week and thus it is not necessary for patients to take this medication the morning of surgery or early in the post-operative period (11,13). If thyroid replacement becomes necessary in a patient who cannot be fed enterally, the equivalent dosing to oral replacement would be half the amount intravenously (i.e. 50 mcg levothyroxine oral is equivalent to 25 mcg intravenous).

THYROID EMERGENCIES

Thyroid hormone emergencies are uncommon. When thyroid emergencies do occur, it is a result of thyroid gland dysfunction or thyroid gland enlargement. Severely elevated thyroid hormone levels (thyrotoxicosis) or markedly decreased thyroid hormone levels (myxedematous coma) can effect cardiovascular, digestive, metabolic, neuro-psychological, musculoskeletal, and integumentary function (14).

Hypothyroid Coma

Hypothyroid coma, also known as myxedematous coma, is the result of severe, untreated hypothyroidism. This condition typically affects females. The following factors can trigger the condition: cerebrovascular events, antidepressants, neuroleptics, congestive heart failure, infections, dyspnea, generalized edema, macroglossia, bradycardia, obesity, constipation, and seizures. In those patients who are treated immediately, the mortality rate is still 15-20% (15). Hypothyroid coma can occur in critically ill patients who present comatose and are unable to relate a history of being on thyroid hormone replacement.

Treatment of hypothyroid coma includes initially replacing thyroid hormone with IV liothyronine or L-thyronine. Often patients may need hydrocortisone supplementation if they incur instability in vital signs or other endocrine abnormalities. Patients must also have electrolyte abnormalities corrected, most frequently hyponatremia, with saline. Hypothermic patients must be passively rewarmed because active rewarming can result in vasodilation and shock. Patients who have respiratory acidosis should have more advanced respiratory management implemented including mechanical ventilation.

Thyrotoxic Storm

Thyrotoxic storm is severe thyrotoxicosis. This emergency can be triggered by withdrawal of antithyroid medication, major surgery, iodide compounds, radioiodine therapy, trauma, infections, pregnancy, diabetic ketoacidosis, emotional stress, cerebrovascular disease, intense exercise or pulmonary embolism. Thyroid storm can develop intraoperatively or within 48 hours post-operatively (16). It is more common in females and affects 1% of patients hospitalized for hyperthyroidism (14). Symptoms of this condition include anxiety, tachycardia, tachypnea, congestive heart failure, hyperhidrosis, tremors, diarrhea, nausea and vomiting.

The first treatment in thyrotoxic storm is resuscitation and maintaining systemic oxygenation. Subsequent treatments include IV beta-blockers (propranolol 1-2 mg IV or 40-80 mg po every 8 hours), thyrostatics to

inhibit thyroid production (propylthiouracil or methimazole), and/or hydrocortisone. Other treatments can include use of concentrated iodine solutions such as Lugol's solution or saturated potassium iodide solution to inhibit thyroid hormone leakage. Lithium carbonate can also be used to inhibit the release of preformed thyroid hormone into the blood system.

For the surgical population, most studies focus on patients who undergo coronary artery bypass surgery and whether thyroid replacement is beneficial with regard to outcome and decreasing morbidity and mortality. The results of such studies are mixed, however, and no clear recommendations can be made.

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