Care Step Pathway – Thyroid Dysfunction

Assessment

Look:
- Appear unwell?
- Changes in weight since last visit?
  - Appear heavier? Thinner?
- Changes in hair texture/thickness?
- Appear hot/cold?
- Look fatigued?
- Sweating?
- Hyperactive or lethargic?
- Tremors?
- Difficulty breathing?
- Swollen neck?
- Proptosis?

Listen:
- Appetite/weight changes?
- Hot or cold intolerance?
- Change in energy, mood, or behavior?
- Palpitations?
- Increasing fatigue?
- Bowel-related changes?
  - Constipation/diarrhea
- Shortness of breath/edema?
- Skin-related changes?
  - Dry/oily

Recognize:
- Other immune-related toxicity?
- Prior thyroid dysfunction?
- Prior history of radiation therapy?
- Signs of thyroid storm (fever, tachycardia, sweating, dehydration, cardiac decompensation, delirium/psychosis, liver failure, abdominal pain, nausea/vomiting, diarrhea)
- Concomitant medications (i.e., beta blocker) or advanced age may mask symptoms of hyperthyroidism
- Signs of airway compression
- Clinical presentation: Occasionally thyroiditis with transient hyperthyroidism (low TSH and high fT4) may be followed by more longstanding hypothyroidism (high TSH and low fT4)
- Differential diagnosis-- Primary hypothyroidism: High TSH with low fT4; secondary (central) hypothyroidism due to hypophysitis: both TSH and fT4 are low (see HCP Assessment below for more detail about testing)

Grading Toxicity

Hypothyroidism

Definition: A disorder characterized by decreased production of thyroid hormones from the thyroid gland

Grade 1
TSH > 4.5 and < 10mIU/L and asymptomatic

Grade 2
Moderate symptoms, able to perform ADLs, TSH persistently > 10 mIU/L

Grade 3-4
Severe symptoms, unable to perform ADLs, medically significant or life-threatening consequences

For normal or low TSH with low free T4 in a symptomatic patient, see hypophysitis CSP (secondary [central] hypothyroidism)

Hyperthyroidism

Definition: A disorder characterized by excessive levels of thyroid hormone in the body

Grade 1
Asymptomatic; clinical or diagnostic observations only; Intervention not indicated

Grade 2
Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADLs

Grade 3 or 4
Severe symptoms, unable to perform ADLs, medically significant or life-threatening consequences

Management

Hypothyroidism

Grade 1 (Elevated TSH, Asymptomatic)
- Continue ICI therapy
- Monitor TSH and fT4 q 4–6 weeks
- Replacement dosing (mild symptoms or TSH <10 mIU/L: Typical dosing: 0.8 – 1.2 mcg/kg/day
- Dosing in patients who are elderly, frail, have coronary artery disease, or multiple comorbidities: total dose ranging from 25-50 mcg/day

Grade 2 (Moderate)
- May continue ICI therapy or hold until symptoms resolve to baseline
- Begin thyroid hormone replacement if symptomatic and with any TSH elevation, or if asymptomatic with TSH persistently > 10 mIU/L (measured 4 weeks apart) to 20 miU/L
  - Levothyroxine dose 1.4 – 1.6 mcg/kg/day
  - Monitor TSH q 6-8 weeks while titrating hormone replacement to goal reference range TSH
- Consider endocrine consult (unusual clinical presentations, concern for central hypothyroidism, or difficulty titrating thyroid hormone therapy)
- Once adequately treated, repeat testing q 6-12 months or if symptomatic

Grade 3 or 4 (Severe or Life-Threatening)
- Hold ICI therapy until symptoms resolve with appropriate thyroid hormone supplementation
- Obtain endocrine consultation and/or emergency in-patient care for rapid hormone replacement (as needed for mental status changes and/or if patient comatose)
- If uncertain about primary or central hypothyroidism, hydrocortisone* should be given before thyroid hormone is initiated
- Supportive care may include hemodynamic support, warming blankets, intravenous thyroid replacement, glucose supplementation, antibiotics if needed
- Post acute care, TSH (option for fT4 as well as TSH may take longer to normalize) will be monitored with dose titration; educate patients about how to take the medication properly and precipitating factors for myxedema coma

Hyperthyroidism

Grade 1 (Mild)
- Continue ICI therapy
- Consider beta blockers for symptomatic patients (e.g., atenolol or propranolol for tachycardia/murmur)
- Monitor thyroid function q 2-3 weeks to catch transition to hypothyroidism (see hypothyroidism management)
- Consult endocrinology for thyrotoxicosis persisting >6 weeks

Grade 2 (Moderate)
- Consider holding ICI therapy until symptoms return to baseline (particularly if acute thyroiditis is threatening an airway)
- Consider endocrine consult
- Consider holding ICI until symptoms improve to baseline
- Consider beta blockers for symptomatic patients (e.g., atenolol or propranolol for tachycardia/murmur)
- Monitor thyroid function q 2-3 weeks to catch transition to hypothyroidism (see hypothyroidism management)
- Thyrotoxicosis persisting >6 weeks requires further evaluation to assess for other causes including Graves' disease: consult endocrinology

Grade 3 or 4 (Severe or Life-Threatening)
- Hold ICI therapy until symptoms resolve with appropriate therapy
- Obtain endocrine consult for all patients
- Hospitalization; inpatient, intensive care management, if needed
- Provide hydration and supportive care
- Thyroid-suppressive therapy to be provided, in some cases steroids
- Anticipate cooling measures, fluid resuscitation, electrolyte replacement, nutritional support
- Antipyretics, beta-blocker management of tachyarrhythmia
- Anticipate medical therapy with corticosteroids, potassium iodide, thioamides, cholesterol-binding resins, and potentially surgery

Implementation:

- Ensure that patient undergoes thyroid function tests (TSH and fT4) prior to first dose. After ICI has been initiated, perform routine screening on asymptomatic patients with TSH and fT4 q 4-6 weeks
- Educate patient that hypothyroidism is generally not reversible
  - Assess patient and family understanding of recommendations and rationale
  - Discuss proper technique for taking thyroid supplementation medication (i.e., without food, separating from interacting medications)
- Assess medication adherence with oral thyroid replacement or suppression
- The hyperthyroid phase of thyroiditis is usually short term, and management is generally supportive
- Explain that history of thyroid disorders does not increase or decrease risk of thyroiditis
- It is important to distinguish between primary and secondary (central) hypothyroidism, since the latter is managed as hypophysitis. ACTH, morning cortisol, FSH, LH, TSH, free T4, and DHEA-S should be tested as well as estradiol (women) and testosterone (men). An MRI of the pituitary should be considered if there is confirmed central thyroid/adrenal insufficiency

*Administering Corticosteroids:

High dose steroids are not indicated in cases of thyroid dysfunction

A short course of oral corticosteroids may be considered for destructive thyroiditis with severe symptoms but generally does not require a taper or long-term administration.

RED FLAGS:
- **Swelling of the thyroid gland causing compromised airway**
- **Thyroid storm (severe end of thyrotoxicosis—mental status changes, extremely elevated heart rate, blood pressure, body temperature, compromised organ function)**
- **Myxedema (changes in behavior/mental status, extreme fatigue/cold intolerance, shortness of breath, swelling of hands or feet)**

ACTH = adrenocorticotropic hormone; ADLs = activities of daily living; DHEA-S = dehydroepiandrosterone sulfate; fT4 = free T4; FSH = follicle-stimulating hormone; ICI = immune checkpoint inhibitor; LH = luteinizing hormone; MRI = magnetic resonance imaging; PD-1 = programmed cell death protein 1; po = by mouth; TFT = thyroid function test; TSH = thyroid stimulating hormone