Care Step Pathway – Thyroiditis (inflammation of the thyroid gland)

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?
- Difficulty breathing?
- Swollen neck?

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

Recognise:
- 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)
- Signs of airway compression
- Clinical presentation: Occasionally thyroiditis with transient hyperthyroidism (low TSH and high free T4) may be followed by more longstanding hypothyroidism (high TSH and low free T4)
- Differential diagnosis-- Primary hypothyroidism: High TSH with low free T4; secondary (central) hypothyroidism due to hypophysitis: both TSH and free T4 are low (see HCP Assessment below for more detail about testing)

Grading Toxicity

HYPOTHYROIDISM

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

Asymptomatic, subclinical hypothyroidism, mildly elevated TSH TSH 4 to <10 mIU/L, normal free T4	**Asymptomatic, subclinical hypothyroidism, moderately elevated TSH** TSH >10, normal free T4	**Symptomatic, primary clinical hypothyroidism** Elevated TSH, low free T4 in symptomatic patient*	**Severely symptomatic, primary clinical hypothyroidism (myxedema)** Elevated TSH, low free T4 in severely symptomatic patient*	**Life-threatening, primary clinical hypothyroidism (myxedema coma)**	**Death**

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

HYPERTHYROIDISM

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

Asymptomatic hyperthyroidism; clinical or diagnostic observation only **OR** **TSH low (or <0.01 mIU/L) with normal T4**	**Symptomatic hyperthyroidism; limiting instrumental ADLs** **OR** **TSH low (or <0.01 mIU/L) with high free T4**	**Severe symptomatic hyperthyroidism in addition to TSH low or <0.01 mIU/L with high free T4 or T3**	**Life-threatening symptomatic hyperthyroidism in addition to TSH low or <0.01 mIU/L with high free T4; urgent intervention indicated**	**Grade 5 (Death)**

Management

HYPOTHYROIDISM

Asymptomatic, subclinical hypothyroidism, mildly elevated TSH
- Continue pembrolizumab, nivolumab, or ipilimumab
- Repeat TFTs in 4–6 weeks

Asymptomatic, subclinical hypothyroidism, moderately elevated TSH
- Continue pembrolizumab, nivolumab, or ipilimumab
- May consider monitoring without intervention and repeating levels in 2–4 weeks if asymptomatic
- Consider thyroid replacement
  - Levothyroxine dosage 1.6 mcg per weight (kg) or 75–100 mcg daily
  - Repeat TSH in 4–6 weeks and titrate dose to reference range TSH

Symptomatic, primary clinical hypothyroidism
- Continue pembrolizumab, nivolumab, or ipilimumab
- Consider co-management with endocrinologist
- Initiate thyroid replacement therapy
  - Levothyroxine dosage 1.6 mcg per weight (kg) or 75–100 mcg daily
  - Repeat TSH in 4–6 weeks and titrate dose to reference range TSH
- Monitor AM cortisol level to exclude concomitant adrenal insufficiency

Severe or life-threatening primary clinical hypothyroidism (myxedema)
- Continue pembrolizumab, nivolumab, or ipilimumab
- Obtain endocrine consultation and/or emergency in-patient care (as needed for mental status changes and/or if patient comatose)
- Laboratory assessment: cell count, electrolytes, glucose, thyroid function, liver function tests, cortisol, blood gas, cardiac workup
- Care may include hemodynamic support, warming blankets, intravenous thyroid replacement, glucose supplementation, antibiotics if needed
- Post acute care, TSH will be monitored with dose titration; educate patients about how to take the medication properly and precipitating factors for myxedema coma

HYPERTHYROIDISM

Asymptomatic hyperthyroidism; clinical or diagnostic observation only
- Continue pembrolizumab, nivolumab, or ipilimumab
- Standard therapy for hyperthyroidism (methimazole treatment)

Symptomatic and severely symptomatic hyperthyroidism
- For symptomatic hyperthyroidism: continue pembrolizumab, nivolumab, or ipilimumab
- For severe symptomatic hyperthyroidism: hold pembrolizumab, nivolumab, or ipilimumab
- Consider collaborative management with endocrinologist
- Consider measuring anti-thyroid antibodies and/or TSH-receptor autoantibodies (TRAB) to establish autoimmune etiology
- If patient has not received IV iodinated contrast within 2 months, can consider a diagnostic thyroid uptake & scan to determine if patient is truly hyperthyroid with Graves-like etiology
- Acute thyroiditis usually resolves or progresses to hypothyroidism; thus, can repeat TFTs in 4–6 weeks
- If TRAB high, obtain a thyroid uptake scan & collaborate with endocrinologist
- Short period of 1 mg/kg prednisone* or equivalent may be helpful in acute thyroiditis
- Work collaboratively with the endocrinologist for management
- Consider use of beta blockers and immunotherapy hold for symptomatic patients (e.g., beta blockers for tachycardia/murmur and immunotherapy holds for patients who have acute thyroiditis threatening an airway)
- Therapy is often restarted when symptoms are mild/tolerable

Life-threatening symptomatic hyperthyroidism (thyroid storm)
- Discontinue nivolumab, pembrolizumab, or ipilimumab
- Hospitalization; in-patient, intensive care management
- Thyroid-suppressive therapy to be provided
- Anticipate cooling measures, fluid resuscitation, electrolyte replacement, nutritional support
- Antipyretics, management of tachyarrhythmia
- Ventilatory support if needed–agitation to be managed carefully to avoid respiratory depression

*Administering Corticosteroids:

Steroid taper instructions/calendar as a guide but not an absolute
- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need & symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down & report them (taper may need to be adjusted)

Long-term high-dose steroids:
- Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1500 mg po daily)
- Consider additional antiviral and antifungal coverage
- Avoid alcohol/acetaminophen or other hepatoxins
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

Implementation:
- Ensure that patient undergoes thyroid function tests prior to first dose, every 12 weeks while on PD-1 therapy and q3 weeks with ipilimumab and periodically in follow-up
- Educate patient that hypothyroidism is generally not reversible
  - Assess patient & 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
- Explain that history of thyroid disorders does not increase or decrease risk of thyroiditis
- Consider reducing starting dose of thyroid hormone supplementation to avoid hyperthyroidism in sensitive patients (e.g., elderly patients, those with comorbidities)
- 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 oestradiol (women) and testosterone (men). An MRI of the pituitary should be considered if there is confirmed central thyroid/adrenal insufficiency

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; FSH = follicle-stimulating hormone; 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