Evaluation and Management of Suspected Immune-Mediated Endocrine Toxicities

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*

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THYROID DYSFUNCTION

PRESENTATION

Patient presents with new onset symptoms of hyperthyroidism[1], hypothyroidism[2], or abnormal TSH, free T4, or total T3 levels 1 week after immune checkpoint inhibitor (ICI)[3] initiation and up to 12 months after initiation. Majority of cases occur within 15 weeks.

ASSESSMENT

Check TSH, free T4, and total T3 levels per package insert or with every cycle[4]

- TSH low with high T4 or T3
- TSH high with normal or low T4 or T3
- TSH low/normal with low T4 or T3

TREATMENT

TSH low with high T4 or T3

Thyrotoxicosis:
- Rule out adrenal insufficiency[5] if patient is symptomatic[6]
- Endocrinology consult/referral
- Beta blockers, if symptomatic[1]
- Hold ICI if CTCAE[7] grade 3+ or Graves' disease
- Follow TSH and free T4 every cycle

Thyrotoxicosis persists for > 6 weeks or severe symptoms[1]?

- Yes → Assess for Graves' disease[8] versus thyroiditis[9]
  - Check total T3, TSH receptor Ab, and TSI
  - I-123/Tc uptake and scan[10]
  - Graves' disease → Hold ICI until hyperthyroidism is controlled; Endocrinology evaluation to initiate methimazole; Consider definitive therapy with radioactive iodine or surgery if indicated
  - Thyroiditis → Monitor for development of hypothyroidism with TSH and free T4 every 2-6 weeks or with every cycle for the next 3-4 months
- No → Monitor for development of hypothyroidism with TSH and free T4 every 2-6 weeks or with every cycle for the next 3-4 months

Labs consistent with primary hypothyroidism?

- Yes → Primary hypothyroidism: Start levothyroxine treatment[11]
- No → Resume routine thyroid function tests monitoring per package insert or with every cycle; Resume ICI if previously held

TSH high with normal or low T4 or T3

Primary hypothyroidism:
- Rule out adrenal insufficiency if patient is symptomatic[6] prior to starting thyroid hormone therapy
- If TSH > 10 mU/L, start levothyroxine per standard guidelines[11]
- Adjust dose every 6 weeks

TSH low/normal with low T4 or T3

Central hypothyroidism:
- Evaluate for hypophysitis, see Page 3
- Endocrinology consult/referral

TSH = thyroid simulating hormone
TSI = thyroid stimulating immunoglobulin

[1] Symptoms include palpitations, tachycardia or tremors
[2] Symptoms fatigue, weight gain, or cold intolerance
[3] PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA-4 inhibitor (ipilimumab)
[4] Consider ongoing monitoring for thyroid dysfunction after patient completes ICI therapy for every 3 months up to 1 year, and annually thereafter
[5] Check for normal morning adrenocorticotropic hormone (ACTH) and cortisol
[6] Symptoms include sever fatigue or low appetite or low blood pressure
[7] Refer to Appendix A for Common Terminology Criteria for Adverse Events (CTCAE)
[8] Positive TSH receptor antibodies/TSI and/or high uptake on I-123/Tc scan
[9] Negative TSH receptor antibodies/TSI and/or low/normal uptake on I-123/Tc scan
[10] Low or normal uptake indicates thyroiditis. High uptake is usually seen with Graves' disease or hot nodule. Uptake scan is contraindicated if IV contrast within 2 months or patient is on amiodarone.
[11] Start levothyroxine at 1.2-1.6 mcg/kg/day in young or healthy patients. For patients age > 60, or those with known heart disease, consider starting at 50 mcg daily and titrate dose based on response

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HYPOPHYSITIS PRESENTATION

After immune checkpoint inhibitor (ICI)[1] initiation:

- Patient presents with new onset of headache, sinus pressure, fatigue **or**
- Patient is asymptomatic **and** has incidental laboratory findings **or** MRI findings concerning for hypophysitis
- Incidental findings consist of any the following:
  - Low T4 with low/normal TSH
  - Low ACTH level with normal or low cortisol
  - MRI findings consistent with hypophysitis

ASSESSMENT

Severe of life-threatening symptoms[2] or adrenal crisis?

Yes

- Hold ICI
- Admit to Acute Cancer Care Center (ACCC) or transfer to local Emergency Department
- Draw urgent labs[3]

No

- Urgent Endocrinology consult with provider-to-provider communication
- Check labs if not already done: TSH, free T4 and total T3, ACTH, and cortisol
- MRI pituitary with and without contrast
- Check testosterone, FSH, and LH in men, and estrogen levels, and FSH, LH in premenopausal women

ACTH or TSH deficiency[4] plus MRI findings **or** ACTH and TSH deficiencies[4] plus symptoms (headache and fatigue) in the absence of MRI?

No → Hypophysitis not confirmed: Further evaluation by Endocrinology

Yes

Hypophysitis confirmed:
Hold ICI until acute symptoms resolve and patient is started on stable replacement doses of hormones (physiological doses of steroids and/or thyroid hormone)

TREATMENT

Acute management of adrenal crises with IVFs and high dose steroids as follows:

- Infuse 2-3 liters of 0.9% normal saline (NS) or 5% dextrose in isotonic saline (D5NS) as quickly as possible. Ensure frequent hemodynamic monitoring.
- Hydrocortisone 100 mg IV for 1 dose, then 50 mg IV every 6-8 hours for 24 hours

Severe headache or vision changes?

Yes → Start high dose steroids: Methylprednisolone 1 mg/kg/day IV until symptoms improve, then taper over 4-6 weeks

No → Replace deficient hormones:

- Physiologic hydrocortisone replacement orally[5]
- Levothyroxine replacement
- Reassess testosterone/estradiol at follow-up[6]
- Resume ICI when patient is asymptomatic and on stable doses of hydrocortisone

ACTH = adrenocorticotropic hormone
FSH = follicle-stimulating hormone
LH = luteinizing hormone
TSH = thyroid simulating hormone

[1] CTLA-4 inhibitor (ipilimumab) single agent or in combination with other systemic anticancer therapies
[2] Severe or life-threatening symptoms include hypotension, persistent nausea/vomiting, extreme fatigue, hyponatremia
[3] Blood draw for ACTH, cortisol, TSH, total T3, Free T4 need to be done BEFORE administration of high dose steroids. Cortisol assay will not be reliable if patient has received most steroids (hydrocortisone, prednisone, methylprednisolone).
[4] ACTH deficiency: low cortisol with low or normal ACTH. TSH deficiency: low free T4 with low or normal TSH
[5] Hydrocortisone 10 mg/m^2 BSA per day (in general, 15 mg in the morning and 5 mg at 3 PM)
[6] Treatment of testosterone and estrogen deficiencies based on clinical indications

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DIABETES/NEW ONSET HYPERGLYCEMIA

PRESENTATION

Patient without history of diabetes presents with new onset grade 2[1] hyperglycemia **or** patient with type 2 diabetes (T2DM) presents with worsening glucose control[2] after immune checkpoint inhibitor (ICI)[3] initiation and up to 12 months after last dose of ICI

ASSESSMENT

- Check BMP, glucose, and C-peptide levels
- Check urinalysis (UA) for ketones

Laboratory findings consistent with DKA[4]?

Yes
- Admit to Acute Cancer Care Center (ACCC) or transfer to local Emergency Department for further management[5]
- Hold ICI until on stable basal/bolus insulin therapy

No

Does the patient have a known diagnosis of T2DM?

Yes

Is C-peptide < 1 ng/mL?

Yes

A

Urgent Endocrinology-Diabetes consult[6]

Concern for T1DM[7]?

Yes
- Hold ICI
- Start a basal/bolus insulin therapy
- Check antibodies[8]
- Diabetes education

- Reassess C-peptide and glucose levels in 4-6 weeks
- Resume ICI once stable on insulin therapy
- Continue diabetes education and insulin dose adjustments

No

B
- Progressive T2DM
- Intensify diabetes regimen, as indicated
- Continue ICI

No

- Routine Endocrinology-Diabetes consult/referral
- Intensify diabetes regimen
- Continue ICI

Is patient still having glucose values > 250 mg/dL after 2 weeks of intensifying regimen?

Yes — See box A on this page

No — See box B on this page

No

Urgent Endocrinology-Diabetes consult[6]

TREATMENT

BMP = basic metabolic panel
CTCAE = Common Terminology Criteria for Adverse Events
DKA = diabetic ketoacidosis
EDKA = euglycemic diabetic ketoacidosis
HHS = hyperosmolar hyperglycemic state
SGLT-2 = sodium-glucose cotransporter-2
T1DM = type 1 diabetes

[1] Grade 2 hyperglycemia as defined by CTCAE as fasting glucose more than 160-250 mg/dL
[2] Worsening glycemic control is defined as change in baseline control of diabetes prior to initiation of ICI with glucose values consistently above 250 mg/dL despite compliance with medication regimen
[3] PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA-4 inhibitor (ipilimumab)
[4] Labs suggestive of DKA: blood glucose > 250 mg/dL, anion gap > 14, arterial pH < 7.3 or bicarbonate < 18 mEq/L, and moderate ketonuria or ketonemia [Note: Blood glucose may be lower than expected in patients on SGLT-2 inhibitors (e.g., empagliflozin, canagliflozin)]
[5] If admitted to MD Anderson, treat according to Hyperglycemic Emergency Management (DKA/HHS/EDKA) algorithm. For patients at outside facilities, direct communication with the admitting service is needed to ensure the patient is discharged on basal/bolus insulin therapy is recommended.
[6] If outpatient page "Endocrinology-Diabetes Consult-Outpt" on the On-Call Calendar for a same day diabetes consultation
[7] Based on clinical judgement, but new onset diabetes, dramatic worsening, and low or inappropriately normal c-peptide levels are suggestive
[8] Glutamic acid dehydrogenase-65 (GAD65) antibody, islet antigen-2 antibody, anti-insulin antibody, and zinc transporter 8 antibodies

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APPENDIX A: Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

Endocrine Disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Adrenal insufficiency A disorder characterized by the adrenal cortex not producing enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypophysitis A disorder characterized by inflammation and cellular infiltration of the pituitary gland.	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Hyperthyroidism A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypothyroidism A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Metabolism and Nutrition Disorders					
Hyperglycemia A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral anti-glycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

SUGGESTED READINGS

Thompson, J. A., Schneider, B. J., Brahmer, J., Andrews, S., Armand, P., Bhatia, S., . . . Engh, A. (2020). NCCN Guidelines Insights: Management of immunotherapy-related toxicities, Version 1.2020. *Journal of the National Comprehensive Cancer Network, 18*(3), 230-241. https://doi.org/10.6004/jnccn.2020.0012

Thyroid Dysfunction

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