ASSESSMENT AND MANAGEMENT OF IMMUNE-RELATED ENDOCRINE EMERGENCIES

NOTE: Endocrine adverse events related to immunotherapy are generally not reversible.

Screening and monitoring for endocrine immune-related adverse events

Evaluate the following at <u>baseline, every 4-6 weeks</u> on immunotherapy, <u>4-6 weeks after last cycle</u> and <u>for at least 1 year after treatment discontinuation</u>:

Laboratory tests:

- Cortisol (AM)*†
- TSH*
- Free T4
- Electrolytes
- Glucose

NOTE: Only screen gonadotropins and sex hormones if symptoms arise

*When not on high-dose glucocorticosteroids as these inhibit ACTH and cortisol and ↓ TSH levels.
† Some clinicians only do ACTH once adrenal insufficiency (AI) is suspected to determine if AI is primary or secondary.

Clinical evaluation for symptoms:

- Weakness
- Fatigue
- Unusual headache pattern
- Vision changes
- Hypotension
- Increased sweating
- Heat intolerance
- Rapid heartbeat
- Weight loss or gain
- Extreme or low hunger
- Constipation or diarrhea
- Deepening of the voice
- Changes in urination
- Polydipsia
- Polyuria
- Nausea or vomiting
- Abdominal pain

Take a menstrual history in premenopausal women

For the following potential endocrine emergencies:

⚠ Refer to endocrinology | **☑ CONTINUE immunotherapy if asymptomatic** | **HOLD if symptomatic until symptoms resolve and/or appropriate therapy (if indicated) is initiated**

Hypophysitis

Assessment / Dx

Suspect if:

↓ TSH and ↓ free T4 * and/or ↓ cortisol
↓ ACTH* ↓ Na+
Or other pituitary hormone abnormalities

Order:

✓ Brain MRI ± contrast with pituitary/sellar cuts if symptomatic

*If ACTH is high, primary adrenal insufficiency (AI) should be suspected. Refer to endocrinology to confirm the dx. Patients with primary AI may require fludrocortisone in addition to hydrocortisone.

Management

RECHALLENGE: After hormone repletion

✓ **Treat with hormone replacement therapy as indicated:**

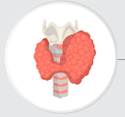
- *Adrenal insufficiency:*
  - → Initiate **hydrocortisone†** 15-30 mg/d in 2-3 split p.o. doses
  - → Patient education on stress dosing and recommend medical alert bracelet
- *Hypothyroidism:*
  - → Initiate **levothyroxine after replacement of glucocorticoids**
    - Start with 1.6 µg/kg/d (use lower doses in elderly/frail patients or in those with severe cardiac disease)
    - Repeat TSH in 4-6 weeks to guide dosing
- *Hypogonadism:*
  - → Consider testosterone (males), estrogen (pre-menopausal women) and progesterone (if patient still has uterus) replacement if needed and not contraindicated

✓ **Consider prednisone ONLY IF SEVERE acute symptoms with PITUITARY mass effect:**

- **1-2 mg/kg/d** until symptoms resolve (1-2 weeks) followed by rapid taper to physiologic replacement

†Hydrocortisone is preferred as it allows for recreation of the diurnal rhythm of cortisol. Longer-acting steroids, such as prednisone, carry risk of over replacement but can be used in certain circumstances. See Glucocorticoid Comparison Chart for equivalencies.

Hyperthyroidism



Assessment / Dx

Suspect if:

↓ TSH ↑ Free T4*

*T3 can be helpful in highly symptomatic patients with minimal free T4 elevations

If severe/persistent symptoms and/or suspicion of Graves' disease:

✓ Consider TSH receptor antibodies and pertechnetate scan to assess for Graves' disease

Management

RECHALLENGE: After symptom resolution

✓ **Consider beta-blocker for symptom relief**

- E.g., propranolol 10-20 mg every 4-6 h as needed

✓ **Thyroiditis usually resolves or evolves to hypothyroidism requiring levothyroxine**

✓ **Repeat TFTs in 4-6 weeks**

- If resolved, no further therapy required
- If persistent, consider further evaluation/management for Graves' disease
  - → Treat with methimazole or PTU, beta-blocker

✓ **If signs of thyroid storm:**

- Urgent endocrinology consult and admission to ICU

Signs and Symptoms of Graves' Disease:

- Diarrhea
- Enlarged thyroid
- Ophthalmopathy
- Tachycardia
- Fatigue
- Heat intolerance/flushing
- Difficulty sleeping
- Hand tremors
- Muscle weakness
- Unexplained weight loss

Autoimmune Diabetes

Assessment / Dx

Suspect if:

✓ Fasting glucose >7 mmol/L
✓ Random glucose >11.1 mmol/L

Investigate for DKA:

✓ Urine and/or serum ketones
✓ Anion gap on metabolic panel
✓ Blood pH
✓ A1C

Note: Endocrinologist to consider ordering anti-GAD or anti-islet cell antibodies and C-peptide levels

Management

RECHALLENGE: Once glucose controlled and insulin initiated

✓ **If severe symptoms or DKA:**

- Admit for inpatient management → will require insulin

✓ **If mild to moderate symptoms:**

- Collaborate with endocrinologist, internist or family physician to start insulin as per local expertise
- Refer to diabetes clinic

✓ **Initiate supportive measures:**

- Hydration
- Correction of electrolytes

Signs and Symptoms of DKA:

- Excessive thirst
- Frequent urination
- General weakness
- Vomiting
- Confusion
- Abdominal pain
- Dry skin
- Dry mouth
- Increased heart rate
- Fruity odour on breath

Glucocorticoid Comparison Chart

	Equivalent glucocorticoid dose (mg)	Potency relative to hydrocortisone		Duration of action (hours)
		Anti-inflammatory	Mineralocorticoid	
Glucocorticoids				
Short acting				
Hydrtocortisone (cortisol)	20	1	1	8 to 12
Cortisone acetate	25	0.8	0.8	8 to 12
Intermediate acting				
Prednisone	5	4	0.8	12 to 36
Prednisolone	5	4	0.8	12 to 36
Methylprednisolone	4	5	0.5	12 to 36
Long acting				
Dexamethasone	0.75	30	0	36 to 72
Betamethasone	0.6	30	0	36 to 72
Mineralocorticoids				
Fludrocortisone	0	15	150	12 to 36

Adapted from UpToDate. Available at: https://www.uptodate.com/contents/image/print?imageKey=ENDO%2F64138&topicKey=ANEST%2F94256&source=outline Accessed February 8, 2022.

Acronyms: A1C, glycated hemoglobin; ACTH, adrenocorticotropic hormone; DKA, diabetic ketoacidosis; Dx, diagnosis; FSH, follicle-stimulating hormone; GAD, glutamic acid decarboxylase; ICU, intensive care unit; LH, luteinizing hormone; MRI, magnetic resonance imaging; Na+, sodium; PTU, propylthiouracil; TFTs, thyroid function tests; TSH, thyroid stimulating hormone

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