Adrenal Insufficiency, primary (a disorder in which the adrenal cortex does not produce enough cortisol, and in some cases, aldosterone, which is caused directly by adrenal inflammation)

Assessment

Look:
Does the patient appear:
- Lethargic?
- Irritable?
- To have lost weight?
- Weak?
- Thinner?
- Sweaty?
- In pain (back, lower legs, abdomen, head)?
- Syncopal?
- Dry skin?
- Cold?
- Forgetful?
- Confused/disoriented

Listen:
- Fatigue
- Weakness
- Hot or cold sensation
- Loss of appetite
- Abdominal pain
- Nausea/vomiting
- Diarrhea
- Faint/dizzy when standing
- Recurrent or severe headaches
- Irregular menstruation (women)
- Loss of libido
- Skin changes: dry, darkening
- Fever
- Persistent or worsening forgetfulness

Recognize:
- AM cortisol
- AM ACTH
- Primary vs secondary adrenal insufficiency (AI)
  - Primary AI: A low morning cortisol (<5 mcg/dL) plus a high ACTH with or without abnormal electrolyte levels and symptoms (other criteria: 30–60-minute cortisol <18 mcg/dL after ACTH stimulation (“cort stim”) with above findings)
  - Secondary AI: low morning cortisol plus a low ACTH level (on ACTH stimulation test)
  - Consider standard dose ACTH stimulation for indeterminate results (AM cortisol < 3 mcg/dL & < 15 mcg/dL)
  - High plasma renin activity (primary) vs normal (secondary)
- Hyponatremia + hyperkalemia is suggestive of primary AI and mineralocorticoid deficiency
- Orthostatic hypotension
- Fever, which may precipitate adrenal crisis
- Symptoms and laboratory findings of adrenal crisis

Grading Toxicity

Primary Adrenal Insufficiency

Grade 1 (Mild)
Asymptomatic; clinical or diagnostic observations only

Grade 2 (Moderate)
Moderate symptoms (able to perform activities of daily living)

Grade 3 (Severe)
Hospitalization indicated

Grade 4 (Life-Threatening)
Urgent intervention indicated

Grade 5 (Death)

Management

Grade 1 (Mild)
- Consider holding ICI therapy until patient is stabilized on replacement hormone
- Consider endocrine consult
- Hydrocortisone (15-20 mg in divided doses [generally 2/3 of the dose in the AM, and 1/3 in the early afternoon] then slowly titrate to lowest dose possible to normalize laboratory values and maintain quality of life) OR prednisone 5-to 10-mg starting dose*
- Consider fludrocortisone, 0.05–0.1mg/day adjust based on volume status, Na+ level and renin response
- Patient education regarding adrenal crisis and requirements for stress doses of corticosteroids

Grade 2 (Moderate)
- Consider holding ICI therapy until patient is stabilized on replacement hormone
- Obtain endocrine consultation
- See in clinic to assess need for hydration, supportive care, and hospitalization
- Initiate outpatient corticosteroid treatment at 2-3 times maintenance (eg, hydrocortisone 30-50 mg total dose or prednisone 20 mg daily) to manage acute symptoms
- Initiate fludrocortisone (0.05-0.1 mg/d)
- Decrease stress-dose corticosteroids down to maintenance doses after 2 days
- Maintenance therapy as in Grade 1
- Patient education regarding adrenal crisis and requirements for stress doses of corticosteroids (if acutely ill, may need to double or triple dose for first 24-48 hours)
- Resume ICI therapy in patients who are no longer symptomatic (Grade 0 to 1)

Grades 3/4 (Severe or Life-Threatening)
- Hold ICI therapy until patient is stabilized on replacement hormone
- Obtain endocrine consultation
- Inpatient management may be needed to provide
  - Normal saline (at least 2L)
  - IV stress-dose steroids (Hydrocortisone 50-100 mg Q 6-8 hours initial dosing)
- Taper stress-dose corticosteroids down to oral maintenance doses over 5-7 days
- Maintenance therapy as in Grade 1
- If not permanently discontinued, resume ICI therapy in patients who are no longer symptomatic (Grade 0 to 1)

Implementation:
- CAUTION: Start corticosteroid first before any other hormone replacement to avoid adrenal crisis as thyroid supplementation increases metabolism of cortisol
- Monitor prior to each dose and check ACTH as indicated based on labs or symptoms
- Rule out other potential causes of primary adrenal insufficiency including infection (TB), adrenal metastases or adrenal hemorrhage, amyloidosis, medications (antifungals), or recent prolonged use of exogenous corticosteroids
- Consider endocrinology referral
- Endocrinology (with reinforcement by the oncology care team) to provide patient/caregiver education regarding:
  - Potential lifelong requirement of replacement steroids (hydrocortisone +/- fludrocortisone)
  - Need for stress dosing for sick days, training on the use of emergency injectables, when to seek medical attention for impending adrenal crisis, and importance of obtaining and wearing a medical alert bracelet or necklace to trigger stress dose corticosteroids by emergency medical personnel

RED FLAGS:
Adrenal crisis:
- **Sudden severe pain in the lower back, abdomen, and legs**
- **Severe weakness**
- **Severe vomiting and diarrhea**
- **Severe hypotension**
- **Severe dehydration**
- **Confusion, delirium**
- **Loss of consciousness**

ACTH = adrenocorticotropic hormone; ICI = immune checkpoint inhibitor; po = by mouth