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

Assessment

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

Listen:
- Fatigue
- Weakness
- Feeling cold all the time
- Loss of appetite
- Abdominal pain
- Nausea/vomiting
- Diarrhea
- Faint/dizzy when standing
- Mood change (irritable/depressed)
- Craving salty food
- Recurrent or severe headaches
- Irregular menstruation (women)
- Loss of libido
- Skin changes: dry, darkening
- Fever
- Persistent or worsening forgetfulness

Recognise:
- AM cortisol, ACTH stimulation test
- 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 with above findings)
  - Secondary AI: **low** morning cortisol plus **low or delayed** ACTH levels (on ACTH stimulation test)
  - High plasma renin activity (primary) vs normal (secondary)
- Hyponatremia, hyperkalemia, hypoglycemia, hypercalcemia
- Orthostatic hypotension
- Imaging of adrenal and pituitary glands consistent with primary vs secondary adrenal insufficiency
- Fever, which may precipitate adrenal crisis
- Symptoms and laboratory findings of adrenal crisis

Grading Toxicity

<u>Primary Adrenal Insufficiency</u>

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

Grade 2 (Moderate)
Moderate symptoms

Grade 3 (Severe)
Hospitalization indicated

Grade 4 (Life-Threatening)
Urgent intervention indicated

Grade 5 (Death)

Management

Grade 1 (Mild)
- Continue pembrolizumab, nivolumab, or ipilimumab
- Fludrocortisone 0.1 mg every other day
- Advise a high sodium diet and adequate calcium/vitamin D intake
- Patient education regarding adrenal crisis and requirements for stress doses of corticosteroids*

Grade 2 (Moderate)
- Withhold pembrolizumab, nivolumab, or ipilimumab
- Administer replacement therapy (corticosteroid therapy such as prednisolone 1 mg/kg/day or equivalent/day until asymptomatic, then continue with physiologic dose in consultation with endocrinologist)
- Advise a high sodium diet and adequate calcium/vitamin D intake
- 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 checkpoint inhibitors in patients who are no longer symptomatic (Grade 0 to 1)

Grades 3/4 (Severe or Life-Threatening)
- Withhold checkpoint inhibitors for Grade 3 and withhold or consider permanent discontinuation for Grade 4
- Patients require hospitalization and potentially intensive care under the guidance of an endocrinologist
- For Grade 3, double or triple oral corticosteroid doses should be initiated for 24-48 hours
- For Grade 4, high-dose steroids should be started immediately (hydrocortisone 100 mg iv immediately followed by hydrocortisone 200 mg/d as a continuous infusion for 24 h, reduced to hydrocortisone 100 mg/d the following day)
- If hemodynamically unstable, may require additional fluids (e.g., rapid infusion of 1000 mL isotonic saline [or more if needed within the first hour] or 5% glucose in isotonic saline, followed by continuous iv isotonic saline guided by individual patient needs)
- Tapering of stress doses of corticosteroids to more physiologic dosing under the guidance of the endocrinologist
- If not permanently discontinued, resume checkpoint inhibitors 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
- Monitor clinical chemistries prior to each dose and check ACTH as indicated based on labs or symptoms
- Consider endocrinology referral
- Rule out other potential causes of primary adrenal insufficiency including infection (TB), adrenal metastases, amyloidosis, medications (antifungals), or inadequate tapering of corticosteroids
- Provide patient/caregiver education regarding:
  - Understanding that the corticosteroids are for physiologic replacement and will be continued indefinitely
  - **Need for stress doses of corticosteroids for surgery, severe injury, or illness**
  - Importance of wearing a medical alert bracelet and carrying corticosteroids at all times in case of adrenal crisis (as well as knowledge of how to administer)

*Administering Corticosteroids:

<u>Steroid taper instructions/calendar as a guide but not an absolute</u>
- 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)

<u>Long-term high-dose steroids</u>:
- Consider antimicrobial prophylaxis
- 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

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; po = by mouth