

Endocrine Toxicities

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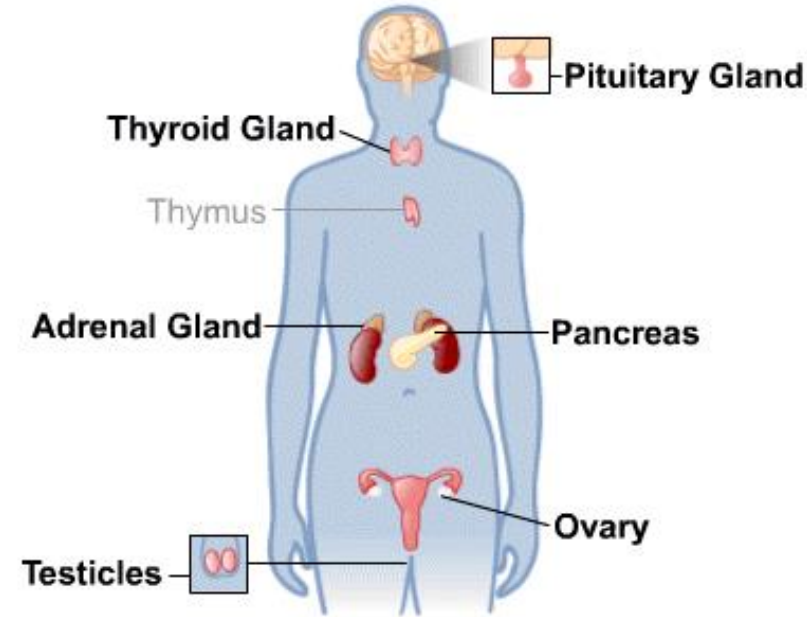
Mass General Cancer Center

Disclosures

- None

Endocrinopathies

- Occurs in 10-40% of patients receiving ICI
- Can present with symptoms of hormone deficiency, hormone excess or both
- Spectrum of clinical presentations ranges from no symptoms to severe life-threatening symptoms
 - Often vague and overlap with common cancer related symptoms



Endocrinopathies

Differ from other irAEs

- Use of high dose steroids do not appear to decrease the severity or duration
- Generally, do not require discontinuing ICI
- Management is based around replacement of the underlying deficiency
- Tend to result in chronic conditions and require lifelong therapies

Pituitary

Hypophysitis

Case

- 71M with stage M1c melanoma s/p 4 cycles ipi + nivo c/b mild rash/pruritus managed conservatively
- 3 days after receiving C4, he reported mild nausea and a “wicked” headache
- Had been started on metformin for hyperglycemia; attributed to med. Held for a few days with improvement, but persistent H/A, and now notable fatigue, loss of appetite, general malaise
- Labs and bMRI arrange

Component	Ref Range	11/23	12/14	12/21
TSH	0.40 - 5.00 uIU/mL	1.25	0.07	0.09
ft4	0.9 - 1.8 ng/dL		1.1	1.1
T3	60 - 181 ng/dL		75	84
Testosterone, Total	249 - 836 ng/dL			<12
Cortisol	Ug/dL			1.0
NA	134 - 145 mmol/L	132	133	129
K	3.4 - 5.0 mmol/L	4.3	4.5	4.2
Creat	0.60 - 1.50mg/dL	0.87	1.07	1.11

Labs and sx suggestive of hypophysitis; he was started on 10mg prednisone

- H/A nearly resolved after 1 dose of prednisone
- Pituitary MRI revealed new diffuse gland enlargement with heterogeneous enhancement compared to a pre-tx MRI
- Prednisone reduced to 5mg once daily, referred to Endocrine

Hypophysitis

- Immune mediated inflammation of the pituitary gland
- Incidence
 - anti-CTLA-4: 1.8 - 18%
 - anti-PD-1/PD-L1: 0.3 - 1.2%
 - anti-CTLA-4 + PD-1/PD-L1: 7 - 10%
- Median onset: 12 weeks (3-76w)
 - hypophysitis due to PD-1/ PD-L1 tends to occur later than in CTLA-4 and is more likely to involve a single hormonal axis

Hypophysitis

- Typically involves the anterior pituitary
- Clinical s/sx are the result of:
 - Primary hormone deficiencies, (most commonly TSH, followed by ACTH)
 - Fatigue (59-73%)
 - Nausea
 - Anorexia
 - Mass effect of the pituitary gland
 - Headache (32-87%)
 - Rarely, visual field defects

Pituitary

Evaluation:

- Baseline screening is controversial
- Labs
 - AM cortisol & ACTH, TSH, fT4, electrolytes
 - Consider LH and testosterone in males and estrogen in symptomatic females
 - Cort-stim for indeterminate results (AM cortisol > 3 and < 15)
 - *Progressive decline in TSH may be indicative of developing pituitary dysfunction*
- Medication reconciliation
 - Opioids, megestrol acetate can affect pituitary function
- Imaging
 - Brain MRI (pituitary protocol) in all patient with new hormonal deficiencies, severe H/A, or vision changes
 - Need to R/O brain metastases
 - Only ½ will see radiologic signs on

Management

- Continue ICI (or temporary hold)
- Replacement of affected hormone(s) due to secondary hypothyroidism or secondary adrenal insufficiency
- High doses of steroids are not necessary and have been associated with worse outcomes
 - Short course may be necessary for those sx from mass effect
- Monitor thyroid function with fT4 for those with central hypothyroidism (↓ TSH, ↓ fT4)

Case- summary

- Diagnosis
 - Hypophysitis
 - TFTs showed mild thyrotoxicosis which resolved without LT4 tx
 - Testosterone level improved to low normal
- Plan
 - 5mg prednisone daily
- Outcome
 - Completed two year of immunotherapy with near CR
- Education
 - Sick day dosing
 - Vigilance monitoring for additional irAEs
 - Likely lifelong replacement

Case

- 85 active male, w/ metastatic cuSCC s/p 4 cycles pembrolizumab 400mg with near CR
- 2 mo after treatment completion he underwent a rather extensive outpatient procedure to excise another SCC- requiring skin graft.
- Shortly thereafter developed weakness, malaise, decreased appetite- big change from baseline.
- Presented to local ED: evaluation unrevealing, received IVH, felt better, D/C home
- Syncopal event the next day with increased lethargy and confusion. anorexia. Family called EMS. Hypotensive on arrival to ED.
- Received IVH, empiric IV abx for possible UTI. Some improvement while hospitalized. D/C home with PT/OT.

- Family contacted office to report events, Given ongoing poor PS and such a change from baseline, suspicion for endocrine tox, specifically AI, either primary or central.
- Random cortisol low. ACTH obtained but pending.
- Empirically started on 10mg prednisone with dramatic and rapid improvement in symptoms.
- Referred for formal endocrine consult; cort stim and pituitary MRI to confirm diagnosis
 - Cort stim: 0.5, 1.9, 3.0
 - ACTH undetectable
 - Pituitary MRI 7/31/23 appears normal and w/o an obvious change from prior head CT

Case - summary

- Diagnosis
 - Adrenal Insufficiency
 - Testing of other axes normal: testosterone, prolactin, IGF-1, TSH/FT4.
- Plan
 - 10mg prednisone daily; later reduced to 5mg daily
- Outcome
 - Ongoing near CR
 - Repeat cort stim in ~ 6 months
- Education
 - Sick day dosing
 - Vigilance monitoring for additional irAEs
 - Likely lifelong replacement

Education

Stress dosing: patient AND caregiver(s)

- Sick days Periop / dental procedures
- Medical alert bracelet/necklace
- Adrenal crisis
- Use of emergency steroid injectables (IM hydrocort)

Guidelines for Stress Dosing & Sick Day Management

KEEP THIS GUIDE HANDY AND REVIEW REGULARLY

Healthy adrenal glands are able to release extra cortisol into the bloodstream when needed, helping the body cope with the demands of extreme physical and mental stress. People with adrenal insufficiency may need to take extra cortisol in addition to their daily doses when they are sick, injured, before surgery or when experiencing physical or emotional stress. This is called stress dosing or sick day dosing.

Keep the following stress dosing guidelines handy and review them regularly. With time, you will learn your own individual needs in various situations.

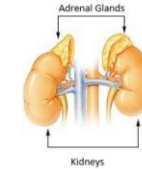
Stress	
Mild injury Exhausting, strenuous physical exercise if a person is not used to it (e.g. hiking, mountain climbing for several hours)	Some individuals take a small dose of hydrocortisone for these events, but it is not universally required. The precise dosing is not known, but it should not exceed 4-10mg hydrocortisone*.
Minor emotional or mental stress (eg. before an important exam)	
Major emotional or mental stress (eg. death of a close relative, witnessing a traumatic event)	Take an additional daily dose
Infection / Fever Note: Infections are the most frequent cause of adrenal crisis, including gastroenteritis. Maintain the extra doses until recovery, then return to the standard doses within 1-2 days.	
Fever of more than 38°C / 100.4°F	Double normal daily dose(s)
Fever of more than 39°C / 102.2°F	Triple normal daily dose(s)
Severe infections (eg. pneumonia)	If you are diagnosed with a severe infection, a hospital admission may be required and your doctor will initiate treatment or advise you how to stress-dose. The recommendations are: Initial 100mg hydrocortisone injection (by a physician) IV* Followed by 50mg every 6 hours until condition stabilizes, then 2 or 3x normal dose
Vomiting / Diarrhoea Note: Vomiting and diarrhoea pose a particularly high risk as the absorption of hydrocortisone is compromised while the demand for cortisol is increased.	
Any illness that includes vomiting and/or diarrhoea	Triple normal daily dose(s), sip rehydration/electrolyte fluids. If vomiting persists and medication cannot be kept down, use emergency injection kit (100mg MDC hydrocortisone**). Then call a emergency department.
Severe sudden illness or injury Note: Go to the nearest emergency department for hydrocortisone injection and fluids.	
Severe illness or injury	Use emergency injection kit (100 hydrocortisone**). Then call a emergency department.

Adrenal Insufficiency and "Stress Dosing"

Adrenal insufficiency is caused when your adrenal glands don't produce enough hormones. The result is fatigue, weight loss, and other problems. Supplements are used to replace missing hormones. During times of stress, you may need extra supplements, known as "stress dosing."

What are adrenal glands?

Adrenal glands are part of the endocrine system. They produce hormones. You have two adrenal glands, one on top of each kidney.



What is adrenal insufficiency?

Adrenal insufficiency is caused when your adrenal glands don't produce enough stress hormones (such as cortisol). The result is fatigue, weight loss, and other problems.

How do I manage my adrenal insufficiency?

- Take your prescribed dose of cortisol replacement (prednisone, hydrocortisone, or

NADF
National Adrenal Diseases Foundation

For more information please visit www.nadf.us, or contact us at NADFMail@nadf.us or 847-738-9010

Patients who rely on daily oral hydrocortisone replacement often need additional oral hydrocortisone to mimic the body's natural stress response. Stress-dose hydrocortisone may be needed in emergencies or before surgery and must be given intramuscularly (IM), subcutaneously (SC), or intravenously (IV) if vomiting or diarrhea is present to prevent death from adrenal crisis. Causes and symptoms of a potential adrenal crisis can vary among people; please consult your endocrinologist for specific recommendations for your care and go to the nearest emergency department if crisis symptoms are evident.

Adrenal Insufficiency Patient Guide to Management of Illness and Stress-Related Medical Events			
	Event	Sub-Event	Dosage Recommendation*
Home Self-management	Stress with fever	Fever >100.4-102°F	Double hydrocortisone replacement dose until recovery (~2-3 days)
		Fever >102.2°F	Triple hydrocortisone replacement dose until recovery (~2-3 days)
	Circumstantial increased physical and/or emotional stress	Unusual work-related stress, increased travel, overexertion, intensive exercise, positively or negatively emotional stress	Dependent on individual and circumstance, but typically requires extra dose of 5-10 mg based on symptoms; proactively consult with endocrinologist at routine visit
	Dental work	Any	Extra hydrocortisone 10-20 mg can be given a few hours before procedure
Healthcare Practitioner Administered	Unable to tolerate oral medications due to illness or trauma	Local anesthesia	Hydrocortisone 100 mg IM or SC and consider EPR; see NADF Guide to Adrenal Crisis Care Medication Information
	Minor to moderate surgery stress		Hydrocortisone 20-75 mg per 24 hours in addition to maintenance dose (~1-2 days)
	Dental work	General anesthesia	Extra hydrocortisone 50 mg IV before anesthesia
	Unable to tolerate oral medications due to illness or trauma	With dehydration or inability to self-inject IM or SC	Hydrocortisone 100 mg IV
Other	Major surgery or major stress from severe infection, sepsis (hospitalized)		Hydrocortisone 100 mg IV and continuous infusion 200 mg/24 hours
	Cardiac stress test or angiogram		
	Catheterization		
	Chemotherapy		Consult your endocrinologist

*Anytime higher than normal amounts of hydrocortisone are given, a slow taper of hydrocortisone down to your routine dosage is important. Consult your endocrinologist for instructions.

Disclaimer: NADF does not engage in the practice of medicine, is not a medical authority, and does not claim medical knowledge. In all cases, NADF recommends that you consult your own physician regarding any course of treatment or medication.