Dana-Farber Cancer Institute

Adrenal Insufficiency in Breast Cancer Patients

Introduction to Adrenal Insufficiency

Adrenal gland function is regulated by the hypothalamic-pituitary-adrenal (HPA) axis.[1]
There are three types of adrenal insufficiency:

1. Primary

caused by dysfunction of **adrenal glands**.[1]
Characterized by:

- Increased corticotropin-releasing hormone (CRH)
- Increased adrenocorticotropic hormone (ACTH)
- Decreased cortisol
- Decreased dehydroepiandrosterone (DHEA)
- Decreased aldosterone

2. Secondary

caused by dysfunction of **pituitary**.[1]
Characterized by:

- Increased CRH
- Decreased ACTH
- Decreased cortisol
- Decreased DHEA
- Normal aldosterone

3. Tertiary

caused by dysfunction of **hypothalamus**.[1]
Characterized by:

- Decreased CRH
- Decreased ACTH
- Decreased cortisol
- Decreased DHEA
- Normal aldosterone

Causes of Adrenal Insufficiency in Cancer Patients

Secondary adrenal insufficiency can be caused by tumors, including primary intracranial tumors (e.g. pituitary adenoma, craniopharyngioma) or metastases (including from breast cancer).[1]

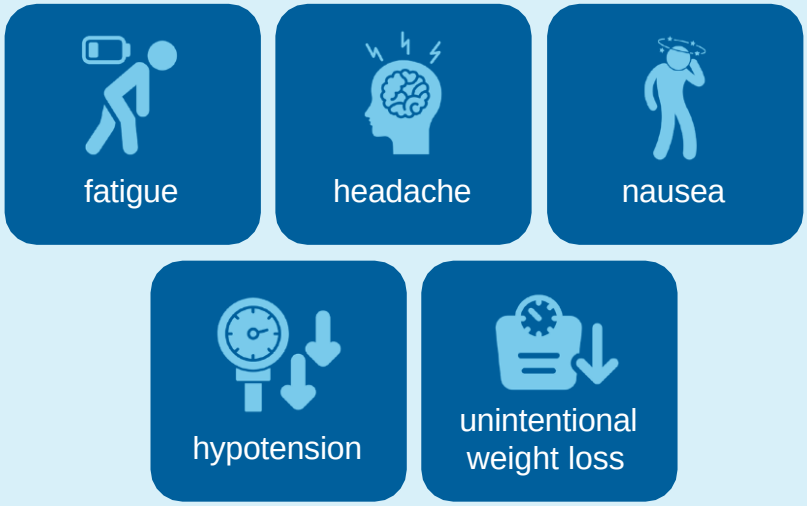
Secondary adrenal insufficiency can also be caused by cancer treatment, including radiation to the brain, systemic therapy (immune checkpoint inhibitors), or other medications (glucocorticoids, opioids).[1]

In a breast cancer patient with adrenal insufficiency, it is crucial to distinguish the cause, whether it is treatment related or caused by metastases to the hypothalamus, pituitary, or adrenal glands.

Immune checkpoint inhibitors can cause endocrine dysfunction, including thyroiditis (both hypothyroidism and hyperthyroidism), hypophysitis, and – very rarely – autoimmune adrenalitis (primary adrenal insufficiency). Hypophysitis can present as secondary adrenal insufficiency.[2]

Diagnosis of Adrenal Insufficiency

Common symptoms of adrenal insufficiency are nonspecific, and include:



Biochemical Tests to Diagnose Adrenal Insufficiency

Morning fasting serum ACTH and cortisol levels
Tests should be performed in the early morning, before 9 a.m.

Factors Affecting Test Results

Steroids, megestrol acetate (Megace), and opiates can interfere with test results.

Steroid Considerations

If the patient is on >5 mg prednisone or equivalent steroid, it is not an appropriate time to assess adrenal insufficiency.
If the patient is on ≤5 mg prednisone or equivalent steroid, hold the steroid for 22-23 hours before the tests.

Medication Instructions

On the day of the tests, opiates should be held from midnight.
Megace should be held for at least 3 days due to its long half-life.

Criteria for Diagnosis[3]

Adrenal insufficiency is diagnosed if cortisol level is less than 5 µg/dL.
Adrenal insufficiency is ruled out if cortisol level is above 15 µg/dL (we use cortisol level above 10 µg/dL). Cortisol levels between 5 and 15 (10) µg/dL are indeterminate.

Interpretation of Test Results[3]

High ACTH and low cortisol: Primary adrenal insufficiency – adrenal gland dysfunction
Low ACTH and low cortisol: Central adrenal insufficiency – dysfunction of pituitary or hypothalamus

ACTH stimulation test

Indications

- Serum cortisol level between 5 to 15 (10) µg/dL
- Clinical symptoms suggestive of adrenal insufficiency

Protocol

- Administer 250 mcg of cosyntropin IV or IM
- Collect blood samples for cortisol at 0, 30, and 60 minutes

Notes: *Patients with newly onset hypophysitis (4-6 weeks) may retain a normal adrenal response to ACTH stimulation*

Interpretation

Post-ACTH stimulation cortisol > 15 µg/dL - adrenal insufficiency is unlikely.

Glucocorticoid-Induced Adrenal Insufficiency

Table 1. Risk Factors for Developing Adrenal Insufficiency, and Susceptibility to Adrenal Crisis, During Glucocorticoid Therapy and Withdrawal from Therapy

Factors	Risk for Adrenal Insufficiency and Crisis		
	Low	Moderate	High
Glucocorticoid potency	Hydrocortisone Cortisone acetate Deflazacort	Prednisone Prednisolone Methylprednisolone Triamcinolone	Dexamethasone Betamethasone Fluticasone
Administration Route	Nasal Topical Ophthalmic	Inhaled	Systemic (oral, intra-muscular, intravenous) Intra-articular Concurrent use of differently administered glucocorticoid
Dose	Low	Medium	High
Duration of use	<3-4 weeks	3-4 weeks – 3 months	>3 months
Body Mass Index	Normal	Overweight	Obese
Age	Younger adults	-	Older adults

Source: European Society of Endocrinology and Endocrine Society Guideline. Reproduced from Beuschlein et al. *2024*[4] *under the Creative Commons CC-BY-NC-ND license (https:// creativecommons.org/licenses/by-nc-nd/4.0/)*

Table 2. Suggested Tapering Regimen Depending on Glucocorticoid Dose

Patient's current daily prednisone equivalent dose	Suggested prednisone decrements	Time interval
>40 mg	5-10 mg decrease	Every week
20-40 mg	5 mg decrease	Every week
10-20 mg	2.5 mg decrease	Every 1-4 weeks
5-10 mg	1 mg decrease	Every 1-4 weeks
5 mg	In absence of clinical symptoms or negative testing for adrenal insufficiency, continue 1 mg decrease (if low dosage prednisolone preparations are not available, alternative: 20 mg hydrocortisone with 5 mg decrease)	Every 4 weeks

Source: European Society of Endocrinology and Endocrine Society Guideline. Reproduced from Beuschlein et al. *2024*[4] *under the Creative Commons CC-BY-NC-ND license (https:// creativecommons.org/licenses/by-nc-nd/4.0/)*

Table 3. Pharmacologic Characteristics of Commonly Prescribed Systemic Glucocorticoids

Glucocorticoids	Approximate equivalent dose	Glucocorticoid potency (relative to hydrocortisone)	Plasma half-life (minutes)	Biological half-life (hours)	Therapeutic indications
Short-acting glucocorticoids with lower potency					
Hydrocortisone	20 mg	1.0	90-120	8-12	Adrenal insufficiency replacement
Cortisone acetate	25 mg	0.8	80-120	8-12	Adrenal insufficiency replacement
Deflazacort	7.5 mg	1.0	70-120	Not defined	Duchenne muscular dystrophy
Intermediate-acting glucocorticoids with moderate potency					
Prednisone	5 mg	4.0	60	12-36	Anti-inflammatory, immunosuppressant; adrenal insufficiency replacement
Prednisolone	5 mg	4.0	115-200	12-36	Anti-inflammatory, immunosuppressant; adrenal insufficiency replacement
Triamcinolone	4 mg	5.0	30	12-36	Anti-inflammatory, immunosuppressant
Methylprednisolone	4 mg	5.0	180	12-36	Anti-inflammatory, immunosuppressant
Long-acting glucocorticoids with highest potency					
Dexamethasone	0.5 mg	30-60	200	36-72	Anti-inflammatory, immunosuppressant; usually reserved for short-term use in severe, acute conditions
Betamethasone	0.5 mg	25-40	300	36-72	Anti-inflammatory, immunosuppressant; usually reserved for short-term use in severe, acute conditions

Source: European Society of Endocrinology and Endocrine Society Guideline. Reproduced from Beuschlein et al. *2024*[4] *under the Creative Commons CC-BY-NC-ND license (https:// creativecommons.org/licenses/by-nc-nd/4.0/)*

European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and Therapy of Glucocorticoid-Induced Adrenal Insufficiency[4]

Who is at risk for glucocorticoid-induced adrenal insufficiency?

Glucocorticoid exposure via oral administration that poses risk for adrenal insufficiency must exceed dose and duration thresholds:

1. Duration of glucocorticoid therapy:	2. Dose of glucocorticoid therapy:
 3-4 weeks or longer	 Any dose greater than daily hydrocortisone equivalent of 15-25 mg (4-6 mg prednisone or prednisolone, 3-5 mg methylprednisolone, 0.25-0.5 mg dexamethasone).

How to discontinue/taper glucocorticoids?

In patients on short-term glucocorticoid therapy (<3-4 weeks, irrespective of dose), glucocorticoids can be stopped without testing due to low concern for HPA axis suppression. Taper is unnecessary.

Glucocorticoid taper can be attempted for patients on long-term glucocorticoid therapy if the underlying disease for which glucocorticoids were prescribed is controlled, and glucocorticoids are no longer required. In these cases, glucocorticoids are tapered until approaching the physiologic daily dose equivalent is achieved (e.g., 4-6 mg prednisolone).

Glucocorticoid withdrawal syndrome may occur during glucocorticoid taper. When glucocorticoid withdrawal syndrome is severe, glucocorticoid dose can be temporarily increased to the most recent dose that was tolerated, and the duration of glucocorticoid taper can be increased.

Routine testing for adrenal insufficiency is unnecessary for patients on supraphysiologic doses of glucocorticoids, or in patients who are still in need of glucocorticoid treatment for the underlying disease.

Patients taking long-acting glucocorticoids (e.g. dexamethasone or betamethasone) should be switched to shorter-acting glucocorticoids (e.g. hydrocortisone or prednisone) when long-acting glucocorticoids are no longer needed.

References

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3. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism 2016;101(2):364-89. DOI: 10.1210/jc.2015-1710.
4. Beuschlein F, Else T, Bancos I, et al. European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and therapy of glucocorticoid-induced adrenal insufficiency. Eur J Endocrinol 2024;190(5):G25-G51. DOI: 10.1093/ejendo/lvae029.