Diagnostic approach and testing for adrenal insufficiency in adults

Who should be tested?
We recommend testing for adrenal insufficiency in patients with the following conditions in their profile or history, or with non-specific symptoms severe enough to interfere with daily function.

<table>
<thead>
<tr>
<th>Patient profile/history PAI</th>
<th>Clinical indications PAI</th>
<th>Patient profile/history SAI/TAI</th>
<th>Clinical indications SAI/TAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pages 3, 4</td>
<td>Weakness, fatigue, hyperpigmentation, vitiligo, weight loss, nausea, abdominal pain, vomiting, hypotension, amenorrhea, volume depletion, musculoskeletal complaints, salt craving, sleep disturbance, diarrhea, visual disturbance, depression/anxiety.</td>
<td>Page 4</td>
<td>Weakness, fatigue, pale complexion, weight gain/loss, cold intolerance, nausea/abdominal pain, pain under ribs/mid-back, hypertension/hypotension, amenorrhea/infertility, musculoskeletal complaints, apathy, sleep disturbance, diarrhea/constipation, headaches/visual disturbance, depression/anxiety.</td>
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<tr>
<td>Pre-testing considerations, Page 5</td>
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<td>Samples drawn between 8 and 9am. The following may interfere with accurate test results.</td>
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<tr>
<td>Glucocorticoids or corticosteroids, including topical, inhaled, injected, and oral tablets/capsules. Birth control or other estrogens, including soybean food products and menopause formulas. Drugs-etomidate, ketoconazole, fluconazole, metryrapone, suramin, phenytoin, barbiturates, mitotane, and rifampin. High dose progestins or chronic administration of opiates. Abnormalities of cortisol-binding globulin (CBG) or albumin, from cirrhosis of nephrotic syndrome, or in patients taking oral estrogens, can lead to incorrect diagnosis.</td>
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Initial Tests
Drawn simultaneously

<table>
<thead>
<tr>
<th>Morning serum cortisol</th>
<th>Baseline ACTH</th>
<th>Comprehensive metabolic panel (CMP)</th>
<th>Aldosterone/plasma renin activity (PRA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pages 6, 7</td>
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<tr>
<td>Drawn between 8 and 9am Fasting</td>
<td>*To determine if the cortisol deficiency is dependent on or independent of corticotropin (ACTH) deficiency.</td>
<td>*To evaluate organ function, electrolytes, hydration, and blood glucose levels.</td>
<td>*To evaluate mineralocorticoid secretion.</td>
</tr>
</tbody>
</table>
Interpretation and further testing

Definitive diagnosis PAI
Page 8
Low cortisol
High ACTH
Abnormal PRA and electrolytes pages 6, 7

Definitive diagnosis SAI/TAI
Page 8
Low cortisol
Low ACTH
History of metabolic/hormone dysfunction common

Indeterminant result Page 9
Morning cortisol < 15 ng/dL (414 nmol/L)
ACTH baseline < 20 -or- > 52 pg/mL (< 4.5 -or- > 12 pmol/L)
Abnormal electrolytes or PRA pages 6, 7
AI indications in profile/history

Adrenal insufficiency excluded Page 8
Morning cortisol > 15 ng/dL (414 nmol/L)
ACTH baseline 20-52 pg/mL (4.5 – 12 pmol/L)
Normal PRA pages 6, 7
Normal electrolytes
No history of adrenal or pituitary dysfunction, or dysfunction of HPA axis resolved

Begin glucocorticoid and mineralocorticoid treatment
See current guidelines ref #’s 1, 6, 7

Determine origin
Adrenal imaging (CT scan)
21-hydroxylase antibody
Page 16
Serum 17-hydroprogesterone, Page 16

Investigate for treatable cause
Pituitary imaging (MRI)
[For HPA axis suppression see ref # 27]

Consider testing hormones affected by pituitary dysfunction
Thyroid panel, thyroid antibodies Pages 24, 25
Gonadotropins Growth hormone Prolactin

Investigate for treatable cause
Infections, Tuberculosis, HIV, Histoplasmosis, Cytomegalovirus, Cryptococcus, and fungal infections.
Infiltrative disorders, Amyloidosis, Sarcoidosis, Hemochromatosis, and Metastatic disease.

Dynamic testing indicated Pages 15, and 17 through 24

SAI/TAI suspected
Metyrapone stim test
Pages 17 - 19
Insulin Tolerance Test (ITT)
Pages 19 – 22
Pituitary imaging (MRI)

Abnormal results
Metyrapone
Page 18
ITT, page 21
SAI/TAI confirmed

Normal results
Metyrapone,
Page 18
ITT, Page 21
SAI/TAI excluded

ACTH stim result
>18 mcg/dL (500 nmol/L) Before or after cosyntropin injection
Primary adrenal insufficiency confirmed

ACTH stim result
<18 mcg/dL (500 nmol/L) After or before cosyntropin injection
Primary adrenal insufficiency excluded.

Patients diagnosed with AI should be educated about the need for stress and illness dosing, (17) (23) medical alert jewelry, and an emergency intramuscular injection in the case of adrenal crisis. (18) Physicians and patients need to create an adrenal crisis plan in the event the patient needs to go to the emergency room (ER). A brief letter with detailed instructions, signed by the physician, can eliminate confusion in the ER. (Please see emergency information at adrenalinsufficiency.org)