Management of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline
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I. Overview of Management of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline
## Epidemiology

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>100–140 cases/million</th>
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<tr>
<td>Incidence</td>
<td>4/million/year</td>
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Clinical Picture: Adrenal Insufficiency

Primary

Before HC

After HC

Secondary
Clinical Features: Primary Adrenal Insufficiency

- Fatigue
- Weight loss
- Abdominal pain
- Hypotension
- Dehydration
- Hyperpigmentation
- Hypoglycemia
- Hyponatremia
- Cortisol ↓
- ACTH ↑
- Confusion
- Hyperkalemia
- Postural dizziness
- Hypotension
- Renin ↑
- Hyponatremia
- Hyperkalemia
- Hypoglycemia
Predisposing Factors: Adrenal Insufficiency

Etiologies:
Primary Adrenal Insufficiency (PAI)

- 90% – Autoimmune
- Infiltration/Injury
- Drug Induced
- Congenital Adrenal Hyperplasia
- Adrenal Hypoplasia
II. Diagnosis
Diagnosing PAI: The Clinical Situation

Low basal serum cortisol: Highly likely if serum cortisol <138 nmol/L (5µg/dl) (Kazlauskaite et al. 2008)

Elevated plasma ACTH: >2-fold over URL

Corticotropin stimulation test: 250µg iv, cortisol at baseline and after 30 min) for confirmation.
  Pitfalls: Cortisol binding globulin, glucocorticoid resistance, and hypersensitivity
# GRADE Classification of Guideline Recommendations

<table>
<thead>
<tr>
<th>QUALITY OF EVIDENCE</th>
<th>High Quality</th>
<th>Moderate Quality</th>
<th>Low Quality</th>
<th>Very Low Quality</th>
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</thead>
<tbody>
<tr>
<td><strong>Description of Evidence</strong></td>
<td><strong>Well-performed RCTs</strong>&lt;br&gt;<strong>Very strong evidence from unbiased observational studies</strong></td>
<td><strong>RCTs with some limitations</strong>&lt;br&gt;<strong>Strong evidence from unbiased observational studies</strong></td>
<td><strong>RCTs with serious flaws</strong>&lt;br&gt;<strong>Some evidence from observational studies</strong></td>
<td><strong>Unsystematic clinical observations</strong>&lt;br&gt;<strong>Very indirect evidence observational studies</strong></td>
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<tr>
<td><strong>STRENGTH OF RECOMMENDATION</strong></td>
<td><strong>Strong (1):</strong>&lt;br&gt;“We recommend...”&lt;br&gt;Benefits clearly outweigh harms and burdens, or vice versa</td>
<td>1</td>
<td>⊕⊕⊕⊕</td>
<td>1</td>
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<tr>
<td></td>
<td><strong>Conditional (2):</strong>&lt;br&gt;“We suggest...”&lt;br&gt;Benefits closely balanced with harms and burdens</td>
<td>2</td>
<td>⊕⊕⊕⊕</td>
<td>2</td>
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</tbody>
</table>
1. **Rule out PAI** in any acutely ill patient with clinical symptoms or signs suggestive of PAI. (Grade 1/★★★★)

2. **Confirmatory testing** with the corticotropin stimulation test in patients with clinical symptoms or signs suggesting PAI when the patient’s condition and circumstance allows. (Grade 1/★★★★)

3. **Immediate therapy** with intravenous hydrocortisone (initially 100 mg as bolus followed by a continuous infusion of 200 mg hydrocortisone/24hrs) prior to the availability of the results of diagnostic tests in patients with severe AI symptoms or AC. (Grade 1/★★★★)
Optimal diagnostic tests: Order of Preference

1. **Standard dose** (250µg iv) corticotropin stimulation over other tests, peak cortisol below 500–550 nmol/l (18µg/dl) indicates PAI. (Grade 2/⊕⊕ΟΟΟ)

2. **Low dose** (1µg) corticotropin stimulation test only if short supply of the substance. (Grade 2/⊕⊕ΟΟΟ)

3. **Random cortisol** level < 138 nmol/l (5µg/dl) preliminary for PAI if corticotropin stimulation test is not feasible. (Grade 2/⊕ΟΟΟΟΟ)
Optimal diagnostic tests: Order of Preference (cont)

4. **Measurement of ACTH** to establish PAI, with baseline sample before corticotropin stimulation or with random cortisol level, ACTH > 2 fold ULN consistent with PAI. (Grade 1/⊕⊕⊕⊕)

5. **Measurement of plasma renin and aldosterone** for mineralocorticoid deficiency. (Grade 1/⊕⊕⊕⊕)

6. **Determining the etiology** in all patients with confirmed disease.
Testing for PAI: Problems and Limitations

- **High cortisol binding globulin**: Pregnancy and oral contraceptives (estrogens)

- **Low cortisol binding globulin**: Nephrotic syndrome, post-operative, and intensive care medicine

- **Rare situations**: Cortisol binding globulin deficiency, glucocorticoid resistance, and hypersensitivity
Diagnostic Approach to the Patient with PAI

Primary Adrenal Insufficiency

17-OH-Progesterone

Infants, selected children and adults

CAH

Genetic syndromes (rare CAH, AHC)

Idiopathic PAI

21-OH Antibody

Infiltrative disease
Adrenal hemorrhage
Infections
Malignant tumors

All > 6 months age

Autoimmune AI
Consider APS-1, APS-2

VLCFA (males)

Adreno-leuko-dystrophy

CT adrenals

(+) (+) (-) (+) (-)

(+)

(-)

(-)

(-)
Adrenal Gland CT Scan

Hematoma of the right adrenal

Normal right adrenal
III. Acute Management
1. **Immediate therapy** with intravenous hydrocortisone (initially 100 mg as bolus followed by a continuous infusion of 200 mg hydrocortisone/24hrs) prior to the availability of the results of diagnostic tests in patients with severe AI symptoms or AC. (Grade 1/★★★★★)
1. **Glucocorticoid mandatory**
   Recommended *(Grade 1/★★★★★)*
   - Hydrocortisone (15 – 25 mg)
   - Cortisone acetate (25 – 37.5 mg)

2. **BID or TID suggestion.** *(Grade 2/★★★★)*
   - Clinical signs, BP, body weight
   - no biochemical monitoring

3. **Prednisolone:** low compliance, diabetics *(Grade 2/★★★★★★)*

4. **Dexamethasone:** not recommended *(Grade 2/★★★★★★)*
Treatment: Mineralocorticoids

1. Recommendation: fludrocortisone in confirmed aldosterone down, starting with 100µg/d. (Grade 1/⊕⊕⊕⊕⊕)

2. Recommendation: monitoring clinical signs, electrolytes, plasma renin. (Grade 1/⊕⊕⊕⊕○)

3. Suggestion: reducing and continuing fludrocortisone in hypertension. (Grade 2/⊕○○○○)
DHEA Treatment: Treating depression, low energy and libido

- Suggested DHEA replacement therapy (Grade 2/⊕ΟΟΟΟΟ)
  - Initial dose 25–50 mg
  - Discontinue after 6 months if no benefit
  - Measurement of DHEAS
Adrenal Crisis Prevention

Steroid emergency card

Education for patients and partners

HC emergency injection kit prescription

Alternative: suppositories prednisolone/HC
IV. Future Research
Future Research: Improving Diagnostics

Utility of salivary cortisol

LC-MS/MS
• Better standardization in the measurement of cortisol
• Free from analytical interferences associated with medications and dietary constituents
• Quantify in a single analysis multiple steroids (up to 15)

Future Research: Improving Treatment

Emerging Formulations
Modified and delayed-release formulation of HC in clinical development aiming to mimic the cortisol circadian rhythm

Subcutaneous Administration
Cortisol replacement by means of continuous subcutaneous infusion

Pulsatile subcutaneous cortisol replacement
Creating a Bioartificial Adrenal Gland

Transplantation of bovine adrenocortical cells encapsulated in alginate.

*Balyura M... Bornstein SR. Proc Natl Acad Sci USA. 2015 Feb 9.*


Bornstein et al. *Science Bx* 2013

External $O_2$ refueling (every 24 hours)
V. Case Discussions
Clinical Practice

- Angiotensin-converting enzyme blockers (ACE)
- Angiotensin-receptor blockers

Hypertension treatment of choice

Dietary Considerations

- Increase mineralocorticoid effect of hydrocortisone
CASE # 1

72 year old man presenting in emergency department with drowsiness, diffuse weakness and postural dizziness after 2 days of anorexia, nausea and vomiting.

Clinical:

- Orientated in place and person, unsure date and time, unsure of medications, dry mouth, healed surgical scars both flanks
- Febrile 37.8°C (101.8°F)
- BP 90/60 mmHg lying, BP 60/- sitting, HR 110/min
- Diffuse abdominal tenderness, no guarding
- Na 132, K 5.6. Serum creatinine 1.414 mg/dL (0.6-1.2 mg/dL)
CASE # 1

What is the best next step?

A. CT/MRI scan of the head for confusion, drowsiness
B. Cortisol, aldosterone and renin levels, await results
C. Measurement of cortisol 30-min after ACTH-stimulation
D. Fluid resuscitation, HC with 100mg i.v. bolus, followed 200mg per day, baseline cortisol if possible
E. Fluid resuscitation, broad spectrum antibiotics, exclude hemorrhage
CASE # 1 - Answer

What is the best next step?

A. CT/MRI scan of the head for confusion, drowsiness
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CASE # 1

Further history from patient’s family:

- Treated with bilateral adrenalectomy for metastatic renal cell carcinoma one year ago
- Medications include:
  - Hydrocortisone 10/10/4 daily
  - Fludrocortisone 0.1 mg daily
Prevent, Treat (acute), Inform

Prevention of Adrenal Crises
Unwell – triple HC dose for 3 days 3x3 rule

Treat: Early adrenal insufficiency symptoms, unable to take oral HC
Injectable hydrocortisone – 100mg IM (SC)
Rectal prednisolone suppository 5mg or hydrocortisone enema

Information for health carers
Card or leaflet to inform on use emergency HC
Medic Alert (unable to communicate)
Adrenal crisis risk in PAI and SAI

Patients requiring hospital admission/IV glucocorticoids since diagnosis

Overall incidence of adrenal crisis: 6.3 per 100 patient-years

Case #2: Pregnancy and PAI

A 36-year-old women with known primary adrenal insufficiency due to Addison’s disease.

Substitution with hydrocortisone 10 – 5 – 0 mg, fludrocortisone 0.1 mg, and levothyroxine 50µg (hypothyroidism).

Pregnant at 10th week of gestation.

Feeling well, no clinical signs of hypocortisolism.
Case #2: Pregnancy and PAI

How to handle with the glucocorticoid replacement during pregnancy?

A. Switch from HC to dexamethasone
B. Immediately increase HC to 15 – 10 – 0 mg
C. Increase HC in third trimester to 15 – 10 – 0 mg
D. No increase of HC during pregnancy
E. Double dosage of HC during labor
Case #2: Pregnancy and PAI - Answer

How to handle with the glucocorticoid replacement during pregnancy?

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Case #2: Pregnancy and PAI

Discussion

Pregnancy

- Clinical monitoring: Normal weight gain, fatigue, postural hypo/hypertension
- Increasing HC on individual course, particularly in the third trimester
- Suggestion: HC over Prednisolone (Grade 2/⊕⊕⊕⊕)
- Dexamethasone not recommended (Grade 1/⊕⊕⊕⊕)
- Recommendation: HC stress dose during labor (Grade 1/⊕⊕⊕⊕)
Case #3: Suspected PAI

A 4-year-old boy with failure-to-thrive. Last 2 months: frequent emesis, anorexia and abdominal pain. Birth weight 4 kg and history of prolonged and difficult labor. Family history unremarkable. On physical examination, weight and height are below the fifth percentile, no dysmorphic features, but dehydrated, hyperpigmented, and lethargic. An abdominal CT reveals adrenal calcifications.
Case #3: Suspected PAI

Laboratory evaluation.
ACTH = 2500 pg/mL (10-60 pg/mL)
AM Cortisol = 3.2 µg/dL

Which of the following tests would most likely be diagnostic?

A. Very long chain fatty acids (VLCFA)
B. 17-hydroxyprogesterone
C. AIRE genetic analysis
D. 21-hydroxylase antibodies
E. None of the above, most likely due to adrenal hemorrhage
Laboratory evaluation.
ACTH = 2500 pg/mL (10-60 pg/mL)
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A. Very long chain fatty acids (VLCFA)
B. 17-hydroxyprogesterone
C. AIRE genetic analysis
D. 21-hydroxylase antibodies

E. None of the above, most likely due to adrenal hemorrhage
Case #3: Child: Suspected PAI
Answer Discussion

Acute Treatment

- Infants: HC 25 mg; School-age: 50 mg; Adolescents: 100 mg
- IVF, ?hypoglycemia

Chronic Therapy

- Suggestion: HC in 2–3 dosages, 8–12 mg/m² body surface area (Grade 2/⊕⊕○○ ○)
- Suggestion: Avoiding long-acting GC (Grade 2/⊕⊕○○ ○)
- Monitoring clinical, not biochemical
- Recommendation: Fludrocortisone, NaCl for newborn up to 12 months (Grade 1/⊕⊕○○ ○)