LEARNING OBJECTIVES

- Diagnose AI and generate an appropriate differential diagnosis
- Recognize other autoimmune conditions that may be coincident with adrenal failure.
- Develop a long-term treatment plan that will prevent adrenal crises and minimize untoward effects of GC and MC replacement.
Physiological replacement therapy is not available.

Modalities for early intervention in autoimmune Addison’s disease are missing.

International guidelines have only recently been published and the best treatment and diagnostic options might not be widely available.
METHOD OF DEVELOPMENT OF EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

Clinical Guidelines Subcommittee

Task force
- Chair
- Eight clinicians experienced with the disease
- Methodologist
- Medical writer

GRADE system
- Determine the strength of recommendation
- Quality of evidence
GRADE SYSTEM

- Strong recommendation
  - “We Recommend” and the number 1

- Weak recommendation
  - “We suggest” and the number 2

- Quality of evidence
  - 4️⃣️️️️️️ - very low quality evidence
  - 3️⃣️️️️️️ - low quality evidence
  - 2️⃣️️️️️️ - moderate quality evidence
  - 1️⃣️️️️️️ - high quality evidence

- Remarks
  - Considered suggestions
• Comparison of the diagnostic accuracy of high-dose ACTH vs low-dose ACTH stimulation tests for the initial dx.
• Five studies evaluated the dx accuracy of the high-dose ACTH stimulation test and none for the low-dose.
• The sensitivity of the high-dose ACTH stimulation test for the dx of PAI was 92% (95% confidence interval, 81–97%).
COMMISSIONED SYSTEMATIC REVIEWS (CONT.)

Second Systematic Review

- Comparison of various glucocorticoid replacement regimens.
- 15 relevant observational studies.
- Poor quality data on mortality, bone density, and incidence of adrenal crisis.
- HRQoL- no statistically significant difference with dosages equal to or higher than 30mg/d of hydrocortisone vs regimens with dosages less than 30/mg/d.
- Very low quality evidence suggests that ER or dual-release forms of GC may have higher HRQoL scores.
OPTIC NERVE
PITUITARY GLAND
HYPOTHALAMUS
CRH
ACTH
CORTISOL
ANDROGENS

17-OH STEROIDS
FREE CORTISOL
17-OH KETO STEROIDS

STIMULATED BY:
\[\downarrow\text{Plasma Cortisol, Hypoglycemia, Pyrogen, and Stress}\]

SUPPRESSED BY:
\[\uparrow\text{Glucocorticoid Level}\]

AVP
HYPOTHALAMUS
OPTIC NERVE
PITUITARY GLAND
ACTH
ANGIOTENSIN
ALDOSTERONE
CORTISOL
ANDROGENS

Pathophysiology
ANGIOTENSINOGEN

-2-GLOBULIN
FROM LIVER

RENIN FROM JGA

ANGIOTENSINOGEN

CONVERTING
ENZYME IN
LUNG

ANGIOTENSINOGEN II

ALDOSTERONE

NA+ AND H2O RETENTION,
HI BLOOD VOLUME + HI BP

Pathophysiology
# Clinical Features of Adrenal Insufficiency and Adrenal Crisis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Routine laboratory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adrenal Insufficiency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Hyperpigmentation (primary only), particularly of sun-exposed areas, skin creases, mucosal membranes, scars, areola of breast</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Low blood pressure with increased postural drop</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Postural dizziness</td>
<td>Failure to thrive in children</td>
<td>Uncommon: hypoglycemia, hypercalcemia</td>
</tr>
<tr>
<td>Anorexia, abdominal discomfort</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adrenal Crisis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe weakness</td>
<td></td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Syncope</td>
<td>Hypotension</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Abdominal pain, nausea, vomiting; may mimic acute abd pain</td>
<td>Abdominal tenderness/guarding</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Back pain</td>
<td>Reduced consciousness, delirium</td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Major Etiologies of PAI

**Autoimmune**
- Isolated
- APS type 1
- APS type 2

**Adrenal-Infiltration/Injury**
- Adrenal hemorrhage
- Metastasis
- Infections: Adrenalitis
- Infiltration
- Bilateral adrenalectomy

**Adrenal hypoplasia congenital**
- X-linked NR0B1
- Xp21 deletion

**CAH**
- 11ß-hydroxylase deficiency
- 11β-hydroxylase deficiency
- 3β-hydroxysteroid dehydrogenase II deficiency

**Infections:**
- Adrenalitis
- Infiltration
- Bilateral adrenalectomy

**Isolated**
- APS type 1
- APS type 2
■ ACTH insensitivity syndromes

- Type 1
- Type 2
- Familial glucocorticoid deficiency
- Allgrove’s syndrome

Drug induced

- Adrenal enzyme inhibitors: mitotane, ketoconazole, metyrapone, etomidate
- Drugs that accelerate cortisol metabolism
- T4
- CTLA-inhibitors

Other metabolic disorders

- Mitochondrial disease
- Adrenoleukodystrophy
- Wolman’s disease
1. WHO SHOULD BE TESTED AND HOW?

- 1.1 We recommend diagnostic testing to exclude PAI in acutely ill patients with otherwise unexplained symptoms or signs suggestive of PAI. (1 OOOO

- 1.2 We recommend confirmatory testing with the corticotropin stimulation test in patients with clinical symptoms or signs suggesting PAI when the patient’s condition and circumstance allow.

- 1.3 In patients with severe adrenal insufficiency symptoms or adrenal crisis, we recommend immediate therapy with iv hydrocortisone at an appropriate stress dose prior to the availability of the results of diagnostic tests.
DELAYED DIAGNOSIS OF ADRENAL INSUFFICIENCY IS COMMON: A CROSS-SECTIONAL STUDY IN 216 PATIENTS

Patients diagnosed with AI within the first 6 months after onset of symptoms

20% of patients had symptoms for >5 years before dx

>67% of patients consulted at least 3 physicians

1. WHO SHOULD BE TESTED AND HOW?

- 1.1 We recommend diagnostic testing to exclude PAI in acutely ill patients with otherwise unexplained symptoms or signs suggestive of PAI.

- 1.2 We recommend confirmatory testing with the corticotropin stimulation test in patients with clinical symptoms or signs suggesting PAI when the patient’s condition and circumstance allow.

- 1.3 In patients with severe adrenal insufficiency symptoms or adrenal crisis, we recommend immediate therapy with iv hydrocortisone at an appropriate stress dose prior to the availability of the results of diagnostic tests.
In 27 patients (o with arrows), all measurements were less than 55 nmol/L. Other symbols and lines represent single patients with detectable cortisol levels.

ACTH-(1-24) (250 mcg) was injected IM immediately after the basal blood sample was taken (0 min).
1. WHO SHOULD BE TESTED AND HOW?

- 1.1 We recommend diagnostic testing to exclude PAI in acutely ill patients with otherwise unexplained symptoms or signs suggestive of PAI.

- 1.2 We recommend confirmatory testing with the corticotropin stimulation test in patients with clinical symptoms or signs suggesting PAI when the patient’s condition and circumstance allow.

- 1.3 In patients with severe adrenal insufficiency symptoms or adrenal crisis, we recommend immediate therapy with IV hydrocortisone at an appropriate stress dose prior to the availability of the results of diagnostic tests.
2.0 OPTIMAL DIAGNOSTIC TESTS

- 2.1 We suggest the standard dose (250 mcg for adults and children ≥ 2 y of age, 15 mcg/kg for infants, and 125 mcg for children <2 y of age) IV corticotropin stimulation (30 or 60 min) test over other existing diagnostics tests to establish the diagnosis of adrenal insufficiency. Peak cortisol levels below 500 nmol/L (18 mcg/dL) (assay dependent) at 30 or 60 minutes indicate adrenal insufficiency.
META-ANALYSIS RESULTS ON COSYNTROPIN STIMULATION TEST FOR PAI DIAGNOSIS

Table 1. The 250-μg Cosyntropin Stimulation Test in Patients with Primary Adrenal Insufficiency*

<table>
<thead>
<tr>
<th>Study (Reference)†</th>
<th>Cosyntropin Route and Time after Injection‡</th>
<th>Serum Cortisol Cutoff Level</th>
<th>Sensitivity§</th>
<th>Specificity§</th>
<th>Positive Likelihood Ratio‖</th>
<th>Negative Likelihood Ratio‖</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speckart et al. (27)</td>
<td>IV, 60</td>
<td>415</td>
<td>100 (6/6)</td>
<td>100 (9/9)</td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td>Nelson and Tindall (14)</td>
<td>IV, 60</td>
<td>415</td>
<td>100 (7/7)</td>
<td>100 (69/69)</td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td>Oelkers et al. (28)</td>
<td>IM, 60</td>
<td>415</td>
<td>100 (41/41)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fiad et al. (29)</td>
<td>IV, 60</td>
<td>415</td>
<td>100 (12/12)</td>
<td>100 (55/55)</td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td>Kong and Jeffcoate (23)</td>
<td>IV, 60</td>
<td>415</td>
<td>75 (6/8)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gonzalez-Gonzalez et al. (20)</td>
<td>IV, 60</td>
<td>415</td>
<td>82 (9/11)</td>
<td>100 (46/46)</td>
<td>&gt;100</td>
<td>0.18</td>
</tr>
<tr>
<td>Soule (30)</td>
<td>IV, 60</td>
<td>415</td>
<td>95 (35/37)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Speckart et al. (27)</td>
<td>IV, 30</td>
<td>415</td>
<td>100 (6/6)</td>
<td>88 (7/8)</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>Dluhy et al. (13)</td>
<td>IM, 30</td>
<td>415</td>
<td>100 (5/5)</td>
<td>100 (12/12)</td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td>Oelkers et al. (28)</td>
<td>IM, 30</td>
<td>415</td>
<td>100 (41/41)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kong and Jeffcoate (23)</td>
<td>IV, 30</td>
<td>415</td>
<td>89 (16/18)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gonzalez-Gonzalez et al. (20)</td>
<td>IV, 30</td>
<td>415</td>
<td>82 (9/11)</td>
<td>100 (46/46)</td>
<td>&gt;100</td>
<td>0.18</td>
</tr>
</tbody>
</table>

DORIN RI, QUALLS CR, CRAPO LM. DIAGNOSIS OF ADRENAL INSUFFICIENCY. ANN INTERN MED. 2003;139;194-204.
Geometric Mean of Post-ACTH Stimulation Cortisol Concentrations in Males, Non-OCP Female And OCP-female Subjects

<table>
<thead>
<tr>
<th>Assay</th>
<th>Males</th>
<th>Non-OCP females</th>
<th>OCP females</th>
<th>P-value*</th>
<th>P-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 60</td>
<td>n = 79</td>
<td>n = 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GC-MS</td>
<td>563 (418–757)</td>
<td>555 (421–731)</td>
<td>870 (643–1177)</td>
<td>0.594</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Centaur</td>
<td>599 (448–802)‡</td>
<td>578 (446–750)‡</td>
<td>763 (619–940)</td>
<td>0.138</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Architect</td>
<td>577 (430–773)‡</td>
<td>542 (416–707)‡</td>
<td>747 (577–967)</td>
<td>0.012</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eli70</td>
<td>772 (574–1039)‡</td>
<td>712 (524–967)‡</td>
<td>1026 (791–1330)</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immulite (2000)</td>
<td>641 (469–874)‡</td>
<td>628 (478–826)‡</td>
<td>850 (688–1051)</td>
<td>0.449</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Access</td>
<td>625 (459–852)‡</td>
<td>594 (455–777)‡</td>
<td>757 (604–948)</td>
<td>0.045</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results are expressed as geometric mean (2.5th–97.5th percentile) in nm.
*P-value for difference between genders.
†P-value for difference between women taking an oral contraceptive pill and those who were not.
‡P-value for immunoassay vs gas chromatography-mass spectrometry (GC-MS) < 0.02.
## Assay-Specific Estimated Lower Reference Limits for Post-Adrenocorticotropic Hormone Cortisol According to Gender and Oral Contraceptive Pill (OCP)-Status

<table>
<thead>
<tr>
<th>Assay</th>
<th>Males</th>
<th>Non-OCP females</th>
<th>Combined male and Non-OCP female subjects*</th>
<th>OCP females</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC-MS</td>
<td>418</td>
<td>421</td>
<td>420</td>
<td>643</td>
</tr>
<tr>
<td>Centaur</td>
<td>448</td>
<td>446</td>
<td>446</td>
<td>619</td>
</tr>
<tr>
<td>Architect</td>
<td>430</td>
<td>416</td>
<td>NA</td>
<td>577</td>
</tr>
<tr>
<td>E170</td>
<td>574</td>
<td>524</td>
<td>NA</td>
<td>791</td>
</tr>
<tr>
<td>Immulite</td>
<td>469</td>
<td>478</td>
<td>474</td>
<td>688</td>
</tr>
<tr>
<td>(2000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access</td>
<td>459</td>
<td>455</td>
<td>NA</td>
<td>604</td>
</tr>
</tbody>
</table>

FACTORS THAT INFLUENCE CBG LEVELS

Increase in CBG

- Pregnancy
- Estrogen therapy
- Chronic active hepatitis
- Inherited abnormality

Decrease in CBG

- Hyperinsulinemic states
- Nephrotic syndrome
- Severe liver disease
- Malnutrition
- Newborn
- Inherited abnormality

Newborn

Inherited abnormality
2.0 OPTIMAL DIAGNOSTIC TESTS

2.2 We suggest the low-dose (1 mcg) corticotropin test for diagnosis of PAI only when the substance itself is in short supply.

Stimulated increase of cortisol after 30 or 60 min in healthy individuals is comparable for both 1 mcg and 250 mcg ACTH test.

The low-dose test adds no further sensitivity or specificity over the high-dose test in the diagnosis of PAI.
2.3 If a ACTH stimulation test is not feasible, we suggest using a morning cortisol <140 nmol/L (5 mcg/dL) in combination with ACTH as a preliminary test suggestive of adrenal insufficiency (until confirmatory testing with corticotropin stimulation is available).

- A cut off threshold for basal cortisol concentrations of <140 nmol/L (5 mcg/dL) drawn in the morning (6 to 10 AM) is suggestive of adrenal insufficiency.
- Most reports detailing this cut off value are not based on subjects with PAI.
- Cortisol level of 5 mcg/dL is at or near the normal limit of the range of normal subjects.
### MORNING CORTISOL FOR THE DIAGNOSIS OF AI

<table>
<thead>
<tr>
<th>Study</th>
<th>Basal cortisol (early morning)</th>
<th>SDCT (30 min/peak)</th>
<th>LDCT (20–30 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n HPAI/n total</td>
<td>HPAI(\mu g/dl)</td>
<td>No HPAI(\mu g/dl)</td>
</tr>
<tr>
<td>Studies with paired data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdu (22)</td>
<td>13/42</td>
<td>≤3.2</td>
<td>≥12.2</td>
</tr>
<tr>
<td>Courtney (16)</td>
<td>11/41</td>
<td>≤3.0</td>
<td>≥11.4</td>
</tr>
<tr>
<td>Gonc (18)</td>
<td>11/29</td>
<td>≤5.7</td>
<td>≥9.0</td>
</tr>
<tr>
<td>Maghnie (19)</td>
<td>14/24</td>
<td>≤9.1</td>
<td>≥15.0</td>
</tr>
<tr>
<td>Mayenknecht (11)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Talwar (7)(\text{a})</td>
<td>13/24</td>
<td>≤10.0</td>
<td>≥13.5</td>
</tr>
<tr>
<td>Tordjman (21)</td>
<td>19/62</td>
<td>≤4.8</td>
<td>≥17.9</td>
</tr>
<tr>
<td>Studies with unpaired data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambrosi (14)</td>
<td>12/57</td>
<td>≤3.6</td>
<td>≥9.3</td>
</tr>
<tr>
<td>Amnari (15)</td>
<td>17/30</td>
<td>≤7.4</td>
<td>≥14.7</td>
</tr>
<tr>
<td>Choi (5)(\text{a})</td>
<td>36/72</td>
<td>≤4.8</td>
<td>≥13.3</td>
</tr>
<tr>
<td>Kane (6)(\text{a})</td>
<td>9/22</td>
<td>≤4.4</td>
<td>≥8.6</td>
</tr>
<tr>
<td>Rose (17)(\text{c})</td>
<td>42/158</td>
<td>≤3.2</td>
<td>≥12.5</td>
</tr>
<tr>
<td>Soule (20)</td>
<td>13/74</td>
<td>≤3.5</td>
<td>≥18.0</td>
</tr>
<tr>
<td><strong>Mean (95% CI)</strong></td>
<td><strong>33%</strong></td>
<td><strong>≤5</strong></td>
<td><strong>≥13</strong></td>
</tr>
<tr>
<td><strong>210/635</strong></td>
<td>(4.7–5.3)</td>
<td>(12.9–13.6)</td>
<td></td>
</tr>
</tbody>
</table>

2.0 DIAGNOSTIC TESTING- PLASMA ACTH LEVEL

- 2.4 We recommend measurement of plasma ACTH to establish PAI. In patients with confirmed cortisol deficiency, a plasma ACTH >2-fold the upper limit of the reference range is consistent with PAI.
  - A plasma ACTH concentration exceeding 300 ng/L (66 pmol/L) provides maximum stimulation of glucocorticoid synthesis.
  - Difficult to establish a specific cut-point for ACTH levels due to analytical bias.
  - Only two studies have reported the ACTH range for PAI at diagnosis with a control reference population, and in these studies the ACTH was typically grossly elevated in PAI.
2.5 We recommend the simultaneous measurement of plasma renin and aldosterone in PAI to determine the presence of mineralocorticoid deficiency.

- In the early phase of evolving PAI mineralocorticoid deficiency may predominate.
- Some etiologies of PAI does not present mineralocorticoid deficiency.
2.0 DIAGNOSTIC TESTING

- 2.6 We suggest that the etiology of PAI should be determined in all patients with confirmed disease. (Ungraded best practice recommendation)
Algorithm for the diagnostic approach to the patient with PAI

Infants, selected children and adults

- Primary Adrenal Insufficiency
  - 17-OH-Progesterone
    - CAH
    - Genetic syndromes (Rare CAH, AHC)
    - Idiopathic PAI
  - CT adrenals
    - Infiltrative Disease, Adrenal hemorrhage, Infections, Malignant tumors
  - 21-OH Antibody
    - Autoimmune AI, Consider APS-1, APS-2
    - VLCFA (Males)
    - Adrenoleukodystrophy

All >6 months of age

(+): Positive
(-): Negative
(+): Positive
(-): Negative
ROLE OF 21-OH ANTIBODIES IN THE DEVELOPMENT OF PAI


- Assess the contribution of different clinical, immunological, genetic, and functional factors in the progression to AAD.
- 100 ACA-positive and 63 ACA-negative patients without AAD were followed for a maximum of 21 yrs.
- About 30% progressed to overt PAI during a 5-year follow-up.


- Levels of adrenal autoantibodies correlate with the degree of adrenal dysfunction.
- 19 ACA-positive subjects with preclinical Addison’s disease.
- The levels of adrenal autoantibodies were positively associated with the severity of adrenal dysfunction (ANOVA, P < 0.0001 for both 21OHAb and ACA).
The 21OH index was significantly lower at stage 0 or 1 than at stage 2 + 3 (corrected P < 0.001 and P < 0.05) or stage 4 (corrected P < 0.001 and <0.01).

ACA titer at stage 4 was significantly higher than stage 0 (P < 0.001), stage 1 (P < 0.001), and stage 2+3 (P < 0.05); and ACA titer at stage 2+3 was higher than stage 0 (P < 0.001) and stage 1 (P < 0.05).
3.0 TREATMENT OF PRIMARY ADRENAL INSUFFICIENCY IN ADULTS
GLUCOCORTICOID REPLACEMENT REGIMEN

- 3.1 We recommend glucocorticoid therapy in all patients with confirmed PAI.
- 3.2 We suggest using hydrocortisone (15–25 mg) or cortisone acetate (20–35mg) in two or three divided oral doses per day.
- 3.3 As an alternative to hydrocortisone, we suggest using prednisolone (3–5 mg/d), administered orally once or twice daily, especially in patients with reduced compliance.
- 3.4 We suggest against using dexamethasone for the treatment of PAI because of risk of Cushingoid side effects due to difficulties in dose titration.
GLUCOCORTICOID REPLACEMENT REGIMENS

<table>
<thead>
<tr>
<th>Optimal hydrocortisone replacement therapy</th>
<th>Twice daily hydrocortisone</th>
<th>Thrice daily hydrocortisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone doses (mg)</td>
<td>20am/10pm</td>
<td>10am/5noon/5pm</td>
</tr>
<tr>
<td>Optimal replacement (% of pts)</td>
<td>10%</td>
<td>66%</td>
</tr>
<tr>
<td>Quality score (1-4)</td>
<td>2.48</td>
<td>3.62</td>
</tr>
</tbody>
</table>

'*Optimal replacement' was arbitrarily defined as that dose which achieved a UFC and 09:00 h cortisol within the reference range for the normal population (to avoid over-replacement) combined with 1230 h and 1730 h cortisol above 50 nmol/l (1.8 mcg/dl), and ideally above 100 nmol/l (3.6 mcg/dl) (to avoid under-replacement)
GLUCOCORTICOID REPLACEMENT REGIMENS

  - Single dose-morning HC adjusted by BSA (5.5 mg/m2) or by weight (0.12 mg/kg) produced integrated cortisol levels over 6 hrs within the healthy control 95% CI.

  - Thrice-daily cortisone acetate lowered ACTH levels and gave 24-hour cortisol curves more similar to the endogenous cortisol rhythm compared with a two-dose regimen.

- **Ekman, et al 2012**
  - Double-blind, randomized, crossover study. Evaluated two-dose vs four-dose regimen with more physiological pharmacokinetics with the four-dose.
3.5 We suggest monitoring glucocorticoid replacement using clinical assessment including body weight, postural blood pressure, energy levels, signs of frank glucocorticoid excess.

3.6 We suggest against hormonal monitoring of glucocorticoid replacement and to adjust treatment only based on clinical response.
MONITORING GLUCOCORTICOID REPLACEMENT

Over-replacement
- Weight gain
- Insomnia
- Peripheral edema

Under-replacement
- Nausea
- Poor appetite
- Weight loss
- Lethargy
- Hyperpigmentation

Detailed questioning...
- Daily habits
- Working patterns
- Energy
- Mental concentration
- Daytime somnolence
- Dips in energy
3.7 We recommend that all patients with confirmed aldosterone deficiency receive mineralocorticoid replacement with fludrocortisone (starting dose, 50–100 mcg in adults) and not restrict their salt intake.

3.8 We recommend monitoring mineralocorticoid replacement primarily based on clinical assessment (salt craving, postural hypotension, or edema), and blood electrolyte measurements.

3.9 In patients who develop hypertension while receiving fludrocortisone, we suggest reducing the dose of fludrocortisone.

3.10 If blood pressure remains uncontrolled, we suggest initiating antihypertensive treatment and continuing fludrocortisone.
MINERALOCORTICOID REPLACEMENT

Assessed clinically
- Salt craving
- Light-headedness
- Blood pressure (sitting and standing)
- Peripheral edema (low sensitivity)

Agents affecting fludrocortisone metabolism
- Licorice
- Grapefruit juice
- Phenytoin

Hypertension
- Evaluate fludrocortisone and glucocorticoid dose
- ACE-I or ARBs preferred
- Avoid diuretics
- Spirinolactone and eplerenone contraindicated
3.11 We suggest a trial of DHEA replacement in women with PAI and low libido, depressive symptoms, and/or low energy levels despite otherwise optimized glucocorticoid and mineralocorticoid replacement.

3.12 We suggest an initial period of 6 months of DHEA replacement. If the patient does not report a sustained, beneficial effect of replacement after 6 months, the DHEA should be discontinued.

3.13 We suggest monitoring DHEA replacement by measuring morning serum DHEAS levels (aiming at the mid normal range) before the intake of the daily DHEA replacement dose.
• Double-blind study
• 24 women with adrenal insufficiency
• 50 mg of DHEA orally each morning for four months and placebo daily for four months, with a one-month washout period.
• DHEA significantly improved overall well-being as well as scores for depression and anxiety. Also improved sexuality.
Random-effects meta-analysis of DHEA on HRQoL, depression, anxiety, and sexual function

General quality of life
- Art, 1999 (2)
- Bilger, 2005 (11)
- Hurt, 2000 (3)
- Libe, 2004 (17)
- Lovas, 2003 (4)
- Johannsson, 2002 (5)
- Van Thiel, 2005 (13)
- Brooke, 2006 (14)
- Dhalia, 2008 (10)

Random effects pooled SMD
- 0.21 (0.08, 0.33); P = 32%

Depression
- Art, 1999 (2)
- Bilger, 2005 (11)
- Hurt, 2000 (3)
- Johannsson, 2002 (5)
- Van Thiel, 2005 (13)
- Brooke, 2006 (14)
- Dhalia, 2008 (10)

Random effects pooled SMD
- 0.23 (0.04, 0.42); P = 57%

Anxiety
- Art, 1999 (2)
- Johannsson, 2002 (5)
- Hurt, 2000 (3)
- Van Thiel, 2005 (13)
- Brooke, 2006 (14)

Random effects pooled SMD
- 0.12 (0.04, 0.27); P = 0%

Satisfaction with sex
- Art, 1999 (2)
- Lovas, 2003 (4)
- Van Thiel, 2005 (13)
- Dhalia, 2008 (10)

Random effects pooled SMD
- 0.27 (-0.11, 0.64); P = 62%
3.14 Monitor clinical symptoms in pregnant patients with PAI for over- and under-replacement with at least one review per trimester.

3.15 Increase dose of hydrocortisone in particular during the 3rd trimester based on clinical course.

3.16 Use hydrocortisone over cortisone acetate, prednisolone, or prednisone. Do not use dexamethasone.

3.17 Hydrocortisone stress dosing during the active phase of labor.
NORMAL CORTISOL VARIATION DURING PREGNANCY

1st to 2nd trimester
- Increase in CBG
- Increase in cortisol

2nd Trimester
- Week 22
  - Increase in free cortisol

3rd Trimester
- Preterm
  - Further rise in free cortisol
  - Fall in CBG
CORTISOL RESPONSE TO ACTH DURING PREGNANCY

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic cortisol cutoffs after ACTH stimulation test</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester</td>
<td>25 mcg/dL</td>
</tr>
<tr>
<td>Second trimester</td>
<td>29 mcg/dL</td>
</tr>
<tr>
<td>Third trimester</td>
<td>32 mcg/dL</td>
</tr>
</tbody>
</table>

3.18 Hydrocortisone in 3 to 4 divided doses (total starting daily dose of 8 mg/m2 BSA)

3.19 Avoid synthetic, long acting glucocorticoids (prednisolone, dexamethasone)

- No published RCT of various treatment regimens for PAI in children.
- No data are available to compare the long-term effects of various formulations of glucocorticoid.

- Hydrocortisone has a short half-life and is easier to titrate.
- Cortisone may be used but understand that activity of 11ß-hydroxysteroid dehydrogenase type 1 activity is variable
- Most data available are in children with CAH
MONITORING GLUCOCORTICOID REPLACEMENT IN CHILDREN

- **Overtreatment**
  - Excessive weight gain
  - Decreased height velocity
  - Signs or symptoms of Cushing’s

- **Underreplacement**
  - Inadequate weight gain
  - Fatigue
  - Anorexia
  - Hyperpigmentation

- In patients with CAH, GC doses >20mg/m²/d in infants and >15-17mg/m²/d in adolescents result in loss of height and shorter adult stature

GRIGORESCU-SIDO A. ET AL. HORMONES.2003; 60:84–90.
3.21 In children with PAI and confirmed aldosterone deficiency, we recommend treatment with fludrocortisone (starting dosage, 100 mcg/d). For infants, we recommend sodium chloride supplements in the newborn period and up to the age of 12 months.
Mineralocorticoid dose does not require adjustment by BSA.

For infants, sodium chloride 1-2 g/d due to mineralocorticoid resistance of the immature kidney.

Dose adjusted based on signs and symptoms of inadequate replacement and renin levels.

Infants require evaluation every 3 to 4 months to assess growth, blood pressure, and general well being.
4.0 MANAGEMENT AND PREVENTION OF ADRENAL CRISIS

Precipitating factors for adrenal crisis

- 423 patients were followed up for 2 years (221 pts had PAI)
- Precipitating factors of adrenal crisis in 46 patients during a prospective follow-up analysis. Multiple answers were possible.
- 8.3 crises per 100 patient-years
- Ten patients died during follow-up; in four cases death was associated with AC (0.5 AC related deaths per 100 patient-years).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Suggested Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home management of illness with fever</td>
<td>Hydrocortisone replacement doses doubled (&gt;$38°C$) or tripled (&gt;$39°C$) until recovery (usually 2 to 3 d); increased consumption of electrolyte-containing fluids as tolerated.</td>
</tr>
<tr>
<td>Unable to tolerate oral medication due to gastroenteritis or trauma</td>
<td>IM or SC hydrocortisone 100 mg</td>
</tr>
<tr>
<td>Minor to moderate surgical stress</td>
<td>Hydrocortisone, 25–75 mg/24 h (usually 1 to 2 d)</td>
</tr>
<tr>
<td>Major surgery with general anesthesia, trauma, delivery, or disease that requires intensive care</td>
<td>Hydrocortisone, 100 mg per IV injection followed by continuous IV infusion of 200 mg hydrocortisone/24h (alternatively 50 mg every 6 h IV or IM). Weight-appropriate continuous IV fluids with 5% dextrose and 0.2 or 0.45% NaCl. Rapid tapering and switch to oral regimen depending on clinical state.</td>
</tr>
<tr>
<td>Acute adrenal crisis</td>
<td>Rapid infusion of 1000 mL isotonic saline within the first hour or 5% glucose in isotonic saline, followed by continuous IV isotonic saline guided by individual patient needs. 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</td>
</tr>
<tr>
<td>Condition</td>
<td>Suggested Action</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Unable to tolerate oral medication due to gastroenteritis or trauma</td>
<td>IM hydrocortisone 50 mg/m² or estimate; infants, 25 mg; school-age children, 50 mg; adolescents, 100 mg</td>
</tr>
<tr>
<td>Minor to moderate surgical stress</td>
<td>IM hydrocortisone 50 mg/m² or hydrocortisone replacement doses doubled or tripled</td>
</tr>
<tr>
<td>Major surgery with general anesthesia, trauma, or disease that requires intensive care</td>
<td>Hydrocortisone 50 mg/m² iv followed by hydrocortisone 50–100 mg/m²/d divided q 6h. Weight-appropriate continuous iv fluids with 5% dextrose and 0.2 or 0.45% NaCl. Rapid tapering and switch to oral regimen depending on clinical state</td>
</tr>
<tr>
<td>Acute adrenal crisis</td>
<td>Rapid bolus of normal saline (0.9%) 20 mL/kg. Can repeat up to a total of 60 mL/kg within 1 h for shock. Children, hydrocortisone 50–100 mg/m² bolus followed by hydrocortisone 50–100 mg/m²/d divided q 6h</td>
</tr>
</tbody>
</table>
Measures for Prevention of Adrenal Crisis

- Identify and define the problem
  - Steroid emergency card (check that card is available and up to date)
  - Medical alert bracelet or necklace: “Adrenal insufficiency – needs steroids!

- Educate patient (and partner/parents)
  - Sick day rule 1: need to double the routine oral glucocorticoid.
  - Sick day rule 2: need to inject a glucocorticoid preparation IM or IV

- Give special attention to:
  - Explaining the rationale for dose adjustment in stress/sickness.
  - Discussing the situations requiring dose adjustment.
  - Discussing symptoms and signs of emergent adrenal crisis.
  - Teaching parenteral self-administration of glucocorticoid preparation.
  - Enforcing the need to go to hospital after emergency injection.

Provide patient with:

- Sufficient supply of hydrocortisone and fludrocortisone (accounting for possible sick days)
- Hydrocortisone emergency injection kit prescription (vials of 100 mg hydrocortisone sodium, syringes, needles)
- Leaflet with information on adrenal crisis and hospitalization to be shown to health care staff

Follow up:

- Reinforce education and confirm understanding during each follow-up visit
IMPORTANT MEDICAL INFO

This patient needs daily replacement therapy with cortisone.

In case of serious illness, trauma, vomiting or diarrhea, hydrocortisone 100 mg iv/r and iv saline infusion should be administered without delay.

Name

Person/number/Date of birth

European Society of Endocrinology
MEDICAL ALERT BRACELET

Pre-engraved "Adrenal Insufficiency" Medical Alert Identification Star of Life Marsala Designer bracelet.

$21.95

Add to Cart

Pre-engraved "Adrenal Insufficiency" Medical Alert Identification Star of Life Black Designer bracelet.

$24.95

Add to Cart

Pre-engraved "Adrenal Insufficiency" Medical Alert Identification Star of Life Black Designer bracelet.

$21.95

Add to Cart

Pre-engraved "Adrenal Insufficiency" Medical Alert Identification Star of Life Black Designer bracelet.

$9.99 - $13.95

See all buying options

Medical ID Bracelet

Waterproof ELITE USB black silicone medical alert ID bracelet with 2 GB USB (Black)

$36.95

Add to Cart

Pre-engraved "Adrenal Insufficiency" Elite Medical Alert Identification Black Advisor/Slim bracelet.

$21.85

Add to Cart

Pre-engraved Acrylic Plate "Adrenal Insufficiency" Elite Medical Alert Identification Bracelet - PINK. Choose from Diabetes, Blood

$27.95

Add to Cart
**Suggested Follow-up Routines For Patients With AI**

### History
- History focused on well-being, capacities in work and social life; sexuality, fertility, adrenal crises
- How much and when medication is taken
- Symptoms and signs of over and under replacement

### Physical examination
- Weight
- Blood pressure sitting/supine and standing
- Look for pigmentation changes, alopecia, vitiligo, goiter, and Cushingoid side effects
Suggested Follow-up Routines For Patients With AI

- **Recommended annual tests**
  - CBC, Na, K, creatinine, ferritin and cobalamin
  - TSH, free T4, anti-TPO
  - HbA1c
  - Renin/renin activity

- **Other tests**
  - Serum or salivary cortisol day curve to check bioavailability
  - Vitamin B12 def? methylmalonic acid, parietal cell and intrinsic factor abs
  - Celiac disease? Transglutaminase abs and total IgA (once)
  - Osteoporosis: DXA scan at start of follow up, around menopause depending on clinical situation

HUSEBYE AE., ADRENAL INSUFFICIENCY: INDIVIDUALIZED MANAGEMENT. 2016 MEET THE PROFESSOR: ENDOCRINE CASE MANAGEMENT. P24
PERSPECTIVES AND DEMAND FOR FUTURE RESEARCH

Diagnostic procedures

Salivary cortisol
- Potential biomarker
- Limitation-collection and analysis perspectives

Cortisol by LC-MS/MS
- Better standardization
- Free from analytical interference
- No cross-reactivity issues seen with IMA
- Ability to quantify multiple steroids

*Dx procedures and tx strategies are still far from being optimal
PERSPECTIVES AND DEMAND FOR FUTURE RESEARCH

- Dual and slow-release formulations of hydrocortisone
  - Aimed to mimic the cortisol circadian rhythm
  - Do not mimic the physiological pulsatile release of cortisol

Rituximab
- Newly diagnosed autoimmune PAI patients

Subcutaneous infusion
- Circadian rhythm
- Mimic early morning increase in cortisol
- Improvement in HRQoL?
- ACTH could be used as a biomarker