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*Hormone Science to Health*

# 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*

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# Epidemiology

| | |
|---|---|
| Prevalence | 100–140 cases/million |
| Incidence | 4/million/year |

*Erichsen et al. 2009, Wallace et al. 2009, Chakera and Vaidya 2010, Laureti et al.1999*

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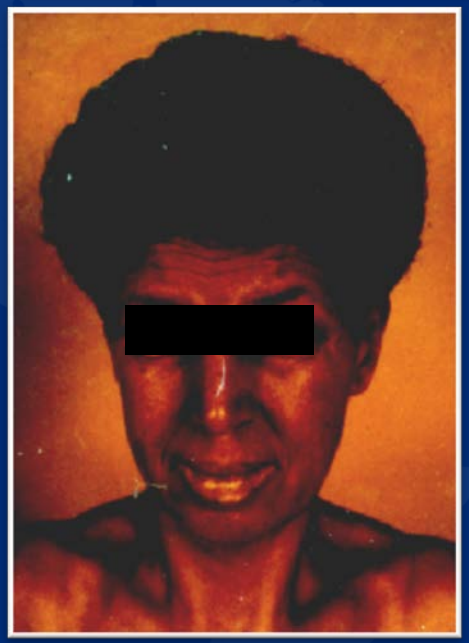
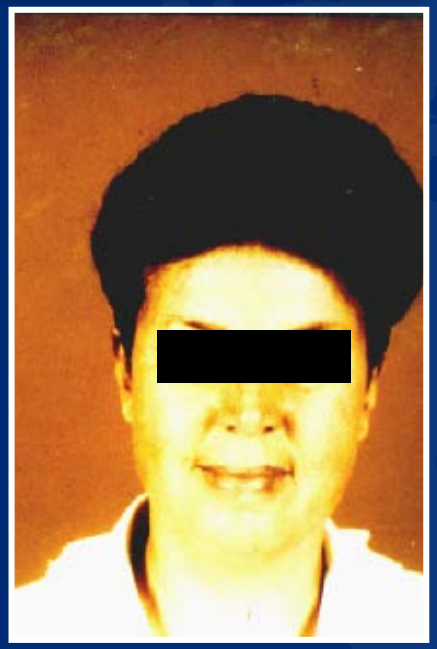
# Clinical Picture:
## Adrenal Insufficiency

Primary

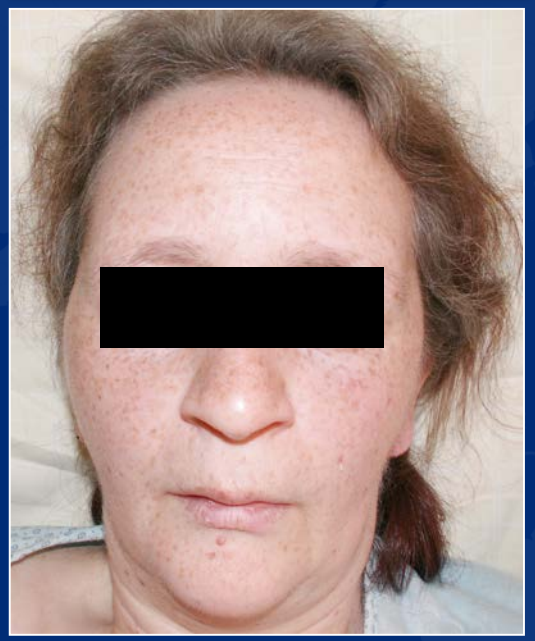


Before HC



After HC

Secondary



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# Clinical Features:
## Primary Adrenal Insufficiency

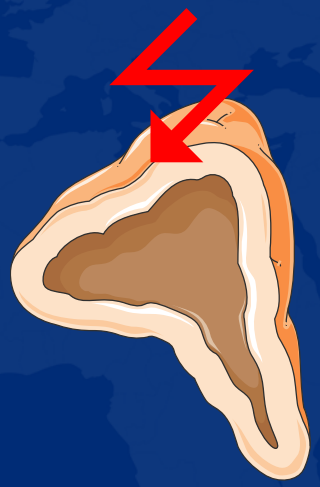
Confusion

Hyperpigmentation

Fatigue

Cortisol ↓

Weight loss



ACTH ↑

Dehydration

Hyponatremia

Abdominal pain

Hyperkalemia

Postural dizziness

Hypoglycemia

Hypotension

Renin ↑

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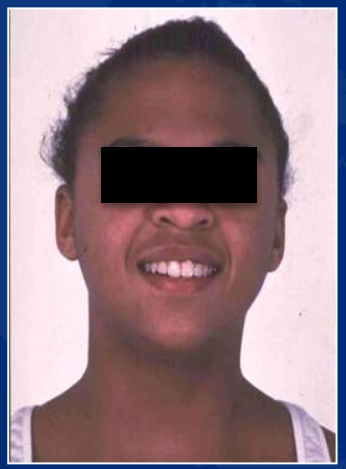
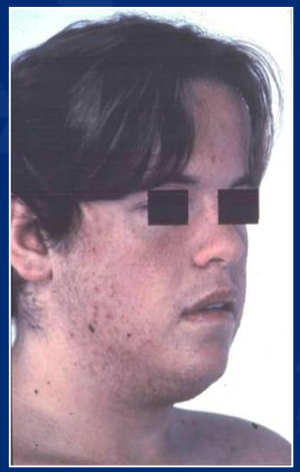
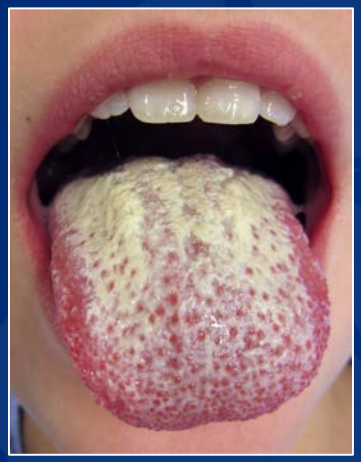
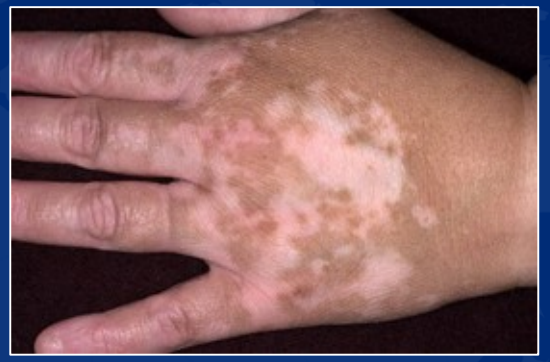
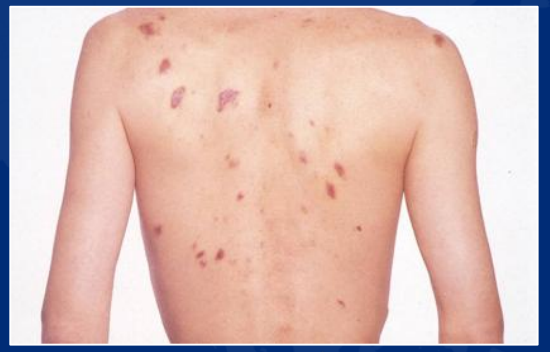
# Predisposing Factors:
## Adrenal Insufficiency



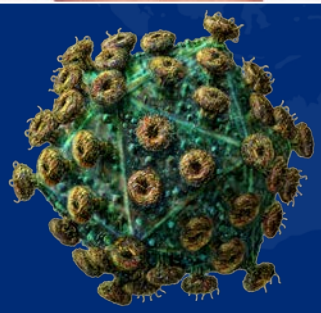












Bornstein SR. N Engl J Med. 2009 May 28;360(22):2328-39.

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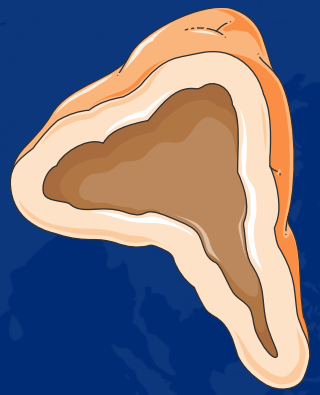
# Etiologies:
## Primary Adrenal Insufficiency (PAI)

- **<u>90% – Autoimmune</u>**
- Infiltration/Injury
- Drug Induced
- Congenital Adrenal Hyperplasia
- Adrenal Hypoplasia



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# II. Diagnosis

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# 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

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# GRADE Classification of Guideline Recommendations

| QUALITY OF EVIDENCE | | High Quality | Moderate Quality | Low Quality | Very Low Quality |
|---|---|---|---|---|---|
| *Description of Evidence* | | • *Well-performed RCTs*<br>• *Very strong evidence from unbiased observational studies* | • *RCTs with some limitations*<br>• *Strong evidence from unbiased observational studies* | • *RCTs with serious flaws*<br>• *Some evidence from observational studies* | • *Unsystematic clinical observations*<br>• *Very indirect evidence observational studies* |
| **STRENGTH OF RECOMMENDATION** | **Strong (1):**<br>**"We recommend…"**<br>*Benefits clearly outweigh harms and burdens, or vice versa* | 1\|⊕⊕⊕⊕ | 1\|⊕⊕⊕O | 1\|⊕⊕OO | 1\|⊕OOO |
| | **Conditional (2):**<br>**"We suggest…"**<br>*Benefits closely balanced with harms and burdens* | 2\|⊕⊕⊕⊕ | 2\|⊕⊕⊕O | 2\|⊕⊕OO | 2\|⊕OOO |

# Who should be tested and how?

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/⊕⊕⊕⊕)

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# 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/⊕⊕◯◯)

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

3. Random cortisol level < 138 nmol/l (5µg/dl) preliminary for PAI if corticotropin stimulation test is not feasible. (Grade 2/⊕◯◯◯)

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# 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.

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# 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

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# Diagnostic Approach to the Patient with PAI

Infants, selected children and adults

Primary Adrenal Insufficiency

All > 6 months age

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)

(+)

Adreno-leuko-dystrophy

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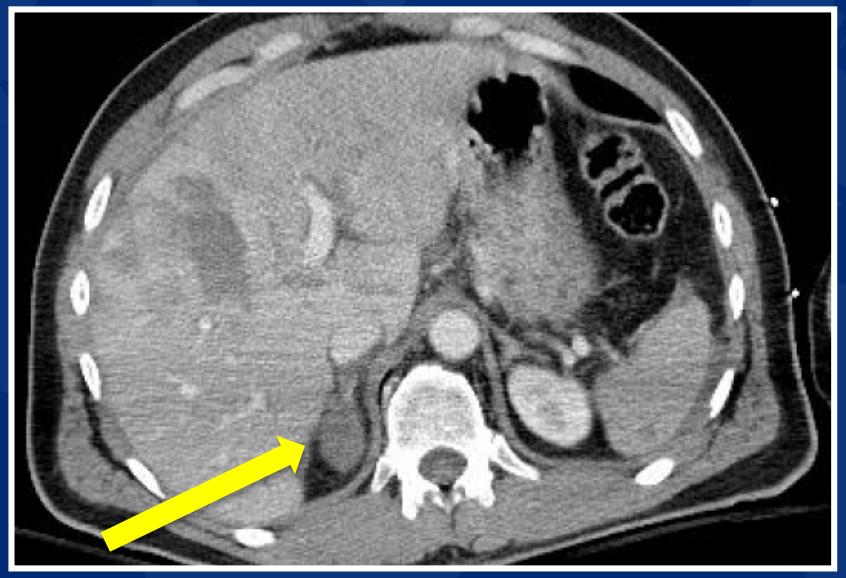
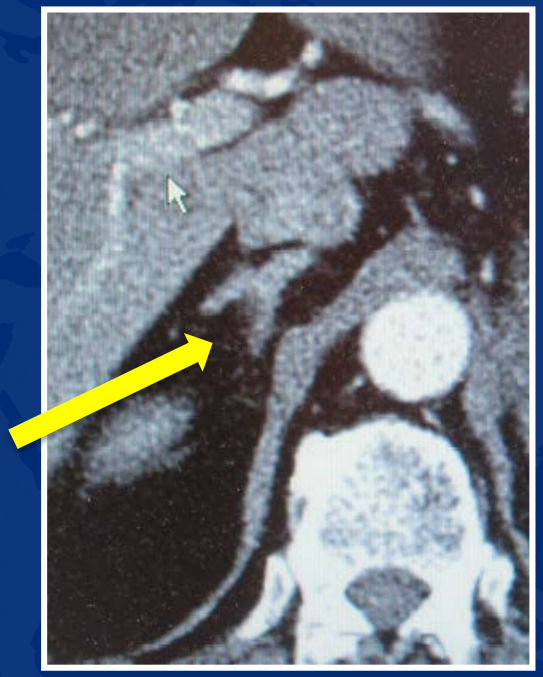
# Adrenal Gland CT Scan



Hematoma of the right adrenal



Normal right adrenal

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# III. Acute Management

# 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/⊕⊕⊕⊕)

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# Treatment: Glucocorticoids

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/⊕⊕○○)

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# Treatment: Mineralocorticoids

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

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

3. Suggestion: reducing and continuing fludrocortisone in hypertension. (Grade 2/⊕◯◯◯)

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# DHEA Treatment:
## Treating depression, low energy and libido

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

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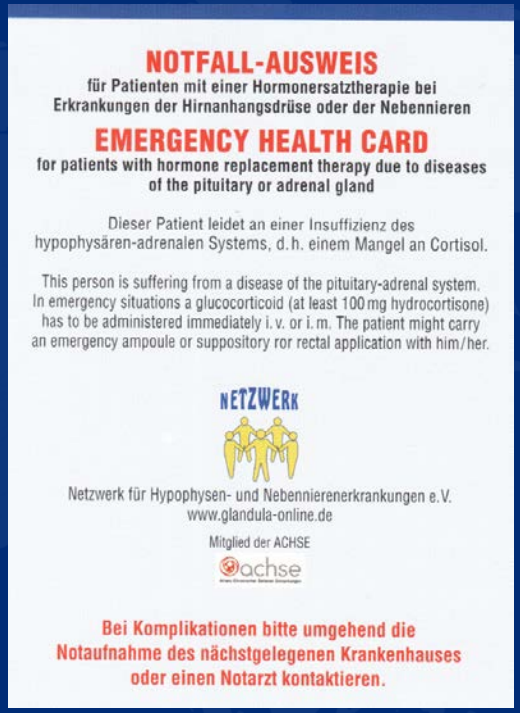
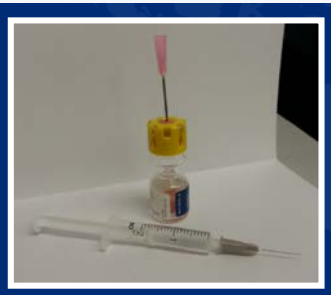
# Adrenal Crisis Prevention


- Steroid emergency card
- Education for patients and partners
- HC emergency injection kit prescription
- Alternative: suppositories prednisolone/HC



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# IV. Future Research

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# Future Research:
## Improving Diagnostics

### Utility of salivary cortisol

*Raff H et al. 2009. J Clin Endocrinol Metab 94:3647-3655*

### 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)

*Keevil BG et al. 2013. Best Pract Res Clini Endocrinol Metab 27:663-674.*

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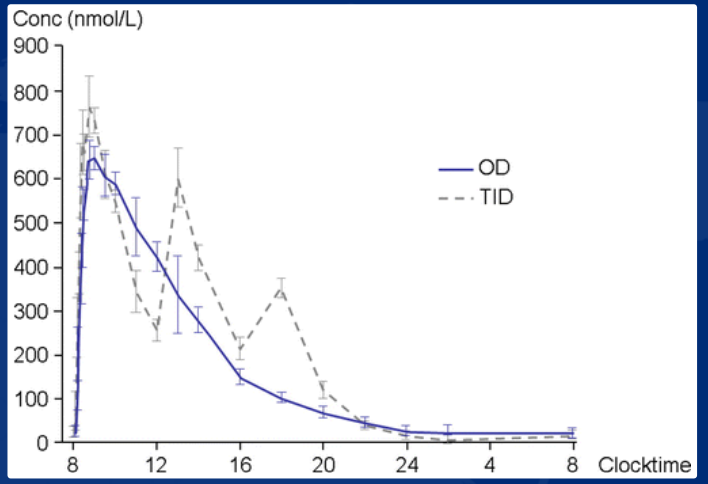
# Future Research:
## Improving Treatment

### Emerging Formulations

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

*Newell-Price J. et al. 2008. Clin Endocrinol 68:130-135.*
*Mallappa A. et al. 2014. J Clin Endocrinol Metab. Epub ahead of print.*




Johannsson G. et al. J Clin Endocrinol Metab. 97:473-481.

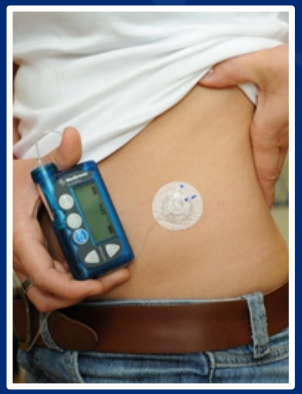
### Subcutaneous Administration

Cortisol replacement by means of continuous subcutaneous infusion

*Løvås K. et al. 2007. 157:109-112.*
*Oksnes M. et al. J Clin Endocrinol Metab 99:1665-1674.*

Pulsatile subcutaneous cortisol replacement

*Russell GM. et al. 2014. Clin Endocrinol (Oxf) 81:289-293.*



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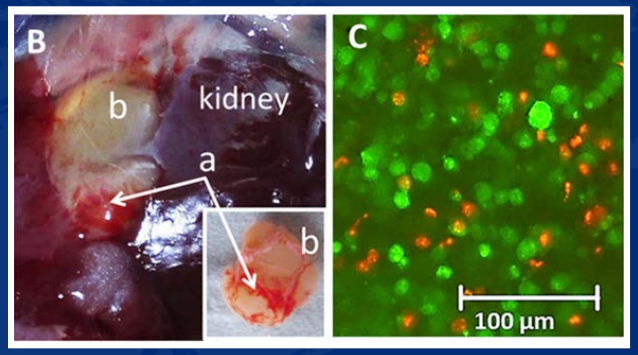
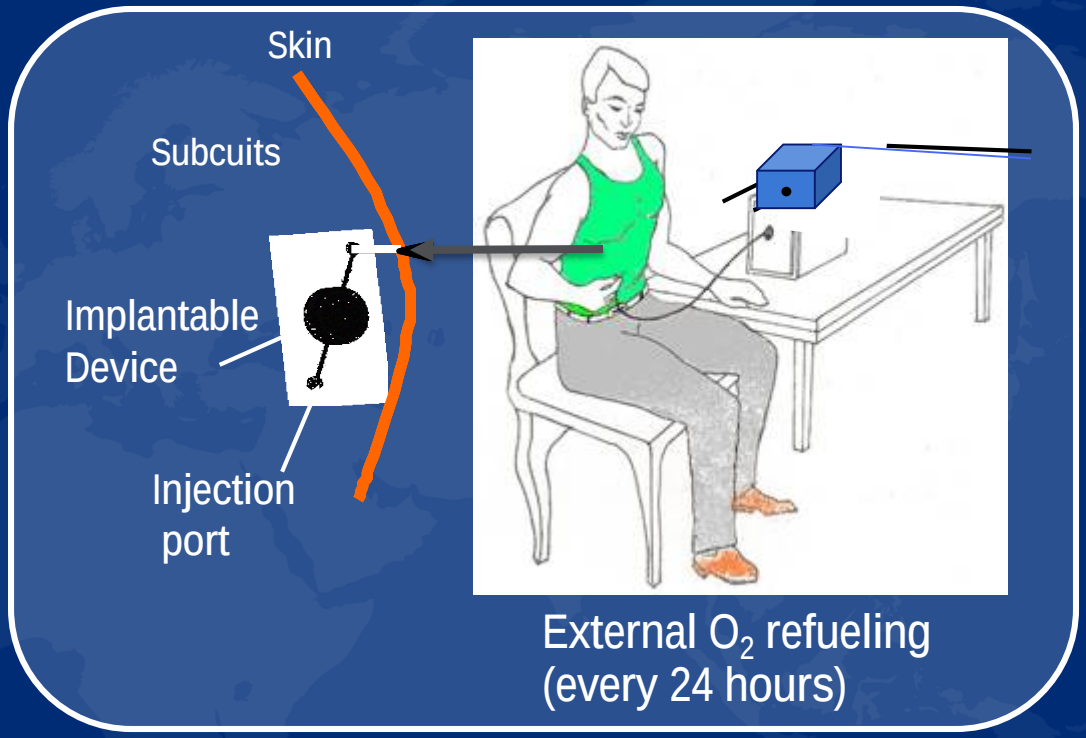
# Creating a Bioartificial Adrenal Gland




Transplantation of bovine adrenocortical cells encapsulated in alginate.

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




*Ludwig B… Bornstein SR. Proc Natl Acad Sci U S A. 2013 Nov19;110(47):19054-8.*
*Bornstein et al. Science Bx 2013*

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# V. Case Discussions

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# Clinical Practice

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

} Hypertension treatment of choice

# Dietary Considerations

! Increase mineralocorticoid effect of hydrocortisone

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# 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)

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# 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

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# CASE # 1 - Answer

## 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

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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

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## Prevent, Treat (acute), Inform

**P**revention of Adrenal Crises
Unwell – triple HC dose for 3 days 3x3 rule

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

**I**nformation for health carers
Card or leaflet to inform on use emergency HC
Medic Alert (unable to communicate)

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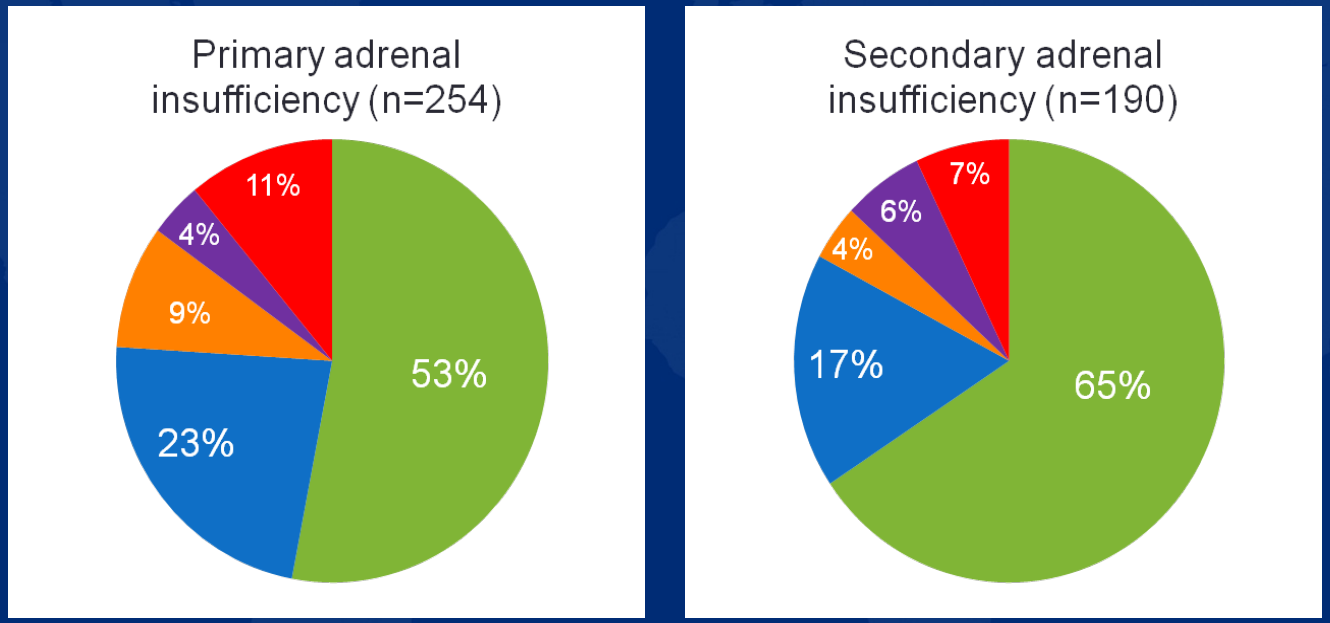
# Adrenal crisis risk in PAI and SAI

## Patients requiring hospital admission/ IV glucocorticoids since diagnosis




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

Hahner S et al. *Eur J Endocrinol* 2010;162:597–602

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# 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.

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# 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

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# Case #2: Pregnancy and PAI - Answer

How to handle with the glucocorticoid replacement during pregnancy?

A. Switch from HC to dexamethasone
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D. No increase of HC 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/⊕⊕◯◯)

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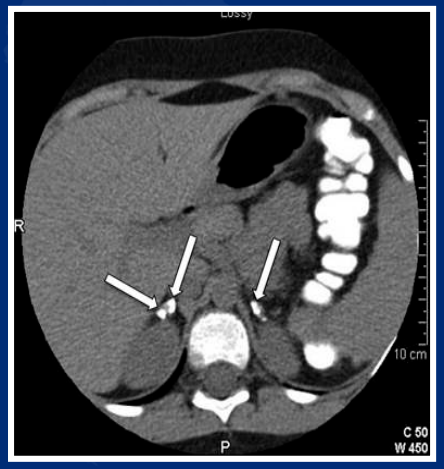
# Case #3: Suspected PAI

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.



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# 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

# Case #3: Suspected PAI - Answer

Laboratory evaluation.

ACTH = 2500 pg/mL (10-60 pg/mL)

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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

# 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/$m^2$ 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/⊕⊕◯◯)

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