Schweizerische Gesellschaft für Endokrinologie und Diabetologie – SGED
Société Suisse d'Endocrinologie et de Diabétologie – SSED
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Update SGED Oral Presentations (Presentation Workshops 2016)

# Treatment of Adrenal Insufficiency (AI)

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# Classification of Adrenal Insufficiency (AI)

| | Primary AI | Central AI (Secondary / Tertiary AI) |
|---|---|---|
| Estimated prevalence | 93-144 cases/mio.[1-4] | 150-280 cases/mio. [2, 5-8] |
| Estimated incidence | 4.4-6.0/mio./year[3] | Secondary AI: 20/mio./year[10] |
| Main etiologies[9] (Western countries) | • **Autoimmune** (Addison's) 85-90%<br>• Post Tb 10-15%<br>• Adrenoleucodystrophy<br>• Congenital adrenal hyperplasia<br>• Other (e.g. adrenal hemorrhage, HIV-infection, anti-phospholipid syndrome, drugs) | • **High-dose glucocorticoids** (tertiary AI)<br>• Hypothalamic-pituitary lesions/tumors: adenoma, craniopharyngeoma, apoplexy, surgery, irradiation, infiltrative diseases (eg. Langerhans-Cell-histiocytosis)<br>• Congenital (rare) |
| Pathogenesis/Consequences | Destruction of adrenal cortex<br>Impaired hormone production/secretion<br>• Glucocorticoid deficiency<br>• Mineralocorticoid deficiency<br>• Androgen deficiency (DHEA) | ACTH-/CRH-deficiency<br>• Glucocorticoid deficiency<br>• Androgen deficiency (DHEA) |


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2 Laureti, J Clin Endocinol Metab, 1999.
3 Lovas, Clin Endocrinol (Oxf), 2002.
4 Erichsen, J Clin Endocinol Metab, 2009.
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8 Tomlinson, Lancet, 2001.
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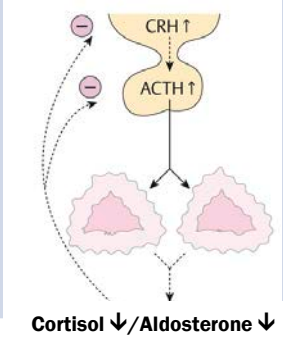
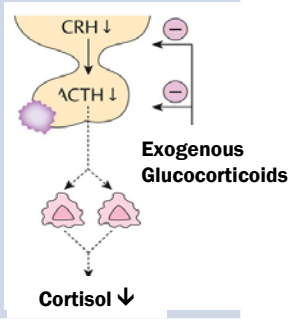
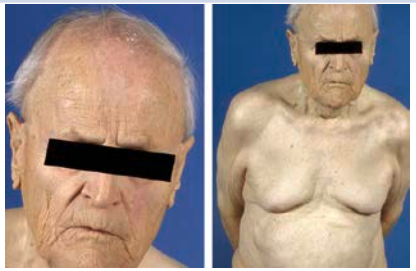


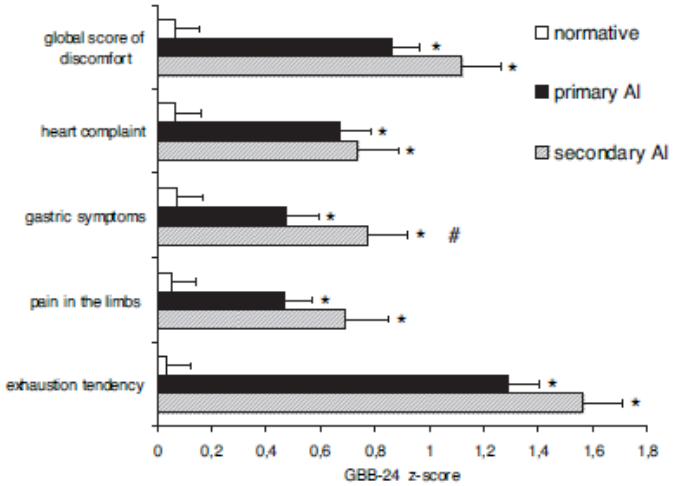
# Clinical Presentation/Treatment of Adrenal Insufficiency

| | Primary AI | Central AI (Secondary / Tertiary AI) |
|---|---|---|
| Signs/Symptoms | • Symptoms of adrenal insufficiency: Malaise, fatigue, GI-symptoms, weight loss, fever<br>• Hyperpigmentation (only primary AI)<br>• Volumedepletion/hypotension/shock<br>• Hypoglycemia (rare in adults)<br>• Signs/symptoms of other autoimmune diseases (e.g. thyorid gland) | • Symptoms of adrenal insufficiency: Malaise, fatigue, GI-Symptoms, weight loss, fever<br>• **No** hyperpigmentation<br>• Hypotension less prominent<br>• Signs/symptoms of pituitary dysfunction and local tumor growth (e.g. visual field deficits) |
| Laboratory parameters | • Low basal/stimulated cortisol<br>• ACTH high<br>• Hyponatremia<br>• Hyperkalemia<br>• Hypercalcemia (rare)<br>• Metabolic acidosis | • Low basal/stimulated cortisol<br>• ACTH low/normal<br>• Hyponatremia (ADH-mediated) |
| Treatment | • Glucocorticoids<br>• Mineralocorticoids | • Only Glucocorticoids |



# Adrenal Insufficiency – Quality of Life and Prognosis

- *Quality of life* and *health status* in patients with primary/central AI – even on current standard replacement – therapy is impaired:
  - Significantly lower quality of life[1-3]
  - Fatigue, lack of energy, affective disorders[4]
  - Higher likelihood of working inability (18-26%)[1,2]
- *Mortality*
  - Primary AI: increased[5,6] / not increased[7] compared to the general population
  - Central AI: increased in patients with hypopituitarism[8,9]; impact of glucocorticoid dose[10,11]




Hahner, J Clin Endocinol Metab, 2009.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3 Bleicken, Eur J Endocrinol, 2008.
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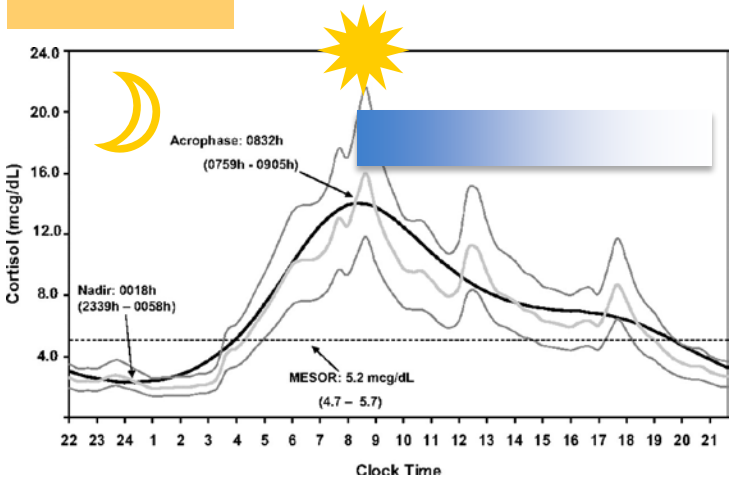
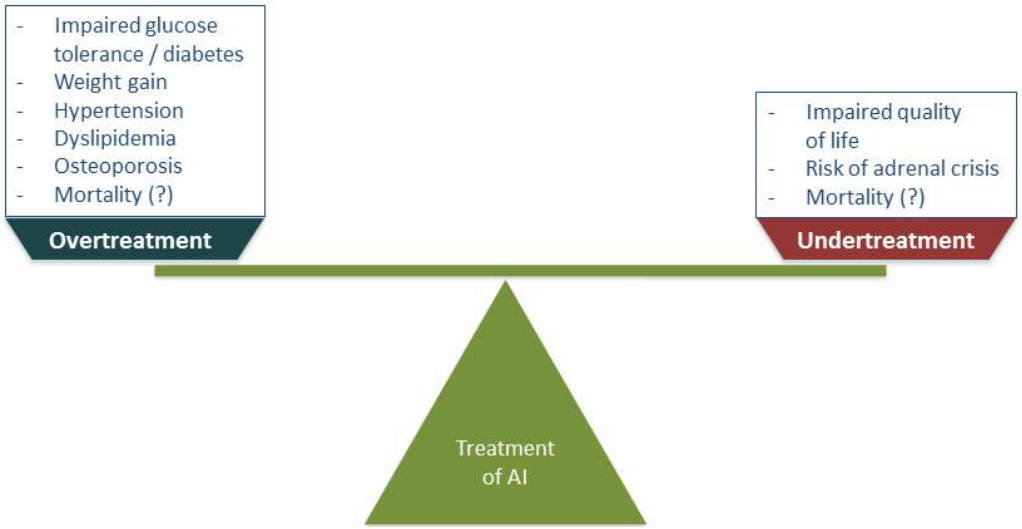
6 Bensing, Clin Endocinol (Oxf), 2008.
7 Erichsen, Eur J Endocrinol, 2009.
8 Rosén, Lancet, 1990.
9 Tomlinson, Lancet, 2001.
10 Sherlock, J Clin Endocrinol Metab, 2009
11 Zueger, J Clin Endocrinol Metab, 2012.

# Treatment of AI – General Principles

- *Goals of an ideal therapy*
  - No/little restriction in activities of daily life/sports
  - Easy and rapid dose adjustment (illness etc.)
  - Minimize the risk of adverse effects of glucocorticoids
  - Mimic the circadian rhythm of physiological cortisol secretion




Debono, J Clin Endocinol Metab, 2009.

# Treatment of AI – Hydrocortisone Treatment

**Average daily cortisol secretion rate[1-4]**

5-10 mg/m²

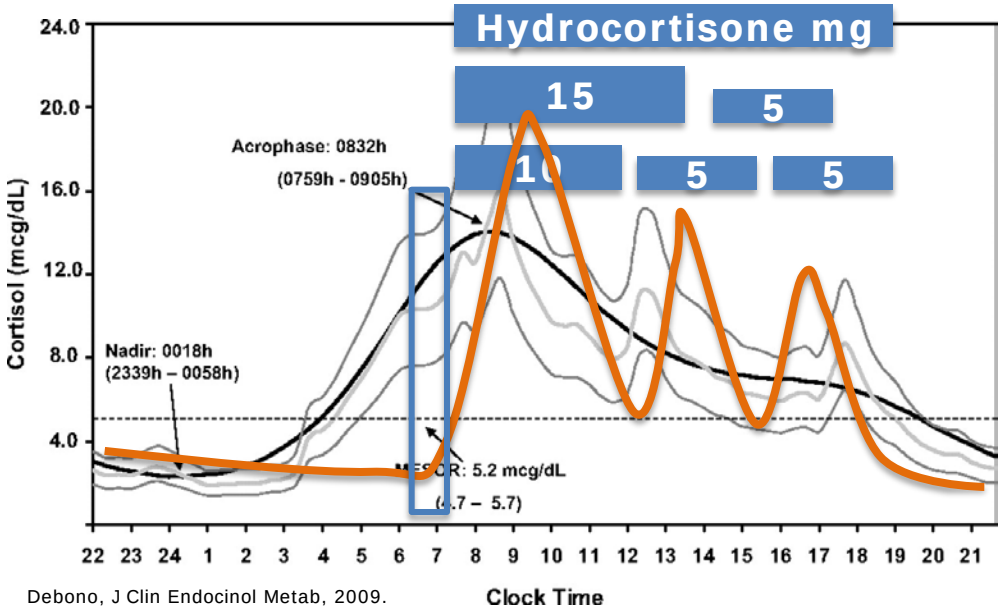
Intraindividual variation of metabolism

**Hydrocortisone -dose[5,6]**

10-12 mg /m²/day

15-25 mg/day

2-3 doses (2/3 → morning after awakening)

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1 Esteban, J Clin Endocrinol Metab, 1991.
2 Kerrigan, J Clin Endocrinol Metab, 1993.
3 Kraan, J Clin Endocrinol Metab, 1998.
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5 Khelet, Clin Endocrinol (Oxf), 1976.
6 Allolio, Akt Endokr Stoffw, 1985.

# Treatment of AI – General Principles

- **Glucocorticoid replacement therapy**
  - Hydrocortisone (Hydrocortison Galepharm®, Hydrocortone® not on SL)
    - 15-25 mg/day in 2-3 doses
    - Doses of ≤ 25 mg/day: BMD not affected[1-3] (DEXA is *not* indicated)
  - Longer acting glucocorticoids only in exceptions (i.e. adherence problems)
    - Prednisolone (e.g. Spiricort®): 1x3-5 mg/day

    → Adverse effects (?) of longer acting glucocorticoid preparations[4,5]
  - Individual dosing important
  - Dual-release hydrocortisone preparation (Plenadren®)[6] is available (not approved in CH)

- **Mineralocorticoid replacement therapy**
  - *Only* in patients with primary AI
  - Fludrocortisone (Florinef®): 0.1-0.2 mg/day (single morning dose)

1 Arlt, Clin Endocrinol (Oxf), 2006.
2 Braatveld, Osteoporosis Int, 1999.
3 Koetz, J Clin Endocrinol Metab, 2012.
4 Falorni, Endocrine, 2013.
5 Arlt, J Clin Endocrinol Metab, 2009.
6 Johannsson, J Clin Endocrinol Metab, 2009.

# Treatment of AI – Monitoring of Therapy

**Glucocorticoid replacement therapy**

- Weight, BP
- Signs/symptoms of overreplacement: i.e. weight gain, hypertension, hyperglycemia
- Signs/symptoms of underreplacement: i.e. fatigue, nausea, weight loss

→ Monitoring relies on clinical not on biochemical (i.e. plasma cortisol) parameters

**Mineralocorticoid replacement therapy**

- BP (sitting and upright)
- Peripheral edema
- Check serum sodium/potassium
- Symptoms of overreplacement: hypertension, hypokalemia
- Symptoms of underreplacement: orthostatic hypotension (postural drop of syst. BP > 20mm Hg)

**General Issues:**

- Self-adjustment necessary?; emergency treatment/hospitalisation?
- Emergency measures (instructions; emergency card; hydrocortisone kit)
- Check TSH, Vit. B12 in primary AI
- Follow-up in endocrinological consultation
- Check for medicamentous interactions

**Interactions**

**CYP3A4 induction** (HC metabolism ↑):
e.g. mitotane, rifampicin, phenytoin, carbamazepine, topiramate, phenobarbital

**CYP3A4 inhibition** (HC metabolism ↓):
e.g. antiretroviral treatment, fluoxetine, grapefruit juice

# Adrenal Crisis

- Adrenal crisis is a *life-threatening event* which is often predictable but under-managed[1] (incidence: 5-10/100 patient years[2-6])
- Remains an important *cause of death* in patients with AI[7-10] (reported mortality is about 0.5/100 pat. years[6])
- *Problems:*
  - Lack of identification of precipitating factors and lack of adjustment of glucocorticoid dose
  - Assessment is impaired due to unspecific, preceeding symptoms (e.g. malaise, GI-symptoms, fever)
  - Delayed administration of i.v.-glucocorticoids[11]

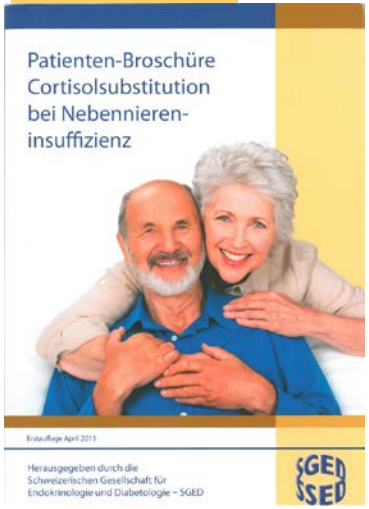
**Triggering factors for adrenal crisis / frequency in %[2]**

| | |
|---|---|
| • GI-infections | 22-33 |
| • Other febrile infections | 17-24 |
| • Surgery | 7-16 |
| • Intense physical activity | 7-8 |
| • Psychological stress | 4-6 |

1 White, European J Endocrinol, 2010.
2 Hahner, European J Endocrinol, 2010.
3 Reisch, European J Endocrinol, 2012.
4 Ritzel, J Clin Endocrinol Metab, 2013.
5 White, European J Endocrinol, 2010.
6 Hahner, European J Endocrinol, 2015.
7 Bergthorsdottir, J Clin Endocrinol Metab, 2006.
8 Bensing, Clin Endocinol (Oxf), 2008.
9 Burman, J Clin Endocrinol Metab, 2013.
10 Erichsen, Eur J Endocrinol, 2009.
11 Hahner, Clin Endocrinol (Oxf), 2015.

# Prevention of Adrenal Crisis[1,2]


- Emergency identification card
- Consider prescribing a hydrocortisone emergency kit (Solu-CORTEF® Act-O-Vial 100 mg); i.m. or s.c.[3]-injection
- Continuing education of patient/family
  - Dose adjustment/«sick-day rules»
  - Identification of triggering factors, symptoms of acute AI
  - Vomiting/diarrhea are urgent indications for parenteral glucocorticoid administration!




1 Allolio, European J Endocrinol, 2015.
2 Quinkler, Dtsch Arzebl Int, 2013.
3 Hahner, European J Endocrinol, 2013.

**Dose adjustments of glucocorticoid therapy in different situations**

**«Minor» Stress**
- Common cold
- Fever 37.5-38°C
- Slight physical activity
- Minor medical procedures (e.g. gastroscopy)

→ *1.5-2x of standard dose*

**«Moderate» Stress**
- Fever 38-39°C
- Strenuous physical acticity
- Medical procedures (e.g. excision in local anesthesia)

→ *2-3x of standard dose*

**«Major» Stress**
- Fever >39°C
- Surgery in general anesthesia
- Childbirth
- Pneumonia

→ *3-4x of standard dose*
→ Consider i.v.-glucocorticoids

→ Return to standard dose within 2-3 days after recovery