Stress dosing for Illness/Surgery/Exercise in Adrenal Insufficiency

L. Kurt Midyett, MD
Medical Director
Midwest Women’s & Children’s Specialty Group
Overland Park Regional Medical Center
Stress & Adrenal Insufficiency

Objectives:

1. Review the function of the adrenal gland and disorders associated with the adrenal gland

2. To discuss the general steroid dosing in patients with adrenal insufficiency

3. Review the lack of precision in the management of adrenal insufficiency

4. Discuss how to approach the dosing of steroids before, during, and after illness, surgery, and exercise
Function of the adrenal gland
Stress & Adrenal Insufficiency

How cortisol is released
Stress & Adrenal Insufficiency

Anatomy of the Adrenal Gland

Transverse Section

Microscopic Section

Capsule

Glomerulosa

Fasciculata

Cortex

Reticularis

Medulla

Chromaffin cells
Medullary veins
Splanchnic nerves

Mineralocorticoids

Glucocorticoids

Adrenal Androgens

Catecholamines
Epinephrine
Norepinephrine
Stress & Adrenal Insufficiency

Type of adrenal insufficiency:

- **Primary** adrenal insufficiency occurs due to damage of the adrenal gland high ACTH levels are present.
  - Autoimmune (Addison’s disease)
  - Damage to the adrenal gland (infection, bleeding, etc.)
  - Congenital Adrenal Hyperplasia (CAH)

- **Secondary** adrenal insufficiency occurs due to damage of the pituitary gland. ACTH levels are low to normal.
  - Disorders of the pituitary gland
  - Long-term steroid use

- **Tertiary** adrenal insufficiency also shows low to normal ACTH levels, but is different from secondary adrenal insufficiency. CRH is released from the hypothalamus.
Stress & Adrenal Insufficiency

Patterns of cortisol release

Diurnal Rhythm

Ultradian Rhythm
Stress & Adrenal Insufficiency

The complex manner in which cortisol is naturally released and converted between active and inactive forms makes it very difficult to achieve a “physiological” replacement therapy with oral steroids such as hydrocortisone.
General steroid dosing in patients with adrenal insufficiency
Stress & Adrenal Insufficiency

How much cortisol to we naturally produce?

In a study of five men (aged 26.2 ± 5.4 years) and seven women (aged 29.1 ± 5.3 years), they estimated the cortisol production rate to be 27.3 ± 7.5 µmol/day (equivalent to 5.7 mg/m²/day or approximately 9.9 mg/day).¹

In a study of 18 males in early and late puberty, the estimated average total daily cortisol production rate was also 5.7 ± 0.3 mg/m²/day.²


As mentioned on the previous slide...

...estimates have established the cortisol production rate to be around 5.7–7.4 mg/m²/day. The recommendation is for oral daily hydrocortisone doses of 10–12 mg/m²/day or 15–25 mg, allowing for first-pass hepatic metabolism and <100% bioavailability.

However, the use of fixed-dose treatment regimens of hydrocortisone is debatable in view of the variability in cortisol kinetics between individual patients.
Stress & Adrenal Insufficiency

After an oral hydrocortisone dose of 10–20 mg, peak concentrations ranged from 422 to 1554 nmol/l and clearance from 0.081 to 0.363 l/hr/kg.¹

Similarly, in 50 patients with adrenal insufficiency, on hydrocortisone, the inter-subject variability in volume of distribution was 39.7% and clearance 23.2%,

AND over 50% of patients had cortisol concentrations outside the physiological range during treatment.²


Stress & Adrenal Insufficiency

The cortisol production rate may also vary up to fivefold from lowest to highest values.

Under stable conditions, there is relatively little intra-individual variance in the circadian rhythm of cortisol, but day to day differences in stressful episodes and lifestyle changes will cause intra-individual variability.

The between-patient variability in cortisol pharmacokinetics could be explained by a number of factors including weight, age, gender, cortisol-binding proteins, sensitivity to cortisol and metabolism of cortisol\(^1\)

---

Glucocorticoid-deficient patient: start hydrocortisone 10 + 5 mg daily

Review need for other hormone replacement therapy

Is the patient feeling well? → YES

NO → Explore other causes (based on history and examination)

Consider TDS split e.g. hydrocortisone 10 + 2.5 + 2.5 mg daily

Is the patient feeling well? → YES

NO → Consider increased dose of hydrocortisone e.g. 10 + 5 + 5 mg daily

Is the patient feeling well? → YES

NO → Consider ‘day curve’ assessment of serum cortisol

Primary hypoadrenalism: fludrocortisone

Secondary hypoadrenalism: assess other axes and replace as indicated

Fig. 1 Algorithm for treatment of the glucocorticoid-deficient patient. Patients should be reassessed at 6–8 week intervals while their treatment is optimized.
Stress & Adrenal Insufficiency

What’s the problem with too much steroids?

It is well recognized that an association exists between glucocorticoid excess and osteoporosis (Cushing, 1932). In patients treated with pharmacological doses of glucocorticoids there was is an increased risk of fractures.

Other potential adverse effects of excessive glucocorticoid replacement therapy have been demonstrated including elevation of plasma glucose and insulin.

Stress & Adrenal Insufficiency

What’s the problem with too much steroids?

For kids and adolescents, too much steroid can also have the effect of slowing their growth

• Important to monitoring linear growth closely in all children with an adrenal imbalance
Stress & Adrenal Insufficiency

What’s the problem with too much steroids?

Unfortunately, much of the data for excess steroid therapy is based on “pharmacological” dosing (meaning doses used to treat patients with other medical problems such as cancer, pulmonary, or rheumatology issues).

“physiological” doses are NOT pharmacological doses
Management of adrenal insufficiency is an imprecise science
Stress & Adrenal Insufficiency

European Adrenal Insufficiency Registry

Table 1. Demographic parameters of patients enrolled into the EU-AIR

<table>
<thead>
<tr>
<th></th>
<th>Primary AI</th>
<th>Secondary AI</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number, n</td>
<td>364</td>
<td>801</td>
<td>1166</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>237 (65-1)</td>
<td>374 (46-7)</td>
<td>612 (52-5)</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>52.0 ± 15-8</td>
<td>55-2 ± 16-0</td>
<td>54.3 ± 16-0</td>
</tr>
<tr>
<td>Disease duration, n (mean ± SD)</td>
<td>364 (17-6 ± 12-8)</td>
<td>800 (15-4 ± 10-9)</td>
<td>1164 (16-1 ± 11-6)</td>
</tr>
<tr>
<td>BMI, kg/m², n (mean ± SD)</td>
<td>321 (26-2 ± 4-8)</td>
<td>695 (28-8 ± 5-1)</td>
<td>1016 (27-0 ± 5-2)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>51 (14-0)</td>
<td>94 (11-7)</td>
<td>145 (12-4)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>92 (25-3)</td>
<td>263 (32-8)</td>
<td>355 (30-4)</td>
</tr>
</tbody>
</table>

AI, adrenal insufficiency; BMI, body mass index; EU-AIR, European Adrenal Insufficiency Registry; SD, standard deviation.

Stress & Adrenal Insufficiency

European Adrenal Insufficiency Registry

- 87.4% of all patients were receiving hydrocortisone
  - 5.1% patients were receiving prednisolone
  - 4.0% cortisone acetate
  - 0.1% were receiving dexamethasone
  - 2.7% steroid dose was unknown
  - 0.7% were on a combination of steroids

- Hydrocortisone was the most commonly utilized glucocorticoid replacement therapy in patients with both primary (84.9%) and secondary AI (88.5%)

Stress & Adrenal Insufficiency

European Adrenal Insufficiency Registry

Hydrocortisone was being taken
once daily by 56 patients (5.5%),
twice daily by 496 patients (48.7%),
three times daily by 444 patients (43.6%)
four times daily by 21 patients (2.1%).

Two patients (0.2%) were taking hydrocortisone at a
higher frequency.

Patients with primary AI were more likely to be receiving
hydrocortisone three times daily than those with secondary
AI 53.7% vs 39.2%, respectively

Murrey RD, et al. Management of glucocorticoid replacement in adrenal insufficiency shows notable heterogeneity – data from the EU-AIR.
Clinical Endocrinology (2017), 86, 340–346
Stress & Adrenal Insufficiency

European Adrenal Insufficiency Registry

• In patients receiving hydrocortisone, the daily dose varied widely, ranging from 5 mg to >45 mg.

• The most common dose range taken by patients with AI was 20 to <25 mg/day

• A greater proportion of patients with primary AI were receiving hydrocortisone doses of 30 mg/day or more compared with those with secondary AI, 21.4% vs 8.8%, respectively

Stress & Adrenal Insufficiency

European Adrenal Insufficiency Registry

Twenty-five different regimens were being used to deliver a daily dose of 20 mg hydrocortisone;

- the most common regimen (used by 28.2% of patients) was 10 mg administered in the morning, 5 mg at midday and 5 mg in the evening

- The second most frequent regimen was use of hydrocortisone as a twice-daily regime: 10 mg in the morning and a further 10 mg at midday (18.0%).

- The third most common regimen was 10 mg administered in the morning, 5 mg at midday and 5 mg in the afternoon (17.2%)

Stress & Adrenal Insufficiency

Use clinical monitoring by asking patients about the symptoms and signs of cortisol under- and over-replacement including fatigue and weight gain, but also recommend a serum cortisol measured approximately 4 h after a morning hydrocortisone dose as this predicts 78% of variability in AUC of cortisol.¹

¹ Debono M, Ross RJ. What is the best approach to tailoring hydrocortisone dose to meet patient needs in 2012? Clinical Endocrinology (2013) 78, 659–664
Steroid dosing and Illness
Stress & Adrenal Insufficiency

Stress dosing guidelines

<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>Adults, im or sc hydrocortisone 100 mg; children, 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>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>Children, im hydrocortisone 50 mg/m² or hydrocortisone replacement doses doubled or tripled Hydrocortisone, 100 mg per iv injection followed by continuous iv infusion of 200 mg hydrocortisone/24 h (alternatively 50 mg every 6 h iv or im)</td>
</tr>
<tr>
<td></td>
<td>Children, hydrocortisone 50 mg/m² iv followed by hydrocortisone 50–100 mg/m²/d divided q 6 h</td>
</tr>
<tr>
<td></td>
<td>Weight-appropriate continuous iv fluids with 5% dextrose and 0.2 or 0.45% NaCl</td>
</tr>
<tr>
<td></td>
<td>Rapid tapering and switch to oral regimen depending on clinical state</td>
</tr>
<tr>
<td></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</td>
</tr>
<tr>
<td></td>
<td>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></td>
<td>Children, 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.</td>
</tr>
<tr>
<td></td>
<td>Children, hydrocortisone 50–100 mg/m² bolus followed by hydrocortisone 50–100 mg/m²/d divided q 6 h</td>
</tr>
<tr>
<td></td>
<td>For hypoglycemia: dextrose 0.5–1 g/kg of dextrose or 2–4 mL/kg of D25W (maximum single dose 25 g) infused slowly at rate of 2 to 3 mL/min. Alternatively, 5–10 mL/kg of D10W for children &lt;12 y old</td>
</tr>
<tr>
<td></td>
<td>Cardiac monitoring: Rapid tapering and switch to oral regimen depending on clinical state</td>
</tr>
</tbody>
</table>

Stress & Adrenal Insufficiency

During illness and stress, the body automatically increases the production of cortisol to react to the stress/illness so that the body can heal faster. With adrenal insufficiency, however, the body is not able to do this on its own. This then needs to be done artificially by increasing the amount of hydrocortisone you are taking.

Stress dosing is given for any of the following reasons:
- Fever 101°F or higher
- Diarrhea
- Vomiting
- Ear infection
- Strep throat
- Pneumonia
- Bronchitis
- Broken bone
- Sprain or strain
- Serious injury/accident
- Surgical procedure Immunizations

Stress dosing: Double your cortisol dose for 3 days.
Stress & Adrenal Insufficiency

- If your fever is 100.4°F or higher, then double your dose (______ mg).

- If your fever is 102°F or higher, then triple your dose (_____ mg).

- If you experience vomiting and/or diarrhea, then double or triple your dose depending on severity. Take a double dose for mild to moderate symptoms and a triple dose for severe symptoms.

- If you vomit, wait half an hour, and repeat the dose. If you are vomiting and cannot keep the hydrocortisone medicine down (vomiting less than one hour after the dose), you need to administer injectable hydrocortisone (Solu-Cortef) or dexamethasone, and contact your physician. Do not delay the injection; give the medicine first, and then call your doctor to discuss when you need to be seen.
Steroid dosing and Surgery
Stress & Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Publication</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller’s anesthesia 8e13</td>
<td>Acknowledge “a precise amount required has not been established”: IV 200 mg/day hydrocortisone phosphate per 70 kg of body weight or for minor procedure 100 mg/day hydrocortisone phosphate per 70 kg of body weight and then decreased at 25% per day until PO intake of maintenance dose can be resumed</td>
</tr>
<tr>
<td>Clinical anesthesia 7e5</td>
<td>Acknowledge both “an extensive review concluded that the best evidence was that patients should receive usual daily dose but no supplementation” and “many clinicians are unwilling to adopt the regimen until further trials have been undertaken in patients receiving physiologic steroid replacement” and ultimately give “popular regimen”: 200–300 mg of hydrocortisone per 70 kg of body weight in divided dose on the day of surgery, with adjustment in dose based on extent and duration of surgery and patients are to take their daily dose of steroids</td>
</tr>
</tbody>
</table>
| Anesthesia and coexisting disease 6e2 | Surgery Recommendations
Superficial | Daily dose only |
Minor | Daily dose plus hydrocortisone (25 mg IV) |
Moderate | Daily dose plus hydrocortisone (50–75 mg, taper 1–2 days) |
Major | Daily dose plus hydrocortisone (100–150 mg, taper 1–2 days) |
| UpToDate: The Surgical Patient Taking Glucocorticoids33 | Non-suppressed (HPA) axis – defined as taking exogenous steroids for less than 3 weeks, or prednisone (<5 mg daily or its equivalent) for any duration, or less than 10 mg of prednisolone or its equivalent every other day; we suggest continuing the same glucocorticoid regimen perioperatively (Grade 2C). These patients are unlikely to have a suppressed HPA axis, and neither preoperative evaluation of the HPA axis nor supraphysiologic doses of glucocorticoids are needed. |
In suppressed patients (defined as equivalent to prednisolone 20 mg/day for 3 weeks or more), recommendations are surgery specific
| Surgery Recommendations
Minor | Morning dose only |
Moderate | Morning dose plus IV 50 mg of hydrocortisone before incision; then IV 25 mg every 8 h for 24 h and then maintenance |
Major | Morning dose plus IV 100 mg of hydrocortisone before induction; then IV 50 mg every 8 h for 24 h; Taper dose by half per day to maintenance level |
| Bornstein et al.: Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society Clinical Practice Guideline6 | Acknowledge the “proposed glucocorticoid regimen in the management of adrenal crisis places a higher value on the prevention of underdosage than on reducing potential negative effects of short-term overdosage” as “under-dosing of glucocorticoids in an adrenal crisis is potentially hazardous. . . . Harm from these doses has not been shown, and direct studies indicating that lower doses are safe do not exist.” |
Glucocorticoid dose adjustment based on severity of illness or magnitude of stressor, as follows:
| Surgery | Recommendations |
Minor to moderate | Hydrocortisone, 25–75 mg/24 h (usually 1–2 days) |
Major surgery, trauma, delivery, disease that requires intensive care, suspected adrenal crisis | Hydrocortisone 100 mg IV followed by continuous IV infusion of hydrocortisone 200 mg/24 h (alternatively 50 mg every 6 h IV/IM) |

HPA = hypothalamic-pituitary-adrenal; IM = intramuscular; IV = intravenous; PO = per os.

Stress & Adrenal Insufficiency

• In 1997, Glowniak and Loriaux studied 18 male patients taking prednisone for at least 2 months for various conditions with baseline secondary adrenal insufficiency as determined by Cosyntropin study.

• Patients underwent various surgical procedures using different anesthetic techniques. Patients were randomized to receive stress-dose steroid injections (100 mg of cortisol in normal saline) versus control (normal saline).

• No significant perioperative differences in hemodynamic parameters were found between groups.

• The authors concluded that patients with secondary adrenal insufficiency as a result of chronic steroid therapy do not experience hypotension in the absence of stress-dose steroid administration and can be maintained on their usual daily dose of steroids in the perioperative period.


Stress & Adrenal Insufficiency

- Thomason et al. studied 20 organ transplant patients on chronic steroid therapy for immunosuppression presenting for gingival surgery under local anesthesia.

- Patients were randomized to receive stress-dose steroids versus placebo. Each patient required at least two operations and thus served as their own control.

- Serum ACTH levels were drawn pre- and postoperatively, and blood pressure was measured at set intervals throughout. No significant differences in blood pressure or ACTH measurements were found between groups.

- The authors concluded that patients on chronic steroids do not require stress-dose steroids before undergoing gingival surgery.

- There were many problems with this study


Stress & Adrenal Insufficiency

“Further complicating this muddied picture is the retraction of a Cochrane review in 2013 that had concluded, largely based on the articles by Glowniak and Loriaux and Thomason et al., that there is “currently inadequate evidence to support the use of supplemental perioperative steroids in patients with adrenal insufficiency. It is likely that in the majority of adrenally suppressed patients undergoing surgery, administration of the patient’s daily maintenance dose of corticosteroid may be sufficient and that supplemental doses are not required.”

This Cochrane review was retracted after comments received “via direct correspondence which have challenged the eligibility criteria and interpretation of the evidence summarized in this review.”

Stress & Adrenal Insufficiency

• In the 2016 Endocrine Society Clinical Practice Guideline on primary adrenal insufficiency notes that

“harm has not been shown from recommended doses of perioperative stress-dose steroids and thus places a higher value on preventing adrenal crisis rather than reducing the potential adverse effects of short-term overtreatment.”

Stress & Adrenal Insufficiency

- “General” guidelines for stress dosing for surgery
  1. Double the oral dose the night before
  2. For “Minor” procedures, can simply double the oral dose for 24 hours, can consider 25-50 mg IV just prior or during the procedure
  3. For “Moderate” procedures, 50 mg IV prior to (or during) the procedure, and then 25 mg IV every 6 hours over the next 24-48 hours
  4. For “Major” procedures, 100 mg IV just prior to (or during) the procedure, and then a continuous infusion of 100-200 mg IV x 24 hours, or 50 mg IV every 6 hours. This may be needed for 48-72 hours.
  5. Resume oral dosing when able to take medications by mouth.
Steroid dosing and exercise
Stress & Adrenal Insufficiency

…however, there are no systematic studies of replacement therapy during strenuous physical activity.*

Stress & Adrenal Insufficiency

A 50-year-old man with a history of autoimmune primary adrenal insufficiency (PAI), diagnosed at age 15 years, reported experiencing extreme nausea, malaise, and fatigue after completing prior marathons and intensive endurance exercise.

His long-term oral adrenal replacement therapy consisted of 0.5 mg dexamethasone for every night and 0.1 mg fludrocortisone daily.

He denied making dose adjustments before these events.

Before competing in a half ironman distance triathlon, consisting of 13.1 miles of running, 56 miles of biking, and 1.2 miles of swimming, the patient presented to his endocrinologist to discuss dose adjustments before the event.

Because of the patient experiencing symptoms of under replacement of glucocorticoids and mineralocorticoids, suggestive of adrenal crisis during prior events, a trial regimen of 1.5 mg dexamethasone every night before the event and 0.3 mg of fludrocortisone daily 3 days before the event was recommended, which is equivalent to 3 times his normal daily dose.

Stress & Adrenal Insufficiency

The patient completed the event in 6 hours and 20 minutes, noting significantly improved performance and greatly reduced fatigue and nausea.

The event conditions featured a temperature of 70°F with low humidity. The patient pre-hydrated before the event and drank approximately 2 L of electrolyte sports drink throughout the event.

He also reported a markedly shorter recovery time after the race when compared with prior events.

Stress & Adrenal Insufficiency

While this case seems to indicate that adjustment of steroid dosing is needed for intensive exercise there unfortunately there is no consensus on this subject.

<table>
<thead>
<tr>
<th>Author</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Husebye ES et al.¹</td>
<td>- All patients may benefit from a small increase in dose of glucocorticoid and mineralocorticoid (2.5-5.0mg hydrocortisone every 3 hours during a marathon)</td>
</tr>
<tr>
<td></td>
<td>- In hot environments, increasing fludrocortisone dose by 50–100 µg per day to compensate for salt and water loss</td>
</tr>
<tr>
<td></td>
<td>- Patients should test out their proposed regimen before the event to assess their response</td>
</tr>
<tr>
<td>Brooks K et al.⁶</td>
<td>- Healthy athletes participating in ultra-marathons were more prone to decreased adrenal responsiveness, and in rare cases, adrenal insufficiency</td>
</tr>
<tr>
<td>Weise M et al.⁹</td>
<td>- In patients with congenital adrenal hyperplasia, stress-dosing steroids are not beneficial when exercising at a normal capacity</td>
</tr>
<tr>
<td>Simunkova K et al.¹⁰</td>
<td>- Strenuous exercise can trigger adrenal crisis in patients with chronic adrenal insufficiency</td>
</tr>
</tbody>
</table>

Primary Adrenal Insufficiency: Managing Mineralocorticoid Replacement Therapy

Conclusions: The commonly used MC replacement in PAI may not be adequate in some patients. Insufficient MC substitution may be responsible for poor cardiometabolic outcome and the failure to restore well-being adequately in patients with PAI. Well-designed studies oriented at optimizing MC replacement therapy are urgently needed.
Stress & Adrenal Insufficiency

Effect of a pre-exercise hydrocortisone dose on short-term physical performance in female patients with primary adrenal failure

- Ten women with Addison’s disease and 10 age-matched healthy females participated in the study.

- All women in the study underwent maximal incremental exercise testing. A stress dose of 10 mg hydrocortisone or placebo was given 1 h prior to exercise on two occasions. Blood samples were drawn before, and 0, 15 and 30 min post exercise. Oxygen uptake, maximal aerobic capacity, endocrine and metabolic responses to physical activity, as well as health status by questionnaires were evaluated.

Stress & Adrenal Insufficiency

Characteristics of the women participating in the exercise study

Table 1 General characteristics of participants. Data are presented as mean (s.d.) or as percentages.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Healthy subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48 (15.9)</td>
<td>48.4 (15.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.9 (4.6)</td>
<td>24.6 (4.8)</td>
</tr>
<tr>
<td>Cortisone acetate daily dose (mg)</td>
<td>30.1 (7.6)</td>
<td>0</td>
</tr>
<tr>
<td>Fludrocortisone daily dose (µg)</td>
<td>0.095 (0.015)</td>
<td>0</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>1 to 33</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>50%</td>
<td>0</td>
</tr>
<tr>
<td>Full-time workers</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Part-time workers</td>
<td>40%</td>
<td>0</td>
</tr>
<tr>
<td>Not working</td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td>Daily physical activity</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Three-times-a-week physical activity</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>No physical activity</td>
<td>20%</td>
<td>0</td>
</tr>
<tr>
<td>Stress dose during common illnesses</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>Stress dose before every physical activity</td>
<td>20%</td>
<td>0</td>
</tr>
<tr>
<td>Stress dose before long-lasting physical activity</td>
<td>20%</td>
<td>0</td>
</tr>
<tr>
<td>Stress dose before stressful event</td>
<td>10%</td>
<td>0</td>
</tr>
</tbody>
</table>

Stress & Adrenal Insufficiency

Exercise differences between those with adrenal insufficiency and healthy subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Wilcoxon's test</th>
<th>Healthy subjects</th>
<th>Mann-Whitney test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Load_{max} (W)</td>
<td>141.0±32.0</td>
<td>142.0±33.0</td>
<td>0.6</td>
<td>186.0±35.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Time_{max} (s)</td>
<td>344.0±108.0</td>
<td>353.0±100.0</td>
<td>0.3</td>
<td>490.0±98.0</td>
<td>0.01</td>
</tr>
<tr>
<td>VO_{2_{max}} (ml/kg per min)</td>
<td>25.7±8.4</td>
<td>26.6±8.1</td>
<td>0.7</td>
<td>25.7±8.7</td>
<td>0.03</td>
</tr>
<tr>
<td>VCO_{2_{max}} (/min)</td>
<td>1.9±0.5</td>
<td>2.0±0.5</td>
<td>0.2</td>
<td>2.7±0.7</td>
<td>0.005</td>
</tr>
<tr>
<td>RER_{max}</td>
<td>1.2±0.1</td>
<td>1.2±0.1</td>
<td>0.4</td>
<td>1.2±0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>BP_{dia_{max}} (mmHg)</td>
<td>94.2±8.6</td>
<td>94.7±11.8</td>
<td>1.0</td>
<td>95.0±13.4</td>
<td>0.8</td>
</tr>
<tr>
<td>BP_{sys_{max}} (mmHg)</td>
<td>186.0±19.0</td>
<td>192.0±19.0</td>
<td>0.2</td>
<td>195.0±26.0</td>
<td>0.3</td>
</tr>
<tr>
<td>HR_{max} (beats/min)</td>
<td>160.0±20.0</td>
<td>159.0±16.0</td>
<td>0.3</td>
<td>172.0±12.0</td>
<td>0.1</td>
</tr>
<tr>
<td>O_{2_{pulse_{max}}} (ml)</td>
<td>9.8±1.8</td>
<td>10.7±2.2</td>
<td>0.2</td>
<td>13.5±3.2</td>
<td>0.01</td>
</tr>
<tr>
<td>E_{max} (kcal/hr)</td>
<td>453.0±205.0</td>
<td>529.0±135.0</td>
<td>0.7</td>
<td>726.0±171.0</td>
<td>0.005</td>
</tr>
<tr>
<td>METS_{max}</td>
<td>11.1±12.3</td>
<td>7.6±2.3</td>
<td>0.8</td>
<td>9.6±2.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Recovery (s)</td>
<td>52.0±34.0</td>
<td>59.0±33.0</td>
<td>0.4</td>
<td>107.0±23.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Load_{AT} (W)</td>
<td>99.6±23.9</td>
<td>104.0±20.5</td>
<td>0.9</td>
<td>137.0±28.2</td>
<td>0.009</td>
</tr>
<tr>
<td>VO_{2_{kg_{max}}} (ml/kg per min)</td>
<td>18.1±5.5</td>
<td>32.0±37.2</td>
<td>0.4</td>
<td>25.1±6.2</td>
<td>0.01</td>
</tr>
<tr>
<td>VCO_{2_{max}} (/min)</td>
<td>1.1±0.3</td>
<td>1.2±0.3</td>
<td>0.2</td>
<td>1.7±0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>RER_{AT}</td>
<td>0.9±0.1</td>
<td>0.9±0.1</td>
<td>0.7</td>
<td>0.9±0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>HR_{AT} (beats/min)</td>
<td>143.0±24.0</td>
<td>148.0±15.0</td>
<td>0.5</td>
<td>134.0±48.0</td>
<td>0.9</td>
</tr>
<tr>
<td>O_{2_{pulse_{AT}}} (ml)</td>
<td>8.1±1.7</td>
<td>8.7±2.0</td>
<td>0.6</td>
<td>11.8±2.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Time_{AT} (s)</td>
<td>228.0±77.1</td>
<td>249.0±55.1</td>
<td>0.4</td>
<td>354.0±79.5</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*P for difference (Treatment vs Placebo).
1P for difference (Treatment vs Healthy subjects).
Max indicates parameter measured at maximal physical activity and AT at anaerobic threshold; Load_{max}, Load max; Time_{max}, duration of exercise; VO_{2_{max}}, oxygen uptake; VO_{kg_{max}}, oxygen uptake per kg; VCO_{2_{max}}, carbon dioxide production; RER_{max}, respiratory exchange rate; BP_{dia_{max}}, peak systolic blood pressure; BP_{sys_{max}}, peak diastolic blood pressure; HR_{max}, peak heart rate; O_{2_{pulse_{max}}} maximum peak of oxygen per pulse; E_{max}, energetic expenditure max; METS_{max}, metabolic equivalents max; Recover-Time of recovery.

Stress & Adrenal Insufficiency

As can be seen in the data from the previous slide

1. While there was not a statistical difference in between treatment and placebo in this small study...

2. There was a significant difference in exercise ability between women with adrenal insufficiency and those with normal adrenal function

3. This would support the idea that perhaps some form of change in therapy may be necessary...
   • ? Glucocorticoids (hydrocortisone)
   • ? Mineralocorticoids (fludrocortisone)
   • ? Catecholamines (stress hormones)
Stress & Adrenal Insufficiency

Given the lack of current evidence and widely variable response to different glucocorticoid dosages in [adrenal insufficiency], endurance athletes should work with their physician to determine an optimal dose increase around intensive endurance exercise.

Stress & Adrenal Insufficiency

So what do we do??

1. Are you having problems with your current steroid dose?
   a. No, then no change
   b. Yes, then what symptoms? (Do you need more or less)

2. If you are having symptoms of too little steroid, then do you need more OR do you need a change how and when the doses are given?
   a. Perhaps a change to 3 or 4x/day dose would work
   b. Changing the time of the doses to better accommodate for activities

3. Are your symptoms only come up with certain activities or are they all the time?
So what to we do??

1. If the symptoms are persistent all the time…
   a. Could consider an increase in the total amount of hydrocortisone
   b. Perhaps measured cortisol levels 4 hours after a regular dose could help to determine if more adjustments are needed

2. If the symptoms are only occurring at specific times or with certain activities…
   a. How do you make adjustments for these unique scenarios?
   b. When is the best time to adjust the dose of the steroid (before, during, or after)?
   c. How much to adjust the dose?
Stress & Adrenal Insufficiency

Stress dosing for activities

- **Important to understand how YOU react to a certain activity**
  - Is there a pattern to how you feel?
  - Was it just one or two times that you felt bad?
  - Are you supposed to feel tired/fatigued?
  - What is your recovery time?
Stress & Adrenal Insufficiency

Stress dosing for activities

1. What are the symptoms?
   a. Fatigue during activity
   b. Heart rate issues
   c. Low blood pressure
   d. Dizziness
   e. Low glucose levels
   f. Slow recovery after activity
Stress & Adrenal Insufficiency

Stress dosing for activities

- **If participating in a strenuous activity**
  - Likely will need a higher dose of the hydrocortisone the night prior to the activity (double or triple dose may be needed)
    - This is where it is important to listen to your body (more is not better if you don’t need it)
  - Double dosing during the activity is a good start.
    - Increasing the frequency of the doses throughout the day can be helpful
      - Sometimes taking a dose of hydrocortisone every few hours is needed to maintain an energy balance.
Stress & Adrenal Insufficiency

Stress dosing for activities

1. Dose adjustment of fludrocortisone can be helpful especially if blood pressure (or symptoms of low blood pressure, such as dizziness, is a problem)
   a. Adding an additional ½ - 1 tablet of fludrocortisone can greatly improve these symptoms.
   b. Splitting the dose into two doses can also be beneficial
Stress & Adrenal Insufficiency

Stress dosing for activities

• Don’t assume you will always need more steroids
  • Try to understand how you will respond (or did respond) to an activity and then try to determine the best adjustment

• My experience has been that everyone reacts differently to the same activity
  • Baseball, Basketball, Football, Wrestling, Running, Gymnastics, Swimming, Final exams, Hard labor, etc.
Stress & Adrenal Insufficiency

Stress dosing for activities

If you know you have issues with a strenuous activity

1. Double/triple dosing the night before activity

2. Increasing the dose of the fludrocortisone by ½ - 1 pill the morning of the activity can help
   a. Adding the fludrocortisone can be helpful if you have secondary adrenal insufficiency (you might only need it during these strenuous activities)

3. It can be better to try and increase the frequency of the hydrocortisone throughout the day as a first start
   a. If that doesn’t help, then increase the dose amount
Stress & Adrenal Insufficiency

Stress dosing for activities

• Try not to let yourself “hit the wall” since it can take longer to recover from this situation.

• Be proactive… as you get more experience you should be able to anticipate the dose you need and therefore likely reduce the time you need the higher steroid dose.
Conclusions

• Dosing of hydrocortisone is difficult. While there are general guidelines there is no “precise scientific method” to determine dosing

• Stress dosing of steroids is even more imprecise.

• The goal for dosing is to provide a steroid dose that allows the person to be able to successfully function in the daily activities that they choose. (more is not always better)

• Communication with your endocrinologist is very important

• Important to advocate for your health!