Emerging Challenges in Primary Care: 2017

Primary Care Endocrinology: The Adrenal and Pituitary
Herding Horses and Zebras

Faculty

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Disclosures

- **Robert S. Busch, MD, FACE** serves as a speaker for Astra Zeneca, Eli Lilly, Boehringer Ingelheim, Novo Nordisk, and Shire. Dr. Busch also serves as a researcher for Astra Zeneca, Novo Nordisk, Janssen, and Amgen.

- **Mark Stolar, MD** serves as a speaker and advisory board member for Astra Zeneca
Learning Objectives

- Differentiate adrenal gland disorders and classify them as either hyperfunctioning or hypofunctioning based on the provided clinical and laboratory information
- Recognize the preferred treatment option(s) for specific adrenal gland disorders
- Learn when clinical symptoms are indicative of functional disorders rather than disease
- Become familiar with ongoing pituitary disorders in primary care patients

Let's start up top:
Getting to know the pituitary

Normal Pituitary Hormone Secretion

[Diagram of normal pituitary hormone secretion]
Prolactinoma

Definition

- Pituitary tumors (also called adenomas) which secrete excessive amounts of prolactin
- Represent most common type of pituitary tumor seen clinically
- May exist "silently" in 5-10% of the adult population
- Micro- vs. macroadenoma (10 mm)

Regulation of pituitary hormones

- Thyroid, cortisol, growth hormone and sex hormones are under stimulatory control
- Prolactin is under inhibitory control by dopamine from hypothalamus. Therefore anything that presses on pituitary stalk will raise prolactin
- When TSH climbs in primary hypothyroidism, prolactin secretion is stimulated
- ADH (antidiuretic hormone) is secreted in hypothalamus and stored in posterior pituitary. Nocturia/polyuria can be a sign of significant pituitary pathology

Hyperprolactinemia

Definition

- Prolactin level > 30 ng/mL
- Prolactin is the hormone that stimulates milk production by the breasts
- Normal prolactin level: 15-25 ng/mL
- Several causes
  - Levels > 200 ng/mL are almost always associated with a prolactin-secreting tumor
Hyperprolactinemia

**CAUSES**
- Modest prolactin elevation (30 - 100 ng/ml)
- Pregnancy (early)/Lactation
- Stress (discomfort, exercise, low blood sugar)
- Hypothyroidism
- Kidney failure
- Liver failure
- Medications
- "Stalk Effect"
- Other

**Drug-Induced Hyperprolactinemia**
- Typically associated with prolactin levels less than 100 ng/mL (rarely > 150 ng/mL)
- Dopamine Antagonists
  - Phenothiazines
  - TCA's
  - Metoclopramide
- SSRIs
- Estrogen/Progesterone
- Methyldopa
- Verapamil
- GnRH analogs (leuprolide, goserelin, naferelin)

**Hyperprolactinemia PRESENTATION**
- **WOMEN** (manifestations of estrogen deficiency)
  - Irregular menstrual periods or amenorrhea
  - Infertility
  - Galactorrhea
  - Reduction in sex drive
  - Vision loss/Headache possible (microadenoma)
  - Osteoporosis (long-term)
Hyperprolactinemia

PRESENTATION

- MEN
  - Manifestation of loss of sex hormone (testosterone) production
  - Loss of libido
  - Erectile dysfunction
  - Loss of body hair
  - Vision loss/Headache more likely (macroadenoma)
  - Osteoporosis (long-term)

Hyperprolactinemia

DIAGNOSIS

- Signs or Symptoms (sex hormone deficiency)
- Elevated Prolactin level (> 30 ng/mL)
- Perform a complete pituitary hormone evaluation (especially if macroadenoma)
- Imaging Studies (MRI, CT) of the pituitary gland
- IMPORTANT RULE: Prolactinomas keep same characteristics. Microadenomas rarely grow into macroadenomas. Serial MR not needed for followup

Prolactinomas

TREATMENT

- Drug Therapy
  - Bromocriptine (Parlodel)
  - Cabergoline (Dostinex)
    - Both drugs are D2 receptor agonists; stimulate postsynaptic dopamine receptors in the hypothalamus to release dopamine; bind to D2 receptors on cell membrane of prolactin-secreting cells, inhibiting release and synthesis of prolactin.
- Surgery
  - Transsphenoidal surgery
- Radiotherapy
  - Stereotactic radiation (Gamma Knife)
  - External beam radiation
Hyperprolactinemia
TREATMENT

- Drug Therapy
  - Bromocriptine
    - Generic
    - 2.5 mg and 5 mg tabs/caps
    - Higher incidence of nausea; preferred for fertility
    - Initiate at 1.25 mg QD-BID (with meal); increase weekly
    - Maximum dose 15 mg per day
  - Cabergoline
    - Often effective in patients whose prolactinomas are resistant to bromocriptine therapy
    - Better GI tolerance
    - 0.5 mg tablets
    - Initiate at 0.25 mg twice a week
    - Max dose of 1 mg twice weekly

Hyperprolactinemia
TREATMENT

- Drug Therapy Effects
  - Normalization of serum prolactin levels
  - Restoration of gonadotropin production
  - Decrease tumor size

- Monitoring
  - Resolution of symptoms
  - Prolactin levels: repeat after 3-4 weeks
  - Tumor size: repeat MRI in 6-12 months

Hyperprolactinemia
TREATMENT

- Drug Therapy
  - Adverse Effects
    - Bromocriptine
    - Cabergoline
      - Nausea, diarrhea
      - Headache
      - Orthostatic hypotension, dizziness
      - Heart valve disorders
    - Contraindications
      - Nursing moms, uncontrolled HTN, orthostasis, heart valve dis’s
  - Drug Interactions
    - Dopamine antagonists, 3A4 metabolism
Prolactinoma
Definition

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- Represent most common type of pituitary tumor seen clinically
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Growth Hormone Excess

Sandy Allen
World’s Tallest Woman
Growth Hormone Excess

- Clinical presentation
  - Children (Giantism) vs. Adults (Acromegaly)
  - Enlarged hands and feet (new ring/shoe size)
  - Excessive sweating
  - Coarse facial features
  - Multiple skin tags
  - Deepened voice
  - Osteoarthritis
  - Carpal tunnel syndrome
  - Sleep apnea
  - Headache/Visual disturbances
  - Increased risk of DM, colonic polyps, colon cancer, and coronary artery disease

Abbreviations Used Throughout

ACC – adrenal cortical carcinoma
ACTH – adrenocorticotropic hormone
APA – aldosterone-producing adenoma
BAH – bilateral adrenal hyperplasia
BUN – blood urea nitrogen
CD – Cushing’s disease
CRH – corticotropin-releasing hormone
CS – Cushing’s syndrome
Dex-CRH – dexamethasone-corticotropin releasing hormone
DST – dexamethasone suppression test
EAB – ectopic ACTH secretion
GRA – glucocorticoid-remediable aldosteronism
h – hour
HPA – hypothalamic – pituitary – adrenal
HTN – hypertension
IAH – idiopathic adrenal hyperplasia
IV – intravenous
MR – mineralocorticoid receptor
PHA – primary hyperaldosteronism
TSS – transsphenoidal surgery
UCF – urine free cortisol
Hypothalamus – Pituitary – Adrenal Axis


The Adrenal Gland

The Big Picture

Adrenal Cortex Disorders

Hyperfunction

- Cushing's Syndrome
- Hyperaldosteronism

Hypofunction

- Addison's Disease
- Congenital Adrenal Hyperplasia
- Hypoaldosteronism
Cushing's Syndrome
(Hyperfunction of the Adrenal Gland)

- **Etiology**
  - Excess levels of glucocorticoids from endogenous production or exogenous sources

- **Classification**
  - ACTH-dependent (80%)
  - Cushing’s disease (85%)
    - A specific type of CS caused by a pituitary adenoma
  - ACTH-independent (20%)
    - Adrenal adenomas
    - Adrenal carcinomas

### Clinical Features and Overlapping Conditions of Cushing's Syndrome

<table>
<thead>
<tr>
<th>Features Discriminating CS</th>
<th>Features Discriminating CS</th>
<th>Overlapping Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial plethora (i.e. redness in the face)</td>
<td>Acne</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Proximal myopathy or muscle weakness</td>
<td>Muscle pain</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Striae, especially if reddish-purple and &gt; 1 cm wide (i.e. stretch marks)</td>
<td>Changes in appetite</td>
<td>Incidental adrenal mass</td>
</tr>
<tr>
<td>Unexplained bruising or osteoporosis</td>
<td>Depression</td>
<td>History of head trauma</td>
</tr>
<tr>
<td>Weight gain and decreased growth velocity (children)</td>
<td>Acne</td>
<td>Polytraumatic injury syndrome</td>
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<td></td>
<td>Fatigue</td>
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</tbody>
</table>

### Cushing's Syndrome Presentation
(Hyperfunction of the Adrenal Gland)

- **A)** Central obesity
- **B)** Facial rounding
  - "Moon Face,"
  - facial plethora,
  - supraventricular fat pads
- **C)** Dorsocervical fat pad
  - "Buffalo Hump"
Cushing’s Syndrome Presentation
(Hyperfunction of the Adrenal Gland)

D) Reddish-purple striae
“Stretch Marks”

Images: https://www-uptodate-com.elibrary.amc.edu/contents/epidemiology-and-clinical-manifestations-of-cushings-syndrome?source=search_result&search=moon+face&selectedTitle=1~150#

Diagnosis of Cushing’s Syndrome
(Hyperfunction of the Adrenal Gland)

- Involves two parts
  - Identifying the presence of hypercortisolism
  - Determining the etiology
- Most patients with Cushing symptoms DO NOT have Cushing’s
- However because Cushing’s can be intermittent a negative workup isn’t always negative


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  - Determining the etiology
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- However because Cushing’s can be intermittent a negative workup isn’t always negative

Involves two parts
- Identifying the presence of hypercortisolism
  - Empty bladder first thing, upon awakening
  - Collect all subsequent voids, including the next day’s first morning void
  - Refrigerate collection, but do not freeze
  - Values over 100 suspicious
- Late-night salivary cortisol
  - Collected between 2300 and 2400
  - Values over 3 suspicious
- Overnight, low-dose dexamethasone suppression test (DST) or 48-hour, 2 mg DST
  - Low Dose DST: 1 mg is taken orally between 2300 and 2400
  - Longer low-dose DST: 0.5 mg taken orally every 6 hours for 48 hours
  - Fasting plasma cortisol is obtained between 0800 and 0900
  - Values over 2.0 suspicious

Cushing’s Syndrome Suspected

Exclude Exogenous Glucocorticoid Use

Perform 1 of the Following

- Late-Night Salivary Cortisol (
  ≥ 2 tests)
- Overnight 1-mg DST or, in
  select patients, the 48-h, 2 mg DST

Any Abnormal Result

- Exclude Physiologic Causes
  - Perform 1 or 2 different tests
    from above. May consider repeating
    abnormal test, Dex-CRH or midnight
    serum cortisol, in select patients

Normal Result

- Cushing’s Syndrome Unlikely

Additional Evaluation

- Discrepant Abnormal
  - Cushing’s Syndrome

Comments on Common Tests Used to Establish Hypercortisolism

<table>
<thead>
<tr>
<th>Test</th>
<th>Benefits</th>
<th>Confounders</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-Night Salivary Cortisol</td>
<td>- Accurate</td>
<td>- Chewing tobacco</td>
<td>Suggestions of CS if salivary cortisol &gt; 145 ng/dL</td>
</tr>
<tr>
<td></td>
<td>- Convenient</td>
<td>- Circadian rhythm can be lost in</td>
<td>- Longer low-dose DST improves specificity</td>
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<td></td>
<td>- Reproducible</td>
<td>- patients with depressive illness,</td>
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<td></td>
<td>- Stable for 1 week</td>
<td>- the critically ill, and</td>
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<td></td>
<td></td>
<td>- shift workers</td>
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<tr>
<td>Serum Cortisol After Low-Dose DST</td>
<td>- Preferred in patients</td>
<td>- Alcohol</td>
<td>Suggestions of CS if serum cortisol &gt; 1.8 mcg/dL</td>
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<tr>
<td></td>
<td>with renal failure</td>
<td>- Estrogen</td>
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<td></td>
<td></td>
<td>- Medications that induce or inhibit</td>
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<td></td>
<td></td>
<td>- CYP3A4 metabolism</td>
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<tr>
<td></td>
<td></td>
<td>- Pregnancy</td>
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<tr>
<td></td>
<td></td>
<td>- Alcoholism</td>
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<td></td>
<td></td>
<td>- ClCr &lt; 60 mL/min</td>
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<td>- Greater than 5 L of H2O per day</td>
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<td>- Medications (carbamazepine,</td>
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<td>- fenofibrate, topical steroids)</td>
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<td></td>
<td></td>
<td>- Starvation</td>
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<td></td>
<td></td>
<td>- Concentrations greater than</td>
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<td>- the upper limit of normal for an</td>
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<td></td>
<td></td>
<td>- assay are suggestive of CS</td>
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<tr>
<td></td>
<td></td>
<td>- Ensure an adequate collection by</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- measuring urine creatinine</td>
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</tbody>
</table>

Diagnosis of Cushing’s Syndrome

(Hyperfunction of the Adrenal Gland)

Involves two parts - Determining the etiology:

- Adrenal vein catheterization
- Cavernous sinus sampling
- Cisternal or abdominal computed tomography (CT)
- Corticotropin-releasing hormone (CRH) stimulation test
- Desmopressin stimulation test
- Hexamethoamine stimulation test
- High-dose dexamethasone suppression test
- Inferior petrosal sinus sampling (IPSS)
- Insulin-induced hypoglycemia

- Jugular venous sampling (JVS)
- Loperamide test
- Metyrapone stimulation test
- Naloxone CRH
- Pulmonary magnetic resonance (MRI)
- Radioimmunassay (RIA) / Immunoradiometric assay (IRMA)
- Used to assess plasma ACTH concentrations
- Somatostatin imaging
- Somatomedin receptor scintigraphy

Abbreviations: CBG – corticosteroid-binding globulin; ClCr – creatinine clearance; CS – Cushing’s syndrome; DST – dexamethasone suppression test; H2O – water; ULN – upper limit of normal; ∴ – therefore
ACTH-Dependent or -Independent Cushing's Syndrome (Hyperfunction of the Adrenal Gland)

Differential Diagnosis (Hyperfunction of the Adrenal Gland)

- Iatrogenic (exogenous) Cushing's syndrome
  - Most common cause
  - Medications to consider
    - Glucocorticoids
    - Medroxyprogesterone acetate
    - Megestrol acetate
- Pseudo-Cushing's syndrome

Treatment of Cushing's Syndrome (Hyperfunction of the Adrenal Gland)

- Goals
  - Normalize cortisol levels or action at its receptors to eliminate signs and symptoms of Cushing's syndrome
  - Prevent or treat comorbidities resulting from hypercortisolism
    - e.g., cardiovascular, diabetes mellitus, mood/cognition, infections, osteoporosis, quality of life
- Treatment of choice
  - Surgical resection by an experienced surgeon
General Monitoring

- Assess for clinical response
- Assess for eucortisolism, except for mifepristone
  - 24-hour urine free cortisol
  - Morning serum cortisol
  - Serum cortisol day curves
- Assess for adrenal insufficiency
  - Severe fatigue, muscle weakness, weight loss, hypotension, nausea, vomiting

Hyperaldosteronism¹,²⁰ (Hyperfunction of the Adrenal Gland)

- Primary hyperaldosteronism
  - Etiology
    - Bilateral adrenal hyperplasia (BAH) [65%]
    - Aldosterone-producing adenoma (APA) [30%]
  - Clinical presentation
    - Arterial hypertension, resistant to medications
    - Hypokalemia in severe cases
    - Muscle weakness
    - Some patients may be asymptomatic
- Secondary hyperaldosteronism

Primary Hyperaldosteronism¹,²⁰ (Hyperfunction of the Adrenal Gland)

- Who should be screened?
  - Moderate or severe HTN
  - HTN resistant to pharmacotherapy
    - Systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg despite ≥3 antihypertensives
    - Hypertensive patients with spontaneous or diuretic-induced hypokalemia
    - HTN with an adrenal incidentaloma
  - Detection
    - Plasma-aldosterone-concentration-to-plasma-renin-activity (PAC-to-PRA) ratio
      - PAC-to-PRA of 30 OR
      - PAC-to-PRA of 20 with aldosterone > 15 ng/dL
    - 24 hr urine aldosterone above 14 on high salt diet


Primary Hyperaldosteronism¹,²,²⁰
(Hyperfunction of the Adrenal Gland)

- Confirmatory testing (no gold standard)
  - Captopril challenge test, fludrocortisone suppression test, oral sodium loading, saline infusion
- Subtype classification, as the management is different
  - Unilateral (i.e. APA or UAH) – the treatment of choice is laparoscopic adrenalectomy
  - Bilateral (i.e. bilateral APA, IAH) - the treatment of choice is a mineralocorticoid receptor (MR) antagonist
  - GRA – the treatment of choice is a long acting glucocorticoid (e.g., dexamethasone, prednisone)

### Therapeutic Options for the Management of Bilateral Adrenal Disease

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Pros</th>
<th>Cons</th>
<th>Comments and Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>- Oral agent (take with food)</td>
<td>- Blood pressure, serum creatinine</td>
<td>- Well tolerated</td>
</tr>
<tr>
<td></td>
<td>- Less effective than spironolactone</td>
<td>- Adverse effects: GI, hypokalemia</td>
<td>- Less effective than spironolactone</td>
</tr>
<tr>
<td></td>
<td>- Adverse effects: GI, hypokalemia</td>
<td>- Titrate every 4 to 8 weeks</td>
<td>- Caution with renal impairment</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>- Less sex steroid-dependent effects</td>
<td>- Blood pressure, potassium, serum creatinine</td>
<td>- Selective aldosterone antagonist</td>
</tr>
<tr>
<td></td>
<td>- CYP3A4 substrate</td>
<td>- Titrate every 4 to 8 weeks</td>
<td>- Caution with renal impairment</td>
</tr>
<tr>
<td></td>
<td>- Adverse effects: hyperkalemia</td>
<td>- 60% MR antagonist potency of spironolactone</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>- Lots of data, preferred MR antagonist</td>
<td>- Consider a thiazide diuretic, amiloride or triamterene to avoid higher spironolactone doses</td>
<td>- Nonselective aldosterone antagonist with active metabolites</td>
</tr>
<tr>
<td></td>
<td>- Adverse effects (dose dependent): GI, rash, gynecomastia, impotence, menstrual irregularities</td>
<td>- Blood pressure, serum creatinine</td>
<td>- Hyperkalemia, hypernatremia</td>
</tr>
<tr>
<td></td>
<td>- Titrate every 4 to 8 weeks</td>
<td>- Titrate every 4 to 8 weeks</td>
<td>- Titrate every 4 to 8 weeks</td>
</tr>
</tbody>
</table>

Abbreviations: GI – gastrointestinal; MR – mineralocorticoid receptor

### The Big Picture

Adrenal Cortex Disorders

- Hyperfunction
  - Cushing’s Syndrome
  - Hyperaldosteronism

- Hypofunction
  - Addison’s Disease
  - Congenital Adrenal Hyperplasia
  - Hypoadaldosteronism
Addison’s Disease
(Hypofunction of the Adrenal Gland)

- Primary adrenal insufficiency
- Etiologies
  - Developed vs. underdeveloped countries
  - Consider autoimmune polyendocrine syndrome (APS)
  - Medication-induced
    - Phenobarbital, phenytoin, rifampin, steroidogenesis inhibitors

Second Adrenal Insufficiency
(Hypofunction of the Adrenal Gland)

- Etiology
  - Many!
  - Exogenous steroid use
    - Decreases ACTH → decreased glucocorticoids
  - Medications to consider
    - Glucocorticoids
    - Medroxyprogesterone acetate
    - Megestrol acetate

Adrenal Fatigue: Not a Real Entity

- Basal cortisol daily secretion is 30mg. Under stress it can climb to 300mg (ten-fold reserve)
- Adrenal function is reduced in the setting of untreated hypothyroidism hence the internet link to Hashimoto’s
- Every adrenal fatigue book lists weight gain as a symptom. Weight loss is a cardinal symptom of adrenal insufficiency
- Unnecessary steroid replacement carries long term risk, even with “natural” adrenal extracts
Diagnosis

- Addison’s disease
- Abnormal corticotropin stimulation test response
- Cosyntropin (Cortrosyn) – synthetic ACTH
- Dehydration, hyponatremia, hyperkalemia, increased BUN and weight loss
- Hyperpigmentation
- Secondary adrenal insufficiency
- Preserved aldosterone secretion

Goals

- Use the lowest effective dose to mimic the diurnal adrenal rhythm

Treatment of choice: exogenous steroids

- Preferred agents (total daily dose)
  - Cortisone acetate (25 to 37.5 mg daily)
  - Hydrocortisone (15 to 25 mg daily)
  - Prednisone (2.5 mg daily)
- Administered twice daily with the majority (67%) given in the morning then dose two, six to eight hours after the morning dose
  - e.g., Hydrocortisone 20 mg by mouth in the morning then 10 mg six to eight hours later

Hyperpigmentation in Addison’s Disease

(Hypofunction of the Adrenal Gland)

Treatment of Addison’s Disease

(Hypofunction of the Adrenal Gland)
**Relative Potencies of Glucocorticoids**

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Antiinflammatory Potency</th>
<th>Equivalent Potency (mg)</th>
<th>Approximate Half-Life (minutes)</th>
<th>Sodium-Retaining Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>25</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>20</td>
<td>90</td>
<td>2</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3.5</td>
<td>5</td>
<td>60</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>5</td>
<td>200</td>
<td>1</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>4</td>
<td>300</td>
<td>0</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>4</td>
<td>180</td>
<td>0</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25</td>
<td>0.6</td>
<td>100 to 300</td>
<td>0</td>
</tr>
<tr>
<td>Desamethasone</td>
<td>30</td>
<td>0.75</td>
<td>100 to 300</td>
<td>0</td>
</tr>
</tbody>
</table>


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**Supplemental Glucocorticoid Use**

(Hypofunction of the Adrenal Gland)

- Very important to educate patients about
- Strenuous activities (e.g., exercise)
- Additional 5 to 10 mg of hydrocortisone before activity
- Illness and injury
  - At minimum, double the daily dose until recovery
  - Parenteral therapy will be necessary if patients experience diarrhea or vomiting
  - e.g., glucocorticoid suppositories or injectable hydrocortisone

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**Treatment of Addison’s Disease**

(Hypofunction of the Adrenal Gland)

- Fludrocortisone acetate
  - “Synthetic aldosterone”
- Not always required
- Some glucocorticoids have sodium-retaining abilities
  - e.g., cortisone, hydrocortisone, prednisone, prednisolone
- Usually 0.05 to 0.2 mg once daily will suffice
- Monitoring
  - Blood pressure and electrolytes (e.g., Na⁺, K⁺)
Principles of Glucocorticoid Therapy

- Oral agents are well absorbed
- Adverse effects
  - Cataracts
  - HPA axis suppression
  - Hypokalemia
  - Hypomagnesemia
  - Iatrogenic Cushing’s syndrome
  - Increased risk for infections
  - Osteoporosis
  - Peptic ulcer disease
  - Seizures
  - Sodium retention → edema

HPA Axis Suppression

- Increased risk with higher doses and longer durations of therapy
  - Assess for HPA axis recovery
    - Morning cortisol every 3 months until ≥ 7.4 mcg/dL
    - Then ACTH stimulation test
    - If either baseline or ACTH stimulation test cortisol levels are ≥ 18 mcg/dL the axis has recovered
- Alternate-day therapy
  - Consideration for stable patients on long-term therapy

Acute Adrenal Insufficiency (Hypofunction of the Adrenal Gland)

- Also known as an Addisonian crisis
- An emergency
- Most common etiology
  - Use of exogenous steroids chronically followed by abrupt withdrawal
- Management
  - Hydrocortisone 100 mg IV bolus then 10 mg/h continuous infusion or intermittent boluses of 100 to 200 mg daily
  - Switch to oral therapy when stable
  - Usually after 24 to 48 h
  - Fluid replacement will be needed
Factors of Successful Glucocorticoid Therapy

<table>
<thead>
<tr>
<th>Counseling</th>
<th>Monitoring</th>
<th>Recognizing Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider the use of a medical alert bracelet</td>
<td>• Bone mineral density scans</td>
<td>• Delayed and moderate atherosclerosis, cataracts</td>
</tr>
<tr>
<td>• During times of stress you will need to increase your dose</td>
<td>• Growth and development (children and adolescents)</td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>• Never stop taking the medication without first talking with your provider</td>
<td>• Ophthalmologic exams</td>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Take with food to decrease stomach upset</td>
<td>• Serum electrolytes</td>
<td>• Likely to occur early in therapy and usually unavoidable: increased appetite, insomnia, weight gain</td>
</tr>
<tr>
<td></td>
<td>• Serum glucose</td>
<td>• Long-term treatment: cushingoid habitus, HPA axes suppression, impaired wound healing</td>
</tr>
<tr>
<td></td>
<td>• Stool tests for occult blood loss</td>
<td>• Peptic ulcer disease</td>
</tr>
</tbody>
</table>

Abbreviations: HPA – hypothalamic-pituitary-adrenal

Pheochromocytoma: When is anxiety more than anxiety??

• Only 2000 cases per year diagnosed in USA
• Rule of tens: 10% in children 10% bilateral 10% non-adrenal 10% malignant
• Most common symptoms are headaches, sweats and palpitations
• Hypertension the rule but orthostatic hypotension can be seen in epinephrine secreting tumors
• Weight loss is a clue. Weight gain is NOT seen in pheo

Diagnosis of Pheochromocytoma

• Since pheo is rare workup is designed to exclude not diagnose
• Plasma metanephrines most specific if over 4 fold elevated. If 2-4 fold elevated doing 24 hr urine catecholamines/metanephrines worthwhile
• If slightly elevated just repeat. 30mins supine usually not needed
• Chromogranin-A if elevated makes neuroendocrine cause more likely but is falsely elevated if taking a PPI
Conclusions

- Adrenal disorders can be classified as either hyperfunctioning or hypofunctioning
- Most patients with adrenal symptomatology don’t have adrenal pathology
- Iatrogenic Cushing’s syndrome is the most common cause of Cushing’s syndrome
- Patients must be educated about the appropriate use of glucocorticoids
  - Not stopping long-term therapy abruptly
  - Increasing supplemental doses, as needed

Endocrinology in Primary Care: Take Home Points

- Most patients with symptoms don’t have an endocrine cause. Horses are more common than zebras. Look for symptoms that just don’t fit before going too far
- Prolactin secreting microadenomas typically remain benign and stable and often needn’t be treated especially post menopausal.
- Adrenal disorders are relatively uncommon. Obesity, fatigue and anxiety are VERY common. Accurate screening tests to exclude disease help clinicians and patients focus on the real issues at hand