DISCLOSURE*

Relevant Financial Relationship(s):
  None

Off Label Usage:
  None

* A provider must disclose the above information to learners prior to beginning of the educational activity (ACCME)
Disclosure of ABIM Service

• I am a member of the Endocrine Exam Committee (July 2013 – present)

• As is true for any ABIM candidate who has taken the certification exam, I have signed a Pledge of Honesty in which I have agreed to keep the ABIM exam confidential

• No exam questions will be disclosed in my presentation
Cushing Syndrome

- Clinical Overview—emphasis on clinical and biochemical phenotypes
- 4 Cases:
  ✓ CPC format
Cushing Syndrome – Why it is so Hard

- Most difficult question:
  - Does the patient have CS?

- Second most difficult question:
  - In ACTH-dependent disease, is it pituitary or ectopic?

- Third most difficult question:
  - If it is ectopic, where is it?

- Fourth—unlike other endocrine disorders, there is no single test – you need to build a wall of evidence
- Weight gain with central obesity & thin extremities
- Facial rounding and plethora – “moon facies”
- Dorsocervical fat pad “buffalo hump” & supraclavicular fat pads
- Easy bruising, fine “cigarette paper thin” skin, poor wound healing, wide (>1-cm) purple-red striae, hirsutism, acne, fungal skin infections
- Proximal muscle weakness & thin extremities
- Emotional and cognitive changes
- Hypertension, diabetes mellitus, osteoporosis
- Gonadal dysfunction
Serial Photographs are Important
Clinical Suspicion of Cushing’s Syndrome (CS)

Case Detection Test:
- 24-hr UFC
- Midnight salivary cortisol
- 1-mg overnight DST
- Diurnal serum cortisols

Dependent on your degree of clinical suspicion, use 1 or all 4

TIP: In the patient with **obvious and severe** CS, don’t waste time with 1-mg DST or salivary cortisol—get 24-hr UFC, a.m./p.m. serum cortisols and serum ACTH
Case Detection Testing for Clinical CS (not for subclinical CS)

- **AM/PM cortisols:**
  - Normal = 18 mcg/dL / 9 mcg/dL
  - Suspect CS if 18 mcg/dL / 18 mcg/dL

- **24-hr UFC**
  - > 200 mcg – must be CS
  - < 45 mcg – unlikely CS

- **MN Salivary cortisol**
  - > 100 ng/dL – suspicious
  - > 200 ng/dL – likely CS

- **1 mg DST**
  - ≤ 1.8 mcg/dL – usually normal
  - > 1.8 mcg/dL – might be abnormal

Oral estrogen
Night shift/jet lag
Depression

High urine volume (>4 L)

If >1000 ng/dL - contamination

Pit CS can suppress <1.8; a lot of false +’s between 1.8 – 5
Example of “Don’t Waste Time”
### Example of “Don’t Waste Time”

<table>
<thead>
<tr>
<th>LAB AG Continuous</th>
<th>Reference Range</th>
<th>MCR 19Aug15 11:00</th>
<th>MCR 19Aug15 09:01</th>
<th>MCR 19Aug15 09:00</th>
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</thead>
<tbody>
<tr>
<td>Prolactin(S)</td>
<td>4.0 - 15.2 ng/mL</td>
<td>21.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol.</td>
<td>a.m. : 7-25; p.m. : 2-14...</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AM Cortisol</td>
<td>7-25 mcg/dL</td>
<td>28</td>
<td></td>
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<tr>
<td>ENDOCRINE 3 AG</td>
<td></td>
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</tr>
<tr>
<td>Insulin-Like Growth Factor ...</td>
<td>83 - 344 ng/mL</td>
<td>203</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticotropin(P)</td>
<td>10-60 (a.m. collection) ...</td>
<td></td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>Calcitonin(S)</td>
<td>Basal: &lt;16; Peak Calcium...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromogranin A, S</td>
<td>&lt;93 ng/mL</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Microbiology

### Metals 63 AG

### URINE CHEMISTRIES AG

<table>
<thead>
<tr>
<th>Creatinine Clearance AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine(U).</td>
</tr>
<tr>
<td>Creatinine Conc....</td>
</tr>
<tr>
<td>Collectn Duration (w/CREAU)</td>
</tr>
<tr>
<td>Urine Volume (w/CTU)</td>
</tr>
</tbody>
</table>

### URINE ENDOCRINE 2 AG

| Cortisol, Free(U)       | 3.5-45 mcg/24 h    | 2104 |    |
| Collectn Duration (w/CORTU) | h                  | 24   |    |
| Urine Volume (w/CORTU)   | mL                 | 2338 |    |
18-Aug-2015 16:24:00

**Indications:** Cushing’s Syndrome; Hypertension (HTN) NOS

EXAM: CT scan of the Chest with IV contrast including 3D maximum intensity projections/volume renderings on a non-independent workstation

COMPARISON: No comparisons available.

**Impression:** 1.5 cm mass in the anterior mediastinum with possible involvement of the aorta and left brachiocephalic vein.

Thymic carcinoid
Cushing CPC

Format:

- 4 Unknown cases
- Brief History of Present Illness
- Diagnostic & Treatment Menus
- 12 minutes per case – including Q & A after each case
26-Year-Old Woman

History of Present Illness:

- 4-year history of:
  - facial and neck plethora
  - acne, easy bruising
  - redistribution of body fat (14# wt gain)
  - fatigue, weakness, insomnia (aerobics instructor)
  - new hypertension (lisinopril)
  - amenorrhea x 4 yrs -- pregnancy with Clomid 1 yr ago -- currently Rx with OCP
26-Year-Old Woman

Physical Exam:
- Height = 158 cm, weight 70.1 kg, BMI = 27.9 kg/m²
- BP 120/85 mm Hg
- Normal muscle strength, no striae
Cushing Syndrome

**Test Menu:**

- Diurnal serum cortisols
- 24-hr UFC
- Serial patient photos
- Low-Dose DST
- Monthly 24-hr UFCs
- Dex-CRH test
- Midnight salivary F
- 1-mg overnight DST
- ACTH level
- DHEA-S

**High-Dose DST**

- CRH test
- Chest XR
- Head MRI
- IPSS with CRH
- Chest CT/MRI
- Adrenal CT/MRI
- Octreotide scan
- FDG-PET scan

**Treatment Menu**
Clinical Suspicion of Cushing’s Syndrome (CS)

Pursue subtype testing ASAP!!!
These pts do die from CS!!

Case Detection Tests:
• 24-hr UFC
• Midnight salivary cortisol
• 1-mg overnight DST
• Diurnal serum cortisol

UFC >1000 mcg

NO RUSH!

Borderline or Normal CS unlikely
Re-evaluate if strong Clinical suspicion
Consider monthly 24-hr UFC
These pts will NOT die from CS!!!

UFC 200 - 1000 mcg + clear CS on exam
Pursue subtype testing promptly

UFC >1000 mcg
Pursue subtype testing ASAP!!!
These pts do die from CS!!!
Clinical Suspicion of Cushing’s Syndrome (CS)

TIP: The “biochemical phenotype” guides the urgency to resolve the diagnosis and treat for a cure.

NO RUSH!

- Diurnal serum cortisols

Borderline or Normal
CS unlikely

Re-evaluate if strong Clinical suspicion
Consider monthly 24-hr UFC
These pts will NOT die from CS!!

UFC 200 - 1000 mcg
+ clear CS on exam

Pursue subtype testing promptly

UFC >1000 mcg

Pursue subtype testing ASAP!!
These pts do die from CS!!

UFC >1000 mcg
Confirmed Cushing Syndrome (CS)

Serum ACTH

Undetectable
Adrenal CT

Unilateral adrenal mass:
- Adenoma
- Carcinoma

Bilateral adrenal masses:
- BMAH
- PPNAD
- Bilateral cortisol-secreting adenomas

Mid-normal to increased
Pituitary MRI

Definite pituitary tumor
Normal or equivocal MRI or picture “does not fit”

If clinical picture fits with pituitary-dependent CS (eg, female, slow onset, mild to moderate CS, UFC <600 mcg) then IPSS usually not needed

IPSS
Cushing Syndrome

Treatment Menu:

- Observation & re-evaluate in 3 to 6 mo
- Transsphenoidal surgery
- Unilateral adrenalectomy
- Bilateral adrenalectomy
- Resect ectopic ACTH tumor
Approach to Glucocorticoid Taper

• Home on prednisone 10-0-5-0 mg (if ectopic use higher dose), then drop total dosage by 2.5 mg every 2 wks:
  ✓ 7.5-0-5-0 → 5-0-5-0 → 5-0-2.5-0 mg

• Then substitute hydrocortisone (HC) 20-0-10-0 mg, then drop total dose by 5 mg every 2 wks:
  ✓ 15-0-10-0 → 15-0-5-0 → 15-0-0-0 mg

• Then, no further dosage taper; but rather check 8 AM cortisol before morning dose of HC every 6 wks

• When morning serum cortisol is >10 mcg/dL (>276 nmol/L), stop HC
Approach to Glucocorticoid Taper

- Home on prednisone 10-0-5-0 mg (if ectopic use higher dose), then drop total dosage by 2.5 mg every 2 wks:
  - 7.5-0-5-0 → 5-0-5-0 → 5-0-2.5-0 mg

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- Then, no further dosage taper; but rather check 8 AM cortisol before morning dose of HC every 6 wks

- When morning serum cortisol is >10 mcg/dL (>276 nmol/L), stop HC

This same approach is used for iatrogenic CS with taper and D/C of exogenous steroids
Case 2: Cushing Syndrome: 41-Yr-Old Man

History of Present Illness:

- Referred for evaluation of “persistent Cushing’s syndrome after stopping prednisone”
- History of Crohn’s disease flare September 2003 – treated with prednisone until March of 2004 (patient is uncertain of dose used)
- After stopping prednisone, his signs & sx related to prednisone therapy did not resolve
- December, 2004 – his “prednisone symptoms” progressed
Case 2: Cushing Syndrome: 41-Yr-Old Man

History of Present Illness (2):

- December, 2004 – his “prednisone symptoms” ↑ed:
  - Increased fatigue; marked proximal muscle weakness
  - 50 pound weight gain; purple/red striae over the lower abdomen
  - New hypertension & diabetes mellitus
  - Scalp hair loss; rapid finger nail growth (clips every other day)
  - Hand tremor
  - Serum potassium was 1.7 mEq/L when Rx with HCTZ
History of Present Illness (3):

- No ETOH or tobacco
- Medications:
  - Metoprolol (Lopressor®) 50 mg twice daily
  - Lisinopril (Prinivil/Zestril®) 20 mg twice daily
  - Amlodipine (Norvasc®) 10 mg once daily
  - Spironolactone (Aldactone®) 50 mg twice daily
  - Potassium chloride 20 mEq twice daily
  - Metformin (Glucophage®) 500 mg twice daily
  - 6-Mercaptopurine 50 mg tabs – 2 ½ tabs daily
  - Balsalazide (Colazal®) 750 mg – 3 tabs 3 times daily

Case 2: Cushing Syndrome: 41-Yr-Old Man
41-Year-Old Man

Physical Exam:

- Ht = 172 cm,
  Wt = 99.6 kg,
  BMI = 33.7 kg/m²
- BP = 159/90 mmHg,
  HR = 74 bpm
- Plethoric face –
  full, round, red;
41-Year-Old Man

Physical Exam:

- Central obesity
- Skin: red striae – lower abdomen & axilla
- Neck: supraclavicular & dorsocervical fat pads
- Extremities: minimal lower extremity edema; + proximal muscle weakness
41-Year-Old Man

Laboratory tests:

- Hemoglobin = 14.0 gm/dL (N, 12.0 – 15.5)
- Sodium = 138 mEq/L (N, 135 – 145)
- Potassium = 4.4 mEq/L (N, 3.6 – 4.8)
- Calcium = 9.8 mg/dL (N, 8.9 – 10.1)
- Glucose = 133 mg/dL (N, 70 – 100)
  - 7.4 mmol/L (N, 3.9 – 5.6)
- Uric acid = 4.1 mg/dL (N, 2.3 – 6.0)
- AST = 61 U/L (N, 12 – 31)
- Creatinine = 0.9 mg/dL (0.6 – 0.9)
Cushing Syndrome

**Test Menu:**

- Diurnal serum cortisols
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- FDG-PET scan
- Treatment Menu
Cushing Syndrome

Treatment Menu:

- Observation & re-evaluate in 3 to 6 mo
- Transsphenoidal surgery
- Unilateral adrenalectomy
- Bilateral adrenalectomy
- Resect ectopic ACTH tumor
Case #3: 20-Year-Old Woman--Jennifer

History of Present Illness:

- College student in Liverpool, England
- Hair thinning, easy bruising, facial flush, & hair loss x 3 yr
- $2^\circ$ amenorrhea x 6 mo; $\uparrow$BP x 3 mo
- Lives in London, consulted with MDs on Harley Street—no answer. Was visiting Aunt in Maiden Rock, WI—had not seen Jen x 3 yrs—and her Aunt said “something must be wrong . . . she is losing her hair, she is weak, I even beat her in a 5K race along the Mississippi River”
- Meds: none
20-Year-Old Woman--Jennifer

Physical Exam:

- 165 cm, 57 kg, BMI = 20.9 kg/m²
- BP 150/102 mm Hg
- Round, flushed face, marked scalp hair loss, small dorsocervical fat pad, striae on inner thighs
  \[\therefore\text{consistent with mild CS}\]
Cushing Syndrome

**Test Menu:**

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- 24-hr UFC
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- Treatment Menu
Cushing Syndrome

Treatment Menu:

- Observation & re-evaluate in 3 to 6 mo
- Transsphenoidal surgery
- Unilateral adrenalectomy
- Bilateral adrenalectomy
- Resect ectopic ACTH tumor
Case #4: 46-Year-Old Woman--Elena

History of Present Illness:

- Travel agent, grew up in Russia, living in Switzerland
- New onset ↑BP, wt gain, easy bruising
- Muscle weakness (stairs)
- Normal menses & normal BMD
- Main concerns are fluid retention & wt gain (83 kg to 103 kg over 4 yr)—spa treatments, liposuction, & herbals all ineffective
- Meds: irbesartan/HCTZ, torsemide
46-Year-Old Woman--Elena

Physical Exam:

- 175 cm, 103 kg, BMI = 33.5 kg/m\(^2\)
- BP 160/90 mm Hg
- Full face, no hirsutism
- No striae
- Proximal muscle weakness
- Edema—ankles bilat
### Cushing Syndrome

**Test Menu:**

<table>
<thead>
<tr>
<th>Test</th>
<th>High-Dose DST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diurnal serum cortisols</td>
<td></td>
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<td>24-hr UFC</td>
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<td>IPSS with CRH</td>
</tr>
<tr>
<td>Dex-CRH test</td>
<td>Chest CT/MRI</td>
</tr>
<tr>
<td>Midnight salivary F</td>
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<td>1-mg overnight DST</td>
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<tr>
<td>ACTH level</td>
<td>FDG-PET scan</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>Treatment Menu</td>
</tr>
</tbody>
</table>

### Treatment Menu
Cushing Syndrome

Treatment Menu:

- Observation & re-evaluate in 3 to 6 mo
- Transsphenoidal surgery
- Unilateral adrenalectomy
- Bilateral adrenalectomy
- Resect ectopic ACTH tumor
Final Thoughts

Pace of Evaluation:

• If the symptoms are mild and biochemical tests borderline, take your time—the goal is NOT to correct laboratory values, but rather to treat signs and symptoms of CS—if you are having trouble confirming CS, there is no RUSH!

• If the patient has severe ACTH-dependent CS and source of ACTH is not evident, don’t waste time—send them to bilateral lap adx!
Final Thoughts

• There is no “one” algorithm for the diagnosis or the subtype evaluation
• The clinical features dictate the tests for confirmatory and subtype evaluation
• No biochemical test should “over rule” clinical intuition!
• Man with ACTH-dependent CS – think ectopic
• Woman with slowly developing and mild to moderate ACTH-dependent CS – almost certainly pituitary tumor
• IPSS is needed in a minority of patients with pituitary-dependent disease