Treatment of Cushing’s Syndrome:
An Endocrine Society Clinical Practice Guideline
Task Force Members

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I. Clinical Case Questions
BH is a 33-year-old woman who complains of a 44 lb (20 kg) weight gain over the past year. She is a former high school gymnast who maintained her weight, including after the birth of her two children (aged 4 and 7).

Other symptoms:
- Irregular menses
- Polyuria
- Dry itchy skin
- Insomnia
- Increased irritability

Other medical history
- Past medical and family history: Unremarkable
- Non-smoker, minimal alcohol usage
- Medications: multivitamin

Physical examination:
- Blood pressure 155/90
- Face round and reddened
- Purplish abdominal striae with generally thin skin
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood sugar</td>
<td>176 mg/dl (9.8 mmol/L)</td>
</tr>
<tr>
<td>[normal &lt;106 mg/dl (&lt;0.88 mmol/L)]</td>
<td></td>
</tr>
<tr>
<td>Cortisol after 1mg Dexamethasone</td>
<td>7.6 mcg/dl (209.8 nmol/L)</td>
</tr>
<tr>
<td>[normal &lt;1.8 mcg/dl (49.7 nmol/L)]</td>
<td></td>
</tr>
<tr>
<td>24-hr Urine free cortisol (UFC)</td>
<td>220 mcg/day (660 nmol/day)</td>
</tr>
<tr>
<td>[normal &lt;45 mcg (124 nmol/L)]</td>
<td></td>
</tr>
<tr>
<td>8 AM ACTH</td>
<td>78 pg/ml (17.2 pmol/L)</td>
</tr>
<tr>
<td>[normal 9-50 pg/ml (1.98-11 pmol/L)]</td>
<td></td>
</tr>
<tr>
<td>Pituitary MRI</td>
<td>9 mm right lateral hypodensity</td>
</tr>
</tbody>
</table>
Clinical Case: BH

Question 1: Therapeutic Intervention

What first therapeutic intervention do you favor?

A. Transsphenoidal surgery
B. Steroidogenesis inhibitors (e.g. ketoconazole, metyrapone)
C. Glucocorticoid blocker (mifepristone)
D. Somatostatin analog (pasireotide)
E. Bilateral adrenalectomy
Clinical Case: BH

Question 1: Therapeutic Intervention

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Clinical Case: BH

Peri-operative Course

- The patient is referred to an experienced pituitary surgeon, who removed the tumor without complication.
  - Pathology reveals a typical pituitary adenoma, which stains only for ACTH.
  - Post-operatively, the cortisol drops to 1.0 mcg/dl (27.6 nmol/L), and the patient feels ill.

- She is given hydrocortisone and discharged on replacement doses. She has no symptoms of diabetes insipidus.

- Her blood sugar and blood pressure normalize.
Clinical Case: BH

Post-operative Course

• Over the next few months, she remains well
  o No anti-hypertensives
  o No anti-diabetic medications

• A follow-up MRI at 6 months shows only post-op changes

• At 9 months, she is weaned off the hydrocortisone and feels well.
Clinical Case: BH

One-year later...

- 20 months post-op, the patient calls the office concerned about recurrence of the Cushing’s syndrome

- She complains of “not feeling well” but is unable to be more specific

- She had lost 40 pounds (18 kg) over the preceding year, but has regained 5 pounds (2.5 kg) over the past few months

- Exam is unremarkable
Clinical Case: BH

Question 2: Diagnostic Testing

Which initial diagnostic test do you favor to assess for disease recurrence?

A. Repeat MRI
B. 24-hr Urine free cortisol (UFC)
C. Dexamethasone suppression test
D. Late night salivary cortisol
Clinical Case: BH

Question 2: Diagnostic Testing

Which initial diagnostic test do you favor to assess for disease recurrence?

A. Repeat MRI
B. 24-hr Urine free cortisol (UFC)
C. Dexamethasone suppression test
D. Late night salivary cortisol
Clinical Case: BH

20–26 months Post-operative

• Biochemical testing returns normal

• 6 months later, the patient has gained another 5 lbs (2.5 kg)

• Exam unremarkable, but screening bloodwork indicates a fasting glucose of 135 mg/dl (7.4 mmol/L)
Clinical Case: BH

Labs at 26 months Post-operation

- **UFC:** 40 mcg/day (110.4 nmol/day)
  - [normal <45 mcg/day (124 nmol/day)]

- 1-mg dex suppression test: 2.3 mcg/dl (63.5 nmol/L)
  - [normal <1.8 ug/dl (49.7 nmol/L)]

- **Late night salivary cortisol:** 180 ng/dL (4.97 nmol/L)
  - [normal <100 ng/dL (2.76 nmol/L)]
Clinical Case: BH

Question 3: Further Interventions

Which intervention would you select at this time?

A. Treat co-morbidities only
B. Repeat pituitary surgery
C. Radiation therapy
D. Medical therapy
E. Bilateral adrenalectomy
Clinical Case: BH

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Which intervention would you select at this time?

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Clinical Case: BH

26–30 months Post-operative

- Patient is placed on metformin with normalization of blood glucose.
- 4 months later, she has gained an additional 10 lbs [5 kg]. She now requires 2 oral medications for her diabetes.
- Exam shows BP 150/90, and she has recurrent moon facies and skin changes.
- UFC 75 mcg/day (207 nmol/day) [normal <45 mcg/day (124.2 nmol/day)]
- Late night salivary 300 ng/dL (8.28 nmol/L) [normal <100 ng/dL (2.76 nmol/L)]
- MRI is stable, showing only post-op changes
Clinical Case: BH

Question 4: Further Interventions

Which intervention would you select at this time?

A. Treat co-morbidities only
B. Repeat pituitary surgery
C. Radiation therapy
D. Medical therapy
E. Bilateral adrenalectomy
Clinical Case: BH

Question 4: Further Interventions

Which intervention would you select at this time?

A. Treat co-morbidities only
B. Repeat pituitary surgery
C. Radiation therapy
D. Medical therapy
E. Bilateral adrenalectomy
Clinical Case: BH

30 months Post-operative

- The surgeon does not feel that further pituitary surgery would be valuable
- The patient is offered radiation therapy but declines.
- She is next offered medical therapy
Clinical Case: BH

Question 5: Medical Therapy

Which medical therapy would you select at this time?

A. Ketoconazole
B. Metyrapone
C. Mifepristone
D. Pasireotide
E. Cabergoline
F. Another option
Clinical Case: BH

Question 5: Medical Therapy

Which medical therapy would you select at this time?

A. Ketoconazole
B. Metyrapone
C. Mifepristone
D. Pasireotide
E. Cabergoline
F. Another option
II. Presentation of Task Force Guidelines
Conversely, in severe CS, treatment may be life-saving and should not be delayed.
Cushing’s Syndrome: Major Points

- Operation by an experienced surgeon is the optimal initial treatment.
- Measurement of cortisol during treatment is a surrogate marker for normalization.
- Normalization of comorbidities is the goal.
- Use late night salivary cortisol to detect recurrence.
- Individualize the choice of second line therapy.
- Know what we don’t know.
III. Review of Treatment Approaches and Special Situations
Subtle Recurrence

Treatment Goals for Cushing’s Syndrome

The benefit of treating to normalize cortisol is not established in the setting of mild hypercortisolemia.

Approach to Long-Term Follow-up

Treat specific comorbidities

Future Research

Evaluate the clinical effects and benefits/risks of treating mild hypercortisolemia.
# GRADE Classification of Guideline Recommendations

<table>
<thead>
<tr>
<th>QUALITY OF EVIDENCE</th>
<th>High Quality</th>
<th>Moderate Quality</th>
<th>Low Quality</th>
<th>Very Low Quality</th>
</tr>
</thead>
</table>
| Description of Evidence    | • Well-performed RCTs  
  • Very strong evidence from unbiased observational studies                 | • RCTs with some limitations                     | • RCTs with serious flaws                        | • Unsystematic clinical observations             |
| STRENGTH OF               |                                                                               |                                                  |                                                  |                                                  |
| RECOMMENDATION             | Strong (1): “We recommend...” Benefits clearly outweigh harms and burdens, or vice versa | 1|⊕⊕⊕⊕ | 1|⊕⊕⊕ | 1|⊕⊕⑤ | 1|⊕⑤   |
|                            | Conditional (2): “We suggest...” Benefits closely balanced with harms and burdens | 2|⊕⊕⊕⊕ | 2|⊕⊕⑤ | 2|⊕⑤   | 2|⊕⑤   |
Obvious Disease Recurrence

- Second line therapeutic options, including surgical and medical options
- In patients with CD who underwent a non-curative surgery or for whom surgery was not possible, we suggest a shared decision-making approach, as there are several available second-line therapies (2|⊕⊕○○)
  - repeat transsphenoidal surgery
  - radiotherapy
  - medical therapy
  - bilateral adrenalectomy
# Medical Therapies

## Steroidogenesis inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/d or g/d)</th>
<th>Administration</th>
<th>Onset of Action</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metyrapone</td>
<td>500 – 6 g/d</td>
<td>Q 6-8 h dosing</td>
<td>Quick</td>
<td>GI, hirsutism, HT, hypokalemia; accessibility variable across countries</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>400-1600 mg/d</td>
<td>Q 6-8 h dosing</td>
<td>Quick</td>
<td>GI, hepatic dyscrasia (death), male hypogonadism; requires acid for biologic activity; DDIs</td>
</tr>
<tr>
<td>Mitotane</td>
<td>Starting dose 250 mg; 500 mg – 8 g/d</td>
<td>Adrenolytic; approved for adrenal cancer</td>
<td>Slow</td>
<td>lipophilic/long half life, teratogenic; GI and CNS: GI, CNS, gynecomastia, low WBC and T4, ↑ LFTs; ↑ CBG, DDIs</td>
</tr>
</tbody>
</table>

## Pituitary-directed

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Onset</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabergoline</td>
<td></td>
<td></td>
<td>asthenia, GI, dizziness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Onset</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasireotide</td>
<td></td>
<td>Most successful when UFC &lt;2-fold normal</td>
<td>diarrhea, nausea, cholelithiasis, hyperglycemia, transient ↑ LFTs; ↑ QTc interval</td>
</tr>
</tbody>
</table>

## Glucocorticoid receptor-directed

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Onset</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone</td>
<td></td>
<td></td>
<td>Difficult to titrate (no biomarker); abortifacient; Adverse effects: fatigue, nausea, vomiting, arthralgias, headache, hypertension, hypokalemia, edema, endometrial thickening</td>
</tr>
</tbody>
</table>

**Note:** DDIs = Drug-drug interactions
Special Cases: Pregnancy

- How would choice of therapies be different if this individual were seeking pregnancy as she began?
  - Hypercortisolism suppresses the gonadal axis → decreased fecundity
  - Some treatment approaches also decrease ovulation/spermatogenesis
  - Others may be abortifacient/teratogenic
  - Choose wisely
Identify biologic markers and tissue factors to:

- Quantify glucocorticoid exposure to guide clinical decision making
- Determine whether the patient is in remission
- Monitor patient response to medical therapy

Ascertain the best follow up strategy to detect recurrence
Evaluate benefits/risks of treating mild hypercortisolemia

Evaluate the utility of thromboembolic prophylaxis before and after remission

Assess long-term quality of life and cognitive changes and determine optimal treatment strategies