

Treatment of Cushing's Syndrome:

An Endocrine Society
Clinical Practice Guideline

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I. Clinical Case Questions

Clinical Case: BH

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

Clinical Case: BH (con't)

Lab Investigations

Test	Result
Fasting blood sugar [normal <106 mg/dl (<0.88 mmol/L)]	176 mg/dl (9.8 mmol/L)
Cortisol after 1mg Dexamethasone [normal <1.8 mcg/dl (49.7 nmol/L)]	7.6 mcg/dl (209.8 nmol/L)
24-hr Urine free cortisol (UFC) [normal <45 mcg (124 nmol/L)]	220 mcg/day (660 nmol/day)
8 AM ACTH [normal 9-50 pg/ml (1.98-11 pmol/L)]	78 pg/ml (17.2 pmol/L)
Pituitary MRI	9 mm right lateral hypodensity

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
 - No anti-hypertensives
 - 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

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

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?

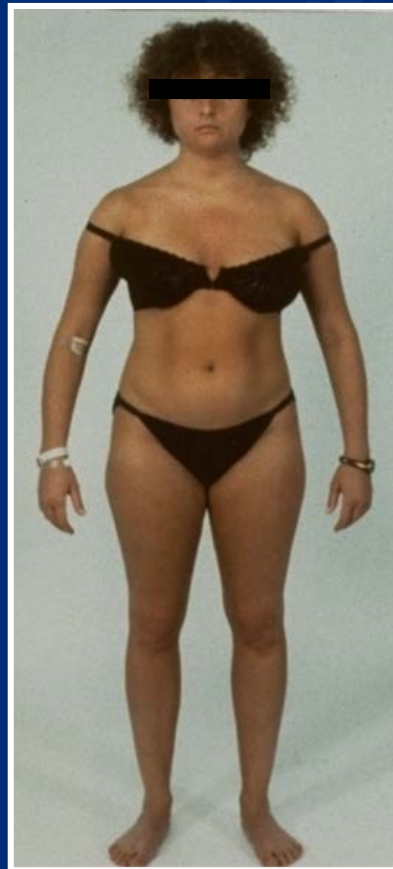
- A. Ketoconazole
- B. Metyrapone
- C. Mifepristone
- D. Pasireotide
- E. Cabergoline
- F. Another option

II.

Presentation of Task Force Guidelines

Cushing's Syndrome: Who to treat?

“Barn Door” Cushing's



If the diagnosis of CS is not clear, do not treat

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

QUALITY OF EVIDENCE		High Quality	Moderate Quality	Low Quality	Very Low Quality
<i>Description of Evidence</i>		<ul style="list-style-type: none"> Well-performed RCTs Very strong evidence from unbiased observational studies 	<ul style="list-style-type: none"> RCTs with some limitations Strong evidence from unbiased observational studies 	<ul style="list-style-type: none"> RCTs with serious flaws Some evidence from observational studies 	<ul style="list-style-type: none"> Unsystematic clinical observations Very indirect evidence observational studies
STRENGTH OF RECOMMENDATION	Strong (1): “We recommend...” Benefits clearly outweigh harms and burdens, or vice versa	1 ⊕⊕⊕⊕	1 ⊕⊕⊕○	1 ⊕⊕○○	1 ⊕○○○
	Conditional (2): “We suggest...” Benefits closely balanced with harms and burdens	2 ⊕⊕⊕⊕	2 ⊕⊕⊕○	2 ⊕⊕○○	2 ⊕○○○

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

Metyrapone 500 – 6 g/d; Q 6-8 h dosing	Quick onset of action	Adverse effects: GI, hirsutism, HT, hypokalemia; accessibility variable across countries
Ketoconazole 400-1600 mg/d; Q 6-8 h dosing	Quick onset of action	Adverse effects: GI, hepatic dyscrasia (death), male hypogonadism; requires acid for biologic activity; DDIs
Mitotane Starting dose 250 mg; 500 mg – 8 g/d	Adrenolytic; approved for adrenal cancer	Slow onset action; lipophilic/long half life, teratogenic; GI and CNS: GI, CNS, gynecomastia, low WBC and T4, ↑ LFTs; ↑ CBG, DDIs
Etomidate Bolus and titrate	Intravenous, quick onset of action	Requires monitoring in ICU

Pituitary-directed

Cabergoline		Adverse effects: asthenia, GI, dizziness
Pasireotide	Most successful when UFC <2-fold normal	Subcutaneous; Adverse effects: diarrhea, nausea, cholelithiasis, hyperglycemia, transient ↑ LFTs; ↑QTc interval

Glucocorticoid receptor-directed

Glucocorticoid receptor-directed Mifepristone		Difficult to titrate (no biomarker); abortifacient; Adverse effects: fatigue, nausea, vomiting, arthralgias, headache, hypertension, hypokalemia, edema, endometrial thickening
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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**

Recommended Future Research Aims

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

Recommended Future Research Aims

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