Adrenal Board Review
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1. A primary care physician refers to you a 35-year-old man with bilateral adrenal enlargement. The physician is concerned about the possibility of bilateral pheochromocytoma because the patient’s initial blood pressure was elevated.

Question 1 (1/4)

You measure plasma free fractionated metanephrines, and the results are normal. The patient’s appetite has been poor and he has lost 11 lb (5 kg) in the past 3 months. He has no family history of endocrinopathy. He is not taking any medications.

On physical examination, his blood pressure is 100/68 mm Hg, pulse rate is 96 beats/min, and temperature is 99.3°F (37.4°C). Height is 72 in (182.9 cm), and weight is 175 lb (79.5 kg). The rest of the examination findings are unremarkable.

Question 1 (3/4)

Additional laboratory test results (sample drawn in the morning):
- Sodium = 131 mEq/L (131 mmol/L)
- Potassium = 4.4 mEq/L (4.4 mmol/L)
- Chloride = 103 mEq/L (103 mmol/L)
- Bicarbonate = 23 mEq/L (23 mmol/L)
- Serum urea nitrogen = 12 mg/dL (4.3 mmol/L)
- Creatinine = 0.6 mg/dL (53.0 μmol/L)
- Calcium = 10.2 mg/dL (2.6 mmol/L)
- Aldosterone = 4 ng/dL (111.0 pmol/L)
- Plasma renin activity = 17 ng/mL per h
- Plasma ACTH = 212 pg/mL (46.6 pmol/L)
- Cortisol = 6.4 µg/dL (176.6 nmol/L)

Question 1 (4/4)

Which of the following diagnostic tests is most likely to be helpful in the further diagnosis and management of this patient?

A. Measurement of 24-hour urinary fractionated catecholamines and metanephrines 15%
B. Measurement of 21-hydroxylase antibodies 30%
C. Pituitary-directed MRI 7%
D. Bilateral adrenal venous sampling for cortisol, aldosterone, and catecholamines 7%
E. CT-guided percutaneous adrenal biopsy 41%
Adrenal Insufficiency: Clinical Presentations

- **Signs/Symptoms**
  - Fatigue
  - GI: weight loss, nausea, anorexia
  - Increased skin pigmentation
  - Hypotension
  - Salt craving

- **Imaging Abnormalities**
  - Bilateral adrenal enlargement/masses
  - Pituitary mass

- **Lab Abnormalities**
  - Hyponatremia
  - Hyperkalemia
  - Hypercalcemia

- **Drugs:** Corticosteroids (oral, parenteral, topical, inhaled), narcotics, adrenostatic/lytic, GR receptor antagonist

- **Genetic:** CAH, ALD

Indications for percutaneous adrenal biopsy*

- Bilateral adrenal enlargement (with or without nodules) with primary adrenal insufficiency
- Adrenal nodule (>2 cm with HU ≥15) with known malignancy that may metastasize to adrenal and information would alter clinical therapy or prognosis

*Pheo exclusion

Diagnostic Testing

CT-guided biopsy of the adrenal glands
- Total replacement of the adrenal parenchyma by confluent necrotizing palisaded granulomas
- PAS and methenamine silver stains revealed numerous yeast consistent with Histoplasma
- Cultures of the biopsy grew *H. capsulatum*

Methenamine Silver Stain of Adrenal Histoplasmosis

2. A 42-year-old woman with a history of Cushing disease asks for your opinion regarding the possibility of a recurrence. Six years earlier, she underwent transsphenoidal pituitary microsurgery for removal of a 5-mm corticotroph adenoma (confirmed with immunocytochemistry). Postoperatively, she had well-documented secondary adrenal insufficiency requiring glucocorticoid support for 11 months. She had complete recovery of her pituitary-adrenal axis. Her signs and symptoms of hypercortisolism resolved, with a 30-lb (13.6-kg) weight loss, resolution of her hypertension, decreased facial fullness and plethora, and resumption of normal menses.

Question 2 (1/2)
During the past 6 months, she has gained 25 lb (11.4 kg) and there has been a slight increase in her blood pressure. Her menses have been normal. She feels more depressed and is having difficulty dealing with the stress of her job. She is not taking any medication. She is convinced that she has Cushing syndrome again. However, her primary care physician measured a urinary cortisol excretion of 28 µg/24 h (77.3 nmol/d).

On physical examination, she has some facial rounding, but no plethora. Her blood pressure is 148/96 mm Hg, and her pulse rate is 78 beats/min. Height is 64.5 in (163.8 cm), and weight is 164 lb (74.5 kg) (BMI = 27.7 kg/m²). She has some nonviolaceous striae. She has good muscle strength and no edema.

Question 2 (2/2)

3. A nephrologist colleague asks you for an opinion regarding deterioration in renal function in a 52-year-old man with primary hyperaldosteronism diagnosed 6 months earlier. His baseline estimated glomerular filtration rate of 93 mL/min per 1.73 m² decreased to 68 mL/min per 1.73 m² after initiation of spironolactone, 50 mg twice daily. A repeated measurement is 61 mL/min per 1.73 m². His blood pressure has been well controlled and he has a normal potassium level without supplementation. Adrenal venous sampling without ACTH stimulation was performed with good catheterization of each adrenal vein and no evidence of lateralization of aldosterone secretion.

Question 3 (1/1)

Which of the following is the best next step to exclude recurrent Cushing disease?

A. 2-day low-dose dexamethasone suppression test (0.5 mg every 6 hours for 48 hours) 11%
B. Pituitary-directed MRI 2%
C. Late-night salivary cortisol measurement 70%
D. Plasma ACTH measurement 5%
E. No further tests are needed; patient should be reassured 12%

Question 2

Sequential Hormonal Changes in Patients with Recurrent Cushing Disease After Successful Pituitary Surgery


Which of the following should you recommend?

A. Ultrasonography of the renal arteries 29%
B. MRI of the adrenal glands 2%
C. Substitution of eplerenone for spironolactone 9%
D. Repeated adrenal venous sampling with ACTH stimulation 20%
E. No change in current treatment 41%

Question 3
Hormonally Induced Transformation of Adrenal Tissue Into Myeloid tissue

Testosterone alone → transformed adrenal cortical cells into ordinary fat cells (only in rats with intact pituitary function)

Addition of ACTH extract transformed the entire deep cortex into fat and hematopoietic tissue


Testicular Adrenal Rest Tumors (TARTs)

- Common in men with CAH found with testicular ultrasound
- May contribute to impaired testicular function because of increased intratesticular pressure and reduced blood flow
- Treatment: increase GC replacement/surgery

4. You are called from the emergency department for advice about a 28-year-old man whom you saw in your office on 1 occasion 2 years ago. The patient is intoxicated, and he has been having some abdominal pain and vomiting. The patient says he has adrenal insufficiency and has a wallet card confirming this. The emergency department physician asks you to electronically review the patient’s abdominal CT scan (see image), which was performed in the emergency department. It reveals bilateral 16-cm heterogeneous adrenal masses (~20 Hounsfield units). When reviewing your note from 2 years ago, you notice that you had appreciated a firm lump in the right testis.

Question 4 (1/2)

After you recommend intravenous hydrocortisone, you explain to the emergency department physician that this man most likely has which of the following?

A. Adrenomyeloneuropathy 21%
B. Congenital adrenal hyperplasia 39%
C. Autoimmune polyglandular syndrome type 2 6%
D. Bilateral adrenal hemorrhage 10%
E. Metastatic testicular carcinoma 24%

Question 4 (2/2)
5. A 47-year-old woman sees you for an annual visit for management of hypothyroidism. She has been on a stable levothyroxine dosage for 9 years and she has always had normal blood pressure at each visit. She is not taking any other prescription medications.

On physical examination, she is a healthy-appearing woman. Her blood pressure is 162/102 mm Hg, pulse rate is 74 beats/min, and BMI is 23.7 kg/m². Her examination findings are normal.

You order studies to exclude hyperaldosteronism and hypercortisolism as possible causes of her hypokalemic hypertension. After receiving the results, you take a thorough dietary history and the patient acknowledges that each day she has been consuming a 10-oz bag of licorice, which contains real licorice extract, 25% glycyrrhizic acid by weight.

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Routine laboratory test results:
- Sodium = 141 mEq/L (141 mmol/L)
- Potassium = 2.8 mEq/L (2.8 mmol/L)
- Chloride = 95 mEq/L (95 mmol/L)
- Bicarbonate = 29 mEq/L (29 mmol/L)
- Glucose = 104 mg/dL (5.8 mmol/L)
- Serum urea nitrogen = 12 mg/dL (4.3 mmol/L)
- Creatinine = 0.7 mg/dL (61.9 µmol/L)
- TSH = 1.2 mIU/L

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Which of the following biochemical profiles is present in this patient?

<table>
<thead>
<tr>
<th>Answer</th>
<th>Plasma Renin Activity</th>
<th>Serum Aldosterone</th>
<th>Late-Night Salivary Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>↑</td>
<td>↑</td>
<td>Normal</td>
</tr>
<tr>
<td>B.</td>
<td>↓</td>
<td>↑</td>
<td>Normal</td>
</tr>
<tr>
<td>C.</td>
<td>↑</td>
<td>↓</td>
<td>Normal</td>
</tr>
<tr>
<td>D.</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>E.</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Answer: A
6. A 49-year-old woman has been referred with a history of estrogen receptor–positive breast cancer diagnosed 3 years earlier. Her only medication is tamoxifen. She has not had any evidence of breast cancer recurrence, but a recent CT of her abdomen showed a 2.8-cm right adrenal nodule with an attenuation value of 46 Hounsfield units. Fluorodeoxyglucose positron emission tomography demonstrated accumulation of fluorodeoxyglucose in the right adrenal nodule, but no significant accumulation in other sites. The patient is asymptomatic and has never had hypertension.

Question 6 (1/2)

Her blood pressure is 128/86 mm Hg, and her pulse rate is 76 beats/min. Her electrolytes and chemistry profile are normal. Biochemical studies document an aldosterone concentration of 16 ng/dL (444.3 pmol/L) and plasma renin activity of 3.5 ng/mL per h. An overnight 1-mg dexamethasone suppression test yields a cortisol concentration of 2.2 µg/dL (60.7 nmol/L).

Question 6 (2/2)

Which of the following would you suggest next?

A. Surgical removal of the right adrenal nodule 5%
B. Measurement of plasma free fractionated metanephrines 80%
C. Bilateral adrenal venous sampling for aldosterone, cortisol, and epinephrine 1%
D. Percutaneous CT-guided aspiration biopsy of the right adrenal nodule 10%
E. High-dose dexamethasone suppression test 5%

Question 6

Pheochromocytoma in Patients Suspected of Harboring Adrenal Metastasis

- Adrenal lesion suspected to be metastasis (n = 30)
- 18 had malignancy (3.5–4.7 cm)
- 8 had adrenal adenoma (1.3–4.0 cm)
- 4 had pheochromocytoma (1.2–10.2 cm)


7. A 33-year-old man has been referred to you for evaluation of Cushing syndrome. He has an 11-year history of HIV infection. He is taking antiretroviral therapy, including didanosine, tenofovir, and ritonavir. His viral load is zero and his CD4 count is normal. He has developed asthma in the past 6 months and has been taking fluticasone/salmeterol twice daily and an albuterol metered-dose inhaler as needed. He has gained 30 lb (13.6 kg) in the past 3 months. Hypertension and fasting hyperglycemia have developed. On physical examination, he has a very cushingoid appearance, with wide, violaceous abdominal striae and proximal muscle weakness.

Question 7 (1/1)
Which of the following laboratory profiles is most likely to be found in this man?

<table>
<thead>
<tr>
<th>Answer</th>
<th>Plasma ACTH</th>
<th>DHEA-S</th>
<th>Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>B.</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>C.</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>D.</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>E.</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Question 7

8. A 33-year-old man is referred to you for the postoperative management of an abdominal catecholamine-secreting paraganglioma. He had hypertension for 10 years before the diagnosis was established and several other family members are reported to have hypertension. On physical examination today, his blood pressure is normal, and his BMI is 25.3 kg/m². His thyroid gland is normal, and you find no evidence of mucosal neuromas, café-au-lait spots, or axillary freckling.

Question 8 (1/2)

His initial urinary catecholamine laboratory test results:

- Metanephrine = 159 µg/24 h (806 nmol/d)
- Normetanephrine = 2200 µg/24 h (12,012 nmol/d)
- Norepinephrine = 434 µg/24 h (2567 nmol/d)
- Epinephrine = 7 µg/24 h (38 nmol/d)
- Dopamine = 245 µg/24 h (1598 nmol/d)

Question 8 (2/2)
In which of the following genes is this man most likely to have a disease-causing mutation?

A. von Hippel-Lindau syndrome gene (VHL) 14%
B. One of the succinate dehydrogenase genes (SDHD, SDHB, SDHC) 66%
C. Neurofibromatosis type 1 gene (NF1) 4%
D. Multiple endocrine neoplasia type 2 gene (RET proto-oncogene) 3%
E. Familial pheochromocytoma gene (FP/TMEM127) 13%

Question 8

Autosomal Dominant Syndromes Associated With Pheochromocytoma and Paraganglioma

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Gene Locus</th>
<th>Protein Product</th>
<th>Protein Function</th>
<th>Gene Locus</th>
<th>Protein</th>
<th>Protein Function</th>
<th>Gene Locus</th>
<th>Protein</th>
<th>Protein Function</th>
<th>Typical Tumor Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDHD (familial paraganglioma type 1)</td>
<td>SDHD</td>
<td>11q23</td>
<td>SDH D subunit</td>
<td>ATP production</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Head and neck, rarely adrenal medulla</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDHC (familial paraganglioma type 2)</td>
<td>SDHC</td>
<td>11q23</td>
<td>SDH C subunit</td>
<td>ATP production</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Head and neck, rarely adrenal medulla</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDHB (familial paraganglioma type 4)</td>
<td>SDHB</td>
<td>1p36.1-35</td>
<td>SDH B subunit</td>
<td>ATP production</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Abdomen and pelvis, rarely adrenal medulla</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laboratory test results:
- Serum electrolytes, normal
- Urinary free cortisol = 532 µg/24 h (1468 nmol/d)
- Late-night salivary cortisol = 1.6 µg/dL (43 nmol/L)
- DHEA-S = 678 µg/dL (18.4 µmol/L)
- Basal plasma ACTH = <5 pg/mL (<1.1 pmol/L)

Question 9 (2/2)

9. A 33-year-old man has been referred to you for evaluation of Cushing syndrome. He has had the rapid onset of signs and symptoms of hypercortisolism over the past 6 months, with a 20-lb (9.1-kg) weight gain, edema, hypertension, and diabetes mellitus.

Question 9 (1/2)

Which of the following radiographic findings is most likely?

A. 8-mm pituitary microadenoma 1%
B. 3-cm right upper lobe lung nodule 10%
C. 3-cm right adrenal mass with low attenuation value (8 Hounsfield units) 22%
D. 6-cm left adrenal mass with high attenuation value (74 Hounsfield units) 63%
E. Bilateral adrenal enlargement without any discrete nodules 5%

Question 9
10. A 27-year-old man has been referred to you for a second opinion regarding endogenous Cushing syndrome. He has a 1-year history of hypertension and has gained 43 lb (19.5 kg) in the past 6 months. He also has facial fullness; muscle weakness; insomnia; and wide, violaceous striae. He is very cushingoid and has a blood pressure of 156/94 mm Hg despite treatment with lisinopril, hydrochlorothiazide, and amlodipine.

 MRI of the pituitary is normal. CT of the chest and abdomen shows a 1.5-cm calcified lesion in the right upper lung lobe and bilateral adrenal enlargement without nodules. A right upper lobectomy has been recommended.

Laboratory test results (ordered by another endocrinologist):
- Sodium = 138 mEq/L (138 mmol/L)
- Potassium = 2.9 mEq/L (2.9 mmol/L)
- Chloride = 98 mEq/L (98 mmol/L)
- Serum urea nitrogen = 24 mg/dL (8.6 mmol/L)
- Creatinine = 1.1 mg/dL (97.2 µmol/L)
- Bicarbonate = 30 mEq/L (30 mmol/L)
- Plasma ACTH = 102 pg/mL (22.4 pmol/L)
- Urinary free cortisol = 1944 µg/24 h (5365 nmol/d)
- Late-night salivary cortisol = 2.4 µg/dL (66 nmol/L)
- Overnight 1-mg dexamethasone suppression test: cortisol = 21.4 µg/dL (590 nmol/L)

Which of the following should you recommend?

A. Bilateral inferior petrosal sinus sampling for ACTH  48%
B. High-dose dexamethasone suppression test (2-mg dexamethasone every 6 hours for 8 doses, with measurement of urine and plasma steroids)  27%
C. Octreotide acetate scintigraphy  13%
D. DDAVP stimulation test  0%
E. Proceeding with the recommended thoracic surgery  13%
**Prenatal Treatment of CAH**

- Female genitalia virilization may start at 6 weeks’ gestation
- Dexamethasone (? dose) as soon as woman is pregnant, but only 1/8 fetuses need to be treated
- Chorionic villous sampling for genetic diagnosis cannot be done until 10-12 weeks’ gestation and knowing parents’ specific mutations may expedite process
- Dexamethasone therapy may eliminate or reduce virilization in 80%

11. A 27-year-old pregnant woman seeks your advice at 6 weeks’ gestation. This is her first pregnancy. She has salt-wasting congenital adrenal hyperplasia due to 21-hydroxylase deficiency, for which she takes hydrocortisone and fludrocortisone. She is concerned that her baby may have the same condition.

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**Congenital Adrenal Hyperplasia (CYP21 deficiency)**

- Autosomal recessive w/ good genotype/phenotype correlation
- Incidence of carriers in the population is 1:50-1:70
- Incidence of CAH is 1:10,000-1:20,000
- Woman with CAH has 1:120 chance of having child w/ CAH
- NCCAH 2/3 cmpd heterozygotes w/ one allele CAH, one NCCAH—milder allele = phenotype: patient w/ NCCAH 1:240 w/ CAH; however, in one study it was 2.5%

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12. A 42-year-old woman is referred for recommendations regarding primary aldosteronism. She developed hypertension and severe hypokalemia during her last pregnancy, at age 29 years. The diagnosis of primary aldosteronism was established at age 32 years, when she was documented to have an aldosterone concentration of 54 ng/dL (1498 pmol/L) and undetectable plasma renin activity. Her urinary aldosterone excretion was 48 µg/24 h (133 nmol/d) on a high-sodium diet. Adrenal imaging showed a 19-mm nodule (7 Hounsfield units) in the right adrenal gland and a normal left adrenal gland. Adrenal venous sampling was performed, but the results (shown below) were considered nondiagnostic. The patient declined a second sampling procedure.

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The patient has been treated for more than 10 years with spironolactone, 100 mg daily, and amlodipine, 10 mg daily, but her blood pressure has been very poorly controlled over the past 1 to 2 years (systolic 140 to 176 mm Hg and diastolic 98 to 110 mm Hg). Persistent hypokalemia has mandated the use of 60 mEq of potassium chloride daily.

Question 12 (2/3)

Which of the following should you recommend?

A. Laparoscopic right adrenalectomy 52%
B. Laparoscopic left adrenalectomy after 2 weeks of α- and β-adrenergic blockade 20%
C. Laparoscopic bilateral adrenalectomy 2%
D. Increasing spironolactone to 100 mg twice daily 18%
E. Replacing spironolactone with eplerenone, 100 mg twice daily 7%

Question 12

13. A 37-year-old woman wants a second opinion regarding her endocrine status. She has a 4-year history of a 56-lb (25.5-kg) weight gain associated with the onset of secondary amenorrhea, hypertension, depression, and diabetes. She has a very cushingoid appearance, with facial fullness and plethora, as well as a marked increase in supraclavicular and dorsocervical fat accumulation. She has truncal obesity; a BMI of 37 kg/m²; and wide, violaceous striae on her abdomen and in her axillae. Her medications include insulin glargine, insulin lispro, metformin, sitagliptin, lisinopril, furosemide, and fluoxetine.

Question 13 (1/3)

Adrenal venous sampling (performed 10 years earlier with ACTH infusion).

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Right Adrenal Vein</th>
<th>Left Adrenal Vein</th>
<th>Inferior Venae Cava</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone</td>
<td>15 mg/dL (416 pmol/L)</td>
<td>427 mg/dL (11,845 pmol/L)</td>
<td>66 mg/dL (1,931 pmol/L)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>28 µg/dL (770 nmol/L)</td>
<td>371 µg/dL (10,120 nmol/L)</td>
<td>28 µg/dL (772 nmol/L)</td>
</tr>
<tr>
<td>Aldosterone-to-Cortisol ratio</td>
<td>0.13</td>
<td>1.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Epiptephrine</td>
<td>&lt;10 µg/mL (&lt;25 pmol/L)</td>
<td>2476 µg/mL (11,864 pmol/L)</td>
<td>16 µg/mL (407 pmol/L)</td>
</tr>
</tbody>
</table>

Repeated adrenal imaging now shows a 21-mm right adrenal nodule. The left adrenal gland remains normal.

Question 12 (3/3)

Unilateral Primary Aldosteronism

Bilateral Adrenal Vein Sampling

- Dominant AV (Aldo:Cort) 3-5x > nondominant AV (Aldo:Cort) ratio
- Nondominant (Aldo:Cort) < IVC (Aldo:Cort)
- And verification of adrenal venous effluent: epinephrine:cortisol

OR

Clinical Prediction Score for Unilateral Disease

- CT presence of a “typical” adrenal adenoma and
- Hypokalemia/eGFR ≥100 mL/min = 100% specificity (53% sensitivity)


Laboratory test results:

- Sodium = 138 mEq/L (138 mmol/L)
- Potassium = 3.6 mEq/L (3.6 mmol/L)
- Chloride = 100 mEq/L (100 mmol/L)
- Bicarbonate = 26 mEq/L (26 mmol/L)
- Serum urea nitrogen = 16 mg/dL (5.7 mmol/L)
- Calcium = 9.6 mg/dL (2.4 mmol/L)
- Hemoglobin Ao2 = 6.9% (0.069)
- Urinary free cortisol = 33 µg/24 h (91.1 nmol/d) and 42 µg/24 h (115.9 nmol/d) (reference range, 4-50 µg/24 h [11.0-138 nmol/d])
- Late-night salivary cortisol = 0.43 µg/dL (12 nmol/l) and 0.62 µg/dL (17 nmol/l) (reference range, <0.13 g/dL [<3.6 nmol/l])

Question 13 (2/3)
Laboratory test results:

- Overnight 1-mg dexamethasone (cortisol) = 8.2 µg/dL (226.2 nmol/L)
- Pregnancy test, negative
- FSH = 1.4 mIU/mL (1.4 IU/L)
- LH = 2.8 mIU/mL (2.8 IU/L)
- Creatinine = 0.9 mg/dL (79.6 µmol/L)
- Estradiol = 42 pg/mL (154.2 pmol/L)
- Prolactin = 12 ng/mL (0.5 nmol/L)
- Free T₄ = 0.7 ng/dL (9.0 pmol/L)
- TSH = 0.31 mIU/L

Question 13 (3/3)

Clinical and Biochemical Screening Criteria for Cushing Syndrome: Sensitivity

**Metabolic syndrome**
- DM/Htn (0.5%-1.0%)
- PCOS (?)

**Osteoporosis (3%)**

**Adrenal nodule (5%-20%)**

14. You are asked to evaluate a 16-year-old adolescent for adrenal insufficiency. He has a 2-year history of attention deficit disorder, for which he is currently treated with methylphenidate. He has had a rapid onset of neurologic symptoms, including weakness in his lower extremities, gait instability, slurred speech, and confusion. On physical examination, he has hyperpigmentation in sun-exposed areas, brisk deep tendon reflexes, clonus in the left ankle, and bilateral Babinski sign.

Question 14 (1/2)

Which of the following studies should you order next?

- A. Pituitary-directed MRI 20%
- B. Dexamethasone corticotropin-releasing hormone test 6%
- C. Plasma ACTH measurement 65%
- D. High-dose dexamethasone suppression test 7%
- E. CT of the adrenal glands 2%

Question 13

There is no family history of any endocrine disorders. Pituitary-adrenal function testing documents a morning basal plasma ACTH concentration of 144 pg/mL (31.7 pmol/L) and a serum cortisol concentration of 3.7 µg/dL (102.1 nmol/L). There is no further increase in cortisol after administration of 250 mcg of intravenous cosyntropin.

Question 14 (2/2)
15. You are referred a 36-year-old man with marked nocturnal spells of palpitation and sweating. Measurement of plasma free fractionated metanephrines shows a normal free metanephrine concentration and an increased free normetanephrine level (201.5 pg/mL [1100 pmol/L]). The 24-hour urinary measurements of fractionated catecholamines and metanephrines are normal. The patient’s primary care physician obtained CT scans of the abdomen and pelvis, which are normal, and 123I-meta-iodobenzylguanidine scintigraphy shows increased uptake in the left adrenal gland compared with that in the right adrenal gland.

Which of the following is the best next management step?

A. Laparoscopic left adrenalectomy 8%
B. Octreotide scintigraphy 10%
C. Adrenal MRI 13%
D. Glucagon stimulation test 6%
E. No further testing or treatment for pheochromocytoma 63%

16. A nephrology colleague asks for your opinion regarding a 32-year-old woman who underwent a successful left laparoscopic adrenalectomy for a 2.1-cm aldosterone-secreting adenoma 4 months earlier. The patient had presented with hypokalemia (potassium, 2.9 mEq/L [2.9 mmol/L]) and severe hypertension (initial blood pressure was 162/102 mm Hg). The patient was not seen by an endocrinologist before surgery. After surgery, her hypokalemia resolved and her blood pressure normalized without any medications. Since her operation, she has been easily fatigued and has had a decreased appetite; she has lost 6.5 lb (3 kg). Her only medication is an oral contraceptive.

Adrenal Imaging for Pheochromocytoma

• MIBG accumulation in NORMAL adrenals L>>R is common!!
• Adrenal pheochromocytoma is always visible with CT imaging
On physical examination, she is a healthy-appearing, obese woman (BMI = 31.3 kg/m²). Her blood pressure is 124/82 mm Hg, and pulse rate is 82 beats/min. She has upper-body obesity, with some increase in supraclavicular and dorsocervical fat. The rest of her examination findings are normal.

Laboratory test results (sample drawn in the morning):
- Sodium = 134 mEq/L (134 mmol/L)
- Potassium = 4.7 mEq/L (4.7 mmol/L)
- Chloride = 100 mEq/L (100 mmol/L)
- Bicarbonate = 24 mEq/L (24 mmol/L)
- Glucose = 91 mg/dL (5.1 mmol/L)
- Serum urea nitrogen = 14 mg/dL (5.0 mmol/L)
- Creatinine = 0.8 mg/dL (70.7 µmol/L)
- Calcium = 9.8 mg/dL (2.5 mmol/L)
- Cortisol = 3.8 µg/dL (104.8 nmol/L)
- Plasma ACTH = 98 pg/mL (21.6 pmol/L)
- Aldosterone = 5 ng/dL (138.7 pmol/L)
- Plasma renin activity = 0.4 ng/mL per h

In addition to initiating hydrocortisone therapy, you recommend which of the following?

A. No further diagnostic studies  47%
B. DHEA-S measurement  5%
C. CT of the adrenal glands  15%
D. MRI of the pituitary gland  4%
E. Discontinuation of oral contraceptives and a rapid ACTH stimulation test the next day  29%

Recovery From Glucocorticoid Therapy

Coexistence of Hyperaldosteronism and Hypercortisolism

Not surprising since...
APA are rarely composed of zona glomerulosa cells only
Both disorders have been associated with aberrant hormone receptor-mediated steroidogenesis

Recovery From Glucocorticoid Therapy

Cortisol
ACTH
Prednisolone
Normal cosyntropin stimulation test
ACTH Normal range
0
10
20
30
40
50
60
70
80
Dec-04
Jan-05
Feb-05
Mar-05
Apr-05
May-05
Jun-05
Jul-05
Aug-05
Sep-05
Oct-05
Nov-05
Dec-05
Jan-06
Feb-06
Mar-06
Apr-06
May-06
Jun-06
Jul-06
Aug-06
0
100
200
300
400
500
600
700
80
ACTH pg/mL
Prednisolone
17. A 24-year-old woman with well-documented primary aldosteronism asks for your opinion after undergoing bilateral adrenal venous sampling. She has a 4-year history of hypertension. An overnight 1-mg dexamethasone suppression test yielded a morning cortisol concentration of 0.7 µg/dL (19.3 nmol/L). Her adrenal CT was normal. Her family history is positive for a paternal aunt with hypertension who had a stroke at age 34 years and a paternal uncle with hypertension and a ruptured cerebral aneurysm at age 24 years. Her father had hypertension and died of an intracerebral hemorrhage at age 46 years.

Question 17 (1/1)

![Glucocorticoid-Remediable Hyperaldosteronism](image)

**Glucocorticoid-Remediable Hyperaldosteronism**

On physical examination, he is a healthy-appearing man with a blood pressure of 122/76 mm Hg, a regular pulse rate of 70 beats/min, and a BMI = 24 kg/m². His skin is well pigmented in sun-exposed areas. Examination findings are otherwise normal.

Laboratory test results:
- Electrolytes, normal
- Plasma renin activity = 2.1 ng/mL per h
- Serum TSH = 2.8 mIU/L

Question 18 (2/2)

**After you initiate a mineralocorticoid receptor antagonist, which of the following should you recommend?**

A. Initiation of mifepristone  0%
B. Laparoscopic right adrenalectomy  2%
C. Laparoscopic bilateral adrenalectomy  2%
D. Genetic testing for glucocorticoid-remediable hypertension  91%
E. Annual CT of the adrenal glands for 5 years  6%

Question 17

**18. A primary care physician refers to you a 32-year-old man because of an elevated plasma ACTH concentration of 312 pg/mL (68.6 pmol/L). He has a 10-year history of primary adrenal insufficiency due to autoimmune adrenalitis. He also has primary hypothyroidism due to Hashimoto thyroiditis. The patient feels well and has no concerns. His medications include hydrocortisone, 12.5 mg every morning and 5 mg every afternoon; fludrocortisone, 50 mcg daily; and levothyroxine, 125 mcg daily.**

Question 18 (1/2)

**In addition to reviewing sick-day corticosteroid management, which of the following should you recommend?**

A. Discontinue hydrocortisone and substitute prednisone, 5 mg in the morning and 2.5 mg in the afternoon  3%
B. Add dexamethasone, 0.75 mg orally at bedtime  1%
C. Increase the hydrocortisone dosage to 20 mg in the morning and 10 mg in the afternoon  10%
D. Increase the fludrocortisone to 100 mcg daily  2%
E. Make no changes in his corticosteroid doses  83%

Question 18
Cortisol Rx for Primary Adrenal Insufficiency

- The adrenal glands only produce 8-12 mg (6-7 mg/m²/day) of cortisol daily...doses of 30 mg of hydrocortisone daily are excessive for most patients
- The adrenal glands do not make prednisone and there is no such thing as physiologic prednisone replacement
- Plasma ACTH should be high-normal/elevated in patients receiving adequate glucocorticoid replacement

Her primary care physician obtained the following laboratory test results:

- Sodium = 134 mEq/L (134 mmol/L)
- Potassium = 2.0 mEq/L (2.0 mmol/L)
- Chloride = 90 mEq/L (90 mmol/L)
- Bicarbonate = 42 mEq/L (42 mmol/L)
- Serum urea nitrogen = 22 ng/dL (7.9 mmol/L)
- Creatinine = 0.7 ng/dL (61.9 µmol/L)

You obtain laboratory test results of an aldosterone concentration less than 1.0 ng/dL (<27.7 pmol/L) and plasma renin activity less than 0.1 ng/mL per h before starting spironolactone, potassium chloride, and valsartan. CT scans of the chest and abdomen show bilateral adrenal enlargement, with a 2-cm left adrenal nodule (10 Hounsfield units), and a large left inferior lobe lung mass.

Which of the following is the most likely cause of hypertension and hypokalemia in this patient?

A. Ectopic ACTH-secreting small cell carcinoma of the lung  83%
B. Liddle syndrome  8%
C. Surreptitious use of diuretics  1%
D. Adrenocortical carcinoma with pulmonary metastases  7%
E. Aldosterone-secreting adrenal adenoma  2%

Differential Diagnosis of Low Aldosterone/Low Renin Hypertension

- Liddle syndrome
- Syndrome of apparent mineralocorticoid excess
- Severe Cushing syndrome
- Exposure to glycyrrhizic acid

19. A 61-year-old woman with a 50-pack-year history of cigarette smoking presents with the recent onset of hypertension and peripheral edema. She appears to be cachectic and chronically ill. Her blood pressure is 182/104 mm Hg, and her pulse rate is 94 beats/min. She has 4+ pretibial edema and severe muscle weakness.
She saw her primary care physician yesterday, and the following laboratory test results were documented:

- Sodium = 134 mEq/L (134 mmol/L)
- Potassium = 2.8 mEq/L (2.8 mmol/L)
- Chloride = 93 mEq/L (93 mmol/L)
- Bicarbonate = 30 mEq/L (30 mmol/L)
- Glucose = 68 mg/dL (3.8 mmol/L)
- Serum urea nitrogen = 22 mg/dL (7.9 mmol/L)
- Creatinine = 1.0 mg/dl (88.4 µmol/L)
- Calcium = 9.8 mg/dL (2.5 mmol/L)
- Cortisol = 57 µg/dL (1573 nmol/L)
- ACTH = 124 pg/ml (27.3 pmol/L)
- TSH = 8.3 mIU/L
- Free T<sub>4</sub> = 1.1 ng/dL (14.2 pmol/L)

**Question 20 (2/3)**

**Which of the following should you recommend?**

A. Perform a pituitary MRI immediately 2%
B. Discontinue mifepristone and administer dexamethasone, 4 mg every 8 hours 85%
C. Initiate ketoconazole, 200 mg every 8 hours 9%
D. Perform a pregnancy test 2%
E. Initiate leveththyroxine, 50 mcg, in combination with liothyronine, 5 mcg daily 1%

**Question 20**

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20. A 38-year-old woman with a history of Cushing disease presents to the emergency department with nausea, weakness, and malaise. The diagnosis of an ACTH-secreting pituitary tumor with endogenous hypercortisolism was established 5 years ago. She had 2 unsuccessful pituitary operations and gamma-knife radiotherapy. Despite these treatments, her hypercortisolism persisted. Mifepristone therapy was started 10 weeks ago with dosage escalation from 300 to 900 mg daily.

**Question 20 (1/3)**

On physical examination, she is a lethargic woman with upper body obesity (BMI = 36.3 kg/m²). Blood pressure is 88/68 mm Hg, pulse rate is 102 beats/min, and temperature is 99.3°F (37.4°C). She has some facial fullness, but no plethora. There is increased supraclavicular and dorsocervical fat accumulation. Her skin pigmentation is normal. Her visual fields are full to confrontation. She has generalized weakness and slight pretibial edema.

The emergency department physician has initiated intravenous isotonic fluids with potassium, and he calls you for directions regarding her continued care.

**Question 20 (3/3)**

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**Mifepristone-Induced Adrenal Insufficiency**

**Rare/Uncommon**

Clinical manifestations are paramount

Nausea, vomiting, weight loss, fatigue, weakness
Some overlap with steroid withdrawal
Hypotension

**Biochemical studies**

Elevation of ACTH/cortisol
Hypokalemia

**Treatment**

Discontinue mifepristone
Dexamethasone (2-4 mg/300 mg mifepristone)
21. A 17-year-old woman is referred for evaluation of hypertension and hypokalemia. Three months earlier, her family physician documented a blood pressure of 142/100 mm Hg. She is asymptomatic, she does not take any medications, and she does not eat licorice. Menarche was at age 11 years, and she has had normal menstrual periods. Her mother and 2 maternal aunts developed hypertension during their third decade of life and all 3 of require potassium therapy with their antihypertensive medications.

Endocrine laboratory test results (sample drawn in the morning):
- Cortisol = 9.9 µg/dL (273.1 nmol/L)
- ACTH = 23 pg/ml (5.1 pmol/L)
- DHEA-S = 152 µg/dl (4.1 µmol/L)
- Plasma renin activity = <0.1 ng/mL per h
- Aldosterone = <1 ng/dl (27.7 pmol/L)

You initiate spironolactone therapy. Two weeks later, she returns with her parents to discuss her endocrine studies. Her blood pressure is 172/102 mm Hg and a potassium level the day before the visit is 2.8 mEq/L (2.8 mmol/L).

Question 21 (1/3)

Question 21 (2/3)

Laboratory test results:
- Sodium = 139 mEq/L (139 mmol/L)
- Potassium = 3.1 mEq/L (3.1 mmol/L)
- Chloride = 95 mEq/L (95 mmol/L)
- Bicarbonate = 27 mEq/L (27 mmol/L)
- Serum urea nitrogen = 12 mg/dl (4.3 mmol/L)
- Creatinine = 0.7 mg/dl (61.9 µmol/L)
- Glucose = 78 mg/dl (4.3 mmol/L)
- Calcium = 9.3 mg/dl (2.3 mmol/L)

A mutation in which of the following genes (and the associated condition) most likely accounts for the familial hypertension and hypokalemia in this young woman?

A. RET (ret proto-oncogene) \(\rightarrow\) multiple endocrine neoplasia type 2 1%
B. SCNN1B or SCNN1G (sodium channel, non-voltage-gated 1, beta or gamma subunit) \(\rightarrow\) Liddle syndrome 70%
C. KCNJ5 (potassium inwardly-rectifying channel) \(\rightarrow\) primary aldosteronism 1%
D. CYP11B1 or CYP11B2 (cytochrome P450, family 11, subfamily B, polypeptide 1 and polypeptide 2) \(\rightarrow\) glucocorticoid-remediable aldosteronism 15%
E. NR1I1 (nuclear receptor subfamily 3, group C, member 1 [glucocorticoid receptor]) \(\rightarrow\) glucocorticoid resistance 8%

Question 21 (3/3)
22. At your hospital’s weekly clinical endocrine conference, a colleague asks for your opinion regarding a 44-year-old man with metastatic pheochromocytoma. He had a left adrenalectomy 2 years earlier to treat a 4.8-cm pheochromocytoma. Postoperative studies showed a solitary metastasis to T12, and CT of the lungs showed two 1.5-cm lesions in the right upper lobe. He underwent external beam radiation therapy for the bone metastasis in T12. He was then lost to follow-up because of lack of health insurance. He is currently asymptomatic. He has continued to take doxazosin, 2 mg daily, and metformin, 500 mg daily (initiated because of hyperglycemia at the time of presentation 2 years ago). He is unaware of any family history of endocrine disorders.

On physical examination, his blood pressure is 128/84 mm Hg, pulse rate is 78 beats/min, and BMI is 24.4 kg/m². He has no mucosal neuromas, café-au-lait spots, or axillary freckling.

Laboratory test results:
- Chemistry profile, normal
- Hemogram, normal
- Hemoglobin A₁c = 4.8% (0.048)
- Thyroid function, normal
- Morning fasting calcitonin, undetectable

Question 22 (1/3)

22. On urine catecholamine studies.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>At Diagnosis 2 Years Ago</th>
<th>At Today Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metanephrine</td>
<td>615 µg/24 h (3118 nmol/d)</td>
<td>587 µg/24 h (3076 nmol/d)</td>
</tr>
<tr>
<td>Normetanephrine</td>
<td>2120 µg/24 h (11,575 nmol/d)</td>
<td>1146 µg/24 h (6257 nmol/d)</td>
</tr>
<tr>
<td>Epi/norepinephrine</td>
<td>56 µg/24 h (305 nmol/d)</td>
<td>58 µg/24 h (316 nmol/d)</td>
</tr>
<tr>
<td>Nor/norepinephrine</td>
<td>565 µg/24 h (3147 nmol/d)</td>
<td>264 µg/24 h (1561 nmol/d)</td>
</tr>
</tbody>
</table>

Imaging with meta-iodobenzylguanidine shows some uptake in the previously described T12 lesion, as well as faint uptake in 2 small (1.5-cm) right upper lobe lung nodules (identical in size to those found 2 years earlier). Fluorodeoxyglucose single-photon emission CT and positron emission tomography show uptake in the same locations, as well as intense segmental uptake in his large intestine.

Question 22 (2/3)

Which of the following courses of action would you suggest?

A. ¹³¹I meta-iodobenzylguanidine therapy 13%
B. External beam radiotherapy to the colon 1%
C. Cyclophosphamide, vincristine, doxorubicin chemotherapy 6%
D. Sunitinib therapy 20%
E. No further treatment 61%

Question 22 (3/3)
23. A colleague whose daughter recently received a diagnosis of Cushing syndrome asks you for a second opinion. The patient is a 25-year-old woman who has gained 20 lb (9.1 kg) in the past 5 months with associated facial fullness and plethora. She has new-onset hypertension and oligomenorrhea. She is not taking any medications.

On physical examination, she is a cushingoid-appearing young woman with a blood pressure of 142/94 mm Hg. Pulse rate is 76 beats/min, and BMI is 28.1 kg/m². She has substantial supraclavicular and dorsocevical fat accumulation. With the exception of some slight edema, the rest of the examination findings are normal.

Laboratory test results:
- Pregnancy test, negative
- Sodium = 141 mEq/L (141 mmol/L)
- Potassium = 3.7 mEq/L (3.7 mmol/L)
- Chloride = 99 mEq/L (99 mmol/L)
- Bicarbonate = 28 mEq/L (28 mmol/L)
- Fasting glucose = 99 mg/dL (5.5 mmol/L)
- Serum urea nitrogen = 15 mg/dL (5.4 mmol/L)
- Creatinine = 0.9 mg/dL (79.6 μmol/L)
- Calcium = 9.5 mg/dL (2.4 mmol/L)

Laboratory test results:
- Late-night salivary cortisol = 0.41 μg/dL (11.3 nmol/L)
- Urinary free cortisol = 129 μg/24 h (356 nmol/d)
- Serum cortisol (8 AM) = 17.6 μg/dL (485.5 nmol/L)
- Serum cortisol (8 AM) after overnight 1-mg dexamethasone suppression test = 17.4 μg/dL (480.0 nmol/L)
- Serum cortisol (8 AM) after overnight 8-mg dexamethasone suppression test = 17.1 μg/dL (471.8 nmol/L)
- DHEA-S = 5.0 μg/dL (0.14 μmol/L)
- Basal plasma ACTH = 17.0 pg/mL (3.7 pmol/L)

Pituitary MRI is interpreted to show a 2-mm hypodense lesion in the left side of the pituitary gland. She has been referred to a neurosurgeon who has scheduled transsphenoidal pituitary surgery.

Which of the following should you recommend?
A. Octreotide acetate scintigraphy  3%
B. Bilateral inferior petrosal ACTH sampling with corticotropin-releasing hormone stimulation  58%
C. CT of the adrenal glands  31%
D. CT of the chest  3%
E. Pituitary surgery as scheduled  4%
ACTH Assay Variability circa 2014

ACTH <10 pg/mL: probably adrenal Cushing syndrome

ACTH >25-30 pg/mL: ACTH-secreting neoplasm

ACTH 10-25 pg/mL: ACTH purgatory

24. You are asked to see a 21-year-old man for preoperative management of a recently discovered right pheochromocytoma. His father had a bilateral adrenalectomy for pheochromocytomas at age 44 years and died 10 years later of influenza and an adrenal crisis. The patient has had the recent onset of hypertension and reports having morning headaches. He has been treated with phenoxycbenzamine for 3 weeks and he just started therapy with a β-adrenergic blocker. On physical examination, his blood pressure is 132/78 mm Hg, pulse rate is 78 beats/min, and BMI is 24.7 kg/m².

Question 24 (1/2)

Which of the following syndromes is most likely responsible for the pheochromocytoma in this young man?

A. Carney complex 4%
B. Neurofibromatosis type 1 13%
C. von Hippel–Lindau syndrome 22%
D. Multiple endocrine neoplasia type 2B 58%
E. Familial pheochromocytoma associated with a TMEM127 mutation 4%

Question 24 (2/2)

He has long, slender arms, arachnodactyly, and pectus carinatum. You also observe the following finding:

Multiple Endocrine Neoplasia Type 2
Autosomal Dominant Mutation RET Proto-Oncogene (Chromosome 10)

Type 2A
90% Medullary thyroid cancer (preceded by multicentric C-cell hyperplasia)
40% Pheochromocytoma (usually bilateral but rarely malignant)
10% Hyperparathyroidism (multigland)
Rare: chronic lichen amyloidosis, Hirschsprung disease

Type 2B
All of the above except HPTH with:
Marfanoid habitus, mucosal neuromas (lips and tongue), intestinal ganglioneuromas, joint laxity, skeletal deformities