Cushing Syndrome

Background

Cushing syndrome is caused by prolonged exposure to elevated levels of either endogenous glucocorticoids or exogenous glucocorticoids.

Individuals with Cushing syndrome can develop moon facies, facial plethora, supraclavicular fat pads, buffalo hump, truncal obesity, and purple striae.

Individuals often complain of proximal muscle weakness, easy bruising, weight gain, hirsutism, and, in children, growth retardation. Hypertension, osteopenia, diabetes mellitus, and impaired immune function may occur.

In an emergency situation, remembering that the most common cause of Cushing syndrome is the use of exogenous glucocorticoids is important. Exogenous steroids may cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis that can last for as long as a year after exogenous steroid administration has ended.

An individual with HPA-axis suppression cannot increase steroid production appropriately during a medical illness or other stress and would need to receive stress doses of steroids to avoid adrenal crisis. Thus, in an emergency situation, the potential for relative adrenal insufficiency should be considered in any patient with Cushing syndrome.

Pathophysiology

Excess levels of either exogenously administrated glucocorticoids or endogenous overproduction of cortisol causes Cushing syndrome. Endogenous glucocorticoid overproduction or hypercortisolism that is independent of adrenocorticotropic hormone (ACTH) usually is due to a primary adrenocortical neoplasm (usually an adenoma but rarely a carcinoma). Bilateral micronodular hyperplasia and macronodular hyperplasia are rare causes of Cushing syndrome.

ACTH-secreting neoplasms cause ACTH-dependent Cushing syndrome. They usually are due to an anterior pituitary tumor, ie, classic Cushing disease (80%). Nonpituitary ectopic sources of ACTH, such as an oat cell, small-cell lung carcinoma, or carcinoid tumor, cause the balance of ACTH-dependent disease. Some rare newly described cases of ectopic corticotropin-releasing hormone (CRH) secretion comprise a very rare group of patients with Cushing syndrome.

Frequency

The majority of cases of Cushing syndrome are due to exogenous glucocorticoids. The annual incidence of endogenous Cushing syndrome has been estimated at 13 cases per million individuals. Of these cases,

approximately 70% are due to Cushing disease, ie, a pituitary ACTH-producing tumor; 15% to ectopic ACTH; and 15% to a primary adrenal tumor.

Mortality/Morbidity

Morbidity and mortality associated with Cushing syndrome are related primarily to the effects of excess glucocorticoids. However, a primary pituitary tumor may cause panhypopituitarism and visual loss.

- In addition, the rare adrenocortical carcinomas are associated with a 5-year survival rate of 30% or less.
- Two catastrophic medical crises that occur in glucocorticoid excess states are perforated viscera and opportunistic fungal infections.
- Exposure to excess glucocorticoids results in multiple medical problems, including hypertension, obesity, osteoporosis, fractures, impaired immune function, impaired wound healing, glucose intolerance, and psychosis.
- Exogenous steroids suppress the HPA axis, with full recovery taking as long as a year after cessation of glucocorticoid administration. Thus, patients who are on or who have taken steroids are at risk for developing an adrenal crisis.

Sex

- The female-to-male incidence ratio is approximately 5:1 for Cushing syndrome due to an adrenal or pituitary tumor.
- Ectopic ACTH production is more frequent in men than in women because of the increased incidence of lung tumors in this population.

Age

- The peak incidence of Cushing syndrome due to either an adrenal or pituitary adenoma occurs in persons aged 25-40 years.
- Ectopic ACTH production due to lung cancer occurs later in life.

History

- Patients with Cushing syndrome may complain of weight gain, especially in the face, supraclavicular region, upper back, and torso.
- Frequently, patients notice changes in their skin, including purple stretch marks, easy bruising, and other signs of skin thinning.
- Women may complain of irregular menses and hirsutism.

- Because of progressive proximal muscle weakness, patients may have difficulty climbing stairs, getting out of a low chair, and raising their arms.

- Psychological problems such as depression, cognitive dysfunction, and emotional lability may develop.

- New-onset or worsening of hypertension and diabetes mellitus, difficulty with wound healing, increased infections, osteopenia, and osteoporotic fractures may occur.

- Patients with an ACTH-producing pituitary tumor (Cushing disease) may develop headaches, polyuria and nocturia, visual problems, or galactorrhea.

- If sufficient mass effect from the tumor is present on the anterior pituitary, hyposomatotropism, hypothyroidism, hyperprolactinemia or hypoprolactinemia, and hypogonadism may develop.

- In addition, look for the following:
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    - Irregular menses or amenorrhea in women and decreased libido, infertility, and impotence in men

    - Polyuria or polydipsia from diabetes mellitus or diabetes insipidus

    - Impaired wound healing or predisposition to infections from immunosuppression

- When rapid onset of glucocorticoid excess occurs, virilization in women or feminization in men may be seen. This scenario suggests an adrenal carcinoma as the underlying cause of the Cushing syndrome.

Physical

- Obesity

    - Patients may have increased adipose tissue in the face (moon facies), upper back at the base of neck (buffalo hump), and above the clavicles (supraclavicular fat pads).

    - Central obesity with increased adipose tissue in the mediastinum and peritoneum; increased waist-to-hip ratio greater than 1 in men and 0.8 in women; and, upon CT scan of the abdomen, increased visceral fat is evident.

- Skin

    - Facial plethora may be present, especially over the cheeks.

- Violaceous striae, usually more than 1 cm in width, is observed most commonly over the abdomen, buttocks, lower back, upper thighs, upper arms, and breasts.
- Ecchymoses may be present.
- Patients may have telangiectasias and purpura.
- Cutaneous atrophy with exposure of subcutaneous vasculature tissue and tenting of skin may be evident.
- Hirsutism and male pattern balding may be present in women.
- Patients may have increased lanugo facial hair.
- Steroid acne, consisting of papular or pustular lesions over the face, chest, and back, may be present.
- Acanthosis nigricans, which is associated with insulin resistance and hyperinsulinism, may be present. The most common sites are axilla and areas of frequent rubbing, such as over elbows, around the neck, and under the breasts.

- Cardiovascular and renal
  - Hypertension may be present.
  - Volume expansion may occur, with edema from sodium and water retention.
  - Diabetes mellitus may be present.
- Gastroenterologic
  - Peptic ulceration may occur with or without symptoms.
  - Particularly at risk are patients given high doses of glucocorticoids (rare in endogenous hypercortisolism).
- Endocrine
  - Hypothyroidism may occur from anterior pituitary tumors, which can interfere with proper thyroid-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) function.
  - Galactorrhea may occur when anterior pituitary tumors compress the pituitary stalk, leading to elevated prolactin levels.
  - Other pituitary function may be interrupted. Possibilities include polyuria and nocturia from diabetes insipidus.

- Menstrual irregularities, amenorrhea, and infertility may occur due to inhibition of pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which likely is due to interruption of luteinizing hormone-releasing hormone (LHRH) pulse generation.
- Low testosterone levels in men may lead to decreased testicular volume from inhibition of LHRH and LH/FSH function.
- Low estrogen levels in women may result from inhibition of LHRH and LH/FSH function.
- Increased synthesis of high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides may occur.
- With severe hypercortisolism, hypokalemic metabolic alkalosis may occur.

- Skeletal/muscular
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    - Proximal muscle weakness may be evident.
    - Osteoporosis may lead to incident fractures and kyphosis, height loss, and axial skeletal bone pain. Avascular necrosis of the hip also is possible from glucocorticoid excess.

- Neuropsychological
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    - Patients may experience emotional liability, fatigue, and depression.
    - Visual-field defects, often bitemporal, and blurred vision may occur in individuals with large ACTH-producing pituitary tumors that impinge on the optic chiasma.

- **Adrenal crisis**
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    - Patients with cushingoid features may present to the emergency department in adrenal crisis. Adrenal crisis may occur in patients on steroids who stop taking their glucocorticoids or neglect to increase their steroids during an acute illness. It also may occur in patients who have recently undergone resection of an ACTH-producing or cortisol-producing tumor.
    - Physical findings that occur in a patient in adrenal crisis include hypotension, abdominal pain, vomiting, and mental confusion (secondary to low serum sodium or hypotension). Other findings include hypoglycemia, hyperkalemia, hyponatremia, and metabolic acidosis.
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Causes

- Exogenous steroid administration
    - Administration of exogenous steroids may lead to the development of Cushing syndrome.
    - Symptoms of glucocorticoid excess generally occur with the administration of oral steroids; however, occasionally injections of steroids into joints and the use of steroid inhalers can cause Cushing syndrome.
    - Suppression of the HPA axis may occur in the absence of obvious signs of glucocorticoid excess.
    - Patients with diseases that respond to steroid therapy are especially likely to receive steroids and thus develop Cushing syndrome. Such disorders include a wide variety of rheumatological, pulmonary, neurological, and nephrologic diseases.
    - Patients who have undergone organ transplants also are at risk for developing Cushing syndrome due to exogenous steroids required as part of graft antirejection medication regimens.
- Endogenous glucocorticoid overproduction
    - ACTH-producing pituitary adenoma
        - Pituitary adenomas that secrete ACTH are derived from corticotrophs in the anterior pituitary.
        - ACTH secreted by corticotrophs is released into the circulation and acts on the adrenal cortex to produce hyperplasia and stimulate the secretion of adrenal steroids.
        - These adenomas, if large, can result in loss of production of other anterior pituitary hormones (TSH, FSH, LH, growth hormone, and prolactin) and the posterior pituitary hormone vasopressin.
        - Pituitary tumors can also compress the hypophyseal stalk leading to hyperprolactinemia from loss of dopamine inhibition.
        - Nelson syndrome is caused by a large ACTH-secreting pituitary tumor; it is often locally invasive, difficult to cure, and associated with hyperpigmentation. In patients who undergo adrenalectomy without pituitary irradiation, the

incidence of Nelson syndrome is about 20-25%.

- Large pituitary adenomas may press on the optic chiasm, causing visual-field deficiencies that often present as bitemporal field cuts.

- Primary adrenal lesions

  - Overproduction of glucocorticoids may be due to an adrenal adenoma, adrenal carcinoma, or macronodular or micronodular adrenal hyperplasia. The zona fasciculata and zona reticularis layers of the adrenal cortex normally produce glucocorticoids and androgens. Glucocorticoid-secreting tumors are derived from these cells and, thus, may secrete both glucocorticoids and androgens.

  - In general, excess androgen secretion is suggestive of an adrenal carcinoma rather than an adrenal adenoma. These glucocorticoid-producing tumors generally do not secrete aldosterone, which is produced in the zona glomerulosa layer of the adrenal cortex.

  - The Carney complex is a familial form of micronodular hyperplasia of the adrenal gland. It is an autosomal dominant disorder and ACTH independent cause of Cushing syndrome. Pigmented skin lesions and mesenchymal and endocrine tumors characterize the disorder. Cushing syndrome may be overt, subclinical, cyclical, or periodic.

  - McCune-Albright syndrome is a rare cause of precocious puberty. It is associated with hyperfunction of the adrenal glands that may lead to Cushing syndrome.

- Ectopic ACTH sometimes is secreted by oat cell or small-cell lung tumors or by carcinoid tumors.

Lab Studies

- Biochemical evaluation of Cushing syndrome

  - The diagnosis of Cushing syndrome due to endogenous overproduction of cortisol requires the demonstration of inappropriately high serum or urine cortisol levels (see Image 1). Currently, 4 methods are accepted for the diagnosis of Cushing syndrome: urinary free cortisol level, low-dose dexamethasone suppression test, evening serum and salivary cortisol level, and dexamethasone–corticotropin-releasing hormone test.

    - Urinary free cortisol (UFC) determination has been widely used as an initial screening tool for Cushing syndrome

because it provides measurement of cortisol over a 24-hour period. A valid result depends on adequate collection of the specimen. Urinary creatinine excretion can be used to assess the reliability of the collection. Urine free cortisol values higher than 3-4 times the upper limit of normal are highly suggestive of Cushing syndrome. Values higher than the normal reference range but less than 3-4 times the upper limit of normal are inconclusive. Values that fall within this range may indicate pseudo–Cushing syndrome or Cushing syndrome and require further testing. Multiple collections are necessary because patients with disease may have values that fall within the normal range.

- Dexamethasone suppression tests are intended to mimic the physiology of the pituitary, which in the presence of steroids decreases the release of ACTH causing a fall in plasma and urine cortisol level. In Cushing syndrome, a loss of sensitivity to glucocorticoids occurs and ACTH is therefore not suppressed and adrenal production of cortisol is not affected. The overnight 1-mg dexamethasone suppression test requires administration of 1 mg of dexamethasone at 11 pm with subsequent measurement of cortisol level at 8 am. In healthy individuals, the serum cortisol level should be less than 2-3 mcg/dL. To enhance the sensitivity of the test, a cutoff value of less than 1.8 mcg/dL (50 nmol/L) excludes Cushing syndrome. Its ease of administration makes the 1-mg dexamethasone suppression test a widely used screening tool.

- Late night serum and salivary cortisol levels take advantage of the alterations in circadian rhythm of cortisol secretion in patients with Cushing syndrome. Normally, nighttime cortisol values are at their lowest level; in patients with Cushing syndrome, elevated nighttime cortisol can be an early but not definitive finding. This test requires hospitalization with blood samples obtained within 5-10 minutes of waking a patient and is not a practical test.

- Measuring salivary cortisol level has gained interest, as it is a simple and convenient way of obtaining a nighttime sample. This measurement allows patients to collect their own samples at home. With repeated measurements, levels less than 1.3 ng/mL (radioimmunoassay) or 1.5 ng/mL (competitive protein-binding assay) exclude Cushing syndrome. Less experience has been gathered for this assay, and it is expensive. Most physicians who

do use this test obtain readings over several evenings to increase accuracy.

- The dexamethasone-CRH test is intended to distinguish patients with Cushing syndrome from those with pseudo-Cushing states. It combines a 48-hour low-dose dexamethasone suppression test with CRH stimulation. Dexamethasone (0.5 mg every 6 hours) is given 8 times, CRH is then administered intravenously and plasma cortisol and ACTH levels are obtained at 15-minute intervals for 1 hour. A cortisol value greater than 50 nmol/L (1.4 mcg/dL) identifies Cushing syndrome. This test is reserved for patients with high clinical suspicion for Cushing syndrome but equivocal results on other diagnostic tests.

- Unfortunately, mild Cushing syndrome is often difficult to distinguish from normal cortisol secretion or pseudo-Cushing states. The aforementioned tests can produce both false-positive and false-negative results. False-positive results are associated with obesity, alcoholism, chronic renal failure, affective disorders, strenuous exercise, or eating disorders. Other potential confounders in the interpretation of tests include the following:
  - Medications that increase corticosteroid-binding globulin, such as estrogen and tamoxifen, may cause appropriate increases in serum cortisol levels.
  - Medications that facilitate the metabolism of dexamethasone, such as phenobarbital, phenytoin, and rifampin, may cause false-positive results with the dexamethasone suppression test.
- Acute illness activates the HPA axis, resulting in increases in ACTH and cortisol. The laboratory workup for Cushing syndrome should not be performed when subjects are acutely ill.

States of Increased HPA Activity	**States of Decreased HPA Activity**
Chronic stress Melancholic depression Anorexia nervosa Obsessive-compulsive disorder Panic disorder Excessive exercise Chronic active alcoholism Alcohol and nicotine withdrawal Diabetes mellitus	Adrenal insufficiency Atypical/seasonal depression Chronic fatigue syndrome Fibromyalgia Hypothyroidism Nicotine withdrawal Post glucocorticoid therapy Post Cushing syndrome Postpartum period Post chronic stress Rheumatoid arthritis

Central obesity Sexual abuse Hyperthyroidism Premenstrual tension syndrome Cushing syndrome Pregnancy	

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- Other laboratory abnormalities seen in Cushing syndrome include the following:
    - Elevated white blood cell count greater than 11,000/mm^3
    - Hypokalemic metabolic alkalosis may occur in patients with urinary free cortisol levels higher than 1500 mcg/24 h.
- Once the diagnosis is established, the next step requires determining the etiology of Cushing syndrome. The logical first step involves identifying if the hypercortisolism is an ACTH-dependent or ACTH-independent disorder.
- A plasma ACTH level that is undetectable is diagnostic of ACTH-independent Cushing syndrome. There are patients with cortisol-producing adrenal adenomas, where the ACTH may be undetectable; therefore, several collections should be obtained. A plasma ACTH (measured by an immunoradiometric assay) of less than 5 pg/mL is suggestive of a primary adrenal tumor. An ACTH level greater than 10-20 pg/mL is consistent with ACTH-dependent Cushing syndrome.
    - The 8-mg overnight dexamethasone suppression test and the 48-hour high-dose dexamethasone test may be useful when baseline ACTH levels are indeterminate. These studies also help in determining whether a patient who has ACTH-dependent disease has pituitary-dependent or ectopic ACTH disease.
        - In the 8-mg overnight dexamethasone suppression test, individuals ingest 8 mg dexamethasone orally at 11 pm, with measurement of an 8 am cortisol level the next day. A baseline 8 am cortisol measurement is required. Suppression of serum cortisol level to less than 50% of baseline is suggestive of a pituitary source of ACTH rather than ectopic ACTH or primary adrenal disease. However, the diagnostic accuracy is only 70-80%.
        - With the 48-hour high-dose dexamethasone suppression test, patients ingest 2 mg dexamethasone every 6 hours for 8 doses. A decrease in urinary free cortisol of greater than 50% is suggestive of an anterior pituitary adenoma

rather than ectopic ACTH or a primary adrenal tumor. Unfortunately, the sensitivity of this test is only 80%, with a specificity of 70-80%. The more stringent criterion of a 90% decrease in urinary free cortisol levels excludes the diagnosis of ectopic ACTH and has almost 100% specificity for anterior pituitary disease.

- Testing with CRH is used in the differential diagnosis of ACTH-dependent Cushing syndrome. In most patients with pituitary ACTH secretion, the intravenous administration of CRH causes a rise in plasma ACTH and cortisol levels. In patients with ectopic secretion of ACTH, CRH does not affect ACTH or cortisol levels. ACTH and cortisol samples are obtained before administration of ovine CRH (oCRH), and subsequently at 15, 30, 45, 60, 90, and 120 minutes after administration of 1 mcg/kg of CRH. A rise of more than 20% in peak plasma cortisol level or a rise of more than 50% in peak ACTH level after oCRH is consistent with pituitary ACTH-dependent Cushing syndrome. Sensitivity and specificity are 91% and 95%, respectively, for cortisol measurements and 86% and 95% for ACTH measurements, respectively.

- If concern for adrenal carcinoma exists, measurement of 17-ketosteroid or other cortisol precursors (such as serum dehydroepiandrosterone sulfate [DHEAS]) is useful.

Imaging Studies

- Imaging studies for Cushing syndrome should be performed after the biochemical evaluation has been performed. The rationale for this is that unguided imaging of the pituitary or adrenal glands may yield a 10% incidence of incidental nonfunctioning pituitary or adrenal adenomas, which may mislead one from proper therapy and surgery. Ideally, the biochemical abnormalities should reconcile with the anatomic abnormalities before definitive therapy is offered.

- An abdominal CT scan is recommended if a primary adrenal problem is suspected. The presence of an adrenal mass larger than 4-6 cm raises the possibility that the mass is an adrenal carcinoma.

- If a pituitary source of excess ACTH is suspected, patients should undergo a contrast-enhanced magnetic resonance imaging (MRI) study of the pituitary. Unfortunately, normal-appearing pituitaries may occur in some patients with Cushing disease due to both diffuse hyperplasia of ACTH-producing cells and small microadenomas that do not appear on imaging studies. In the latter case, ACTH lateralization during an inferior petrosal sinus (IPS) sampling study may be useful in lateralizing the occult lesion and in guiding surgical therapy.

- Chest and abdominal CT scans should be performed in patients with suspected ectopic ACTH production.

- Octreotide scintigraphy may be helpful in detecting ectopic ACTH tumors because some neuroendocrine tumors typically have cell surface receptors for somatostatin.

Procedures

- Inferior petrosal sinus sampling (IPSS) is useful in distinguishing a pituitary source from an ectopic source of ACTH. An experienced interventional radiologist should perform this procedure to decrease the incidence of neurological complications.
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    - Bilateral IPSS and simultaneous peripheral ACTH measurements are made at baseline and 2-3 min, 5 min, and 10 minutes after intravenous administration of oCRH at 1 mcg/kg.
    - A baseline and/or stimulated IPS-to-peripheral ACTH ratio of less than 1.8 is suggestive of ectopic ACTH, while an IPS-to-peripheral ACTH ratio of greater than 2 is consistent with Cushing disease.
    - In approximately 70% of patients, a ratio of greater than 1.4 between the right and left inferior petrosal sinuses is predictive of the location of the microadenoma.

Medical Care

- Overview
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    - Treatment of Cushing syndrome is directed by the primary cause of the syndrome.
    - In general, therapy should reduce the cortisol secretion to normal to reduce the risk of comorbidities associated with hypercortisolism. A culprit tumor should be removed if possible. The treatment of choice for endogenous Cushing syndrome is surgical resection of the causative tumor. The primary therapy for Cushing disease is transsphenoidal surgery, and the primary therapy for adrenal tumors is adrenalectomy.
    - When surgery is not successful or cannot be used, as often occurs with ectopic ACTH or metastatic adrenal carcinoma, control of hypercortisolism may be attempted with medication. However, medication failures are common, and adrenalectomy may be indicated in ACTH-mediated Cushing syndrome.
    - Pituitary radiation may be useful if surgery fails for Cushing disease.
    - The treatment for exogenous Cushing syndrome is gradual withdrawal of glucocorticoid.

- Cushing syndrome
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    - Agents that inhibit steroidogenesis, such as mitotane, ketoconazole, metyrapone, aminoglutethimide, trilostane, and etomidate, have been used to cause medical adrenalectomy. These medications are used rarely and often are toxic at the doses required to reduce cortisol secretion. Thus, medical treatment should be initiated cautiously and, ideally, in conjunction with a specialist. Efficacy of these medical interventions can be assessed with serial measurements of 24-hour urinary free cortisol.

    - Patients receiving these medications may require glucocorticoid replacement to avoid adrenal insufficiency. Patients should be counseled on the signs and symptoms of adrenal insufficiency when starting these drugs.

    - Metyrapone and trilostane are agents that competitively inhibit a single steroidogenic enzyme. Ketoconazole and aminoglutethimide act at several sites. If enzymatic blockade is not complete, ACTH secretion overcomes the blockade so that hypercortisolism persists.

    - Because ACTH production may persist or increase in patients with Cushing disease, radiation therapy of the pituitary often is required after unsuccessful initial therapy, either surgical or medical. These agents have higher efficacy when used in combination because they may act synergistically.

    - Ketoconazole probably is the most popular and effective of these agents for long-term use and usually is the agent of choice. It acts on several of the P450 enzymes, including the first step in cortisol synthesis, cholesterol side-chain cleavage, and conversion of 11-deoxycortisol to cortisol.

    - Adverse effects of ketoconazole include headache, sedation, nausea, irregular menses, decreased libido, impotence, gynecomastia, and elevated liver function tests. The drug is contraindicated during pregnancy.

    - Ketoconazole is ineffective in patients on H2 blockers or proton-pump inhibitors because gastric acidity is required for metabolism. If this agent is ineffective at controlling hypercortisolism, the dose may be maintained while another steroid enzyme inhibitor, typically metyrapone, is initiated.

    - Metyrapone blocks 11-beta-hydroxylase activity, the final step in cortisol synthesis. Therapy is begun at 1 g/d divided into 4 doses and increased to a maximum dose of 4.5 g/d. Adverse effects are from increases in androgen and mineralocorticoid precursors, including hypertension, acne, and hirsutism.

- Aminoglutethimide is an anticonvulsant agent that blocks cholesterol side-chain cleavage to pregnenolone. It is a relatively weak adrenal enzyme inhibitor at doses that patients can tolerate. Aminoglutethimide typically is initiated at 250 mg twice daily, and increased to 2 g 4 times daily.

- Adverse effects of aminoglutethimide include somnolence, headache, a generalized pruritic rash, hypothyroidism, and goiter. In rare cases, it may cause bone marrow suppression. Aminoglutethimide increases the metabolism of dexamethasone but not cortisol.

- Trilostane is not widely available and is not as well studied. Trilostane inhibits the conversion of pregnenolone to progesterone, which decreases the synthesis of cortisol, aldosterone, and androstenedione. It is not a first-choice agent because it is a weak inhibitor of steroidogenesis. In addition, trilostane interacts with some assays, causing a false elevation of cortisol measurements.

- Etomidate, an imidazole-derivative anesthetic agent, blocks 11-beta-hydroxylase. It is used intravenously at 0.3 mg/kg/h. Its use is limited by the requirement for chronic administration by the intravenous route.

- Mitotane is an adrenolytic agent that acts by inhibiting 11-beta hydroxylase and cholesterol side-chain cleavage enzymes. This drug also leads to mitochondrial destruction and necrosis of adrenocortical cells in the zona fasciculata and reticularis. For this reason, it is used in treatment of adrenal cancer. Its survival benefit is unclear. It can be used in addition to radiation therapy for treatment of Cushing disease and in combination with metyrapone or aminoglutethimide for treatment of ectopic ACTH secretion.

- Unfortunately, mitotane is expensive, and its utility is limited by adverse gastrointestinal and neurologic effects, including nausea, diarrhea, dizziness, and ataxia. Other adverse effects include rash, arthralgias, and leukopenia. It is taken up by adipose tissues and persists in the circulation long after discontinuation. It is a potential teratogen and can cause abortion; therefore, it is relatively contraindicated in women interested in remaining fertile.

- Mifepristone (RU 486) is an antiprogestational agent, which, at high doses, competitively binds to the glucocorticoid and progesterone receptors. It currently is used only on an investigational basis for treatment of Cushing syndrome.

- Agents that decrease CRH or ACTH release have been studied for the treatment of Cushing disease. Such agents include

bromocriptine, cyproheptadine, valproic acid, and octreotide. Currently, use of these agents is investigational.

Surgical Care

- Cushing disease
    - Treatment of choice for classic Cushing disease is transsphenoidal surgery by an experienced neurosurgeon. The goal of surgery is to remove the adenoma, preserving as much pituitary function as possible.
    - The more extensive the mass and the resulting resection, the greater the risk for loss of pituitary function. Successful amelioration of hypercortisolism occurs in 60-80% of cases. Both open and laparoscopic techniques are possible. If unsuccessful, MRI-guided pituitary surgery, a new procedure, may be indicated. Lateralization of ACTH secretion via IPS catheterization and sampling sometimes is helpful in difficult cases.
    - Pituitary irradiation is employed when transsphenoidal surgery is not successful or not possible. The procedure is less successful than surgery in adults, with a 45% cure rate in adults and 85% cure rate in children. Late-onset adverse effects include hypopituitarism.
    - Bilateral adrenalectomy is an option if transsphenoidal surgery, pituitary irradiation, and medical therapy fail or if rapid normalization of cortisol levels is required. The patient then requires lifelong glucocorticoid and mineralocorticoid therapy.
    - In individuals who undergo bilateral adrenalectomy, Nelson syndrome, ie, symptomatic enlargement of the pituitary gland and adenoma, may occur in one quarter to one half of adults not treated with pituitary irradiation and in as many as one quarter of patients pretreated with radiation therapy.
- Ectopic adrenocorticotropic production
    - Surgical resection of the source of ACTH production may not always be possible. Ectopic ACTH-producing tumors often are difficult to locate.
    - Medical therapy or bilateral adrenalectomy may be required.
- Adrenal source
    - Adenomas may be removed with unilateral adrenalectomy, often with a laparoscopic approach.

- Carcinomas should be resected for possible cure and palliation.
- Micronodular or macronodular hyperplasia causing Cushing syndrome may be treated effectively by bilateral adrenalectomy. Unilateral or subtotal adrenalectomy may lead to recurrence.

- Hormone replacement
  - Patients with endogenous Cushing syndrome who undergo resection of pituitary, adrenal, or ectopic tumors should receive stress doses of glucocorticoid in the intraoperative and immediate postoperative period.
  - Typically, hydrocortisone is infused intravenously, either continuously (10 mg/h) or in boluses (80-100 mg q8h) starting prior to surgery and for the first 24 hours afterward.
  - If the patient does well, intravenous glucocorticoid replacement may be tapered over 1-2 days and replaced with an oral formulation. The rate of steroid taper may be slowed if severe preoperative hypercortisolism was present.
  - In the event of pituitary destruction or bilateral adrenalectomy, lifelong steroid replacement is necessary.

Complications

- Osteoporosis
- Increased susceptibility to infections
- Hirsutism
- Diabetes mellitus
- Hypertension
- Risk for adrenal crisis
- Panhypopituitarism
- Diabetes insipidus

Prognosis

- Prognosis is favorable if surgery is curative