- No human-to-human transmission, except in cases of contaminated transplant tissue
- The most accurate diagnosis method is a LFA, which relies on antibody detection of the fungal glucuronoxylomannan in the capsule.

Usual Treatment

- An essential step in the treatment of cryptococcosis is first being able to make an accurate diagnosis and to so as quickly as possible.
- It has been shown that 89% of the pts with a relapse of cryptococcosis are reinfected by the original strain for a second time, raising concerns for gains in drug resistance (temporarily through heteroresistance or permanently through genetic mutations) or inefficiency of current drug regimens to clear fungus.
- Multiple challenges to effective antifungal treatment may include diagnosis, timing of treatment, cost of treatment, efficacy of the drugs, and availability of drugs.
- Cryptococcal meningitis/meningoencephalitis or CNS infection: The gold standard antifungal regimen is the combination of IV amphotericin B deoxycholate (polyene antifungal agent AMB) 0.7–1 mg/kg/day (or its liposomal derivatives, such as liposomal amphotericin B [AmBisome] 3–6 mg/kg/day with less nephrotoxicity) with 5-fluorocytosine (pyrimidine analogs 5-FC) 100 mg/kg/day for 2–4 wk. Adding flucytosine to amphotericin B reduces the rates of failure and relapse compared with amphotericin B monotherapy. Then fluconazole 400–800 mg/day for at least 8–10 wk. In HIV pts, maintenance fluconazole 200–400 mg/day PO therapy lifelong. Currently the issue of using azoles is developing resistance. Itraconazole is the second drug chosen for a maintenance dose. New-generation azoles (voriconazole, posaconazole) have demonstrated potent activity against *Cryptococcus* species.
- Despite the effectiveness of AMB, it has a high toxicity causing nephrotoxicity, hepatotoxicity, and myelotoxicity. In addition, 5-FC has hematologic toxicities.
- In resource-limited regions, fluconazole is the commonly used alternative therapy to AMB. However, fluconazole is fungistatic and not fungicidal and has been shown less effective than AMB-based therapy.
- Corticosteroids not recommended for the treatment of cryptococcal meningitis.
- Raised ICP is an extremely common complication of cryptococcal meningitis. Control of increased ICP (external drainage or CSF shunt, or surgical drainage of abscesses) to avert irreversible morbidity.
- Antiretroviral therapy in HIV pts or augmentation and restoration of host immunity through reversal of immunosuppression in other immunocompromised hosts.
- Pulmonary disease: fluconazole 400–800 mg/day for 6–12 mo.
- For more severe disease and immunocompromised hosts, treat like CNS disease.
- Echinocandins have no clinically useful activity against *Cryptococcus*.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
ENT	Laryngeal infection	Hoarseness, cough, or acute airway obstruction	Laryngeal edema and erythema, exophytic lesions	Laryngoscopy, stains, biopsy, cultures, serum cryptococcal antigen
RESP	Pneumonia	Fever, chest pain, cough, weight loss, dyspnea, sputum production	Signs of infection	ABGs, CXR, sputum culture, bronchoscopy, lung biopsy, serum cryptococcal antigen, LFA
CV	Endocarditis, myocarditis	Rare vascular instability		ECG, ECHO
HEME/IIMMUNO	Cryptococcemia		Signs of infection	Blood cultures, serum cryptococcal antigen, LFA
GU	Prostatitis, renal cortical abscess		Signs of infection	UA, urine cultures
CNS	Meningitis, abscesses, dementia	Headache, fever, nausea vomiting, cranial nerve palsies, lethargy, coma, seizures, or memory loss	Mental status, focal signs	CSF India ink stain, CSF cultures and cryptococcal antigen, LFA,CT, MRI

Key References: Perfect JR: Cryptococcosis (*Cryptococcus neoformans* and *Cryptococcus gattii*). In Bennett JE, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, PA, 2015, Elsevier, pp 2934–2948; Idnurm A, Lin X: Rising to the challenge of multiple *Cryptococcus* species and the diseases they cause. *Fungal Genet Biol* 78:1–6, 2015.

Perioperative Implications

Preoperative Preparation

- Disposable anesthetic delivery circuits with bacterial filters.
- Protect and maintain airways for altered mental status, seizures, focal neurologic signs, and cranial nerve palsies.
- Organ system effects of HIV infection or underlying immunocompromised conditions.

Monitoring

- ARDS network low tidal volume protocol in severe ARDS patients.
- Consider monitoring increased ICP.

Airway

- None

Induction/Maintenance

- Anesthetic drugs associated with lower ICP and having neuroprotective qualities
- Possible interaction of antiretroviral drugs with the anesthetics and/or toxicity

Extubation

- Consider if can adequately protect airway.

Adjuvants

- None

Postoperative Period

- Careful observation for respiratory and neurologic compromise

Cushing Syndrome

Kathleen A. Smith | Justin L. Rountree

Risk

- Onset generally occurs in third and fourth decades.
- Approximately 3–5 times more common in women than men.
- 5-y mortality rate from adrenal carcinomas has been estimated to be >70%.

Perioperative Risks

- Lyte abnormalities
- Consequences of untreated Htn
- Hyperglycemia
- Cardiovascular disease more common

Worry About

- Challenges related to obesity, including airway management and IV access.
- Significant osteopenia secondary to impaired calcium absorption, making positioning difficult.
- Htn due to fluid retention.
- Increased risk of infection as a result of corticosteroids' immunosuppressive qualities.
- Hypokalemic alkalosis, commonly seen in ectopic ACTH production.
- Cushing syndrome may also occur with other disease states, including pheochromocytoma, sarcoidosis, pancreatic carcinoma, sarcoidosis, carcinoid lung tumors, and other neuroendocrine carcinomas.

Overview

- Most common cause of Cushing syndrome is iatrogenic administration of exogenous glucocorticoids.
- Spontaneous Cushing syndrome can result from adrenal gland hyperplasia secondary to increased ACTH production from a pituitary tumor or an ectopic nonendocrine ACTH tumor. Pituitary tumors may present with visual disturbances and have symptoms of increased ICP.
- Other causes include primary gland disorders, such as adrenal adenoma or carcinoma.
- Symptoms including Htn, hyperglycemia, increased intravascular volume, hypokalemia, abdominal striae, truncal obesity, telangiectasias, muscle weakness and/or wasting leading to thin extremities, osteoporosis due to impaired calcium absorption, depression, and insomnia.
- Severe metabolic alkalosis is often the first clinical manifestation of ectopic ACTH-secreting tumors and may result in significant hypoventilation, myocardial depression, arrhythmias, decreased cerebral blood flow, and neuromuscular excitability.

- A 24-h urine cortisol test can demonstrate elevated cortisol levels.
- Dexamethasone suppression test is used to aid in differentiating pituitary adenomas from adrenal tumors. Dexamethasone causes depression of cortisol and 17-hydroxycorticosteriod levels due to a negative feedback response, which is absent with ectopic ACTH or primary gland disease.
- ACTH plasma levels can also be tested directly.
- Radiologic evaluation including abdominal CT scan to evaluate the adrenal glands, pituitary MRI scan with gadolinium contrast to evaluate the pituitary gland, and a chest CT scan when ectopic ACTH is the suspected etiology.

Etiology

- ACTH dependent (excessive ACTH secretion, stimulating adrenal production of cortisol).
  - Pituitary microadenoma (Cushing syndrome) occurs in 70% of cases.
  - Ectopic ACTH production from a nonendocrine tumor (e.g., tumors of the lungs, pancreas, thyroid, or thymus).
- ACTH independent (excessive cortisol production by adrenals and suppression of ACTH production).
  - Adrenocortical adenoma or carcinoma (15%).
- Exogenous administration of glucocorticoids (e.g., treatment of asthma); these pts will likely need periop stress dose steroids.

Usual Treatment

- ACTH-dependent Cushing syndrome:
  - Transsphenoidal resection of pituitary microadenoma.
  - Radiation therapy.
  - Bilateral adrenalectomy in refractory cases.
- ACTH-independent Cushing syndrome:
  - Unilateral or bilateral adrenalectomy (laparoscopic is the preferred method).
  - Medical adrenalectomy.

1. Etomidate inhibits 17α-hydroxylase, 11α-hydroxylase, and 11-deoxycortisol β-hydroxylase, all of which are important in steroidogenesis.
   - Adrenal suppression may occur approximately 30 min following a single dose of etomidate and may last for 24 h.
   - Subhypnotic infusion of etomidate (0.03–0.1 mg/kg/h) can also be used to reduce cortisol levels to within normal limits in 24–48 h.
2. Other drugs that may be used to either inhibit steroidogenesis or prevent the release of glucocorticoids include ketoconazole, metyrapone, mitotane, or aminoglutethimide.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Htn, hypervolemia	HA, visual disturbances		Noninvasive BP
FEN	Hypokalemia Metabolic alkalosis	Weakness, constipation, nausea, arrhythmias, potentiate neuromuscular blockade Hypoventilation	Decreased strength	Basic metabolic panel, flat T waves on ECG
RENAL	Fluid retention	Leg swelling	Peripheral edema	Serum/urine osmolarity
ENDO	Hyperglycemia	Thirst, frequency		Fasting blood glucose
MS	Muscle wasting Impaired calcium absorption	Proximal weakness Osteoporosis	Thin extremities Easy fracture	Difficulty rising from chair/climbing stairs Bone density scan
CNS	Pituitary adenoma	Elevated ICP	Somnolence, papilledema	CT scan

Key References: Heyn J, Geiger C, Hinske CL, et al.: Medical suppression of hypercortisolemia in Cushing's syndrome with particular consideration of etomidate, *Pituitary* 15(2):117–125, 2012; Domi R: Cushing's surgery: role of the anesthesiologist, *Indian J Endocrinol Metab* 15(Suppl 4):S322–S328, 2011.

Perioperative Implications

Preinduction, Induction, and Maintenance

- Prior to induction, normalize volume status, lytes, BP, and blood glucose levels. Spironolactone can be used to mobilize fluid and normalize potassium levels.
- Anxiety can cause increased secretion of cortisol. This response may be blunted by premedication.
- Make preparations to deal with a potentially difficult airway.
- Cortisol secretion is unlikely to be affected by the type of anesthesia used.
- Choice of anesthetic agents used for induction and maintenance of anesthesia are not affected by the presence of Cushing syndrome.
- Etomidate can be used at induction for its temporary suppression of the adrenal gland. This effect may be overcome by the significant cortisol release with surgical stimulation.
- Maintain blood glucose levels between 120–180 mg/dL; SQ insulin or infusion.

Monitoring

- Intraoperative monitoring should be based on the pt's current clinical state
- Arterial catheter may be indicated in cases of poorly controlled systemic Htn
- CVP monitoring is often used to aid in fluid administration, particularly in transsphenoidal tumor resections
- Intraop blood glucose levels and electrolytes

General Anesthesia

- GA is often the anesthetic of choice in pts with significant skeletal muscle weakness/wasting due to the need for mechanical ventilation
- Dose of muscle relaxant may need to be reduced in pts with skeletal muscle weakness
- Pneumoperitoneum, obesity, and lateral decubitus position may worsen hypoxia and hypercarbia
- The pneumoperitoneum should be kept as low as possible to decrease the risk of hemodynamic changes

Regional Anesthesia

- Regional anesthesia offers no significant advantage over general anesthesia in patients with Cushing syndrome

Postoperative Period

- Bilateral and unilateral adrenal resections require glucocorticoid and mineralocorticoid supplementation for life or until the remaining adrenal gland is able to compensate.
- Treatment doses start with 100 mg of IV hydrocortisone every 24 h, starting the day of surgery with titration over a week until a maintenance dose (20–30 mg/day) is reached. Hydrocortisone given in these quantities usually provides adequate mineralocorticoid activity.
- Bilateral adrenalectomy often requires the addition of fludrocortisone for mineralocorticoid supplementation.
- Close observation for pneumothorax when open adrenal resection is performed.
- Meningitis and transient DI are possible postop complications following a transsphenoidal microadenomectomy.
- Glucocorticoids decrease the tensile strength of healing wounds. Topical administration of vitamin A may improve wound healing in the face of increased glucocorticoids.

Anticipated Problems/Concerns

- Meningitis following microadenomectomy
- Obesity leading to a possible difficult airway
- Increased susceptibility to infection
- Hyperglycemia
- Increased risk of hypercoagulability and periop thromboembolic events
- Increased risk for intraop pneumothorax with open adrenal resection when compared with laparoscopic approach