Cushing's Syndrome

A syndrome of high circulating cortisone with characteristic resultant changes in physique and physiology that result in obesity, muscle weakness, glucose intolerance and hypokalemia.

ANESTHETIC CONSIDERATIONS:

- Potential difficult airway and BMV
  - OSA, obesity
  - buffalo hump, large tongue, friable airway mucosa
- Systemic Effects of excess glucocorticoid:
  - HTN, CAD, obesity, hyperglycemia/glucose intolerance, hypokalemic alkalosis
- Difficult IV access
- Osteopenia with risk for fractures (cautious positioning)
- Increased infection risk (aseptic technique)
- Altered pharmacology
  - Sensitive to NDMR, due to decreased muscle mass
  - Sensitive to catecholamines
  - Risk of adrenal insufficiency if exogenous steroid replacement not given during surgery

ANESTHETIC GOALS:

- Preoperative optimization of end organ dysfunction and electrolyte abnormalities
- Management of difficult airway
- Cautious titration of NMBAs
- Maintain BP within 20% of baseline if chronic HTN to preserve end organ perfusion
- Perioperative glucose control

HISTORY AND PHYSICAL

- History of extended steroid exposure during last year
  - Mainly glucocorticoid – Cushingoid appearance etc.
- History of excess ACTH
  - Source of ACTH is important:
    - Excess anterior pituitary production – gradual onset of predominantly glucocorticoid but also mineralocorticoid symptoms
    - Excess non-pituitary ACTH production – predominantly mineralocorticoid (hypokalemic alkalosis and skeletal muscle weakness)
- Respiratory – breathing difficulty; snoring (d/t altered fat deposition around face and neck)
- CVS – HTN; angina; CHF (increased intravascular volume / edema, PND / orthopnea)
- CNS – personality changes, euphoria
- Endocrine – glucose intolerance; electrolyte abnormalities (↑ Na, ↓ K → mineralocorticoid suppression); metabolic alkalosis
- GI – gastric ulceration
- MSK – osteoporosis; muscle wasting / weakness, delicate skin, thin extremities, AVN
- Hematologic – easy bruising; ecchymosis
- **PHYSICAL**
  - **HEENT** – moon facies (possible difficult ventilation / intubation) → uvula visible, neck & mandible ROM
  - **CVS** – HTN; CHF (increased JVP, S3 gallop, crackles / basilar rales)
  - **GI** – central obesity; abdominal striae
  - **CNS** – affect (euphoria)

INVESTIGATIONS

- Check electrolyte balance and glucose pre-op (ABG); other investigations as suggested by history and physical
  - Hb, lytes, BUN / Cr (↑ Na, ↓ K,↑ glucose)
  - ABG (metabolic alkalosis)
  - +/- ACTH stimulation test (baseline plasma cortisol level; another level 30-60min following 250 mcg cosyntropin; cortisol level should rise appropriately)
  - Random cortisol level
- Laboratory diagnosis of hyperadrenocorticism:
  - 24-hour urinary cortisol and 17-hydroxycorticosteroids
  - ACTH dependent (primary pituitary disease) or ACTH independent (primary adrenal disease)?
    - Plasma ACTH and simultaneous plasma cortisol levels
    - High-dose dexamethasone suppression test
      - Pituitary adenomas -depression in cortisol and 17-hydroxycorticosteroid levels (tumor retains some negative feedback control)
      - Adrenal tumors –complete resistance
- Imaging -does not provide information about adrenal cortex function (useful only for determining location of a tumor)

OPTIMIZATION

- Consult Endocrinology for post-operative glucocorticoid/mineralocorticoid replacement
- Consider ketoconazole if unstable prior to OR
- Treat hypertension and diabetes, and normalize intravascular fluid volume and electrolyte abnormalities
  - Continue antihypertensives and H2-blockers
  - Diuresis with spironolactone helps mobilize fluid and normalize the potassium concentration
- Aspiration prophylaxis—H_2 blocker, Na citrate preoperatively
- For patients taking corticosteroids for long periods, perioperative steroid supplementation is indicated to cover the stresses of anesthesia and surgery
  - Patients who have had only a short course of steroids within the 12 months prior to surgery, the use of steroid supplementation is controversial, although most clinicians would favor their use preoperatively

Table 23-10 Perioperative Corticosteroid Coverage

For minor surgery	The patient should take 1.5–2 times his or her usual prednisone dosage on the morning of surgery. The following day the patient should take his or her normal prednisone dose (or parenteral equivalent if gut cannot be used). The surgeon and anesthesiologist should be aware that the patient is glucocorticoid-dependent and should be prepared to administer more "steroids" if the surgery becomes prolonged or more extensive.
For moderate surgery	The patient should be given 2 times his or her usual glucocorticoid dosage orally (if possible) on the morning of surgery and/or 25 mg hydrocortisone IV before the operation, then 75 mg hydrocortisone IV during the operation, and 50 mg hydrocortisone IV after the operation; then the dose should be rapidly tapered over 48 hr to the usual dose—if the postoperative course is uncomplicated.
For major surgery	The patient should be given 2 times his or her usual glucocorticoid dosage orally (if possible) on the morning of surgery and/or 50 mg hydrocortisone IV before the operation, then 100 mg hydrocortisone IV during the operation. After the operation, 100 mg IV q 8 hr × 24 hr should be administered and then rapidly tapered (over 48–72 hr) to the patient's usual glucocorticoid dosage—if the postoperative course is uncomplicated.

IV, intravenously.
Adapted from Brussel T, Chernow B: Perioperative management of endocrine problems: Thyroid, adrenal cortex, pituitary. Am Soc Anesthesiol 1990; 3: 48.

- Ectopic ACTH secretion where primary tumor is unresectable
  - Administration of inhibitors of steroid synthesis, such as metyrapone or mitotane may ameliorate some symptoms but may not improve survival
  - Ketoconazole po
  - Aldosterone antagonists
  - Patients given these adrenal suppressants are also prescribed chronic glucocorticoid replacement therapy (i.e., the goal of therapy is complete adrenal suppression - glucocorticoid replacement should be increased perioperatively

ANESTHETIC OPTIONS

- General, Local, regional (neuraxial may be challenging if vertebral body collapse secondary to osteoperosis)

ANESTHETIC SETUP

- **Drugs**
  - Standard emergency drugs
  - Etomidate has been used for temporizing medical treatment of severe Cushing syndrome because of its inhibition of steroid synthesis
- **Monitors**
  - Standard CAS + PNS (TOF)—may be more sensitive to NDMR
  - May add intraoperative monitoring after evaluation of the patient's cardiac reserve and consideration of the site and extent of the proposed surgery
    - Eg. CVP monitoring for transsphenoidal tumor resection (Cushing's patients tend to have a higher CVP -anecdotal) –maintain CVP at the low end of normal range

MANAGEMENT OF ANESTHESIA

- The choice of drugs for preoperative medication, induction of anesthesia, and maintenance of anesthesia is not influenced by the presence of hypercortisolism
- **Induction:**
  - IV access often difficult due to thin, weak integument
  - Etomidate transiently decreases synthesis and release of cortisol
  - Potentially difficult airway due to "cushingoid" habitus
    - May require planned awake FOB intubation
    - If no concerns with airway exam, intubation with RSI if history of GERD
  - Will likely require mechanical ventilation as skeletal muscle weakness, with or without co-existing hypokalemia, may decrease strength in the muscles of breathing
    - Potential difficult ventilation
  - If OSA, expect exquisite sensitivity to opiods
  - Careful positioning because of the high incidence of severe osteopenia and the risk of fractures
- **Maintenance:**
  - Watch for intraoperative hyperglycemia which is likely
  - Monitoring of BP with judicious use of pressors to maintain normotension
    - Watch for blood loss- patient with Cushing's disease inclined to bleed more easily
  - For transsphenoidal microadenoidectomy/bilat adrenalectomy → dropping cortisol levels will require a continuous infusion of hydrocortisone 100mg/day IV, initiate intraoperatively
  - May be sensitive to NDMR due to decreased muscle mass +/- hypokalemia
    - Decrease dose or give doses based on twitch monitor
  - Surgical stimulation predictably increases the release of cortisol from the adrenal cortex but unlikely that this stress-induced release would produce a different effect from that in normal patients
    - Attempts to decrease adrenal cortex activity with opioids, barbiturates, or volatile anesthetics are probably futile, as any drug-induced inhibition is likely overridden by surgical stimulation
    - Even regional anesthesia may not be effective in preventing increased cortisol secretion during surgery
- **Emergence:**
  - Assess neuromuscular blockade prior to emergence

DISPOSITION & MONITORING

- Depends on surgery and patient

COMPLICATIONS

- Transient DI and meningitis may occur post microadenomectomy
- Mineralocorticoid and glucocorticoid deficiency; Addisonian crisis if no further cortisol
- Glucocorticoids are lympholytic and immunosuppressive and thus increase the patient's susceptibility to infection

PATHOPHYSIOLOGY

- Cushing's syndrome is categorized as ACTH-dependent Cushing's syndrome (inappropriately high plasma ACTH concentrations stimulate the adrenal cortex to produce excessive amounts of cortisol) and ACTH-independent Cushing's syndrome (excessive production of cortisol by abnormal adrenocortical tissues causes the syndrome and suppresses secretion of CRH and ACTH)
- ***4 types***:
  - ↑ACTH by anterior pituitary adenoma = Cushing Disease (70%)
  - Ectopic production of ACTH by malignant tumors of the lung, kidney, pancreas or thyroid
  - Excessive cortisol production by benign or malignant adrenal tumors
  - Exogenous cortisol administration (>21 days, risk of perioperative Addisonian crisis)
- Functions of cortisol:
  - Conversion of norepinephrine to epinephrine in adrenal medulla → maintain BP
  - Gluconeogenesis + inhibition of peripheral cellular glucose uptake → hyperglycemia
  - Retention of Na + excretion of K → hypokalemia (mineralocorticoid effects)
- Physiologic effects of excess cortisol secretion (Table 16-11 Coexisting):
  - Systemic hypertension
  - Hyperglycemia
  - Skeletal muscle weakness
  - Osteoperosis
  - Obesity
  - Menstrual disturbances
  - Poor wound healing
  - Susceptibility to infection
- The treatment of choice for patients with Cushing's disease is transsphenoidal microadenomectomy if a clearly circumscribed microadenoma can be identified and resected
  - Alternatively, patients may undergo 85% to 90% resection of the anterior pituitary
  - Pituitary radiation and bilateral total adrenalectomy are necessary in some patients
  - Surgical removal of the adrenal gland is the treatment for adrenal adenoma or carcinoma.
- Glucocorticoid excess
  - Exogenous administration of steroid
  - Pituitary (adenoma) or non-pituitary (ectopic ACTH-secreting tumor → small cell lung cancer, carcinoid, pancreatic, adrenal, thyroid) ACTH overproduction (rare)
  - Adrenal glucocorticoid overproduction d/t adrenocortical tumors, either adenoma or carcinoma (rare)
- Exogenous steroid > 2 weeks can suppress adequate pituitary ACTH secretion for up to 1 year
  - Prednisone 20-30 mg/d for < 1 week seems to have no effect in some reviews, others have reported minor effects
  - Mineralocorticoid secretion usually normal thus no fluid and electrolyte abnormalities (only when overproduction of ACTH
- Addisonian crisis triggered if period of stress (infection, trauma, surgery) and no supplemental steroid:
  - Circulatory collapse
  - Fever
  - Hypoglycemia
  - Decreased mentation
  - Treat with hydrocortisone 100 mg q8h, fluid + electrolyte replacement; prevent with stress dose of steroid
- Rationale for Stress-Dose Steroids
  - Major surgery increases cortisol
    i. Usual daily production: 10-20 mg/d
    ii. Minor Surgery: 50 mg/d
    iii. Major surgery: 75-150 mg/d
  - Enhanced survival through:
    i. Increased cardiac contractility
    ii. Increased cardiac output
    iii. Increased sensitivity to catecholamines
    iv. Ability to mobilize energy sources
  - Any patient who has received more than 20 mg of prednisone daily (or equivalent) for more than 3 weeks within the previous year should be considered incapable of mounting such a response
  - Doses between 5 and 20 mg daily may also cause adrenocortical suppression
  - Doses less than 5 mg/d have not shown suppression of HPA

CONSIDERATIONS IN PREGNANCY

- Nothing in Chestnut!

REFERENCES

- Barash Pg 313, 1018-1019, 1288
- Miller Chpt 35
- Coexisting Chpt 16