

# Adrenal Insufficiency, Acute or Secondary

## Risk

- Risk of adrenal insufficiency: 1/1000 to 1/10,000 (if steroids used in prior y).
- With steroids >20 mg/d (cortisol equivalent), >7 to 14 d within 1 y (large variability in pt response to dose, route(s), duration and timing of prior steroid use).
- Clinical signs worsen with stress, such as trauma, surgery, or infection.

## Perioperative Risks

- Increases CV instability, fever, CHF, lyte abnormalities.
- High cardiac output failure, or low-output state (hypovolemia) with signs of tissue hypoperfusion.
- Often evidence of systemic vasodilation with decreased reactivity to fluid or vasopressors.

## Worry About

- GI: N/V, dehydration (adrenal crisis).
- Anemia; neutropenia with androgen deficiency: Rare.
- CV response; decreased SVR, decreased left ventricular stroke work index and decreased vascular responsiveness to maintain perfusion pressure; steroids necessary for blood vessel responsiveness to catecholamines.
- Hyperkalemia with or without hyponatremia (usually aldosterone deficiency); hypoglycemia, acidosis, hypercalcemia, and anemia; cardiac conduction abnormalities.

## Overview

- Adrenal insufficiency results from inadequate production of glucocorticoids (cortisol), mineralocorticoids (aldosterone), and/or androgens.
- Adrenal insufficiency can be acute or chronic, primary or secondary.
- Primary adrenal insufficiency: Associated with >90% destruction of the adrenal glands and deficiency in both cortisol and aldosterone.
- Secondary adrenal insufficiency develops from the HPA axis dysfunction or failure.
- Inadequate mineralocorticoid production can cause hyperkalemia, hyponatremia, and metabolic acidosis, with or without signs of dehydration.

- Inadequate glucocorticoid production may cause signs of hemodynamic instability (hypotension) during stress.
- Acute adrenal (Addisonian) crisis may develop in periop period when another stress is present (infection, hemorrhage, or major or prolonged surgery), leading to hyponatremia, hyperkalemia, dehydration, abdominal symptoms, and shock. (See also Addison Disease.)
- May present without symptoms until stress.
- Adrenals secrete around 5 to 20 mg of cortisol daily at baseline, 150 mg in periop period, and up to 300 mg during the maximal stress.
- Recovery of the adrenal function may take up to 9 to 12 min after withdrawal of exogenous steroids (>20 mg/d of prednisone  $\times$  5 d) and the supplementation of daily cortisol production is advised.
- Critical illness may produce a state of relative adrenal dysfunction. Critically ill pts may appear to have sepsis without an obvious source of infection.
- Chronic adrenal insufficiency from use of steroids in prior year may manifest as weakness, fatigue, nausea, emesis, weight loss, and a variety of psychiatric disturbances.

## Etiology

- Primary adrenal insufficiency: Autoimmunity, infection (TB, HIV, CMV), hemorrhage (meningococcal sepsis, trauma, HIT, anticoagulants), drugs (etomidate, antifungals), infiltration (sarcoidosis, amyloidosis, histoplasmosis), metastatic disease (breast, lung, melanoma).
- Secondary adrenal insufficiency: Glucocorticoid therapy (systemic, inhaled, topical), drugs (fluticasone, megestrol, medroxyprogesterone, ketorolac tromethamine), brain injury, pituitary or hypothalamic tumors.
- Pts on corticosteroids (even topical) have a reduced basal secretion of cortisol and a reduced response to stress as a result of negative feedback of the HPA axis.
- Workup: Screening test) AM cortisol: Should be greater than 10 mg/dL; if lower, Cortisol stimulation test (ICU setting; suspected perioperative hypocortisolism should be treated empirically): The baseline cortisol level is measured. Synthetic ACTH at a dose

of 250  $\mu$ g IV is administered, and plasma cortisol levels are measured at 30 and 60 min. Usually the plasma cortisol rises at least 9 mg/dL or to a total of at least 18 g/dL at 60 min.

## Usual Therapy

- Mild stress (e.g., colonoscopy): 25 mg/m<sup>2</sup> of hydrocortisone IV on day of surgery only
- Moderate stress (e.g., appendectomy, lobectomy): 50 to 75 mg/m<sup>2</sup> or about 2  $\times$  normal production on day of surgery, taper quickly to usual dose over 1 to 2 d (usually a loading dose of 50 with induction and then 25 mg/m<sup>2</sup> divided every 4 h IV or every 8 h oral)
- Major stress (major trauma, major surgery): 100 mg/m<sup>2</sup> of hydrocortisone (if IV divided Q4, if oral divided Q8) on day of surgery, taper quickly to usual dose over 1 to 2 d (usually a loading dose of 50 with induction and then 50 mg/m<sup>2</sup> divided every 4 h IV or every 8 h oral)
- Septic shock in pts who remain hypotensive despite adequate administration of fluids and vasopressors: 50 mg/m<sup>2</sup> (for adults 50 mg) IV q 6 h or 100 mg/m<sup>2</sup> (for adults 100 mg) IV q 8 h for at least 7 d, then taper. No mortality benefit shown, but vasopressor requirements decreased with treatment.
- Early ARDS: Controversial benefit of steroids. Potential benefit in early ARDS (<72 hours after onset): 1 mg/kg methylprednisolone for more than 14 days, followed by taper to usual dose. Increased mortality in late ARDS (>14 days after onset).
- Aldosterone deficiency (manifested by abnormalities in Na<sup>+</sup>/K<sup>+</sup> or dehydration): Fludrocortisone (Florinef), 50 to 200  $\mu$ g/d. Consider concomitant furosemide in pts with CHF.
- Only one very small RCT examines the benefit of supplemental steroids in pts undergoing GA for invasive procedures (Glowniak, 1997, PMID 9037222). The 18-participant study showed no clear benefit but was at high risk of bias; was underpowered to identify any possible benefit.

## Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Dehydration, hypotension, high-output failure Fluid/Pressor unresponsive shock	Postural symptoms, fatigue; Wt loss, Hx of surgery on adrenals, pituitary	Low BP, postural drop, signs of dehydration	Hct, BUN/Cr, adrenal, AM cortisol, ACTH stimulation CRH stimulation, insulin tolerance, metyrapone test
RESP	CHF (high or low output)	DOE, SOB	S <sub>3</sub> , rales	CXR
GI	Dehydration, nausea, emesis	Appetite, Hx of emesis	See CV	Lytes
HEME	Anemia, neutropenia		Hyperpigmentation (excess corticotropin)	Hct, WBC
CNS	Depression, confusion, psychosis			Reverses with replacement
MS	Weakness, potentiation of neuromuscular blockage			Nerve stimulator

**Key References:** Marik P: Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the ACCCM, *Crit Care Med* 36(6):1937–1949, 2008; Schwartz J: Endocrine function. In Barash PG, editor: *Clinical anesthesia*, ed 6, Philadelphia, PA, 2009, Lippincott Williams and Wilkins, pp 1279–1304.

## Perioperative Implications

### Preoperative Preparation

- Consider perioperative steroid coverage if benefits outweigh risks if high index of suspicion of adrenal depression (e.g., prednisone >20 mg/d  $\times$  5 d).
- Correct lyte abnormalities, hypoglycemia, and dehydration prior to elective surgery.
- Fludrocortisone with resistant aldosterone (K<sup>+</sup> and Na<sup>+</sup>) abnormalities; glucose for hypoglycemia

### Monitoring

- ECG for signs of abnormal conduction (QRS duration, u waves with hypokalemia)
- Consider CVP, PCWP, or TEE if fluid/lyte and hemodynamic abnormalities
- Sodium, potassium, bicarbonate, and glucose

### Airway

- None

### Premedication/Induction

- Consider volume status with regard to hydration and choice of agents. Have vasopressors available.

### Maintenance

- No hemodynamic instability; follow with lytes and glucose as needed.
- Hemodynamic instability (hypotension):
  - R/O other causes, then consider hydrocortisone hemisuccinate, 25–100 mg IV, then 100 mg q 12–24 h for 2 or 3 d. In septic shock, consider 200–300 mg IV daily in divided (q 4 h) doses.
  - Fluid resuscitation as needed.

### Extubation

- Possible potentiation of nondepolarizing muscle relaxants with use of high-dose steroids; ensure adequate muscle relaxant reversal.

### Adjuncts

- Glucose, fluids, careful monitoring of temperature to avoid hyperthermia.

### Postoperative Period

- Stress-dose steroids possibly required several days postop.
- High steroid doses may be associated with decreased wound healing and immunosuppression with increased infection risk. Unclear risk if used short-term.
- Consider prolonged steroid coverage if severe stress continues (e.g., severe trauma with multiple operations).

- Mineralocorticoid administration as needed; many glucocorticoids have significant mineralocorticoid action (hydrocortisone, prednisone, prednisolone). Methylprednisolone and dexamethasone have no mineralocorticoid activity.

### Anticipated Problems/Concerns

- Severe resistant hypotension, hyperthermia, and CNS abnormalities, such as confusion, coma, lethargy, may occur intraop or postop and may be unpredictable.

- Syndrome may occur in severely traumatized pts without history of steroid use, with clinical picture of sepsis and associated abnormalities in adrenal function; Rx is life saving.

## Alagille Syndrome

Christopher J. Cullom | Alan David Kaye | Amit Prabhakar

### Risk

- Also known as syndromic bile duct paucity
- Affects cardiac, musculoskeletal, ocular, facial, and neurodevelopmental systems
- Most common inherited disorder that causes chronic liver disease in children
- 1:100,000 births with equal gender incidence

### Perioperative Risks

- Cardiac congenital anomaly and hemodynamic instability
- Coagulopathy
- Liver dysfunction
- Musculoskeletal injury from positioning

### Worry About

- Vertebral abnormalities
- Facial anomalies
- Ocular abnormalities
- Vitamin deficiencies: A, D, E, K
- Neurologic deficits (neuropathy, mental retardation, cerebellar defect)

### Overview

- In addition to liver involvement, includes congenital cardiac disease (97%), dysmorphic face (96%), ocular abnormalities (78%), vertebral anomalies (51%), and kidney malformation (40%).

- Disease ranges from mild cholestasis to progressive liver failure.
- Liver involvement results in the loss of intralobar ducts over months to years.
- Elevated serum bile acids, conjugated bilirubin, alkaline phosphatase, and GGT typically seen.
- Malnutrition and growth failure is common, leading to delayed pubertal development.
- Malnutrition may lead to protuberant abdomen, making pts more prone to regurgitation.
- Ineffective absorption of dietary lipids, essential fatty acids, fat-soluble vitamins.
- Vitamin deficiencies: vitamin K (coagulopathy), vitamin D (rickets), vitamin E/A (retinopathy and neuropathy).
- Vitamin K deficiency and liver dysfunction lead to prolonged PT and PTT as well as thrombocytopenia.
- Cardiac abnormalities: Pulm vascular stenosis (most common with up 90% pts), tetralogy of Fallot, truncus arteriosus, patent ductus arteriosus, VSDs.
- Facial characteristics: Prominent forehead, hypertelorism, saddle or straight nose.
- Vertebral anomalies: Butterfly vertebrae (splitting of the bodies sagittally), spina bifida, fusion of adjacent vertebrae.
- Ocular abnormalities: Posterior embryotoxon, microcornea, macular dystrophy.
- Posterior embryotoxon progresses to glaucoma in 50% of pts.

- Neurologic effects: Cerebellar ataxia and peripheral neuropathy usually due to vitamin E and A deficiency. Mental retardation is also associated with the syndrome.
- There is a 12–14% risk of spontaneous intracranial bleed.
- Renal dysplasia found in 40% of pts.
- Halothane should be avoided as it has a myocardial depressant effect, lowering hepatic blood flow.
- Perfusion pressure to liver and kidney should be maintained with periop hydration and blood pressure control.

### Etiology

- Characterized by chronic cholestasis, decreased number of interlobar bile ducts, and variety of congenital malformations
- Autosomal dominant mode of transmission involving mutation in *JAG1* gene

### Usual Treatment

- Pts typically require procedures to correct various congenital abnormalities, biliary diversion, and ileal exclusion; may also require biopsy or liver transplantation.
- Symptomatic relief of pruritus can be provided with rifampicin or ursodeoxycholic acid.

### Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Pulm arterial stenosis, tetralogy of Fallot, truncus arteriosus, patent ductus arteriosus	Dizziness Palpitations	Murmur	ECG, ECHO
RENAL	Renal dysplasia			Cr, GFR, UA
GI	Cholestasis, liver failure/cirrhosis	Pruritus	Hepatomegaly, splenomegaly	LFTs, abdominal CT
HEME	Coagulopathy			CBC, PT, PTT, INR
MS	Osteodystrophy		X-ray of extremities/DXA	
NEURO	Intracranial hemorrhage, vertebral anomalies		Cervical spine evaluation	X-ray of vertebrae
HEENT	Xerophthalmia, posterior embryotoxon		Ophthalmoscopic exam	
GENERAL	Facial abnormalities		Prominent forehead, hypertelorism	

**Key References:** Choudhry D, Rehman M, Schwartz R, et al.: The Alagille's syndrome and its anaesthetic considerations, *Paediatr Anaesth* 8(1):7–82, 1998; Subramaniam K, Myers L: Combined general and epidural anesthesia for a child with Alagille syndrome: a case report, *Paediatr Anaesth* 14(9):787–797, 2004.

### Perioperative Implications

#### Preoperative Preparation

- Assessment of airway and neck mobility.
- Standardized bleeding history as well as clotting profile.
- ECHO and ECG to prepare for cardiovascular abnormalities.
- Evaluate neurologic status.
- Avoid succinylcholine if peripheral neuropathy is present.

#### Monitoring

- Avoid invasive monitoring whenever possible due to bleeding risk.

#### Airway

- Neck mobility may create difficulties.

#### Preinduction/Induction

- Potential usage of rapid sequence induction as pts are prone to regurgitation.
- Careful positioning due to osteodystrophy.
- Eye care paramount due to vitamin A deficiency and dry eyes.

#### Maintenance

- Use of sevoflurane or isoflurane as they have less myocardial depressant effects and preserve hepatic blood flow.
- Blood pressure control and adequate hydration to maintain liver perfusion.
- Use of cisatracurium for muscle relaxation as metabolism is independent of liver and renal function.

#### Extubation

- Usual criteria

#### Postoperative Period

- Careful positioning in PACU

#### Regional Anesthesia

- Used cautiously due to potential risk of bleeding and vertebral anomalies, but not contraindicated

### Anticipated Problems/Concerns

- Cardiac pathology/anomalies
- Hemodynamic instability and hypotension
- Airway difficulty due to vertebral anomalies
- Coagulopathy
- Nerve and soft tissue injury due to positioning
- Liver and renal dysfunction
- Ocular abnormalities requiring extra eye protection
- Various neurologic abnormalities to be aware of before anesthesia