Absite Review Series: Adrenal Gland Disorders

Sean Rim
7/11/2008
Which of the following are effective initial treatments of acute adrenal insufficiency?

A. Normal saline bolus
B. Potassium
C. IV glucocorticoids
D. IV mineralocorticoids
E. A and C
F. All of the above
The most common cause of congenital adrenal hyperplasia is related to which enzyme deficiency?

A. 11-hydroxylase  
B. 17-hydroxylase  
C. 3-hydroxyhydrogenase  
D. 21-hydroxylase
Which of the following is the most common cause of endogenous Cushing’s syndrome/disease?

A. Adrenal adenoma
B. Adrenal carcinoma
C. Pituitary adenoma
D. Ectopic ACTH
A CT scan demonstrates an 8 cm right adrenal mass extending into liver and kidney. Which of the following are appropriate?

A. En bloc resection
B. Radiation followed by en bloc resection
C. Mitotane followed by en bloc resection
D. Chemoradiation followed by en bloc resection
Questions

Which of the following are contraindications to laparoscopic adrenalectomy?

A. Pheochromocytoma
B. Adrenocortical cancer
C. Bilateral adrenal lesions
D. Prior abdominal surgery
E. A and B
Adrenal Glands

- Paired glands with two distinct functional organs
- Third most highly perfused organ behind kidney and thyroid, 2000mL/kg/min

- **Cortex**
  - Mesodermal

- **Medulla**
  - Ectodermal
Adrenal Glands

- Paired glands with two distinct functional organs
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**Cortex**
- Mesodermal
- 4th to 5th week

**Medulla**
- Ectodermal
- 5th to 6th week
Adrenal Glands

- Paired glands with two distinct functional organs
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Cortex
- Mesodermal
- 4th to 5th week
- Glucocorticoids, mineralocorticoids, sex steroids

Medulla
- Ectodermal
- 5th to 6th week
- Catecholamines
Adrenal Glands

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Cortex
- Mesodermal
- 4th to 5th week
- Glucocorticoids, mineralocorticoids, sex steroids
- Hyperaldosteronism, Cushing’s, virilization

Medulla
- Ectodermal
- 5th to 6th week
- Catecholamines
- Pheochromocytoma
Anatomy
Anatomy

- Arterial supply is diffuse
  - Inferior phrenic artery
  - Juxtaceliac aorta
  - Renal artery
Anatomy

- Inferior vena cava
- Right and left inferior phrenic arteries
- Right adrenal gland
- Right adrenal vein
- Right renal artery and vein
- Left adrenal gland
- Left inferior phrenic vein
- Left inferior adrenal artery
- Left adrenal vein
- Left kidney
- Left renal artery and vein

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Anatomy

- Venous drainage is solitary
  - Left vein ~2 cm into renal
  - Right ~0.5 cm into IVC
  - 20% variable
Anatomy
Histology

- Cortex is 2 mm
- >80% mass
- Medulla has extensive autonomic fibers and ganglion cells
Series of oxidative reactions via cytochrome P-450 membrane associate enzymes
Steroid hormones

- Low molecular weight, lipophilic signaling molecules
- Enter cells and bind to intracellular receptors
- Slower response than membrane binding peptides
- Levels altered by pregnancy, nephrotic syndrome, cirrhosis
- Metabolized in liver and excreted via kidney
Mineralocorticoids

- Aldosterone regulates circulating fluid volume and electrolyte balance
- Promotes Na and Cl retention in distal tubule
- K and H secreted
- Will see expansion of BP and intracellular volume with aldosterone
Mineralocorticoids

- Renin-angiotensin-aldosterone axis is responsive to delivery of sodium to the DCT
- Low sodium delivery triggers release of renin from JGA
  - Shock
  - Renal artery vasoconstriction
  - Hyponatremia
- Renin cleaves angiotensinogen (liver) to angiotensin-1
- ACE (lungs) cleaves to angiotensin-2
Glucocorticoids

- Generate a catabolic state in response to stress
- Alters carbohydrate, protein, and lipid metabolism to increase blood glucose
- Increase gluconeogenesis
- Decrease peripheral glucose uptake
- Sensitizes arterial smooth muscle to beta-adrenergic stimulation
Glucocorticoids

- Potent anti-inflammatory and immunosuppressive agents
- Reduce circulating lymphocyte and eosinophils and increase neutrophils
- Decrease cytokine and Ig production
- Suppress histamine release
- Inhibit phospholipase A2 to reduce prostaglandins
Glucocorticoids

- Hypothalamus release CRF into pituitary
- Results in ACTH secretion
- ACTH bind G protein coupled receptors on adrenocortical cell surface
- Steroidogenesis is upregulated
Glucocorticoids

- ACTH is released in a pulsatile fashion, circadian rhythm
- Peak in AM
- Negative feedback occurs at both hypothalamic and pituitary levels
Exclusive to chromaffin cells
Stable metabolites used for markers
Catecholamines

- **Alpha-1**: Vasoconstriction of skin and GI tract
- **Alpha-2**: Attenuate sympathetic outflow in presynapse
- **Beta-1**: Increase HR and contractility
- **Beta-2**: Smooth muscle relaxation in uterus, bronchi, skeletal muscle arterioles
Congenital Adrenal Hyperplasia

- Six enzyme defects have been identified
- 90% caused by CYP21A2 deficiency (21-hydroxylase)
- Usually manifests as salt-wasting form
Congenital Adrenal Hyperplasia

- Decreased negative feedback
- Hypovolemia, hyperkalemia, hyperreninemia
- Shunts towards adrenal androgens
- Ambiguous genitalia in females
- Dx via elevated 17-hydroxyprogesterone
- Tx via glucocorticoid and mineralocorticoid replacement
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Primary Adrenal Insufficiency

- Addison’s disease
  - Weakness
  - Fatigue
  - Anorexia
  - Nausea
  - Weight loss
  - Hyperpigmentation
  - Hypotension
  - Electrolyte disturbance
Primary Adrenal Insufficiency

- Congenital adrenal dysgenesis
- Defective steroidogenesis
- Adrenal destruction
  - Autoimmune
  - Infectious (TB, fungal, viral)
  - Metastases
  - Adrenal hemorrhage (Waterhouse-Friderichsen syndrome)
Secondary Adrenal Insufficiency

- Steroid withdrawal
- Surgical cure of Cushing’s
- Panhypopituitarism
  - Neoplasm
  - Granulomatous disease
  - Sheehan’s syndrome
Adrenal Crisis

- Life-threatening
- Occurs in patients with marginal function subjected to significant physiologic stress
- Initial treatment is volume and glucocorticoids
- Mineralocorticoid effects take several days
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Adrenal Insufficiency in Sepsis

- Acute reversible dysfunction of HPA axis
- >30% in critically ill patients
  - Adrenal ACTH resistance
  - Decreased sensitivity of target tissues
- Vasopressor dependent septic shock may benefit from 5 to 7 day course of physiologic dose steroids

Meta-analysis: The effect of steroids on survival and shock during sepsis depends on the dose

<table>
<thead>
<tr>
<th>Total Steroid Dose Administered</th>
<th>Duration of Therapy</th>
<th>Steroid Taper?</th>
<th>Indication for Therapy</th>
<th>Time to Initiation of Therapy after Shock or Indication for Enrollment</th>
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<tbody>
<tr>
<td>mg</td>
<td>h</td>
<td></td>
<td></td>
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<tr>
<td>1050</td>
<td>6 d</td>
<td>No</td>
<td>Severe infection</td>
<td>Immediate</td>
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<tr>
<td>7000</td>
<td>3 d</td>
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<td>Severe infection</td>
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<td>42 000</td>
<td>24 h</td>
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<tr>
<td>11 200</td>
<td>48 h</td>
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<td>Shock</td>
<td>Immediate</td>
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<td>24 h</td>
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<tr>
<td>42 000</td>
<td>24 h</td>
<td>No</td>
<td>Shock</td>
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<td>Vasopressor-dependent shock</td>
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<td>3 d</td>
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<td>Median: &lt;2</td>
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<tr>
<td>Median, 1209</td>
<td>Median, 6 d</td>
<td>Ratio, 3/5</td>
<td>Median: Vasopressor-dependent shock</td>
<td>Median: 23</td>
</tr>
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A patient has abdominal pain, T 102, systolic BP 60, HR 120, labored breathing.
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- A. The sepsis protocol is stupid
- B. The ER never sent it
A patient has abdominal pain, T 102, systolic BP 60, HR 120, labored breathing. Dr. Kurtz asks you what the cortisol level. Your response is

- A. The sepsis protocol is stupid
- B. The ER never sent it
- C. It’s pending but the patient was already started on steroids (physiologic dose)
Suspected adrenal insufficiency

8 AM serum or salivary cortisol

Serum cortisol ≤ 15 μg/dL or salivary cortisol ≤ 5.8 ng/mL

- Adrenal insufficiency possible

Serum cortisol > 15 μg/dL or salivary cortisol > 5.8 ng/mL

- Adrenal insufficiency unlikely

250 μg ACTH (cosyntropin) stimulation test

Post cortisol < 18 μg/dL

- Adrenal insufficiency possible

Post cortisol ≥ 18 μg/dL

- Adrenal insufficiency unlikely

8 AM serum ACTH

Increased ACTH

- Primary adrenal insufficiency

Decreased or normal

- Secondary adrenal insufficiency
Primary Hyperaldosteronism

- Resistant hypertension and hypokalemia
- 1% of patients with hypertension
- Mean age at diagnosis ~50
- Slight male predilection
- Symptoms usually related to hypokalemia
Primary Hyperaldosteronism

- Potentially curable cause of significant cardiovascular disease
- Higher risk for stroke, MI, a-fib, LV hypertrophy compared to age and systolic BP matched controls
- Risks decrease with successful removal of aldosteronoma
- Responsiveness to spironolactone is a good prognostic sign

Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism

- 124 patients with primary hyperaldosteronism over a three year period
- 465 age and BP matched controls
- Stroke: 12.9% vs 3.4%
- MI: 4% vs 0.6%
- Atrial fibrillation: 7.3% vs 0.6%

Primary Hyperaldosteronism

- Aldosteronoma (unilateral) and idiopathic (bilateral) account for >90%
- Goal is to identify and lateralize
Ratio <30

PAC/PRA

Discontinue interfering medications*

Ratio >30

Suppression of urine aldosterone

24-hr urine free aldosterone
Urinary potassium excretion

Oral or IV sodium loading

No suppression

Probable primary hyperaldosteronism

Unilateral adrenal mass >1 cm, normal contralateral adrenal, age ≤40 years

Thin cut adrenal CT

Nonlateralizing CT
Consider for age >40 years

Adrenal vein sampling

Failed study

Nonlateralizing (bilateral adrenal hyperplasia)

Lateralizing (aldosteronoma)

Observation, consider repeat testing if suspicion remains

Medical management

Adrenalectomy

*Including spironolactone, ACE inhibitors, diuretics, β-blockers.
Primary Hyperaldosteronism

- Laparoscopic adrenalectomy is the preferred method
- Cure in 75% to 95%
  - Normalize BP
  - Normalize plasma and urine aldosterone
  - Resolve hypokalemia
- 24 hours to weeks

Cushing’s Syndrome

- Obesity
- Hirsuitism
- Amenorrhea
- Easy bruising
- Extreme muscle weakness

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Emotional disturbance
Enlarged sella turcica
Moon facies
Osteoporosis
Cardiac hypertrophy (hypertension)
Buffalo hump
Obesity
Adrenal tumor or hyperplasia
Thin, wrinkled skin
Abdominal striae
Amenorrhea
Muscle weakness
Purpura
Skin ulcers (poor wound healing)
Cushing’s Syndrome

- Most common cause is exogenous
- Endogenous is rare
  - 5 to 10 per million
  - 75% have Cushing’s disease
    - ACTH-secreting pituitary adenoma
  - 15% Primary adrenal
  - 10% Ectopic ACTH
    - Neuroendocrine tumors
    - Bronchogenic malignancies
Cushing’s Syndrome

- 5x increase in mortality
  - Hypertension
  - Diabetes
  - Truncal obesity

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High does dexamethasone will not suppress ectopic ACTH
Cushing’s Syndrome

- Laparoscopic adrenalectomy
- 90% successful
- Perioperative stress dose
- Hydrocortisone 100 mg IV every 8H for 3 doses
- Tapered to physiologic replacement doses over weeks to years
- Failure may be due to local or distant recurrence
Adrenocortical Carcinoma

- One per million
- Nearly all occur at 40 to 50 years
- Mean size at discovery 9-12 cm
- 5 year survival 15% to 20%
- >50% functional
  - Cushing’s
  - Virilization

Adrenocortical Carcinoma

- Radical OPEN surgery
- En bloc resection of adjacent organs and regional lymphadenectomy
- Right sided tumors >9 cm have high chance of invading into IVC and right heart
- May need cardiopulmonary bypass
Adrenocortical Carcinoma

- Incomplete resection
  - <1 year survival
- Mitotane
  - Derivative of DDT
  - Direct adrenocortical toxin
  - Adjuvant and primary therapy
  - GI and neurologic toxicity

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Incidentaloma

- 2.1% of autopsies
- 1% to 4% of abdominal imaging studies
Incidentaloma

- Size and risk of carcinoma
  - <4 cm = 2%
  - 4 cm to 6 cm = 6%
  - >6 cm = 25%

Adrenal incidentaloma

Hormonal evaluation

24-hr urine metanephrines and catecholamines
Low-dose (1 mg) dexamethasone suppression test
PAC/PRA if hypertensive

Functioning adrenal tumor?

Yes

Consider tumor size:

<3 cm
>5 cm
3-5 cm

Consider case-specific factors:
- Suspicious imaging features
- Young patient
- Few surgical risk factors
- Interval tumor growth
- Patient preference

No

Yes

Size criteria, risk/benefit assessment

Interval CT in 6 months
Adrenalectomy

Management
Autopsy studies reveal 25% of adrenal involvement in patients with carcinoma.

50% are bilateral.

Lung, GI, breast, kidney, pancreas, skin.

Resection of isolated mets increases survival:
- 20 to 30 months median survival for complete resection.
- 12 months for incomplete resection.
- 6 months for no resection.

Positioning
Port Placement
Right Adrenalectomy

1. Division of triangular ligament
2. Divide plane between adrena and IVC
Right Adrenalectomy

1. Identify and ligate adrenal vein and arteries
2. Dissect off diaphragm superiorly, kidney inferiorly
Left Adrenalectomy

1. Mobilize spleen and splenic flexure
2. Leave kidney in place
3. Mobilize tail of the pancreas
Left Adrenalectomy

1. Ligate vessels
2. Dissect off kidney and diaphragm
Open adrenalectomy

1. Used for cancer operation
2. En Bloc removal may include stomach, spleen, pancreas
3. Take periadrenal fat and lymphatic tissue
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