

Relative Adrenal Insufficiency: Case Examples & Review

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Abstract

Several cases of adrenal insufficiency are reviewed in this article.

CASE EXAMPLE 1

A 21 year old morbidly obese man s/p motor vehicle crash presented to the E.R. with a SBP 70, P 128, RR 20 and complaining of chest pain and pelvic pain. Physical examination revealed crepitus along the right chest wall and a right chest tube was placed (with a minimal air leak). A dislocated right shoulder and an abdominal wall contusion with diffuse pelvic tenderness was also noted. Blood work revealed a Hct 40 with ABG's of 7.29/42/151. Further studies (after following initial ATLS protocol) included a CXR (showing a small Right-sided PTX with Chest Tube in position), multiple rib fxs; Bilateral rami fractures on pelvic film; negative C-spine series; a normal Cystogram; and an abdominal C.T. demonstrating a left perinephric hematoma and pelvic hematoma.

Crystalloids and blood products were administered and the patient was admitted to the Surgical ICU. ICU admission vitals were: T 39 C, SBP 90, P 112, and UOP < 30 cc/hr. Within the first 2-3 hours, the patient developed progressive respiratory distress with tachypnea and hypoxemia. He was intubated and started on dopamine and norepinephrine in an attempt to maintain a mean arterial pressure greater than 70 mmHg.

At this point, what is your working diagnosis and treatment plan?

An EKG and cardiac echo (TTE) were obtained and interpreted as normal. A PA catheter was inserted to help guide further management and the initial numbers were: CVP 4, PWP 11, CI 8.5, and SVR 494. Pan-cultures (blood, urine, sputum) were sent and the patient was prepared for surgery (the decision was made based on persistent hypotension despite 9 units of PRBC's, 2 units FFP, and 6 liters of crystalloid.

During the exploratory laparotomy, a nonexpanding retroperitoneal hematoma was identified. There were no other traumatic findings.

At this point, what is your working diagnosis and treatment plan?

Upon returning to the SICU, a cortisol level was drawn and a "stim test" was performed. After finishing the test, Dexamethasone (6 mg IV) was empirically given. Within 1 hour of administration, the patient's MAP > 80 and all Vasopressors were weaned off. The patient's vital signs normalized and began an impressive diuresis (UOP > 500 cc/hr - lasting 6 hours, then falling to greater than 100 cc/hr through the next 24 hours).

The cortisol level that was initially drawn returned at 1.2. Results of the cosyntropin stimulation test were: baseline 1.6, 30 min 2.2, and 60 min. 2.3. The patient was continued on glucocorticoids and mineralocorticoids. After 3 weeks in the ICU, he was discharged to the floor; one week later he was transferred to a short-term care facility for further orthopedic rehabilitation.

CASE EXAMPLE 2

A 63 year old male was admitted with large cell diffuse lymphoma after a C.T. scan revealed massive retroperitoneal lymphadenopathy. He had been started on 4-drug chemotherapy and was experiencing intermittent fevers to 39 C, lethargy, and abdominal pain. On diagnostic work-up, the patient was found to have free-air on plain abdominal radiograph.

At this point, what is your working diagnosis and treatment plan?

At celiotomy, an involved-segment of small bowel

lymphoma was found to be perforated. Resection and primary anastomosis was performed. The patient was extubated on post-operative day #1 and doing fairly well overall. On POD #3, the patient went into a profound episode of hypotension, tachycardia, fever, and respiratory distress. A stat CXR demonstrated diffuse pulmonary edema and the patient was emergently intubated.

At this point, what is your working diagnosis and treatment plan?

A PA catheter was inserted (CVP 14, PWP 22, C.I. 6, SVR 350) and an EKG, TTE and cardiac enzymes were checked (all negative for acute ischemia). Pan-cultures were collected and sent. Despite all measures (fluid boluses, dopamine, norepinephrine, IV-antibiotics, and bronchoscopy), the patient continued to worsen. A repeat laparotomy was performed to evaluate the small bowel anastomosis and rule-out associated peritonitis; the exploration was negative.

At this point, what is your working diagnosis and treatment plan?

Upon return to the SICU, a cortisol level and “stim test” was done. Then Dexamethasone (8 mg IV) was empirically given. Several hours later, the patient began showing dramatic improvement: SBP 140 and weaned from all vasopressors. On PA, his SVR was 1000 dynes. The cortisol baseline was 6, and his 60 minute cosyntropin stim test was 7. The patient was continued on hydrocortisone 100mg IV q 8hrs. After 1 month in the SICU, the patient was successfully discharged with a full-recovery and all organ systems functioning. The chemotherapy regimen was altered by Oncology and he was continued on oral glucocorticoids.

The patient died 4 months later from his underlying systemic lymphoma.

CASE EXAMPLE 3

A 57 year old male s/p XRT for recurrent invasive bladder Transitional Cell Carcinoma underwent a radical cystectomy and ileal loop urinary diversion. On POD #4, the patient was found to have a DVT in his left leg. The patient was started on a heparin qtt and had a prompt decrease in his lower extremity swelling.

On POD #6, the patient began having LGI bleeding and dropped his HCT 31 to 19. The heparin was discontinued and FFP/Vit k were administered. A tagged red cell scan demonstrated a positive blush at the ileoileal anastomosis. The patient was transfused and HCT stabilized at 32 and

PLT 292K Despite this, he started complaining of progressive pain and discomfort in his left leg and thigh. The patient was restarted on heparin for a new goal of 40 -50.

The following day, he developed a fever to 39.5 C, nausea, and significant LUQ pain. His breath sounds were noted to be decreased at the left lung base and he was diffusely distended.

At this point, what is your working diagnosis and treatment plan?

A series of diagnostic studies were then undertaken: CXR was negative, EKG was negative, VQ scan was negative. LFT/amylase/lipase were all normal. PLT count decreased to 60K and the heparin drip was stopped and an IVC filter was placed.

By POD #9, the patients abdominal complaints had resolved but he was noted to be confused and disoriented. All labs were repeated and found to be within normal limits with a slowly resolving thrombocytopenia. A head C.T. and cardiac work-up were also unremarkable.

On POD #10, the patient developed hypotension, tachypnea, and fever 39.8C. He required reintubation and dopamine/norepinephrine drips were started. EKG and electrolytes were again checked and were normal. The patient’s WBC was elevated at 23K. Cultures were collected and sent and broad-spectrum antibiotics were started. A Chest, abdominal, and pelvis C.T. was done and were unremarkable. A pulmonary angiogram was also done but did not reveal an acute embolus.

At this point, what is your working diagnosis and treatment plan?

The patient continued to deteriorate with fever/hypotension. A Gallium scan demonstrated increased uptake in the left pelvis and an exploratory laparotomy was performed. The celiotomy was negative for any acute findings. Hydrocortisone had been given prior to the OR and the patient promptly improved in the immediate post-operative setting (“released evil humors-theory”?).

The patient’s fever resolved and blood pressure returned to normal. All pressors were weaned off and the patient was placed on dexamethasone. He required fludrocortisone for hyponatremia and hyperkalemia over the next several days.

The patient did recover after a prolonged course in the SICU and was discharged on low-dose prednisone and coumadin.

ADRENAL DISEASE

All three of these cases demonstrate significant episodes of hypotension. Clinically, the main causes of such episodes can be divided into: Hemorrhage, Intravascular hypovolemia, Sepsis, Cardiac failure, and Adrenal insufficiency. ICU scenarios associated with adrenal-based hypotension can be further divided into: Adrenal insufficiency (AI), Pheochromocytoma and “Pheo-crisis”, and Aldosterone deficiency.

Incidence of adrenal insufficiency (A.I.) in the general population ranges between 40-60 events/million population. In the ICU, there is a 1-20% incidence pattern depending on how aggressive one looks for it.

Adrenal Insufficiency (A.I.) can be divided into: Primary, Central, and Relative. Primary A.I. involves a pathological process within adrenal gland leading to destruction of at least 90% of the gland. Specific risk factors for developing Primary A.I. include coagulopathy, thromboembolic disease, and the postoperative state. (Rao et al , Ann Intern Med, 1989)

Etiologies can include:

- Autoimmune - 65-80%
- Infectious - 35%
- Hemorrhagic

Central A.I. involves, as the name suggests, a central dysfunction either in the pituitary (“Secondary A.I.”) or the hypothalamus (“Tertiary A.I.”). Etiologies can include:

- “common”: long-term glucocorticoid therapy
- “uncommon”: post-partum pituitary necrosis (Sheehan’s syndrome)
- transient ACTH deficiency (alcoholics)
- pituitary radiation
- empty sella syndrome

Relative A.I. involves an increased degradation of glucocorticoids (in relation the surrounding need of the system) which can be seen with:

- drugs that activate hepatic metabolism

- treatment of hypothyroidism
- resistance to glucocorticoid activity
- AIDS
- increased demand (the stress response)

The general risk factors for developing adrenal insufficiency include: Age > 55; Malnutrition; Prolonged hospital or ICU stay; Chronic alcoholism; High APACHE score; Stress in form of trauma, surgery, infection, and dehydration.

Presentation of A.I. in non-ICU settings can be insidious and nonspecific (weakness, wt loss, lethargy, GI symptoms). In ICU settings, presentation of A.I. can be as an acute adrenal crisis with actual signs and symptoms altered by co-existing disease. Onset is usually precipitated by physical stressors (trauma, surgery, infection, dehydration) but other causes should be considered (AIDS, TB, or pituitary tumor).

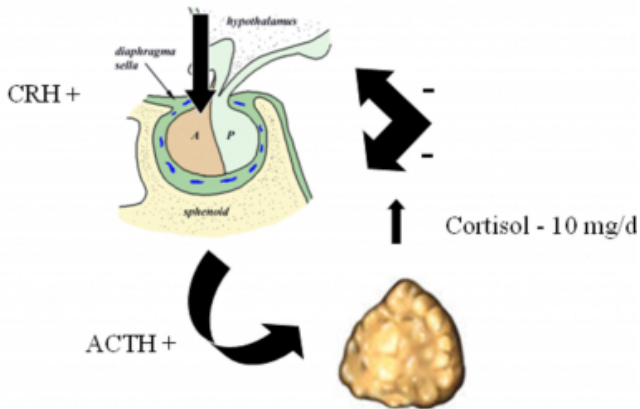
Clinical presentation in the ICU usually involves refractory hypotension. High-output circulatory failure (CI > 4, tachycardia, and a low SVR with normal wedge) is classically associated with AI. Electrolytes disturbances (high K , low Na, and low glucose) and fevers (> 39C), mental status changes, dehydration, with or without GI disturbances are all common in the presence of AI.

“Clues” to A.I. include the history, other endocrine abnormalities, a family history of endocrine abnormalities, and unexplained eosinophilia. AI differential diagnosis should include:

- Sepsis
- Neurogenic shock
- Overdose of vasodilator agent(s)
- Severe anemia
- AV shunt
- Thyrotoxicosis
- Beriberi
- Pregnancy

Figure 1

Hypothalamus-Pituitary-Adrenal Axis



Testing the HPA-Axis includes:

1. 1H-P Axis and Adrenal
2. Low-dose ACTH stimulation (1 ug)
3. 2Adrenal only
4. Short ACTH stimulation test (250 ug)
5. 3H -P Axis only
6. Insulin-induced hypoglycemia test
7. Metyrapone
8. CRH stimulation

Laboratory Assessment of AI classically starts with a random cortisol level drawn before steroids given (and between 6-8 am). Dexamethasone generally considered to be non-reactive. A “positive result” is one that is < 10 in normal or < 15 in critically ill (10-20 indeterminate). Cosyntropin testing (“stimulation testing” has replaced the random cortisol level. Cosyntropin stimulation test involves a standard approach:

- 1st - baseline cortisol level
- 2nd - 0.25 mg cosyntropin with level 60 minutes later
- 3rd - peak > 20 or rise of 7 in critically ill

Other cosyntropin tests include the “short approach” (more sensitive for central AI, and is more accurate and physiologic than the “standard”). This uses the same regimen as above but only 1 ug dose instead of 250 ug. The

“Long approach” helps to differentiate primary vs central AI. and has been replaced by measuring ACTH levels directly. Other measures to assess AI include measuring Corticotropin-releasing hormone (CRH), plasma rennin, and aldosterone levels.

Figure 2

Diagnosis - AI in Critical Illness

Adrenal deficit	Baseline	ACTH
Severe	< 10	none
Moderate	10-19	<30
Mild	20-30	<30
None	> 30	>>30

TREATING AI

- Hemodynamically unstable
 - Baseline cortisol & Stim-testing
 - Treat with Hydrocortisone 100 IV bolus and q8
 - Isotonic IVF with D5
 - treat underlying disease or precipitating factors
- Hemodynamically stable
 - same as above
 - cosyntropin testing
 - treat only if AI is present

Treating with Steroids:

- Hydrocortisone
 - provides glucocorticoid and mineralocorticoid
 - physiological doses
 - max 300 mg/day
 - normal daily adrenal output
 - AM 25 mg /PM 12.5 mg
- Dexamethasone
 - not cross-reactive with cortisol assays

- no mineralocorticoid activity
- useful while diagnostic testing being completed
- Fludrocortisone (Florinef)
 - uncommonly required for mineralocorticoid activity

- negatively correlated to survival

Figure 3

Glucocorticoid vs Mineralocorticoid Effect (a general guide):

Steroid	Glucocorticoid	Mineralocorticoid
Hydrocortisone	1	1
Prednisolone	4	0.7
Dexamethasone	40	2
Aldosterone	0.1	400
Fludrocortisone	10	400

Potential for HPA Suppression:

- higher glucocorticoid potency
- short frequency of dosing
- evening dosing
- systemic therapy
- duration > 1 week

OUTCOME OF AI PATIENTS

- Untreated = 100% mortality
- Treated in critically ill = 50% mortality
- Cortisol level
 - positively correlated to severity of illness

PREVENTION OF AI

Susceptible within 1-2 years of high dose glucocorticoids treatment. Presurgical screening should be considered in:

- elderly patients
- prolonged previous hospitalizations
- malnourished or alcoholic patients
- risk factors for adrenal insufficiency: prednisone doses > 5 mg/d
 - subnormal ACTH-stimulation test
 - previous adrenal insufficiency

PROPHYLACTIC STEROID THERAPY

Universal coverage is the most common method utilized to avoid AI. Lowest possible dose in the perioperative setting should be employed.

* Glowniak et al , Surgery, 1997: prednisone maintenance dosing only

Salem et al, Ann Surgery, 1994:

- minor surgery (hernia) = 25-50 mg HC x 1 d
- moderate (chole, TAH) = 50 -100 mg HC/d x 1-2
- major (Whipple, CABG) = 100-150 mg HC/d x 2-3 d

References

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