

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

ADRENAL INSUFFICIENCY OF CRITICAL ILLNESS

SUMMARY

Critically ill patients are at risk for the development of adrenal insufficiency of critical illness (AICI). This may present as hypotension, unresponsiveness to catecholamine infusions, and/or ventilator dependence. Such patients may benefit from administration of exogenous steroids to restore their hemodynamic stability. Critically ill patients who were on chronic steroid therapy prior to injury or illness may also require steroid supplementation.

RECOMMENDATIONS

- **Level 1**
 - **Adrenal insufficiency of critical illness (AICI) should be suspected in high-risk critically ill patients with a random serum cortisol level < 20 mcg/dL.**
- **Level 2**
 - **Consider AICI and obtain a serum cortisol level in any critically ill patient who demonstrates hypotension, refractory shock, hypoglycemia, persistent systemic inflammation, and/or marked eosinophilia.**
 - **When AICI is present, initiate steroid replacement using:**
 - **Hydrocortisone 50 mg IV q 6hrs OR 100 mg IV q 8 hrs**
 - **Fludrocortisone 50 mcg PO q day x 7 days**
- **Level 3**
 - **For patients on steroid therapy for ≤7 days, steroid weaning is not necessary.**
 - **For patients on steroid therapy for >7 days, wean steroid replacement by 25-50% per day as tolerated by the patient's response.**

INTRODUCTION

Cortisol is vitally important to the maintenance of vascular tone, endothelial integrity, vascular permeability, and total body water distribution. It also potentiates the vasoconstrictor actions of both endogenous and exogenous catecholamines. Appropriate activation of the hypothalamic-pituitary-adrenal (HPA) axis in the critically ill patient is essential to stress adaptation and maintenance of homeostasis. Common causes of adrenal insufficiency in the critical care setting include infection, systemic inflammation, previous glucocorticoid use, and sepsis (1).

While the incidence of AICI in the critically ill has been underappreciated, the detrimental impact of such dysfunction is well recognized. AICI may be characterized by any of the following findings with delayed weaning from mechanical ventilation and hypotension refractory to fluids and vasopressors being most common (1-3):

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

- Hypotension
- Unresponsiveness to catecholamine infusions
- Ventilator dependence
- Abdominal or flank pain
- High fever with negative cultures and unresponsive to antibiotic therapy
- Unexplained mental changes (i.e., apathy or depression)
- Electrolyte abnormalities (hypoglycemia, hyponatremia, hyperkalemia)
- Neutropenia, eosinophilia

Diagnostic criteria for AICI in the critically ill are not well established, but evidence suggests that modifications from standard testing are warranted. A cortisol level obtained in the presence of severe endogenous stress (hypotension, shock, sepsis) evaluates the entire HPA axis and can be considered superior to traditional ACTH stimulation testing. Random serum cortisol levels that are < 20 mcg/dL are sufficient to diagnose AICI in such patients (4).

LITERATURE REVIEW

Barquist and Kirton prospectively evaluated 1054 trauma, general surgery, urology, and OB/GYN patients requiring intensive care unit admission over a 9-month period (2). They defined adrenal insufficiency as either a baseline cortisol level of < 15 mcg/dL regardless of stimulated cortisol levels OR a 30-minute post-stimulation cortisol level of ≤ 25 mcg/dL. Of the 1054 admissions, 7 patients (0.66%) were diagnosed as adrenally insufficient with an in-hospital mortality rate of 57%. Data were further stratified by age and ICU length of stay (Class II) (2).

<u>Patient Population</u>	<u>AICI (%)</u>
All ICU admissions	0.66
ICU LOS < 14 days	0.1
ICU LOS > 7 days	3.3
ICU LOS > 14 days	6.0
Age > 55 yrs	1.7
Age > 55 yrs, ICU LOS > 7 days	6.9
Age > 55 yrs, ICU LOS > 14 days	11.0

Schroeder et al. prospectively examined the HPA axis in surgical intensive care patients with severe sepsis. An IV bolus of human CRH was administered to test response to cortisol in survivors and nonsurvivors. Baseline cortisol levels in those with severe sepsis were lower in nonsurvivors (10.3 mcg/dL) than in survivors (16.8 mcg/dL). Nonsurvivors were also found to have an impaired response to CRH stimulation, which may reflect endocrine dysfunction in patients with severe sepsis (Class II) (5).

Schein and colleagues measured plasma cortisol concentrations in patients with septic shock (6). Levels were found to be highly variable with a median value of 51 mcg/dL (range 16-400 mcg/dL). Only 8% of patients had a serum cortisol concentration < 25 mcg/dL (Class II). Additional data demonstrate that cortisol levels are elevated in septic shock (7).

A review by Cooper et al. suggested a new definition for AICI consisting of a baseline cortisol of < 15 mcg/dL. They postulated that AICI was highly unlikely if the random serum cortisol was > 34 mcg/dL and likely if < 15 mcg/dL. For cortisol levels falling between these limits, further evaluation using 250 mcg of ACTH was recommended (12).

The use of hydrocortisone and fludrocortisone in patients with septic shock and adrenal insufficiency was examined by Annane et al. Study patients were defined as having septic shock with a systolic blood pressure ≤ 90 mm Hg for more than one hour despite fluid and vasopressor therapy. The investigators

found that seven days of treatment with low dose steroids significantly reduced the risk of death in nonresponders to the corticotropin test, as well as in the overall treatment population, which included corticotropin responders. There was no significant increase in adverse events in the steroid group (Class I). (8)

The CORTICUS trial, performed by Sprung et al., compared hydrocortisone 50 mg IV every 6 hours versus placebo in patients with septic shock who did (50.9%) and did not (46.7%) have a response to corticotropin (9). A response to corticotropin was defined as an increase of > 9 mcg/dL after administration of 250 mcg Cosyntropin®. After day five, hydrocortisone was gradually tapered until discontinuation on day 12. At 28 days, there was found to be no significant difference in mortality between groups. There were a similar proportion of patients with shock reversal, but a significantly shorter time to reversal in the hydrocortisone group in all patient populations. The use of the ACTH test did not predict faster shock resolution. A post-hoc analysis showed an increased rate of death in patients receiving etomidate (20.3% vs 18.1%). An increased incidence of super-infections (new episodes of sepsis or septic shock within 48 hours of drug initiation) was seen in the hydrocortisone group, as well as increased rates of hyperglycemia and hypernatremia. Due to the weaning schedule over 7 days, patients were exposed to hydrocortisone for a longer duration than seen in previous trials, which may have contributed to the increased incidence of adverse events (Class I) (8,9).

Case reports by Albert et al. describe a possible association between high-dose fluconazole and adrenal insufficiency in critically ill patients (10). Although impaired steroidogenesis is well described with ketoconazole, it has not been associated with fluconazole administration. However, higher doses are now commonly used due to the emergence of resistant *Candida* strains. The authors suggest that although their data are preliminary and anecdotal, the possibility of adrenal insufficiency in symptomatic patients on high-dose fluconazole therapy should be investigated (Class III) (10).

According to a retrospective study in critically injured patients by Cotton et al., exposure to etomidate may increase the risk of adrenal insufficiency (11). Etomidate inhibits 11- β -hydroxylase which results in blockage of adrenal cortisol production for 4-8 hours in the general population, and up to 24 hours in the ICU or elderly population. In light of this trial and results of the CORTICUS trial post-hoc analysis, patients receiving etomidate for rapid sequence intubation may be at greater risk of adrenal insufficiency (Class III) (11).

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS TESTING

If AICI is suspected in an adequately stressed ICU patient, obtain a random serum cortisol level. There is no need to wait until morning since diurnal variation is lost in the critically ill. A random level of < 20 mcg/dL in the presence of hemodynamic instability is diagnostic of AICI and glucocorticoid replacement therapy should be initiated. In patients with indeterminate cortisol levels (20-35 mcg/dL), AICI should be considered and glucocorticoid replacement therapy initiated based upon the patient's clinical condition and severity of illness. Patient outcomes have not been shown to be affected by response to ACTH testing; thus, it is not recommended in this setting. Cortisol levels > 35 mcg/dL are sufficient to confirm adequate adrenal function (8,9,13).

GLUCOCORTICOID REPLACEMENT THERAPY

If AICI is detected, patients should be immediately started on corticosteroid replacement therapy. Dexamethasone is no longer recommended secondary to its prolonged suppression of the HPA axis and offers no benefit in the absence of an ACTH stimulation test (14). Glucocorticoid administration during stress should be based upon the magnitude of the stress and the known glucocorticoid production rate associated with it (12).

Mineralocorticoid replacement is seldom necessary in the acute setting, but electrolyte and fluid status should be followed closely. Whereas patients who are found to be adrenally insufficient will require full adrenal replacement therapy, patients who have been on steroid therapy chronically do not necessarily need full replacement dosages. Further, studies have demonstrated that steroid replacement therapy

does not need to be continued for weeks to months as has historically been performed. Suggested dosages and durations of therapy for steroid replacement are listed in Tables 1 and 2.

STEROID WEANING

Once the patient is stable and no longer in need of vasopressor therapy, steroids may be discontinued or tapered. Suppression of the HPA-axis can occur with the long-term administration of systemic corticosteroids. This results in a decrease in endogenous ACTH secretion. Suppression increases with increasing dose and duration of therapy. Less potent corticosteroids such as hydrocortisone are not as likely to cause suppression as more potent agents such as methylprednisolone or dexamethasone. Steroid therapy for less than 7 days is unlikely to cause clinically significant HPA-axis suppression (15). Trials have successfully treated patients for 7-10 days with no gradual dosage decrease and no increase in adverse events (8,16). Tapering therapy results in an increased duration of treatment that may increase the incidence of adverse events (9). For patients on steroid therapy for less than or equal to 7 days, steroid weaning is not necessary. For patients on steroid therapy for greater than 7 days, the dose should be decreased by 25-50% per day as tolerated by the patient's hemodynamic status.

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Table 1. Recommendations for Steroid Replacement Therapy (12)

Indications	Total Daily Dosage	Duration
Minor Surgical Stress • Inguinal herniorrhaphy • Breast biopsy • Laparoscopic cholecystectomy	Hydrocortisone 10 mg IV q 8 hours	If procedure is uncomplicated, patient may resume preoperative steroid dose on POD # 1
Moderate Surgical Stress • Open cholecystectomy • Fem-pop bypass • Total joint replacement • Abdominal hysterectomy	Hydrocortisone 25 mg IV q 8 hours	If procedure is uncomplicated, patient may resume preoperative steroid dose on POD # 2
Major Surgical Stress • Pancreaticoduodenectomy • Major trauma • Sepsis • ARDS	Hydrocortisone 100 mg IV q 8 hours	If procedure is uncomplicated, patient may resume preoperative steroid dose on POD # 3

Table 2. Corticosteroid Equivalencies

Drug	Equivalent Dose (mg)	Route of Administration	Relative Anti-inflammatory Potency	Relative Mineralocorticoid Potency	Half-life (hrs)
Betamethasone	0.6-0.75	IM,IV,PO	20-30	0	36-54
Dexamethasone	0.75	IM,IV,PO	25-30	0	36-54
Hydrocortisone	20	IM,IV,PO	1	2	8-12
Methylprednisolone	4	IM,IV,PO	5	0	18-36
Prednisolone	5	PO	4	1	18-36
Prednisone	5	PO	4	1	18-36