Surgical Critical Care.net

CRITICAL ILLNESS-RELATED CORTICOSTEROID INSUFFICIENCY

Evidence Based Medicine Guideline

Primary Author: Emily Helmick DO
Co-Authors: Jason Miller; Alexis Schlosser, MD; Kara Birrer, PharmD; Evan Westrick, MD
Editors: Michael L. Cheatham MD, Chadwick Smith MD
Approved: 06/21/2022 Previous Revision dates: 04/03/2001, 03/29/2005, 10/24/2009

SUMMARY
Critically ill patients are at risk for Critical Illness-Related Corticosteroid Insufficiency (CIRCI) (previously known as "Relative Adrenal Insufficiency" and "Adrenal Insufficiency of Critical Illness"). This may present as hypotension, unresponsiveness to catecholamine infusions, and/or ventilator dependence. Such patients may benefit from administration of exogenous steroids to restore hemodynamic stability until their adrenal glands recover sufficient function. Critically ill patients on chronic steroid therapy prior to injury or illness may also require steroid supplementation.

RECOMMENDATIONS

- **Level 1**
  - **Consider CIRCI and obtain a random serum cortisol level in any critically ill patient who demonstrates hypotension, refractory shock, hypoglycemia, persistent systemic inflammation, and/or marked eosinophilia.**
- **Level 2**
  - **When CIRCI is present and when clinically indicated, initiate steroid replacement using hydrocortisone 50 mg IV q6 hours.**
  - **Testing should not delay treatment in unstable patients where CIRCI is strongly suspected.**
  - **CIRCI is strongly suspected with a random serum cortisol of <10 mcg/dL and can be relatively ruled out with a random serum cortisol >34 mcg/dL.**
  - **Consider stimulation testing with 250 mcg ACTH with values between 10-34 mcg/dL in patients who can tolerate delayed treatment.**
    - **CIRCI should be suspected in critically ill patients with a delta serum cortisol of <9 mcg/dL.**
- **Level 3**
  - **For patients receiving steroid therapy for ≤ 7 days, steroid weaning is not necessary.**
  - **For patients receiving steroid therapy for >7 days, wean steroid replacement by 25-50% per day as tolerated by the patient's hemodynamic response.**
  - **Stimulation testing with 1 mcg cosyntropin may be more appropriate to avoid false negative results.**

INTRODUCTION

Serum 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 (1-3).

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.

While the incidence of CIRCI in the critically ill has been under appreciated, the detrimental impact of such dysfunction is well recognized. CIRCI 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 (1-4):

- 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
- Nausea, vomiting

Diagnostic criteria for CIRCI in the critically ill are not well established, but evidence suggests that modifications from standard testing are warranted. Random serum cortisol levels, free cortisol, and delta cortisol (change in baseline cortisol after ACTH stimulation) are all methods to evaluate for CIRCI. Free cortisol level testing is not available at most hospitals. Most experts will agree that a random serum cortisol <10 mcg/dL is low and >34 mcg/dL is high. Controversy of how to interpret levels between 10 and 34 mcg/dL exists (5,6).

Hypothalamic-pituitary-adrenal axis testing

If CIRCI 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 < 10 mcg/dL in the presence of hemodynamic instability is diagnostic of CIRCI and glucocorticoid replacement therapy should be initiated. In patients with indeterminate random cortisol levels (10-34 mcg/dL), a delta cortisol level is diagnostic. However, the adrenocorticotrophic hormone stimulation test should not be used to identify those patients with septic shock who should receive glucocorticoids (6,7). If the patient can clinically tolerate further testing before treatment, this may be performed (8). To perform a stimulation test for CIRCI when the initial cortisol level is indeterminate (random cortisol between 10-34 mcg/dL), a second cortisol level is drawn 60 minutes after the administration of 250 mcg of intravenous cosyntropin. The T60 cortisol minus the T0 cortisol results in the delta value. Cortisol levels > 34 mcg/dL and a delta of >9 mcg/dL are sufficient to confirm adequate adrenal function (7,8). Arguments have been made that 250 mcg is a supraphysiological dose and can lead to misdiagnosing true adrenal insufficiency. Studies have been performed that suggest using 1 mcg of cosyntropin is sufficient to stimulate cortisol production (9).

Glucocorticoid replacement therapy

If CIRCI is detected, patients should be immediately started on corticosteroid replacement therapy. Dexamethasone is not recommended secondary to its prolonged suppression of the HPA axis and offers no benefit in the absence of an ACTH stimulation test (10). Glucocorticoid administration during stress should be based upon the magnitude of the stress and the known glucocorticoid production rate associated with it (11).

Mineralocorticoid replacement is seldom necessary in the acute setting, but there are recommendations that suggest mineralocorticoid replacement should begin when the patient is tolerating hydrocortisone doses of 50 mg/24 hours (12). 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 (12). Trials have successfully treated patients for 7-10 days with no gradual dosage decrease and no increase in adverse events (13,14). Tapering therapy results in an increased duration of treatment that may increase the incidence of adverse events (11). 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. In addition, beginning mineralocorticoid therapy can be considered (9).

LITERATURE REVIEW

In a meta-analysis by Rygard et al., randomized controlled trials evaluating 7,297 patients with septic shock were reviewed in the context of low-dose corticosteroids vs. placebo in patients with septic shock (8). Their measured outcomes included mortality, adverse events, and durations of shock, mechanical ventilation, and ICU length of stay. They found that short- and long-term mortality were unaffected by low-dose corticosteroids, but durations of shock, mechanical ventilation, and ICU stay are reduced.

Much controversy still exists regarding a single test that can reliably diagnose CIRCI. The Society of Critical Care Medicine and European Society of Intensive Care Medicine recognize that plasma cortisol of <10 mcg/dl or delta cortisol of <9 mcg/dl after 250 mcg cosyntropin administration may identify CIRCI. For patients with septic shock unresponsive to fluids and moderate-to-high-dose vasopressor therapy, they agree upon IV hydrocortisone <400 mg/day for >3 days at full dose. The consensus statements suggest against corticosteroids for patients with major trauma (15).

Alternatively, different metrics have been proposed to assess relative adrenal insufficiency by comparing low-dose and conventional corticotropin tests by Siraux et al (16). They evaluated 46 consecutive patients with septic shock and measured serum cortisol levels at 0, 30, 60, and 90 min after 1 mcg corticotropin vs. 250 mcg corticotropin test. Nonresponders to the low-dose test had a lower overall survival than responders to both tests. The response to the combined low-dose and high-dose tests was an independent predictor of survival whereas basal or maximal cortisol levels were not predictors of survival. Thus, a new group was identified with the low-dose test that would have otherwise been missed by the high-dose test.

Karir et al. examined the practice variability in the assessment and treatment of CIRCI at their tertiary-care academic institution (17). They found the treatment and evaluation of CIRCI to be inconsistent. Many patients with vasopressor dependent septic shock did not receive either treatment or evaluation for CIRCI, and patients who did not meet the current criteria were being evaluated and/or treated for CIRCI.

Burry et al. examined the incidence of CIRCI in patients with septic shock using a 1 mcg corticotropin (ACTH) test to describe their clinical outcomes (18). They retrospectively identified 219 consecutive patients with septic shock assessed for CIRCI with a 1 mcg ACTH test. Standardized testing involved plasma cortisol measurements at baseline (T0) and at 30 min (T30) and 60 min (T60) after ACTH administration. The maximal increase in cortisol (delta max) was calculated as the difference between T0 and the highest cortisol value at T30 or T60. CIRCI was defined as a delta max <9 mcg/dL after ACTH administration. Patients with CIRCI had similar ICU mortality whether or not they received corticosteroids (46% vs. 25% p=0.17). The highest mortality rates were observed in patients with high baseline cortisol and in those who failed to respond appropriately to ACTH. The administration of corticosteroids was not associated with a reduction in mortality. It also was proposed that false negative results were avoided compared to the 250 mcg dose of ACTH.

Molenaar et al. set out to study the value of free vs. total cortisol levels in assessing relative adrenal insufficiency during CIRCI (19). This single center prospective study included 49 septic and 69 non-septic patients with treatment-insensitive hypotension in whom an adrenocorticotropic hormone (ACTH) test (250 mcg) was performed. They found that subnormal increments in total cortisol upon ACTH suffice in assessing relative adrenal insufficiency, particularly in sepsis.

Marik et al. published a consensus statement that coined the term critical illness-related corticosteroid insufficiency (CIRCI) (20). They defined adrenal insufficiency in critically ill patients as a delta total serum cortisol of <9 mcg/dL after adrenocorticotrophic hormone (250 mcg/dL) administration or a random total cortisol of <10 mcg/dL. They also stated that the stimulation test should not be used to identify those patients with septic shock or acute respiratory distress syndrome who should receive glucocorticoids.

Yang et al. investigated the prevalence, time course, and effect of CIRCI on the outcome of critically ill patients with multiple injuries (21). They prospectively found that the CIRCI patients with a delta cortisol of less than 9 mcg/dL had a significantly higher 28-day mortality (39.3%) compared with those with a baseline cortisol level of less than 10 mcg/dL (10%) and non-CIRCI patients (6.3%).

Schroeder et al. prospectively examined the HPA axis in surgical intensive care patients with severe sepsis (13). An IV bolus of human corticosteroid releasing hormone (CRH) was administered to test response to cortisol in survivors and non-survivors. 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.

Cooper et al. suggested a new definition for CIRCI consisting of a baseline cortisol of < 15 mcg/dl (14). They postulated that CIRCI 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.

The use of hydrocortisone and fludrocortisone in patients with septic shock and adrenal insufficiency was examined by Annane et al (22). Study patients were defined as having septic shock with a systolic blood pressure ≤ 90 mmHg 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.

If the patient is clinically stable, tapering of hydrocortisone to replacement doses can be initiated usually within 24–72 hrs of stabilization (11).

The CORTICUS trial, performed by Sprung et al., compared hydrocortisone 50 mg IV every 6 hours vs. placebo in patients with septic shock who did (50.9%) and did not (46.7%) have a response to corticotropin (11). A response to corticotropin was defined as in 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 (23). The recommended initial dosing for patients in CIRCI with a large systemic inflammatory response is 200 mg/24 hours, most commonly divided into 4 doses. A dose of 100-300 mg at one time is considered a large stress dose and most patients do not need this dose (24).

According to a retrospective study in critically injured patients by Cotton et al., exposure to etomidate may increase the risk of adrenal insufficiency (25). 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.

More recent studies have hinted at a small improvement in mortality. Rochwerg et al. published a systematic review and meta-analysis addressing the efficacy and safety of corticosteroids in the context of sepsis in critically ill patients (26). A total of 10,194 patients from 42 RCTs were included. There was a small reduction or no reduction in the relative risk of death within the first month (RR 0.93; 95% CI, 0.84-1.03; 1.8% ARR; 95% CI, 4.1% reduction to no effect). There were small reductions in ICU length of stay and hospital stay. Additionally, they found better recovery from shock and improvement in SOFA scores. Adverse events were also reviewed and noted that risks of hypernatremia, hyperglycemia, and neuromuscular weakness may be increased with corticosteroid use.

REFERENCES

1. Zaloga GP, Marik P. Hypothalamic-pituitary-adrenal insufficiency. *Crit Care Clinics* 2001;17(1):25-41.
2. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). *Intensive Care Med* 2017; 43(12):1781-1792.
3. Barquist E Kirton O. Adrenal insufficiency in the surgical intensive care unit patient. *J Trauma* 1998; 41(1):27-31.
4. Lamberts SWJ, Bruining HA, deJong FH. Drug therapy: Corticosteroid therapy in severe illness. *N Engl J Med* 1997; 337(18):1285-1292.
5. Cohen J, Venkatesh B. Relative adrenal insufficiency in the intensive care population; background and critical appraisal of the evidence. *Anaesth Intensive Care* 2010; 38(3):425-436.
6. Moraes RB, Friedman G, Toneietto et al. Comparison of low and high dose cosyntropin stimulation tests in the diagnosis of adrenal insufficiency in septic shock patients. *Horm Metab Res* 2012; 44(4):296-301.
7. Carella MJ, Srivastava LS, Gossain VV, Rovner DR. Hypothalamic-pituitary-adrenal function one week after a short burst of steroid therapy. *J Clin Endocrinol Metab* 1993; 76(5):1188-91.
8. Rygard SL, Butler E, Granholm A, Moller MH, Cohen J, Finfer S et al. Low-dose corticosteroids for adult patients with septic shock: a symptomatic review with meta-analysis and trial sequential analysis. *Intensive Care Med* 2018; 44(7):1003.
9. Naykky Singh Ospina, Alaa Al Nofal, Irina Bancos, Asma Javed, Khalid Benkhadra, Ekta Kapoor, Aida N. Lteif, Neena Natt, M. Hassan Murad, ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis, *J Clin Endocrin Metab* 2016; 101(2):427–434.
10. Cotton BA, Guillamondegui OD, Fleming SB, Carpenter RO, Patel SH, Morris JA et al. Increased risk of adrenal insufficiency following etomidate exposure in critically injured patients. Arch Surg 2008; 143(1):62-67.
11. Sprung CL, Annane D, Kah D, Moreno R, Singer M, Freivogel K et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358(2):111-124.
12. Dineen R, Thompson CJ, Sherlock M. Adrenal crisis: prevention and management in adult patients. *There Adv Endocrinol Metab* 2019; 10:2042018819848218.
13. Schroeder S, Wichers M, Klingmuller D, Hofer M, Lehmann LE, von Spiegel T, et al. The hypothalamic-pituitary-adrenal axis of patients with severe sepsis: Altered response to corticotropin-releasing hormone. *Crit Care Med* 2001; 29(2):310-16.
14. Cooper M.S., Stewart P. Corticosteroid Insufficiency in Acutely Ill Patients. *N Engl J Med* 2003; 348:727-734.
15. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med* 2017; 43(12):1751-1763.
16. Siraux V, De Backer D, Yalavatti G, Melot C, Gervy C, Mockel J, Vincent JL. Relative adrenal insufficiency in patients with septic shock: comparison of low-dose and conventional corticotropin tests. *Crit Care Med* 2005; 33(11):2479-86.
17. Karir, V. Cooke, CR. Andersson, L. et al. Practice variability in the assessment and treatment of critical illness-related corticosteroid insufficiency. *J Crit Care* 2010; 25(2):363.
18. Burry L, Little A, Hallett D, Mehta S. Detection of critical illness-related corticosteroid insufficiency using 1 mcg adrenocorticotropic hormone test. *Shock* 2013; 39(2):144-148.
19. Molenaar N, Johan G, et al. Assessing adrenal insufficiency of corticosteroid secretion using free versus total cortisol levels in critical illness. *Intensive Care Med* 2011; 37(12):1986-1993.
20. Marik PE, Pastores SM, Anane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American college of Critical Care Medicine. *Critical Care Medicine* 2008; 36:1937-1949.
21. Yang Y, Liu L, Jiang D, et al. Critical illness-related corticosteroid insufficiency after multiple traumas: a multicenter, prospective cohort study. *J Trauma Acute Care Surg* 2014; 76(6):1390-1396.
22. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288(7):862-871.
23. Toma A, Stone A, Green RS, Gray S. Steroids for patients in septic shock: the results of the CORTICUS trial. *CJEM* 2011 12(4):273-276.
24. Briegel J, Kilger E, Schelling G. Indications and practical use of replacement dose of corticosteroids in critical illness. Curr Opin Crit Care 2007; 13:370–375.

25. Cotton BA, Guillamondegui OD, Fleming SB, Carpenter RO, Patel SH, Morris JA et al. Increased risk of adrenal insufficiency following etomidate exposure in critically injured patients. *Arch Surg* 2008; 143(1):62-67.
26. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, D'Aragon F et al. Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. *Crit Care Med* 2018; 46(9):1411-1420.

Table 1: Recommendations for Steroid Replacement Therapy (15)

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 50 mg IV q 6 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