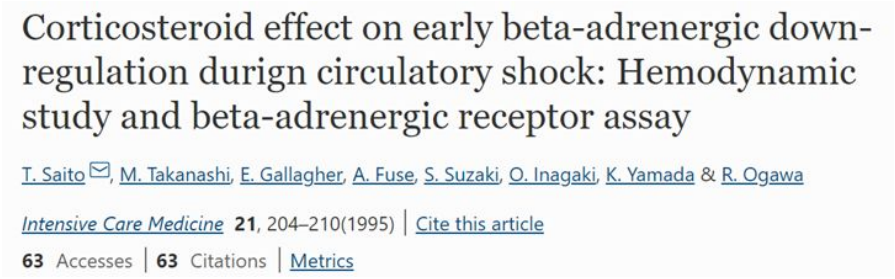
Critical illness-related corticosteroid insufficiency (CIRCI)

Glucocorticoids:

- regulate metabolic, cardiovascular (vascular tone), immune, and behavioral processes.
- The physiological effects of glucocorticoids are mediated by a cytosolic protein, the glucocorticoid receptor (GR).
- Widely distributed throughout the brain and peripheral tissues.
- Steroids enter the cells by passive diffusion
- Signals from body (cytokine release, tissue injury, pain, hypotension, hypoglycemia, hypoxemia) are sensed by CNS and transmitted to the hypothalamus/
- Hypothalamus integrates a response → CRH → ACTH secretion → cortisol secretion
- Glucocorticoids play a prominent role in regulating the magnitude and duration of HPA axis activation.
- Decreased cortisol results in increased CRH-ACTH release, whereas elevated levels inhibit its secretion.
- Cortisol circulates 90% bound to corticosteroid-binding globulin. Unbound form is physiologically active.
- Hemodynamic benefits of cortisol:
    - Up-regulate synthesis of β-adrenergic receptors
    - Increase density of β-adrenergic receptors
    - Prevents β adrenergic desensitization



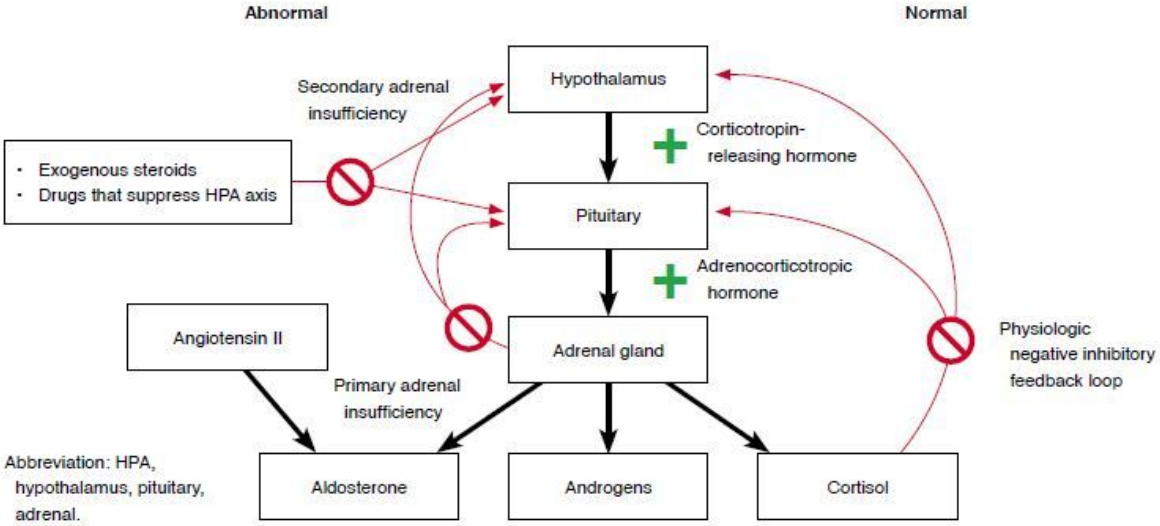
Corticosteroid effect on early beta-adrenergic down-regulation durign circulatory shock: Hemodynamic study and beta-adrenergic receptor assay

T. Saito, M. Takanashi, E. Gallagher, A. Fuse, S. Suzaki, O. Inagaki, K. Yamada & R. Ogawa

Intensive Care Medicine **21**, 204–210(1995) | Cite this article

63 Accesses | **63** Citations | Metrics

Figure 1. Hypothalamic-Pituitary-Adrenal Axis and Feedback Loops



› Intensive Care Med. 2018 Apr;44(4):474-477. doi: 10.1007/s00134-017-4951-5. Epub 2017 Oct 31.

Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017

Definition of CIRCI

- Impairment of the hypothalamic pituitary axis (stress response) during critical illness.
- Characterized by dysregulated systemic inflammation resulting from inadequate intracellular glucocorticoid-mediated anti-inflammatory activity for the severity of the patient's critical illness (sepsis or septic shock)
- Associated w increasing levels of biological markers of inflammation and coagulation over time, morbidity, length of ICU stay and mortality.

Pathogenesis

- increasingly being recognized in human critically ill patients with systemic inflammation associated with sepsis, ARDS/ALI, severe hepatic disease, trauma, acute myocardial infarction, or following cardiopulmonary bypass.

- Insufficient adrenal and/or pituitary function has been identified in dogs with sepsis/septic shock, trauma, gastric volvulus-dilatation, neoplasia, and genetic mutation of the multidrug resistance gene ABCB1 (MDR1)
- Insufficient adrenal function has been identified in cats with neoplasia (lymphoma), trauma, and sepsis/septic shock
- Not been documented in stable patients
- HPA dysfunction in CIRCI is relative and transient. The adrenal glands produce and secrete cortisol, but the quantity is inadequate for the degree of physiological stress or illness. Following recovery from critical illness, HPA dysfunction resolves.
- Pathogenesis of CIRCI in dogs is unknown, most likely multifactorial
- Possible mechanisms for the development of CIRCI include:

  1. Proinflammatory cytokine mediated inhibition of CRH and ACTH secretion resulting in decreased cortisol production.

  2. Proinflammatory cytokine (TNF) mediated glucocorticoid receptor dysfunction and reduction in receptor numbers. This results in a reduced ability of cells to respond appropriately to cortisol.

  3. Corticostatin-mediated ACTH receptor antagonism. Corticostatin, a peptide produced by immune cells, impairs adrenocortical function by competing with ACTH and binding to its receptor.

  4. Leptin-mediated inhibition of the HPA axis during stress or illness.

  5. Tissue resistance to the actions of glucocorticoids (decreased glucocorticoid activity while serum cortisol concentrations appear appropriate). Several factors:
     - decreased access of cortisol to tissues secondary to a reduction of circulating cortisol-binding globulin concentrations
     - increased cytokine (IL-2, IL-4 and IL13)-mediated conversion of cortisol (active) to cortisone (inactive)

  6. Disruption of pituitary and/or adrenal gland function secondary to extensive tissue destruction of these organs by infection, infarction, hemorrhage, or thrombosis

  7. ABCB1 gene mutation resulting in the lack of P-glycoprotein, the ABCB1 gene product, at the blood–brain barrier:

     a) P-glycoprotein normally restricts the entry of cortisol into the brain, limiting cortisol's feedback inhibition of CRH and ACTH.

     b) In ABCB1 mutant dogs, P-glycoprotein is not present, allowing greater concentrations of cortisol to be present within the brain, thus augmenting feedback inhibition of the HPA axis and, ultimately, impedance of sufficient cortisol secretion.

     c) Thus, the mutation may lead to the inability to appropriately respond to critical illness and stress.

Clinical Signs

- Vague and nonspecific, (depression, weakness, fever, vomiting, diarrhea, and abdominal pain). Additionally, clinical signs of the underlying disease process responsible for CIRCI (e.g., septic shock, hepatic disease, trauma, etc.) can mask the clinical features of CIRCI.
- The most common clinical abnormality associated with CIRCI in human patients with septic shock is hypotension that is refractory to fluid resuscitation and requiring vasopressor therapy.

Diagnosis

- CIRCI should be considered as a differential diagnosis in all critically ill patients requiring vasopressor support.
- Hyponatremia and hyperkalemia are uncommon in humans with CIRCI, and to date, have not been reported in vet med patients with CIRCI
- Human patients with CIRCI typically have **normal or elevated basal serum cortisol concentrations and a blunted response to ACTH stimulation.** Similar findings have been documented in critically ill dogs with sepsis/septic shock, trauma, and gastric dilatation-volvulus as well as in critically ill cats with sepsis/septic shock, trauma, and neoplasia.
- No consensus exists regarding the identification of patients with CIRCI in human or vet med. A variety of tests have been advocated: measurement of a random basal cortisol concentration, ACTH-stimulated cortisol concentration, delta cortisol concentration (i.e., the difference obtained when subtracting basal from ACTH-stimulated cortisol concentration), the ratio of cortisol concentration to that of endogenous ACTH, etc

- The optimal way to identify critically ill veterinary patients with CIRCI has yet to be determined:

1. Evaluation of adrenal function typically involves performance of an **ACTH stim test**:
    a. Most commonly used protocol in dogs: IV administration of 5µg cosyntropin/kg up to a maximum of 250µg.
    b. In cats, IV administration of 125µg of cosyntropin/cat
    c. Serum or plasma is obtained for measurement of cortisol concentration before and 60min after ACTH administration in both dogs and cats.
2. The standard doses of cosyntropin (5µg/kg in dogs and 125µg/cat) currently used in ACTH stim testing are greater than that necessary to produce maximal adrenocortical stimulation in healthy small animals:
    a. Doses as low as 0.5µg/kg in healthy dogs and 5µg/kg in healthy cats have been shown to induce maximal cortisol secretion by the adrenal glands.
    b. The use of higher doses may be supraphysiologic and may mask subtle decreases in adrenal gland reserve and hinder identification of dogs and cats with CIRCI.
3. Low-dose (0.5µg/kg IV) ACTH stim testing has been compared to standard-dose (5µg/kg IV) ACTH stim testing in critically ill dogs:

a. In the study, every critically ill dog that was identified by the standard-dose ACTH stim test to have insufficient adrenal function (i.e., ACTH-stimulated serum cortisol concentration below the reference range or <5% greater than the basal cortisol concentration) was also identified by the low-dose test.
b. Additional dogs were identified with adrenal insufficiency by the low-dose ACTH stimulation test, which were not identified by the standard-dose test.
c. Thus, ACTH administered at a dose of 0.5µg/kg IV appears to be at least as accurate in determining adrenal function in critically ill dogs as the IV administration of ACTH at 5µg/kg. The low-dose ACTH stimulation test may even be a more sensitive diagnostic test in detecting patients with insufficient adrenal gland function than the standard-dose test.

4. **Serum free cortisol** concentration:
    a. Assays that measure cortisol concentration typically measure total hormone concentration (i.e., serum free cortisol concentration plus a protein-bound fraction).
    b. However, the serum free cortisol fraction is believed to be responsible for the physiologic function of the hormone. Therefore, serum free cortisol concentrations may be a more precise predictor of adrenal gland function.
    c. The relationship between free and total cortisol varies with serum protein concentration:
        1) In human critically ill patients, cortisol-binding globulin and albumin concentrations can decrease by approximately 50% due to catabolism at inflammatory sites and inhibition of hepatic synthesis via cytokines
        2) Therefore, serum total cortisol concentration may be falsely low in hypoproteinemic patients, resulting in overestimation of CIRCI.
        3) Serum free cortisol concentration is less likely to be altered in states of hypoproteinemia. Consequently, serum total cortisol concentrations may not accurately represent the biological activity of serum free cortisol during critical illness.
    d. Several human studies suggest that serum free cortisol concentrations are a more accurate measure of circulating glucocorticoid activity than total cortisol concentrations.
    e. Canine and feline studies are lacking and the ability to measure serum free cortisol concentration is not widely available:
        1) Serum free and total cortisol concentrations have been compared in one study of critically ill dogs
        2) Fewer critically ill dogs with adrenal insufficiency (i.e., an ACTH-stimulated serum cortisol concentration below the reference range or <5% greater than the basal cortisol concentration) were identified by serum free cortisol concentration than serum total cortisol concentration. However, basal and ACTH-stimulated serum total cortisol concentrations were not lower in hypoproteinemic patients when compared to normoproteinemic patients.
5. **Delta cortisol concentration** has been advocated in both human and veterinary medicine:

a. A study in human patients with septic shock found that a basal cortisol concentration ≤34µg/dL (938nmol/L) combined with a delta cortisol concentration ≥9 µg/dL (250nmol/L) in response to a 250µg/person ACTH stimulation test were associated with a favorable prognosis:

1) Additionally, a basal cortisol concentration >34µg/dL combined with a delta cortisol concentration <9µg/dL were associated with a poor prognosis.

2) Since these values successfully predicted outcome, a delta cortisol concentration of <9µg/dL is frequently used as a diagnostic criterion for CIRCI in human critically ill patients.

b. Veterinary studies have also assessed delta cortisol concentrations as a criterion for diagnosing CIRCI in critically ill patients:

1) One study found that septic dogs with delta cortisol concentrations ≤3µg/dL (83nmol/L) after a 250µg/dog ACTH stimulation test were more likely to have systemic hypotension and decreased survival.

2) Another study investigating acutely ill dogs (i.e., dogs with sepsis, trauma, or gastric volvulus-dilatation) found that dogs with delta cortisol concentrations ≤3µg/dL (83nmol/L) after a 5µg/kg ACTH stimulation test were more likely to require vasopressor therapy as part of their treatment plan.

3) Whether or not delta cortisol concentrations of ≤3µg/dL (83nmol/L) can be used as a criterion to diagnose all populations of veterinary critically ill patients with CIRCI has yet to be determined.

- Normal reference ranges do not exist for basal and ACTH-stimulated cortisol concentrations in critically ill dogs and cats.
- There are **three scenarios** which may indicate the presence of CIRCI in critically ill dogs:

1. Dogs with a normal or elevated basal cortisol concentration and an ACTH-stimulated cortisol concentration less than the normal reference range.
2. Dogs with a normal or elevated basal cortisol concentration and an ACTH-stimulated cortisol concentration that is <5% greater than the basal cortisol concentration (flatline response)
3. Dogs with a delta cortisol concentration ≤3µg/dL (83nmol/L).

- CIRCI appears to occur in cats. Diagnostic criteria are undetermined

J Vet Intern Med. Mar-Apr 2007;21(2):226-31. doi: 10.1892/0891-6640(2007)21[226:raiidw]2.0.co;2.

Relative Adrenal Insufficiency in Dogs With Sepsis

Jamie M Burkitt [1], Steve C Haskins, Richard W Nelson, Philip H Kass

Affiliations + expand

PMID: 17427381 DOI: 10.1892/0891-6640(2007)21[226:raiidw]2.0.co;2

Free article

- septic dogs with a delta cortisol 3 ug/dL following a standard 250 ug/dog ACTH stim test were more likely to be hypotensive and had decreased survival com-pared to dogs with a cortisol increase > 3 ug/dL

J Am Vet Med Assoc. 2008 Jul 1;233(1):87-95. doi: 10.2460/javma.233.1.87.

Pituitary–adrenal Function in Dogs With Acute Critical Illness

Linda G Martin [1], Reid P Groman, Daniel J Fletcher, Ellen N Behrend, Robert J Kemppainen, Valerie R Moser, Kathy C Hickey

Affiliations + expand

PMID: 18593315 DOI: 10.2460/javma.233.1.87

- patients with a delta cortisol 3 ug/dL 1 hour after 5 ug/kg cosyn-tropin administration were more likely to be pressor-dependent than dogs with delta cortisol > 3 ug/dL

Differential Diagnosis

A. To hypotension that is poorly responsive to fluid and/or vasopressor therapy:

1. Sepsis/septic shock/systemic inflammatory response syndrome without the presence of CIRCI.
2. Absolute spontaneous hypoadrenocorticism.
3. Decompensated hypovolemic shock.
4. Cardiovascular disease:
    a. Cardiogenic shock.
    b. Overdose of vasodilator therapy.
5. Hypermagnesemia.
6. Diabetic ketoacidosis.
7. Anaphylaxis.

Treatment

- Steroids in humans:

  1. Most human protocols have used dosages of 200–300mg IV q 24h of hydrocortisone for an average 70kg person (2.9–4.3mg/kg IV q 24h). The total daily dose is typically given as either a constant rate infusion or divided and given every 6h.
  2. A human study found that repeated bolus injections of HC causes a significant increase in blood glucose that was not observed with CRI administration. As such, the

current Surviving Sepsis Campaign guidelines recommend using a CRI over repeated bolus doses for avoidance of these side effects.

- It is reasonable to start volume-resuscitated, vasopressor-dependent animals on corticosteroid therapy after performing an ACTH stim test:
  1. When the test results are available, treatment can be withdrawn in animals that responded normally to the ACTH stim test.
  2. Steroids can be continued in patients that have:
     (a) a normal or elevated basal cortisol concentration and an ACTH-stimulated cortisol concentration less than the reference range
     (b) a normal or elevated basal cortisol concentration and an ACTH-stimulated cortisol concentration that is <5% greater than the basal cortisol concentration (flat line response)
     (c) a delta cortisol concentration ≤3µg/dL (83nmol/L)
     (d) demonstrated a significant improvement in cardiovascular status within 24h of starting corticosteroid therapy.

- Dosage, duration, and type of steroid therapy are **unknown in vet med**:
  1. supplemental doses of corticosteroids at physiological to supraphysiological dosages (1 – 4.3mg/kg IV q 24h of hydrocortisone [divided into four equal doses q 6h or as a constant rate infusion], 0.25–1mg/kg IV q 24h of prednisone [divided into two equal doses]).
  2. Two case reports used HC (0.5 mg/kg IV q6hr) in a dog and dexamethasone (0.08 mg/kg, IV, q24hr) in a cat
  2. The American College of Critical Care Medicine Task force recommended **against the use of dexamethasone** for the treatment of CIRCI, because it may interfere with ACTH stimulation testing

- HPA dysfunction in CIRCI is transient, lifelong therapy is not required. Steroid dose can be tapered by 25% per day following the resolution of the critical illness. The ACTH stimulation test should be repeated following the resolution of critical illness and discontinuation of steroids.

Prognosis

- Human critically ill patients with CIRCI have a worse prognosis than those with normal HPA function:
  1. Nonsurvivors typically have low basal cortisol concentrations (<9µg/dL), very high basal cortisol concentrations (>44µg/dL or 1215nmol/L), and/or a low cortisol response to ACTH stimulation (delta cortisol concentration <9µg/dL).
  2. Prior to corticosteroid therapy, a poor cortisol response to ACTH stimulation (delta cortisol concentration <9µg/dL) is associated with poor response to vasopressor therapy.

3. In some patients, replacement therapy with corticosteroids (i.e., 200–300mg hydrocortisone or equivalent per day) improved survival without causing overt harm (e.g., infection or gastrointestinal hemorrhage).

- Prognosis is not fully known for dogs with CIRCI:

1. Delta cortisol concentrations ≤3μg/dL after ACTH stimulation in septic dogs were associated with systemic hypotension and decreased survival.

2. Acutely ill dogs (i.e., had sepsis, trauma, or gastric volvulus-dilatation) with delta cortisol concentrations ≤3μg/dL after ACTH stimulation were more likely to require vasopressor therapy.

3. Elevated basal serum cortisol and decreased basal serum thyroid concentrations at 24 and 48h after hospital admission were associated with death in dogs with parvoviral enteritis.

4. Elevated basal serum cortisol and endogenous ACTH concentrations with decreased basal serum thyroid concentrations were associated with death in dogs suffering from Babesia canis rossi babesiosis.

Case Report

Journal of Veterinary Emergency and Critical Care **17**(2) 2007, pp 197–201
doi: 10.1111/j.1476-4431.2006.00211.x

Suspected relative adrenal insufficiency in a critically ill cat

Samuel Durkan, DVM, Armelle de Laforcade, DVM, DACVECC, Elizabeth Rozanski, DVM, DACVIM, DACVECC and John E. Rush, DVM, MS, DACVIM (Cardiology), DACVECC

- A cat recovering from polytrauma developed hypotension unresponsive to intravenous fluidsupport and vasopressor therapy
- Stim test documented insufficient adrenal function
- Treatment with exogenous low-dose glucocorticoids in addition to standard therapies resulted in rapid hemodynamic and clinical improvement
- The cat ultimately recovered and was weaned from supplemental glucocorticoids

Clinical Case Reports

Open Access

CASE REPORT

Hydrocortisone therapy in a cat with vasopressor-refractory septic shock and suspected critical illness-related corticosteroid insufficiency

Simone R. R. Pisano[1], Judith Howard[1], Horst Posthaus[2], Alan Kovacevic[1] & Ivayla D. Yozova[3]

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[3]Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Palmerston North, New Zealand

- A 27-month-old female cat was presented with septic peritonitis secondary to a ruptured pyometra and subsequent pyothorax
- Vasopressor-refractory septic shock led to a suspicion of critical illness-related corticosteroid insufficiency, successfully treated with intravenous hydrocortisone

- Previous megestrol acetate administration may have played a role in the development of adrenocortical dysfunction

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Total cortisol vs plasma or serum cortisol?

- Recommend against using plasma free cortisol level rather than plasma total cortisol for diagnosis of CIRCI. Very low quantity of evidence, conditional recommendation

Is the hemodynamic response to hydrocortisone superior to stim test for diagnosis of CIRCI?

- Suggest the use of stim test rather than the hemodynamic response to hydro for diagnosis of CIRCI. Conditional recommendation, very low quality of evidence

Should steroids be administered among hospitalized adult patients with sepsis without septic shock?

- Suggest against use of steroids in patients with sepsis without septic shock. Conditional recommendation, moderate quality of evidence. HYPRESS trial.

Should steroids be administered among hospitalized adult patients with septic shock?

- Suggest using steroids in patients with shock that is not responsive to fluid and moderate to high-dose vasopressor therapy. Conditional recommendation, low quality of evidence

Recommended dose of steroids?

- Suggest long course and low dose: IV hydro <400 mg/day for 3 or more days

JOURNAL OF Veterinary Emergency AND Critical Care

Clinical Practice Review

Journal of Veterinary Emergency and Critical Care **25**(1) 2015, pp 107–112
doi: 10.1111/vec.12270

Controversies surrounding critical illness-related corticosteroid insufficiency in animals

Jamie M. Burkitt Creedon, DVM, DACVECC