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Controversies surrounding critical illness-related corticosteroid insufficiency in animals

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Abstract

Objectives – To describe the controversies surrounding critical illness-related corticosteroid insufficiency (CIRCI) and the use of hydrocortisone in critically ill patients, and to present published diagnostic and therapeutic strategies in companion veterinary species.
Etiology – Critical illness-related corticosteroid insufficiency may be due to hypothalamic-pituitary-adrenal (HPA) axis dysfunction, alterations in cortisol-plasma protein binding, target cell enzymatic changes, changes in glucocorticoid receptor (GR) function, or a combination of these or other factors present during critical illness.
Diagnosis – Appropriate tests to diagnose CIRCI are unknown. The diagnosis in people is currently based on response to treatment with hydrocortisone. There is currently no consensus on appropriate diagnostic feature(s) in veterinary species.
Therapy – Low-dose hydrocortisone is the treatment of choice for patients with CIRCI.
Prognosis – If the patient survives the critical illness, prognosis for resolution of CIRCI and hydrocortisone dependence is very good.

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Keywords: glucocorticoid, hydrocortisone, relative adrenal insufficiency, septic shock

Abbreviations

11β-HSD	11β-hydroxysteroid dehydrogenase
ACTH	adrenocorticotropic hormone
CBG	cortisol binding globulin
CIRCI	critical illness-related corticosteroid insufficiency
CRH	corticotropin releasing hormone
GR	glucocorticoid receptor
HPA	hypothalamic-pituitary-adrenal
ICU	intensive care unit
IV	intravenous
RAI	relative adrenal insufficiency

Introduction

In 1977, Sibbald reported unexpected baseline plasma cortisol concentrations with or without blunted response to synthetic adrenocorticotropin hormone (ACTH) in a subset of 26 human patients with severe sepsis.[1] Survival was not statistically evaluated, but the authors noted that only 1 of 9 patients (11%) with unexpected plasma cortisol findings survived, and that the single survivor had been treated with steroids following ACTH stimulation testing. Of the 17 septic patients with expected cortisol concentrations and ACTH responsiveness, 8 survived (47%). Since Sibbald's report, other groups have confirmed a relationship between altered HPA axis function and mortality in severe sepsis and septic shock.[2–6] These investigations suggested that severely septic patients with altered HPA axis function may have a form of adrenal insufficiency. The term "relative adrenal insufficiency" (RAI) came into use to describe septic patients with either unexpectedly low basal plasma cortisol concentrations or those whose response to exogenous ACTH (termed "delta cortisol": serum cortisol concentration 1 hour after exogenous ACTH administration minus baseline serum cortisol concentration) was deemed inadequate regardless of basal cortisol concentration.[7–10]

Suggestions that some severely septic or septic shock patients have RAI raised the natural next question: Could glucocorticoid supplementation lead to improved survival in these individuals? In 2002, in a multicenter,

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randomized, placebo-controlled investigation of 300 adults in intensive care units (ICUs) across France often referred to as "the French study," Annane et al[11] demonstrated improved survival in septic shock patients with low delta cortisol who were treated with hydrocortisone and fludrocortisone. Corticosteroid treatment in the RAI group improved survival to match that of patients without RAI, and patients with normal ACTH responsiveness did not experience a corticosteroid treatment effect. Results of this investigation appeared to confirm that the ACTH stimulation test was a useful diagnostic test for RAI, and that corticosteroid treatment was helpful to RAI patients but not to those with more robust response to exogenous ACTH. However, issues such as the relatively small sample size;[12] the fact many subjects received etomidate, a drug known to suppress cortisol production, shortly before study inclusion;[13] persistent questions about appropriate diagnostic criteria for RAI and whether the diagnosis of RAI should dictate which septic shock patients receive steroids;[14–17] inclusion of fludrocortisone;[18] and lack of data about adverse effects of corticosteroids in the study population[12,15] plagued the landmark study. The solution was a larger, multicenter, international, randomized, double-blinded, placebo-controlled study to help address these remaining questions; along came CORTICUS.

The CORTICUS investigation[19] (performed by the Corticosteroid Therapy of Septic Shock – CORTICUS – group) was a multicenter, international, randomized, double-blinded, placebo-controlled trial that set out to investigate the usefulness of the standard ACTH stimulation test and hydrocortisone treatment in 800 people with septic shock. The investigation ultimately included only 499 people because of slow recruitment and subsequent expiration of study medications. A major reason for slow enrollment may have been the fact the Surviving Sepsis Campaign guidelines at the time recommended treatment with low-dose hydrocortisone in patients with vasopressor-dependent septic shock;[20] thus, clinicians may have elected not to enroll patients and risk their placement in the placebo group. The primary findings of CORTICUS were that low-dose hydrocortisone treatment led to more rapid pressor weaning regardless of ACTH stimulation test results, that hydrocortisone had no survival benefit despite more rapid pressor weaning in the treatment group, and that hydrocortisone treatment was associated with more incidents of superinfection than placebo.[19] Shortly after publication of these findings, an international task force by the American College of Critical Care Medicine replaced the term "relative adrenal insufficiency" with the phrase "critical illness-related corticosteroid insufficiency" ("CIRCI") to better reflect current understanding of corticosteroid insufficiency in critically ill patients.[21]

Unfortunately, the CORTICUS study has drawn no less criticism than the French study. Concerns include difficulty in CORTICUS subject enrollment such that the study fell significantly short of target sample size, leaving it underpowered to detect a relative reduction in mortality;[18,22] and the fact that the CORTICUS study population was less severely ill and its control group mortality was lower than that of the French study.[23] An elegant summary of this concern came in Dr. Marik's letter to the editor of the *New England Journal of Medicine* about CORTICUS, in which he wrote, "... the fairest conclusion might be that corticosteroids were not likely to benefit patients with septic shock when their physicians had already decided that they were not sufficiently ill to warrant such therapy."[24] Regarding the CORTICUS trial, there was also concern again about some patients having received etomidate,[25,26] and continued questions about appropriate diagnostic testing for and definition of "adrenal insufficiency" in septic shock.[25] The apparently dichotomous results of the French study and CORTICUS have led to continued controversy over adrenal function testing and the use of glucocorticoids in patients with severe sepsis and septic shock.

Unfortunately, even less is known and understood about normal and abnormal corticosteroid metabolism and the possible benefit of corticosteroid therapy in critically ill veterinary patients. The purposes of this review are to describe the controversies surrounding CIRCI and the use of hydrocortisone in critically ill patients and to present published diagnostic and therapeutic strategies in companion veterinary species.

Etiology

The adrenal glands secrete cortisol in a circadian rhythm and in increased concentrations in times of stress or illness. Cortisol secretion is controlled by the hormonal cascade and negative feedback loops of the HPA axis. The hypothalamus secretes corticotropin-releasing hormone (CRH), which binds receptors in the anterior pituitary, leading to release of ACTH. Circulating ACTH stimulates the adrenal cortices to produce and secrete cortisol. Cortisol has negative feedback control over the release of both CRH and ACTH such that increased plasma cortisol concentration leads to decreased CRH and ACTH release, and thus decreased cortisol production and release.

In health, at least 90% of plasma cortisol circulates bound to corticosteroid-binding globulin (CBG). Unbound or "free" plasma cortisol is the biologically active fraction. Cortisol crosses cell membranes freely into target cells; intracellular cortisol concentration can then be affected by the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzyme system. The 11β-HSD1 enzyme has

the capability to convert inactive cortisone to active cortisol, and under some conditions, to convert active cortisol to inactive cortisone.[27] Active intracellular cortisol binds the cytoplasmic glucocorticoid receptor (GR). Once bound, the GR-cortisol complex moves to the nucleus, where cortisol exerts genomic effects, altering protein production and cell function.

The etiology of CIRCI is unknown. There is almost certainly interindividual variation in its pathophysiology[28] and more than one mechanism may be present concurrently in the same patient. It is also unknown whether different mechanisms may be at play in different species, as very limited to no data regarding appropriate corticosteroid metabolism are available in veterinary species. The hypothalamus, pituitary, or adrenal glands may be inhibited or damaged by cytokines, reactive oxygen species, hemorrhage, or other deleterious events during septic shock,[29–34] leading to inadequate cortisol production or inadequate response to administered ACTH. Plasma CBG is damaged by neutrophil elastase; therefore, during systemic inflammatory states, an increased fraction of total plasma cortisol is in its active form.[35] Since standard tests for cortisol concentration measure only total plasma cortisol,[36] true cortisol activity potential may be underestimated in patients with sepsis. The 11β-HSD1 enzyme system is stimulated by proinflammatory cytokines and by high concentrations of glucocorticoids,[37] leading to increases in active intracellular cortisol that are not reflected by measurement of plasma cortisol concentration. Finally, systemic inflammation inhibits GR-cortisol binding, impairs translocation of the complex to the nucleus, and alters cortisol-dependent gene transcription.[36] The variety of ways in which systemic inflammation can potentially affect the secretion and biological activity of cortisol makes the precise mechanism(s) of CIRCI difficult to know, and complicates definitive diagnosis of the syndrome in the individual.

Diagnosis

The complicated and likely multifactorial nature of CIRCI's pathogenesis as discussed above has led to significant controversy regarding the best way to identify patients with the syndrome. Baseline cortisol concentration, delta cortisol concentration using standard vs low-dose ACTH stimulation test protocols, endogenous hormone ratios, measurement of total vs free cortisol, response to treatment, and other methods have been advocated by various authors as appropriate method(s) for detecting cortisol insufficiency or resistance in critical illness in people.

It is probably most accurate to say that due to disparate data from different studies and resultant clinical equipoise, the human critical care community does not advocate any method of diagnosis for CIRCI at present. In a practical sense, the "diagnosis" of CIRCI in people is currently made by evaluating response to treatment with low-dose hydrocortisone, because current guidelines recommend treating pressor-resistant septic shock patients with hydrocortisone without or with no regard to HPA axis assessment.[21,38] Both the 2012 Surviving Sepsis Campaign guidelines[38] and the 2008 recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients[21] recommend against using the ACTH stimulation test to determine which patient should receive hydrocortisone therapy; the 2008 recommendations advise against using free cortisol measurements at all, since the reference interval during critical illness has not been established.[21] Marik et al's 2008 recommendations state that adrenal insufficiency in critically ill people should be diagnosed by a delta cortisol of < 9 μg/dL or a random total cortisol concentration of < 10 μg/dL, but that this diagnosis should not be used to determine which patients may benefit from hydrocortisone therapy.[21]

Little is known about the best way to detect CIRCI in critically ill dogs. One investigation found that septic dogs with a delta cortisol ≤ 3 μg/dL following a standard 250 μg/dog ACTH stimulation test were more likely to be hypotensive and had decreased survival compared to dogs with a cortisol increase > 3 μg/dL.[39] This difference would suggest that dogs with cortisol increase ≤ 3 μg/dL may have CIRCI. Similarly, a study in septic and nonseptic critically ill dogs found that patients with a delta cortisol ≤ 3 μg/dL 1 hour after 5 μg/kg cosyntropin administration were more likely to be pressor-dependent than dogs with delta cortisol > 3 μg/dL.[40] Findings from these 2 studies suggest that ACTH responsiveness may be a marker of illness severity in critically ill dogs and raises the question of whether they may benefit from glucocorticoid replacement. Schoeman et al also found that dogs infected with *Babesia rossi* had significantly higher basal cortisol concentrations and attenuated responses to 5 μg/kg exogenous ACTH compared to control dogs.[41] However, dogs in this study with a delta cortisol < 83 nmol/L (3μg/dL) following ACTH administration had significantly higher baseline cortisol-to-endogenous ACTH ratios than dogs with more robust cortisol responses to ACTH. The authors stated that higher cortisol-to-ACTH ratios meant that a 3 μg/dL delta cortisol cutoff is not associated with CIRCI in this population of acutely ill dogs, since these dogs manifested relatively higher concentrations of cortisol for relatively lower concentrations of endogenous ACTH.

Less is known about the appropriate method of CIRCI diagnosis in the cat. At the time of this writing, only

abstract data were available on the subject. In a study of 20 critically ill cats, Prittie et al[42] found that critically ill cats had higher baseline cortisol concentrations than normal cats, as would be expected in response to physiologic stress. However, there was no significant difference between baseline cortisol, post-ACTH stimulation cortisol, or delta cortisol concentrations in cats that died and those that survived. Cats with neoplastic disease were found to have lower delta cortisols compared to other critically ill cats in the study. Costello et al studied 19 septic cats and reported significantly lower delta cortisols in septic cats compared to normals; however, there was no difference in delta cortisol between survivors and nonsurvivors in this investigation.[a] Neither of these studies were able to provide diagnostic criteria for CIRCI in the cat, which remain unknown at this time.

Alterations in HPA axis function have been found in septic foals, though as with cats, no specific diagnostic criteria for CIRCI have yet been suggested. Multiple investigators have conducted studies over the last decade to determine expected HPA axis function in foals. Baseline ACTH, baseline cortisol, and ACTH-stimulated cortisol concentrations change over the first 12 weeks of life in normal foals.[43] Baseline cortisol concentrations[43–45] and expected ACTH stimulation test results have been published for 0.1 μg/kg,[43] 10 μg/foal,[44,45] 100 μg/foal,[44,45] and 250 μg/foal[44] doses of cosyntropin for healthy foals at various ages. Septic foals have been found to have significantly higher concentrations of endogenous ACTH and baseline cortisol than normal foals,[46–49] as would be expected during physiologic stress of illness. However, Wong et al reported no differences in these endogenous hormone concentrations when comparing septic and nonseptic sick, or when comparing sick and healthy foals.[50] Endogenous ACTH concentrations[47,48] and ACTH-cortisol ratios appear to be significantly higher in nonsurviving septic foals than in survivors,[46,48] suggesting their adrenal glands may be inadequately responsive to ACTH. Dembek et al reported that septic nonsurviving foals had lower baseline cortisol concentrations than survivors,[48] while Armengou et al found that critically ill nonsurviving foals (both septic and nonseptic) had higher admission cortisol concentrations than survivors.[49] Lastly, Hart et al found that approximately half of sick foals had inappropriately low delta cortisol compared to healthy control foals.[51] In this study, inadequate response to exogenous ACTH was associated with shock and multiple organ dysfunction, and with decreased survival in septic foals. No specific criteria for the diagnosis of CIRCI in critically ill foals have been determined.

Treatment

It is widely accepted that hydrocortisone dose should not exceed 300 mg per adult person (~70 kg) per day for treatment of CIRCI. The dose is referred to as "low," "physiologic," "stress," or "replacement," depending on author, and calculates to no more than ~4.3 mg/kg/day of hydrocortisone. As hydrocortisone has approximately ¼ the potency of prednisone, the daily dose should not exceed ~1 mg/kg of prednisone equivalent. Whether this approach is appropriate in horses, dogs, and cats is unknown. The required dose for any individual patient (human or veterinary) is unknown, as the precise glucocorticoid deficiency or responsiveness in any critically ill individual cannot be determined. Meta-analyses confirm that while these lower doses of corticosteroids may confer benefit in people with septic shock, higher doses are not beneficial and may be detrimental.[52–55]

The main controversy in the human literature surrounding treatment of CIRCI is whether to institute treatment at all. The American College of Critical Care Medicine task force on CIRCI states that hydrocortisone should be *considered* in treating septic shock, particularly in fluid-loaded patients who are poorly responsive to vasopressor therapy.[21] Current Surviving Sepsis Campaign guidelines actually phrase their first statement on glucocorticoids as a negative recommendation: "We suggest not using intravenous hydrocortisone ... if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability ..."[38] Though the recommendations are weak, fortunately they agree: Glucocorticoid treatment in sepsis should be reserved for patients in fluid-loaded, vasopressor-resistant septic shock. If a clinician chooses to treat, the guidelines' recommendations again basically agree that adult humans should be treated with 200 mg IV hydrocortisone daily.[21,38] The task force's recommendations state that the 200 mg of hydrocortisone should either be divided into 4 daily doses or given as an initial 100 mg bolus followed by 10 mg/hr as a constant rate infusion for 24 hours (total 240 mg/day with this method),[21] while the Surviving Sepsis Campaign guidelines recommend 200 mg hydrocortisone be given specifically as a constant rate infusion to help avoid hyperglycemic episodes.[38] Both sets of guidelines make the nonspecific recommendation of tapering the steroid rather than abruptly discontinuing. Duration of treatment, and whether to begin tapering before or after discontinuation of pressors are not addressed, and so remain at clinician's discretion. Enough uncertainty remains regarding the decision to use corticosteroids in this patient population that in a recent survey of 125 North American human intensivists, only 52% of respondents said they would "almost always"

prescribe corticosteroids in patients with vasopressor-refractory septic shock.[56]

As would be expected, the decision to treat is murkier and the treatment methods more variable in veterinary medicine. Treatment regimens have been published primarily in case reports, reviews, and book chapters, with no reliable clinical trial data available in veterinary species. A single case report in a dog with pressor-refractory septic shock describes the use of hydrocortisone 0.5 mg/kg IV q6h to treat suspected CIRCI.[57] Pressors were discontinued within hours of starting the hydrocortisone, and the steroid dose was tapered over many days beginning 4 days after pressor independence. One small study in 8 dogs with septic shock administered the treatment group hydrocortisone 1 mg/kg IV q6h for 5 days with a 6 day tapering regimen.[b] A single case report in a critically ill cat describes the use of dexamethasone 0.08 mg/kg IV q24h to treat fluid-loaded, pressor-dependent hypotension.[58] Interestingly, the American College of Critical Care Medicine task force has since strongly recommended against the use of dexamethasone for treatment of septic shock, specifically because its profound HPA axis suppression may complicate accurate ACTH stimulation testing.[21] Since it is currently not recommended to use the ACTH stimulation test to guide CIRCI treatment decisions, dexamethasone may be a reasonable treatment choice; however, dexamethasone is highly structurally altered from the parent cortisol molecule and may therefore carry excessive immunosuppressive effects without the benefit of hydrocortisone's modest mineralocorticoid effect. For small animals, other authors recommend 1–4.3 mg/kg hydrocortisone daily, either divided into 4 equal IV doses administered every 6 hours or delivered as a constant rate infusion;[59] or 0.5 mg/kg hydrocortisone IV every 6 hours or 0.08 mg/kg/hr as a constant rate infusion.[60]

One case report has been published regarding the case of a 3-day-old foal that developed clinical signs and electrolyte abnormalities most consistent with classic hypoadrenocorticism; this horse was treated supportively and with prednisone 50 mg IV and then with prednisone 40 mg PO q12h tapered over the course of weeks.[61] Hart et al recommend hydrocortisone 1.3 mg/kg/day divided every 4 hours IV on a short tapering course in foals suspected to have CIRCI.[62]

Prognosis

For individuals that recover from the acute or critical illness, prognosis for return of normal HPA axis function following an episode of CIRCI is very good.[8,57,58,61]

Future Directions

Considering the substantial controversy and uncertainty that still surround the syndrome of CIRCI, it is fortunate that another large-scale, multicenter trial investigating the use of hydrocortisone in septic shock is currently underway.[63] This trial began enrollment in February 2013, and aims to include 3800 people with septic shock. Results of this investigation may significantly influence CIRCI identification and management in people. However, because of species differences in endogenous cortisol metabolism and in responsiveness to exogenous steroids, studies in individual veterinary species will be required to make specific recommendations in companion animals. Until further data become available, practitioners will continue to make clinical judgments regarding the diagnosis and treatment of corticosteroid insufficiency in critically ill patients.

Footnotes

[a] Costello MF, Fletcher DJ, Silverstein DC, et al. Adrenal insufficiency in feline sepsis. In Proceedings of the ACVECC Postgraduate Course 2006: Sepsis in Veterinary Medicine. 2006.

[b] Burkitt Creedon JM, Hopper K. Low-dose hydrocortisone in dogs with septic shock. In Proceedings of the 17th International Veterinary Emergency and Critical Care Symposium. 2011.

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