Critical Illness–Related Corticosteroid Insufficiency in Small Animals

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Acute illness can produce dramatic changes in endocrine function.¹–³ Activation of the hypothalamic-pituitary-adrenal (HPA) axis, as evidenced by an increase in secretion of adrenocorticotropic hormone (ACTH) and cortisol during illness, is presumed to be a vital part of the physiologic stress response and is essential for maintenance of homeostasis and adaptation during severe illness. Cortisol has been shown to increase after a variety of stressors, and the response is thought to be proportional to the magnitude of the injury or disease process.³,⁴ However, human and animal studies have revealed marked heterogeneity in adrenocortical function in critically ill patients.⁵,⁶

The syndrome of critical illness–related corticosteroid insufficiency (CIRCI), previously referred to as relative adrenal insufficiency, has been proposed to describe these endocrine abnormalities associated with illness. This syndrome is characterized by an inadequate production of cortisol in relation to an increased demand during periods of severe stress, particularly in critical illnesses such as sepsis or septic shock.⁷–⁹ In patients with CIRCI, cortisol concentrations, despite being normal or high in some patients, may still be inadequate for the current physiologic stress or illness, and the patient is unable to respond to additional stress. CIRCI is usually defined by an inadequate response to exogenous ACTH stimulation.⁸,¹⁰ This failed response indicates reduced functional integrity of the HPA axis and may lessen the patient’s ability to cope with severe illness and stress. In the setting of human and veterinary critical illness, CIRCI appears to be a transient condition secondary to

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doi:10.1016/j.cvsm.2011.03.021 vetsmall.theclinics.com
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severe illness with adrenal function normalizing after recovery. For these patients, life-long replacement of glucocorticoids is not anticipated. This article reviews the physiology and pathophysiology of the corticosteroid response to critical illness and the incidence, clinical features, diagnosis, and treatment of CIRCI.

NORMAL REGULATION OF THE HPA AXIS DURING ILLNESS

Cortisol secretion by the adrenal cortex is under the control of the hypothalamic-pituitary axis. Signals from the body (eg, cytokine release, tissue injury, pain, hypotension, hypoglycemia, and hypoxemia) are sensed by the central nervous system and transmitted to the hypothalamus. The hypothalamus integrates these signals and increases the release of corticotropin-releasing hormone (CRH). CRH circulates to the anterior pituitary gland, in which it stimulates the release of ACTH, which acts on the adrenal cortex stimulating the release of cortisol. Cortisol, released from the adrenal glands or from exogenous sources, feeds back on the HPA axis to inhibit its secretion (negative feedback). Thus, decreased cortisol concentrations (lack of negative feedback) result in increased CRH-ACTH release and conversely elevated cortisol concentrations inhibit CRH-ACTH release. By these mechanisms, the body can control the secretion of cortisol within narrow limits and can respond with increased secretion of cortisol to a variety of stressors and other signals.

Cortisol circulates in the blood in both bound and unbound forms. Almost 90% of cortisol is bound to corticosteroid-binding globulin (CBG). It is the unbound or free cortisol that is physiologically active and homeostatically regulated. Although relative concentrations of free cortisol have not been well investigated in critically ill patients, studies suggest that there is a decrease in cortisol binding rather than an increase. The reduced binding results in elevated free cortisol concentrations in the acute phase of illness. The cause for this decrease in binding is unknown, but likely increases cortisol availability to cells and tissues during stress and illness.

ABNORMAL RESPONSE OF THE HPA AXIS DURING ILLNESS

The HPA axis, along with the adrenergic and sympathetic nervous systems, is the main mediator of the stress response. During acute illness, circulating proinflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and IL-1β, stimulate the production of CRH and ACTH. Simultaneously, vagal afferent fibers detect the presence of cytokines such as IL-1β and TNF-α at the site of inflammation and activate the HPA axis. Subsequently, this results in an immediate rise in circulating cortisol concentrations. Cortisol then binds to specific carriers, CBG and albumin, to reach the target tissues. It is generally accepted that CBG-bound cortisol has restricted access to the target cells. At the inflammatory sites, elastase produced by neutrophils liberates cortisol from CBG, allowing localized delivery of cortisol to the cells. Subsequently, cortisol can freely cross the cell membrane or interact with specific membrane-binding receptor sites. Cytokines may also increase the affinity of receptors for glucocorticoids. Dysfunction at any 1 of these steps can result in diminished cortisol action. Alternatively, cortisol can be inactivated by conversion to cortisone by 11β-hydroxysteroid dehydrogenase type 2. CIRCI may result from decreased glucocorticoid synthesis or reduced access of glucocorticoids to the target tissues and cells.

Decreased Glucocorticoid Synthesis

Subsequent to the secretion of ACTH, glucocorticoids are synthesized by the adrenal cortex from cholesterol. The amount of glucocorticoid found in adrenal tissue is not
sufficient to maintain normal rates of secretion for more than a few minutes in the absence of continuing biosynthesis. Thus, the rate of secretion is directly proportional to the rate of biosynthesis. In other words, any disruption in glucocorticoid synthesis will immediately result in glucocorticoid insufficiency.16

Critical illness may result in decreased CRH, ACTH, or cortisol synthesis through damage to the hypothalamus, pituitary gland, and/or adrenal glands. Necrosis and hemorrhage of the hypothalamus and pituitary gland have been reported in human sepsis because of prolonged hypotension or severe coagulopathy.17 Thrombosis and hemorrhage of the adrenal glands have also been proposed as a cause of CIRCI in human critically ill patients.3,11 Animal studies have shown that septic shock can produce extensive pathology of the adrenal glands.11,18 For example, hemorrhagic necrosis, massive hematomas, microthrombi, and platelet aggregation have been documented in the adrenal cortices of study animals with septic shock.18 Bilateral adrenal hemorrhage has been found in up to 30% of human critically ill patients who do not survive septic shock.19 Occasionally, CIRCI can result from pituitary infarction secondary to traumatic injury or thrombosis.3,11,20

Suppression of CRH synthesis during sepsis may result from neuronal apoptosis, which may be triggered by elevation in substance P or inducible nitric oxide synthase in the hypothalamus.21,22 Circulating proinflammatory mediators such as TNF-α may block CRH-induced ACTH release.23 Similarly, local expression of TNF-α and IL-1β may interfere with CRH and ACTH syntheses.22 TNF-α may also inhibit ACTH-induced cortisol release.24 In addition, corticostatins, such as α-defensins, compete with ACTH at their membrane-binding receptor sites and exert an inhibitory effect on adrenal cells.25

Numerous drugs that are commonly used in critically ill patients are known to affect the HPA axis and may ultimately decrease cortisol synthesis. It is suspected that these drugs contribute, at least in part, to CIRCI.16 Benzodiazepine administration results in a dose-dependent decrease in serum cortisol concentrations.26 Opioid administration also results in decreased cortisol concentrations.27 Anesthesia in humans with high-dose diazepam and fentanyl inhibits the early increase in ACTH and cortisol that occurs in response to surgery, suggesting that these drugs act at the level of the hypothalamus.16,28 Discontinuing or reducing the dose of these drugs may result in clinical improvement in patients with CIRCI.29

Cortisol is synthesized via a series of cytochrome-mediated enzymatic reactions from cholesterol. Statins are thought to decrease the available substrate for cortisol synthesis, thereby decreasing overall cortisol secretion. A recent study in humans with diabetes demonstrated a dose-dependent effect of statins on cortisol production.30

Several drugs are known to block enzymic steps such as the partial or complete inhibition of 11β-hydroxylase by etomidate, ketoconazole, or high-dose fluconazole.16,31 Etomidate inhibits steroidogenesis by blocking mitochondrial cytochrome P450 enzymes, and this effect may persist as long as 24 hours after a single dose of etomidate in human critically ill patients.32 A study of canine surgical patients demonstrated that adrenocortical function was depressed for up to 6 hours after a single intravenous (IV) bolus injection of etomidate for inducing anesthesia.33 A similar study demonstrated that response to ACTH stimulation was also depressed 2 hours after a single IV bolus injection of etomidate in canine surgical patients.34 In addition, a feline study found profound cortisol suppression up to 5.5 hours after the administration of a single IV bolus injection of etomidate to induce anesthesia.35 Aza...
suppression is best documented with ketoconazole, and although in vitro data suggest that adrenal suppression is unlikely with triazole antifungals (eg, fluconazole and itraconazole), several human case reports have documented reversible adrenal suppression in association with these agents.\textsuperscript{36,37} Dexmedetomidine, a highly selective and potent alpha-2 agonist, is increasingly being used for perioperative sedation and analgesia. It is an imidazole compound, and in vitro and in vivo canine studies have shown that dexmedetomidine inhibits cortisol synthesis.\textsuperscript{38}

P-glycoprotein appears to be an important component of the HPA axis in dogs.\textsuperscript{39} P-glycoprotein restricts the entry of cortisol into the brain, limiting cortisol’s feedback inhibition of CRH and ACTH. In ABCB1 (formerly referred to as MDR1) mutant dogs, P-glycoprotein is not present, allowing greater concentrations of cortisol to be present within the brain, resulting in greater feedback inhibition of the HPA axis and, ultimately, inhibition of sufficient cortisol secretion. Plasma basal and ACTH-stimulated cortisol concentrations are significantly lower in ABCB1 mutant dogs compared with ABCB1 wild-type dogs, indicating that the HPA axis is suppressed in ABCB1 mutant dogs compared with ABCB1 wild-type dogs.\textsuperscript{39} This may lead to an inability to appropriately respond to critical illness and stress in dogs that harbor the ABCB1 mutation. The ABCB1 mutation has been identified in herding breed dogs, such as Collies, Shetland Sheepdogs, Old English Sheepdogs, and Australian Shepherds. It has also been found at a higher frequency in sight hounds, such as Long-haired Whippets and Silken Windhounds, and also in McNabs.\textsuperscript{40}

### Reduced Access of Glucocorticoids to the Target Tissues and Cells

CBG is crucial in transporting cortisol to tissues and cells. Reductions in circulating CBG result in decreased access of cortisol to the sites of inflammation and to immune cells.\textsuperscript{16} In human critically ill patients, CBG and albumin concentrations can decrease by approximately 50% because of catabolism at inflammatory sites and inhibition of hepatic synthesis via cytokine induction.\textsuperscript{14} In addition, the presence of elastase is essential for cortisol cleavage and release from CBG.\textsuperscript{16} Therefore, drugs that inhibit elastase (eg, protease inhibitors such as amprenavir, lopinavir, nelfinavir, and ritonavir) could prevent cortisol release from CBG and subsequent access to the tissue.\textsuperscript{16} At present, protease inhibitors are not commonly used as therapeutic agents in veterinary medicine. Tissue concentrations of cortisol are also regulated by enzymatic conversion of cortisol to its inactive form, cortisone, by 11β-hydroxysteroid dehydrogenase type 2. Cytokines such as IL-2, IL-4, and IL-13 have been shown to stimulate 11β-hydroxysteroid dehydrogenase type 2 activity, converting cortisol to cortisone.\textsuperscript{41} This inappropriate response to inflammation could be detrimental to the patient’s response to illness or stress if cortisol is preferentially being converted to an inactive form. In addition, there may be a cytokine-mediated response, resulting in a decrease in the number and activity of the glucocorticoid receptors. Mechanisms may include inhibition of glucocorticoid receptor translocation from cytoplasm to nucleus and reduction in glucocorticoid receptor–mediated gene transcription.\textsuperscript{42} This decrease would reduce the ability of cells to respond to cortisol. These different mechanisms responsible for reducing glucocorticoid access to tissues and cells could account for a decreased activity of glucocorticoids, although serum cortisol concentrations appear appropriate.\textsuperscript{16}

### Incidence of CIRCI

The incidence of CIRCI in human critically ill patients is variable and depends on the underlying disease and severity of the illness. The overall incidence of CIRCI in
high-risk critically ill patients (eg, those with hypotension, shock, and sepsis) approx-
imates 30% to 45%. The incidence increases with severity of illness (sepsis >elective
surgery >ward admits), with most studies of critically ill patients reporting incidences
between 25% and 40%. The incidence also depends on the specific tests and criteria
used to diagnose CIRCI. The ACTH stimulation test is usually used to assess
adrenocortical function, but this is an area of great controversy in the human critical
care arena. At present, there is no consensus for appropriately interpreting the results
of ACTH stimulation testing in seriously ill patients, as accepted reference ranges are
derived from healthy populations. Lack of an appropriately high basal cortisol concen-
tration or a negligible response to ACTH may actually represent CIRCI or an insuffi-
cient response to stress in a critically ill patient.

At present, little information is available regarding the incidence of CIRCI in critically
ill animals with severe disease or injury. To date, there have only been a few studies
that have investigated pituitary-adrenal function in populations of critically ill dogs
and cats. Earlier studies evaluating pituitary-adrenal function in critically ill dogs
and in dogs with severe illness attributable to non–adrenal gland disease did not
identify any dogs with adrenal insufficiency. Prittie and colleagues measured serial
plasma concentrations of basal cortisol and ACTH-stimulated cortisol in 20 critically
ill dogs within 24 hours of admission to an intensive care unit (ICU) and daily until
death, euthanasia, or discharge from the ICU. ACTH stimulation testing was per-
formed by IV administration of 250 μg of cosyntropin/dog. The study population
was heterogeneous and consisted of animals with a variety of acute and chronic
illnesses. Only 40% of the dogs enrolled in this study were acutely ill. The investigators
found that basal and ACTH-stimulated cortisol concentrations were within or above
the reference range in all the blood samples collected, concluding that none of the crit-
ically ill dogs developed adrenal insufficiency during hospitalization in the ICU. Delta
cortisol concentrations (ACTH-stimulated cortisol concentration minus basal cortisol
concentration) were not evaluated in this study. Kaplan and colleagues also investi-
gated a general population of severely ill dogs with a wide array of diseases. Most
dogs studied had chronic diseases with the duration of morbidity ranging from 1
week to 1 year (mean, 5.8 ± 1.4 weeks). ACTH stimulation testing was performed
by IV administration of 10 μg/kg of cosyntropin. Investigators did not identify any
dogs with basal or ACTH-stimulated cortisol concentrations below the reference
range. In this study, delta cortisol concentrations were not assessed.

In a more recent study, Burkitt and colleagues assessed pituitary-adrenal function
in 33 septic dogs admitted to an ICU. Dogs were included in the study if they had
a known or suspected infectious disease and demonstrated signs consistent with
systemic inflammatory response syndrome. Systemic inflammatory response
syndrome was considered present if dogs demonstrated at least 2 of the following
abnormalities at the time of inclusion in the study: rectal temperature more than
103.0°F or less than 100°F, heart rate more than 120 beats/min, nonpanting respiratory
rate more than 40 breaths/min or PCO2 (arterial or venous) less than 32 mm Hg, and total
white blood cell count more than 16,000/μL, less than 6000/μL, or more than 3%
bands. Serum cortisol and plasma endogenous ACTH concentrations were measured
before and serum cortisol concentration was measured 1 hour after intramuscular
administration of 250 μg of cosyntropin/dog. Basal plasma endogenous ACTH and
ACTH-stimulated serum cortisol concentrations below the reference range were
detected, and delta cortisol concentrations of 3 μg/dL (83 nmol/L) or less were associ-
ated with systemic hypotension and a decrease in survival. The mortality rate in dogs
with delta cortisol concentrations of 3 μg/dL (83 nmol/L) or less was 4.1 times higher
than that of dogs with delta cortisol concentrations more than 3 μg/dL (83 nmol/L).
The study identified CIRCI in 48% of the septic dogs enrolled in the study; however, the investigators never clearly defined the criteria used to diagnose CIRCI in their study population. Their definition was likely based on the delta cortisol concentration.

In a multicenter study performed to evaluate pituitary-adrenal function in 31 acutely ill dogs with sepsis, severe trauma, or gastric dilatation-volvulus, biochemical abnormalities of the HPA axis indicating adrenal or pituitary gland insufficiency were found to be common. Serum cortisol and plasma endogenous ACTH concentrations were measured before and serum cortisol concentration was measured 1 hour after IV administration of 5 μg/kg of cosyntropin (up to a maximum of 250 μg/dog). Basal and ACTH-stimulated serum cortisol concentrations and basal plasma endogenous ACTH concentrations were assayed for each dog within 24 hours of admission to the ICU. Delta cortisol concentrations were also assessed for each patient. Overall, 55% of the critically ill dogs had at least 1 biochemical abnormality suggesting adrenal or pituitary gland insufficiency (ACTH-stimulated cortisol concentration less than the reference range, no response to ACTH stimulation [delta cortisol concentration ≤1 nmol/L], and plasma endogenous ACTH concentration less than the reference range). Only 1 dog had an exaggerated response to ACTH stimulation. Acutely ill dogs with delta cortisol concentrations of 3 μg/dL (83 nmol/L) or less were 5.7 times more likely to be receiving vasopressors than dogs with delta cortisol concentrations more than 3 μg/dL (83 nmol/L). In addition, dogs with delta cortisol concentrations of 3 μg/dL (83 nmol/L) or less had a slight, but not significant, increase in mortality. No differences were detected among dogs with sepsis, severe trauma, or gastric dilatation-volvulus with respect to mean basal and ACTH-stimulated serum cortisol concentrations, delta cortisol concentrations, and basal plasma endogenous ACTH concentrations.

Canine studies examining HPA axis function have also been performed in dogs with neoplasia (lymphoma and several different types of nonhematopoietic tumors), Babesia canis rossi babesiosis, parovirus, and the ABCB1 genetic mutation. Boozer and colleagues investigated HPA function in dogs with lymphoma and with nonhematopoietic tumors (transitional cell carcinoma, hepatocellular adenoma, hepatocellular carcinoma, hemangiosarcoma, mammary carcinoma, jejunal adenocarcinoma, anal sac apocrine gland adenocarcinoma, insulinoma, osteosarcoma, and pheochromocytoma). None of the dogs had received any drugs known to affect adrenal function within 30 days before evaluation. Of the dogs with lymphoma and nonhematopoietic tumors, 5% and 13%, respectively, had basal cortisol concentrations below the reference range; 20% of the dogs with lymphoma and 13% of the dogs with nonhematopoietic tumors had ACTH-stimulated cortisol concentrations below the reference range. Endogenous ACTH concentrations were below the reference range in 10% of the dogs with lymphoma and 7% with nonhematopoietic neoplasia. Delta cortisol concentrations were not assessed as part of the study, and the investigators did not distinguish between dogs that had absolute adrenal insufficiency or CIRCI in the tumor-bearing dogs that had HPA axis abnormalities.

Two studies have examined the endocrine response to canine babesiosis. The first study was designed, in part, to determine the association between the hormones of the pituitary-adrenal axis and outcome in dogs with naturally occurring Babesia canis rossi babesiosis. In this study, basal cortisol and endogenous ACTH concentrations were measured; ACTH stimulation testing was not performed. The results indicated that serum cortisol and endogenous ACTH concentrations were significantly higher in dogs with babesiosis that died, compared with hospitalized dogs with babesiosis that survived and dogs with babesiosis that were treated as outpatients. Mortality was significantly associated with high serum cortisol and high endogenous ACTH.
concentrations in the dogs suffering from babesiosis. In the second study investigating endocrine response to babesiosis, basal serum cortisol and plasma endogenous ACTH concentrations were measured, ACTH stimulation testing was performed, and delta cortisol concentrations and cortisol-to-ACTH ratios (which is thought by some to assess the whole pituitary-adrenal axis) were calculated. Basal serum cortisol concentrations, but not ACTH-stimulated serum cortisol concentrations, were significantly higher in the dogs with babesiosis compared with the control dogs. Basal and ACTH-stimulated serum cortisol concentrations were significantly higher in the dogs that died, compared with hospitalized dogs that survived and dogs treated as outpatients. Basal plasma endogenous ACTH concentrations were not significantly different between the 3 babesiosis groups (hospitalized dogs that died, hospitalized dogs that survived, and dogs treated as outpatients). Dogs with delta cortisol concentrations less than 83 nmol/L had significantly higher cortisol-to-ACTH ratios compared with dogs with delta cortisol concentrations more than 83 nmol/L. The investigators concluded that the findings of increased basal and ACTH-stimulated cortisol concentrations and increased cortisol-to-ACTH ratios confirmed the absence of CIRCI and demonstrated upregulation of the HPA axis in this population of dogs with acute canine critical illness.

In a study that examined puppies with parvovirus and endocrine response to illness, daily IV ACTH stimulation tests were performed. Investigators found that on days 1 and 2, nonsurviving puppies with parvovirus had significantly lower delta cortisol concentrations than surviving puppies. However, on day 3, there was no statistical difference in delta cortisol concentrations between the nonsurvivors and survivors, mainly because of reduction in basal cortisol concentrations (and therefore increased delta cortisol concentrations) in the nonsurvivors, illustrating that the test results obtained on a single day do not necessarily reflect the findings on subsequent days.

The HPA axis has also been evaluated in dogs possessing the ABCB1 genetic mutation. The investigators found that basal cortisol and ACTH-stimulated cortisol concentrations were significantly lower in ABCB1 mutant dogs compared with ABCB1 wild-type dogs. Plasma ACTH concentrations after dexamethasone administration were significantly lower in ABCB1 mutant dogs compared with ABCB1 wild-type dogs. The investigators concluded that the HPA axis in ABCB1 mutant dogs that lack P-glycoprotein is suppressed compared with that in ABCB1 wild-type dogs. In addition, this may explain some clinical observations in breeds known to harbor the genetic mutation, including Collies, Shelties, and Australian Shepherds. There is a clinical impression that many of these dogs have worse outcomes in response to stress and, at times, respond poorly to appropriate therapy. HPA axis suppression, secondary to the ABCB1 mutation, could result in a CIRCI-like state during times of severe stress and illness. However, further studies are required to determine the exact relationship between the ABCB1 genotype and CIRCI.

Studies investigating the presence of CIRCI in critically ill cats have also been performed. Prittie and colleagues have investigated the effects of critical illness on adrenocortical function in a feline population. Twenty critically ill cats with different diseases were admitted to an ICU and constituted the study population. Plasma concentrations of basal cortisol and ACTH-stimulated cortisol were analyzed, and delta cortisol concentrations were calculated. Initial samples for basal cortisol concentrations were collected within 24 hours of admission. Samples for ACTH-stimulated cortisol concentrations were collected 1 hour after IV administration of 125 μg of cosyntropin/cat. ACTH stimulation tests were performed every other day for each cat until death or discharge from the hospital. Established reference ranges for 10 healthy cats were used for comparative purposes. The investigators found
that critically ill cats had higher basal cortisol concentrations than the control group. ACTH-stimulated cortisol concentrations did not differ significantly between the 2 groups. Basal cortisol, ACTH-stimulated cortisol, and delta cortisol concentrations did not differ significantly between cats that survived and cats that died, or between the septic and nonseptic cats. However, critically ill cats with neoplasia had lower delta cortisol concentrations and were more likely to die than other cats in the study population. Based on these findings, the investigators postulated that critically ill cats with neoplasia may develop CIRCI.

Pituitary-adrenal function has been evaluated in cats with lymphoma. In this study, cats with cytologic or histologic confirmation of lymphoma were investigated. None of the cats were thought to have invasion of their lymphoma to the adrenal glands, and none had received any drugs known to affect adrenal function within 30 days before evaluation. However, it should be noted that a limitation of this study was that ultrasonography was used to make the determination that there was no invasion of the lymphoma to the adrenal glands. All study cats had normal adrenal gland size, as assessed by ultrasonography. No histologic or cytologic analysis was performed to confirm that the adrenal glands were normal. Samples for basal serum cortisol, ACTH-stimulated serum cortisol, and plasma endogenous ACTH concentrations were collected and analyzed. ACTH-stimulated cortisol concentrations were collected 1 hour after IV administration of 125 μg of cosyntropin/cat. Of the 10 cats studied, 9 had a subnormal cortisol response to ACTH stimulation and 5 had elevated plasma endogenous ACTH concentrations. Based on these findings, the authors concluded that many of these cats had CIRCI. Basal cortisol concentrations and serum sodium-to-potassium ratios remained within the normal range in almost all cats, and none of the cats displayed any signs typical for complete adrenal crisis. The investigators speculated that the CIRCI present in some cats with untreated lymphoma may cause the dramatic clinical response to glucocorticoid supplementation before the induction of chemotherapy.

In a prospective multicenter study, cats were enrolled if they had a known or suspected focus of infection combined with 2 or more of the following criteria: temperature more than 103.5°F or less than 100°F, heart rate less than 225 beats/min or less than 140 beats/min, respiratory rate more than 40 breaths/min, white blood cell count more than 19,500/μL, less than 5000/μL, more than 5% bands; or Doppler (systolic) blood pressure less than 90 mm Hg. Nineteen septic cats were included in the study, and 19 healthy cats served as controls. ACTH stimulation testing was performed using 125 μg of cosyntropin/cat intramuscularly. Cortisol and aldosterone concentrations were measured before and 30 minutes after ACTH administration. Delta cortisol and aldosterone concentrations were also assessed. Delta cortisol concentrations were significantly lower in septic cats (64 ± 69 nmol/L) compared with healthy cats (180 ± 129 nmol/L). Basal and post-ACTH median aldosterone concentrations were significantly higher in the septic cats (1881 and 2180 pmol/L) compared with the healthy cats (101 and 573 pmol/L), but delta aldosterone concentrations were not significantly different between the 2 groups. There was no significant difference in either delta cortisol or delta aldosterone concentration when survivors were compared with nonsurvivors.

**CLINICAL SIGNS**

Clinical signs of CIRCI can be vague and nonspecific, such as depression, weakness, fever, vomiting, diarrhea, and abdominal pain. In addition, clinical signs that are secondary to the underlying disease process responsible for CIRCI (ie, septic
shock, hepatic disease, trauma, etc) can mask the clinical features of CIRCI.11 The most common clinical abnormality associated with CIRCI in human critically ill patients is hypotension refractory to fluid resuscitation, requiring vasopressor therapy.3,8,11 Hyponatremia and hyperkalemia are uncommon in humans with CIRCI and, to date, have not been reported in canine or feline critically ill patients with insufficient adrenal or pituitary function.3,46,47,52–54,57–59 Laboratory assessment of human critically ill patients with CIRCI may demonstrate eosinophilia and/or hypoglycemia, but these abnormalities are not consistently found in humans with CIRCI.3,11,56 Eosinophilia and hypoglycemia have not been reported in veterinary critically ill patients with CIRCI.

**DIAGNOSIS**

CIRCI should be considered as a differential diagnosis in all critically ill patients requiring vasopressor support. Human patients with CIRCI typically have normal or elevated basal serum cortisol concentrations and a blunted response to ACTH stimulation.10,60,61 These findings have also been documented in critically ill dogs with sepsis/septic shock, trauma, and gastric dilatation-volvulus and in critically ill cats with sepsis/septic shock, trauma, and neoplasia.46,47,53,62,63 At present, there is no consensus regarding the identification of patients with CIRCI in human or veterinary medicine, and normal reference ranges do not exist for basal and ACTH-stimulated cortisol concentrations in critically ill dogs and cats.

A variety of tests have been advocated, including random basal cortisol concentration, ACTH-stimulated cortisol concentration, delta cortisol concentration (the difference when subtracting basal from ACTH-stimulated cortisol concentration), the cortisol-to-endogenous ACTH ratio, and combinations of these methods. The optimal way to identify critically ill veterinary patients with CIRCI has yet to be determined. Evaluation of adrenal function in veterinary patients typically involves administration of an ACTH stimulation test. The most commonly used protocol for ACTH stimulation testing in dogs involves the IV administration of 5 μg cosyntropin/kg up to a maximum of 250 μg. In cats, IV administration of 125 μg of cosyntropin/cat is commonly used. Serum or plasma is then obtained for cortisol analysis before and 60 minutes after ACTH administration for both dogs and cats. The standard doses of cosyntropin (5 μg/kg in dogs and 125 μg/cat) currently used in ACTH stimulation testing are greater than that necessary to produce maximal adrenocortical stimulation in healthy small animals.64,65 Doses as low as 0.5 μg/kg in dogs64 and 5 μg/kg in cats65 have been shown to induce maximal cortisol secretion by the adrenal glands. The use of higher doses is considered supraphysiologic and may hinder the identification of dogs and cats with CIRCI. Low-dose (0.5 μg/kg IV) ACTH stimulation testing has been compared with standard-dose (5 μg/kg IV) ACTH stimulation testing in a group of critically ill dogs.66 In this study, every critically ill dog that was identified to have insufficient adrenal function (ie, ACTH-stimulated serum cortisol concentration below the reference range or less than 5% greater than the basal cortisol concentration) by the standard-dose ACTH stimulation test was also identified by the low-dose test. Additional dogs with adrenal insufficiency were identified by the low-dose ACTH stimulation test and not by the standard-dose test. ACTH administered at a dose of 0.5 μg/kg IV appears to be at least as accurate in determining adrenal function in critically ill dogs as the IV administration of ACTH at 5 μg/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.

Assays that measure cortisol concentration typically measure total hormone concentration (ie, serum free cortisol concentration plus a protein-bound fraction).
However, the serum free cortisol fraction is thought to be responsible for the physiologic function of the hormone.67–71 Therefore, serum free cortisol concentrations may be a more precise predictor of adrenal gland function. The relationship between free and total cortisol varies with serum protein concentration.68,69 In human critically ill patients, cortisol-binding globulin and albumin concentrations can decrease by approximately 50% because of catabolism at the inflammatory sites and inhibition of hepatic synthesis via cytokine induction.69 Therefore, serum total cortisol concentration may be falsely low in hypoproteinemic patients, resulting in overestimation of CIRCI.68 Serum free cortisol concentration is less likely to be altered in states of hypoproteinemia. Consequently, serum total cortisol concentrations may not accurately represent the biologic activity of serum free cortisol during critical illness. Several human studies suggest that serum free cortisol concentrations are a more accurate measure of circulating corticosteroid activity than total cortisol concentrations.67–70 At this time, abundant canine and feline studies are lacking and the ability to measure serum free cortisol concentration is not widely available. However, serum free and total cortisol concentrations have been compared in a group of 35 critically ill dogs having 1 of the following diseases: sepsis, severe trauma, or gastric dilatation-volvulus.66 Fewer critically ill dogs with adrenal insufficiency (ie, an ACTH-stimulated serum cortisol concentration below the reference range or less than 5% greater than the basal cortisol concentration) were identified by serum free cortisol concentration than by serum total cortisol concentration. However, basal and ACTH-stimulated serum total cortisol concentrations were not lower in the hypoproteinemic dogs compared with the normoproteinemic dogs. The significance of this is unknown and warrants further investigation in veterinary patients.

The delta cortisol concentration has been advocated as a method to identify critically ill patients with CIRCI in both human and veterinary medicine.46,72,73 A study in human patients with septic shock72 found that basal cortisol concentrations of 34 μg/dL (938 nmol/L) or less combined with delta cortisol concentrations of 9 μg/dL (250 nmol/L) or more in response to an IV 250 μg/person ACTH stimulation test were associated with a favorable prognosis. In addition, basal cortisol concentrations more than 34 μg/dL (938 nmol/L) combined with delta cortisol concentrations less than 9 μg/dL (250 nmol/L) were associated with a poor prognosis. Because this protocol was successful in predicting outcome, a delta cortisol concentration less than 9 μg/dL (250 nmol/L) is frequently used as the diagnostic criteria for CIRCI in human critically ill patients.

Veterinary studies have also assessed delta cortisol concentration as a criterion for diagnosing CIRCI in critically ill patients.46,47 One study found that septic dogs with delta cortisol concentrations of 3 μg/dL (83 nmol/L) or less after an intramuscular 250 μg/dog ACTH stimulation test were more likely to have systemic hypotension and decreased survival.46 In addition, another study investigating acutely ill dogs (ie, dogs with sepsis, severe trauma, or gastric volvulus-dilatation) found that dogs with delta cortisol concentrations of 3 μg/dL (83 nmol/L) or less after an IV 5 μg/kg ACTH stimulation test were more likely to require vasopressor therapy as part of their treatment plan.47 Sensitivity of delta cortisol concentrations of 3 μg/dL (83 nmol/L) or less in the diagnosis of veterinary critically ill patients with CIRCI has yet to be determined.

Based on the current veterinary literature, there are 3 scenarios that may indicate the presence of CIRCI in critically ill dogs (especially in the presence of refractory hypotension): (1) dogs with a normal or an elevated basal cortisol concentration and an ACTH-stimulated cortisol concentration less than the normal reference range; (2) dogs with a normal or an elevated basal cortisol concentration and an ACTH-stimulated cortisol concentration that is less than 5% greater than the basal cortisol
concentration (flatline response); and (3) dogs with a delta cortisol concentration of 3 μg/dL (83 nmol/L) or less. Based on a few clinical studies and case reports, CIRCI appears to occur in cats.\textsuperscript{52–54,63} However, a consensus regarding the diagnostic criteria in cats is undetermined at this time.

**TREATMENT**

Human critically ill patients with CIRCI who are treated with supplemental doses of corticosteroids are more likely to be quickly weaned from vasopressor therapy and ventilatory support, and some treated populations of critically ill patients are more likely to survive than patients with CIRCI who do not receive corticosteroid supplementation.\textsuperscript{50,73–76} The optimal dose and duration of treatment with corticosteroids in human patients with CIRCI have yet to be determined. The dosages of corticosteroids used to treat human patients with CIRCI are referred to as supplemental, physiologic, supraphysiologic, low dose, stress dose, or replacement.\textsuperscript{3,8,60,73–75,77} Most human protocols have used dosages of 200 to 300 mg IV every 24 hours of hydrocortisone for an average person of 70 kg (2.9–4.3 mg/kg IV every 24 hours). The total daily dose is typically either given as a constant-rate infusion or quartered and given every 6 hours.\textsuperscript{3,78,79} Hydrocortisone is one-fourth as potent as prednisone and one-thirtieth as potent as dexamethasone. Therefore, this supplemental corticosteroid dosage is 0.7 to 1 mg/kg every 24 hours of prednisone equivalent or 0.1 to 0.4 mg/kg every 24 hours of dexamethasone equivalent. The hydrocortisone dose currently recommended for CIRCI in human patients is supraphysiologic (the human physiologic dose of hydrocortisone is 0.2–0.4 mg/kg every 24 hours), resulting in a serum cortisol concentration several times higher than that achieved by ACTH stimulation. This regimen of therapy was initially based on the maximum secretory rate of cortisol found in humans after a major surgery.\textsuperscript{80}

At present, there are no consensus guidelines for the treatment of CIRCI in veterinary critically ill patients. However, it is reasonable to start volume-resuscitated vasopressor-dependent animals on corticosteroid therapy after performing an ACTH stimulation test. When the test results are available, treatment can be withdrawn in those animals that responded normally to the ACTH stimulation test. Corticosteroids can be continued in those patients that have (1) a normal or an elevated basal cortisol concentration and an ACTH-stimulated cortisol concentration less than the normal reference range, (2) a normal or an elevated basal cortisol concentration and an ACTH-stimulated cortisol concentration that is less than 5% greater than the basal cortisol concentration (flatline response), (3) a delta cortisol concentration of 3 μg/dL (83 nmol/L) or less, or (4) clinically demonstrated a significant improvement in cardiovascular status within 24 hours of starting corticosteroid therapy.

The appropriate dosage, duration, and type of corticosteroid therapy are unknown in veterinary patients with CIRCI. However, it is reasonable to give supplemental doses of corticosteroids at physiologic to supraphysiologic dosages (1–4.3 mg/kg IV every 24 hours of hydrocortisone [the total daily dose can be divided into 4 equal doses and given every 6 hours or as a constant-rate infusion], 0.25–1 mg/kg IV every 24 hours of prednisone equivalent [the total daily dose can be divided into 2 equal doses and given every 12 hours], or 0.04–0.4 mg/kg IV every 24 hours of dexamethasone equivalent). Because the HPA dysfunction in CIRCI is thought to be transient, lifelong therapy with corticosteroids is not required and is tapered after resolution of critical illness. The corticosteroid dose can be tapered by 25% each day. An ACTH stimulation test should be repeated to confirm the return of normal adrenocortical function following the resolution of critical illness and discontinuation of corticosteroid supplementation.
Evaluating adrenal function in human and veterinary critically ill patients can be challenging, and at present, there is no consensus regarding the identification of patients with CIRCI in human or veterinary medicine. Detection of abnormal responses will continue to be debated until standard diagnostic methods are developed and validated. At present, there are no guidelines for the treatment of CIRCI in veterinary critically ill patients, and the question as to whether supplemental doses of corticosteroids are beneficial for the treatment of CIRCI in these patients remains unanswered. Practitioners should rely on both biochemical and clinical assessment to optimize patient management.

REFERENCES