INTRODUCTION
Critical illness-related corticosteroid insufficiency (CIRCI), previously known as relative adrenal insufficiency, is a syndrome of relative, as opposed to absolute adrenal dysfunction observed in critically ill patients. Initially observed in septic patients, CIRCI has been documented in many other forms of critical illness, primarily in human medicine, such as pancreatitis and trauma. Recognition, diagnosis, and treatment are essential to affect survival in this relatively small patient population.

The hypothalamic-pituitary-adrenal axis is a complex system of negative feedback loops and hormones controlling the release and restraint of cortisol. As cortisol receptors are present in almost every cell in the body it seems apparent that tight regulation of this hormone is in order. The hypothalamus responds initially to insults from the body (such as stress, hypoglycemia, etc) and release coricotropin releasing hormone (CRH). CRH travels from the hypothalamus to the anterior pituitary where it’s agonist affects stimulate the release of adrenocorticotrophic hormone, or ACTH. Once ACTH is released it traverses the body, via the bloodstream, to the adrenal glands. There its agonist activity stimulates the release of free cortisol into systemic circulation. Once adequate cortisol levels are established ACTH, and subsequently CRH, levels dwindle as they are inhibited by the presence of cortisol.

BACKGROUND
During times of physiologic stress the hypothalamic-pituitary-adrenal, HPA, axis increases plasma concentrations of adrenocorticotrophic hormone, ACTH, and subsequently raises plasma cortisol levels. Initially documented in critically ill human patients, CIRCI appears to be a relative, or reversible, state of adrenal dysfunction whereas the body’s ability to release cortisol during a stressful period, such as a septic insult, is blunted. The adrenal cortex is intact and functioning, as evidenced by a basal cortisol level and cortisol production post-ACTH challenge, but this level is insufficient to maintain homeostasis. In contrast to absolute adrenal failure, Addison’s disease, long-term glucocorticoid and mineralocorticoid replacement is not required in these patients, after they have recovered from their critical state. Cortisol is a highly important and complex molecule with effects on the cardiac, renal, hematologic, vascular, and metabolic systems. Many body processes rely on cortisol for effective function. Cortisol is involved with nutrient metabolism, maintenance of cell membranes, maintenance of vascular tone, catecholamine activity, cardiac contractility, and immune system and endothelial cell function.

CIRCI is thought to originate from underlying systemic inflammation and cytokine release. Pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-a) potentially suppress the HPA axis causing this transient disturbance in cortisol release and activity.
PRESENTATION AND CLINICAL SIGNS
Adrenal deficiency (relative or absolute) could, theoretically, present with any clinical signs that an “Addisonian” crisis patient might present with: collapse, hypotension, hypovolemia, dehydration, bradycardia, hyperkalemia, hyponatremia. In addition, in cases of sole glucocorticoid deficiency, waxing and waning signs such as vomiting, diarrhea, lethargy, anorexia, may also be present. However, with regards to relative adrenal dysfunction, as is the case in CIRCI, these clinical signs are usually masked in the face of critical illness. The most reproducible clinical manifestations of CIRCI is refractory hypotension in the face of severe illness; despite volume-loading and vasopressor therapy. A patient with persistent hypotension, despite initial interventions such as fluids and a vasopressor, should be considered suspicious for the CIRCI complex.

The incidence of CIRCI in critically ill humans varies greatly from study to study. This is due, in part, to the lack of standardization of diagnosing/identifying adrenal dysfunction. Yet, these incidences range from 30-50% with varied population sizes (Cohen and Vankatesh, 2010). A 2007 veterinary study identified an incidence of 48% of critically ill dogs (Burkitt et al, 2007).

DIAGNOSIS
Diagnosis of adrenal dysfunction in critical illness is hotly debated in human medicine. Several methods of clinicopathologic identification of relative adrenal dysfunction in the critically ill exist in human medicine and these include: random cortisol screening, corticotropin testing, free cortisol estimation, metapyrone testing, and glucocorticoid trial and response assessment. The typical method involved in diagnosing CIRCI in veterinary patients involves using a standard synthetic ACTH stimulation test. It is not the basal or post-stimulation cortisol values that are explicitly important, rather the difference between these two values, termed the delta cortisol (Δ cortisol). When this value is <9 mg/dL, this is considered, in addition to clinical signs, to point towards CIRCI. It has also been suggested that a narrowed criteria of a Δ cortisol of ≤ 3 mg/dL is highly suggestive of CIRCI.

Standard ACTH testing (protocol below) was compared to low-dose ACTH administration in critically ill patients. Using a 0.5ug/kg (vs. standard 5ug/kg) dose of ACTH proved to identify adrenal insufficiency in this population. This regimen identified several dogs with adrenal dysfunction not previously identified with the standard protocol. Thus, using an ACTH dose of 0.5ug/kg would be recommended in the diagnosis of patients with CIRCI.

Additional testing modalities to identify transient adrenal dysfunction in the critically ill include using a cortisol assay aimed at providing a true cortisol level- not a pre and post-stimulated value. As in many adrenal testing protocols, measuring a free-cortisol level would be ideal, as a total value can encompass free hormone with hormone that is protein-bound.

Criteria for establishing CIRCI in a critically ill veterinary patient:

- Patients with a normal/elevated basal cortisol level whose post-stimulation cortisol does not increase greater than 5% of the baseline.
- Patients with a delta cortisol ≤ 3 mg/dL
TREATMENT
There are several studies documenting increased survival rates in critically ill vasopressor-dependent septic patients who receive steroids after bouts of refractory hypotension. Steroid doses used in this case should be at physiologic or replacement doses. These are subsequently less than those used for anti-inflammatory or immunosuppressive effects. Hydrocortisone is used in human medicine most frequently. The dose is typically 200–300 mg for an average adult per day. This equates to a 3–4mg/kg/day dose. Using relative potencies to determine doses of other steroids yields equivalent doses of prednisone at 0.7–1mg/kg/day and dexamethasone at 0.1–0.4mg/kg/day (see Figure 1). This daily dose is typically divided into 4 doses given every 6 hours.

Figure 1

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Dose per day</th>
<th>Dose every 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>3–4 mg/kg/day</td>
<td>0.75–1 mg/kg</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.7–1 mg/kg/day</td>
<td>0.18–0.4 mg/kg</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.1–0.4 mg/kg/day</td>
<td>0.025–0.1 mg/kg</td>
</tr>
</tbody>
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It seems plausible to also administer a “loading” dose of a steroid and administer a CRI for the remainder of the daily amount.

CASE DISCUSSION
- **Signalment**: Mabel 12 year old, spayed female wheaten terrier 15.8kg
- **Presenting Complaint**: Acute weakness, two episodes of vomiting, one episode of diarrhea
- **Initial Assessment**: Mabel was tachycardic, hypothermic, and hypotensive (Doppler measured 30mmHg on right pelvic limb), with no Doppler blood pressure obtainable on the left pelvic limb. She had pale/cold mucous membranes, and a capillary refill time of 3 seconds. She had a 2/6 heart murmur of unknown etiology. Her extremities were also cool. She lacked left femoral arterial pulses.
- **Interventions**: Mabel presented in early decompensated shock. A mixed acid-base disorder consisting of a metabolic acidosis and a respiratory acidosis was diagnosed. Brief ultrasound showed no free abdominal or thoracic fluid. Initial packed cell volume was 43% and the total solids was 7.6 g/dL. After a 40mL/kg bolus of a balanced isotonic crystalloid (Normosol-R®), the repeat Doppler blood pressure obtained was 60mmHg and the packed cell volume was 24% with a total solids of 4.0 g/dL. A 5mL/kg artificial colloid (Hetastarch) bolus was also given. Coagulation times revealed a prothrombin time of 16 seconds (normal is 12–17) and an activated partial thromboplastin (aPTT) time of 121 seconds (normal is 70–102). The delayed aPTT time may be a dilutional effect and/or poorly understood effects of synthetic colloids. After initial stabilization, plans

**ACTH Stimulation Protocol:**
- Draw 2mL pre-sample
- Administer 0.5ug/kg of synthetic ACTH (Corsynotropin)
- Obtain a 1 hr. post-ACTH sample
were made to admit her to the ICU. Blood pressures continued to temporarily improve with boluses of crystalloids and colloids, but did not stabilize for several hours. Her blood pressure finally stabilized 8 hours after admission with a Doppler systolic holding at 90 mmHg. Broad spectrum antimicrobials were started to treat a possible septic focus and gastrointestinal (GI) translocation. A central line was placed in a saphenous vein for administration of additional fluids and repeated blood draws. Packed red blood cell and fresh frozen plasma transfusions were started for anemia and a potential dilutional coagulopathy after resuscitation with multiple blood volumes of crystalloids and colloids. Hematochezia was noted and gastrointestinal blood loss was added to her problem list. Pain control was instituted using buprenorphine (0.015mg/kg) administered intravenously. Gastrointestinal protectants and anti-emetics were also added to address vomiting and gastrointestinal hemorrhage. Enoxaparin, a low-molecular weight heparin, was started to prevent further clot formation.

- **Presence of criteria for CIRCI:** By day 4, Mabel had been tentatively diagnosed with Acute Pancreatic Necrosis and SIRS. Her initial blood pressure reading of the day revealed hypotension (64 mmHg via Doppler). Her CVP was 6 cm H2O so her preload/volume status was judged to be adequate. In lieu of this information Dopamine was started at 5ug/kg/min. Because she had some previous bouts of fluid unresponsive hypotension the attending clinician sent out an ACTH stimulation test the evening prior. Results revealed an improper response to ACTH stimulation: resting cortisol level was 2.2mg/dL (ref range: 1.0-5.0 mg/dL) and post-ACTH cortisol level of only 4.2 mg/dL (ref range: 8-17 mg/dL). She did not fit the criteria of primary hypoadrenocorticism (Addison’s disease) because her resting cortisol level was within the reference range. However, her delta cortisol was 2 (4.2 – 2.2) revealing an inadequate physiologic response to adrenal stimulation. Based on meeting the criteria of a delta cortisol of < 3 and the presence of refractory hypotension despite fluid and pressor therapy Mabel was started on hydrocortisone (Solu-Medrol®) at 2mg/kg/day divided into 4 doses. A dose of 0.5mg/kg was given initially and within 15 minutes her blood pressure increased to 75mmHg. It began to slowly climb and held at around 90-100mmHg for a few hours until Mabel unfortunately arrested; most likely due to a cerebral thromboembolic event.

**CONCLUSION**

Adrenal dysfunction in human patients remains somewhat controversial- with several camps opposed and several touting the “real-ness” of this syndrome. As this syndrome has been identified in veterinary patients, and the prognostic importance of correcting hypo-adrenal related hypotension in critically ill patients it remains plausible to incorporate CIRCI into the “critical care syndromes” such as: DIC, MODS, ARDS, etc. Veterinary technicians can assist with the intervention and treatment of patients with CIRCI by being diligent about monitoring blood pressure and understanding vasopressor pharmacology, knowing proper testing protocols for adrenal axis testing, and being ready to prepare and administer steroid CRI’s.


