

## **Addison's Update: A Case-Based Approach**

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Hypoadrenocorticism ("Addison's disease") is an uncommon disease in dogs. However, because of the potential for acute death in dogs with severe acid/base and electrolyte abnormalities, and the excellent prognosis with treatment, prompt diagnosis is crucial.

### **BACKGROUND**

The adrenal cortex is divided into 3 different layers. In order of outermost to innermost, they are the *zona glomerulosa*, *zona fasciculata*, and *zona reticularis*. Only the *zona glomerulosa* can make aldosterone, while the *z. fasciculata* and *reticularis* are responsible for the production of cortisol. Cortisol's function is primarily catabolic, in that it stimulates the breakdown of fat, muscle, and glycogen for use in gluconeogenesis. It's one of the four "anti-insulin" hormones that protect the body from hypoglycemia.

Cortisol secretion is regulated by the hypothalamic-pituitary-adrenal axis (HPAA). Physiologic, psychologic, and/or emotional stress initially stimulates the hypothalamus to secrete CRH (corticotrophin releasing hormone). CRH then stimulates the pituitary gland to release adrenocorticotrophic hormone (ACTH) into systemic circulation. When ACTH reaches the adrenal cortex, it stimulates the synthesis of cortisol.

As with other endocrine axes, the synthesis of cortisol is controlled by feedback inhibition. Cortisol itself inhibits further release of CRH and ACTH. Thus, when an abundance of cortisol is present in the body, that cortisol prevents additional stimulation of cortisol secretion in normal animals.

Aldosterone is a mineralocorticoid that stimulates the resorption of sodium, chloride, and water; and excretion of potassium, from the distal renal tubules. A deficiency in aldosterone can lead to hyponatremia, hypochloremia, hypovolemia, and hyperkalemia. Secretion of aldosterone is controlled by the renin-angiotensin-aldosterone (RAS) system. Note that physiologic doses of ACTH do NOT appear to play a significant role in the regulation of aldosterone synthesis; therefore, pituitary pathology resulting in ACTH deficiency should not result in aldosterone deficiency.

### **ETIOLOGY**

In dogs, Addison's is most commonly caused by adrenocortical failure, usually secondary to immune-mediated destruction of >90% of the adrenal cortex. Most patients exhibit signs of both cortisol and aldosterone deficiency. Neoplastic, infectious, and inflammatory infiltration of both adrenal cortices may also result in combined deficiency. Secondary hypoadrenocorticism due to ACTH deficiency results in isolated cortisol deficiency. Iatrogenic administration of exogenous glucocorticoids is the most common cause of secondary hypoadrenocorticism; however, pituitary neoplasia or trauma, in addition to idiopathic causes, may also result in secondary hypoadrenocorticism.

In patients with “atypical” hypoadrenocorticism (eunatremic, eukalemic hypoadrenocorticism), clinical signs of cortisol deficiency occur without concurrent electrolyte abnormalities. The etiology of atypical Addison’s is unclear; ACTH deficiency has been ruled out in most cases. It may be the result of partial immune-mediated destruction of the adrenal cortex, sparing the zona glomerulosa. Alternatively, some dogs with aldosterone deficiency may compensate via an unknown mechanism. Although some have speculated that atypical hypoadrenocorticism is simply an early manifestation of “typical” hypoadrenocorticism, many patients never lose their ability to secrete aldosterone.

## **CLINICAL PRESENTATION AND CLINICOPATHOLOGIC ABNORMALITIES**

Clinical presentation of hypoadrenocortical patients varies from patients with chronic “failure to thrive” (ADR) and/or gastrointestinal signs (anorexia, vomiting, diarrhea, melena, etc.), to patients that present acutely in hypovolemic shock. Both groups of patients may have a history of improvement with fluid administration and/or glucocorticoid therapy.

Physical examination findings can also vary from almost normal to hypovolemic shock. Hyponatremia and hyperkalemia are the classic laboratory findings in dogs. However, these findings may be absent early in the disease process, and in dogs with atypical hypoadrenocorticism. Additionally, atypical Addisonians rarely present in hypovolemic shock; however, excessive gastrointestinal blood loss can lead to hypovolemic shock in these patients.

Regurgitation may be seen in rare Addisonian patients with megaesophagus, and seizures have also been reported secondary to hypoglycemia. Polyuria and polydipsia occur infrequently in dogs with hypoadrenocorticism; the mechanism is unknown.

Additional laboratory abnormalities may include azotemia, hypoglycemia, hyponatremia, hypocholesterolemia, hypercalcemia and metabolic acidosis (decreased  $tCO_2$ /bicarbonate). Hypoadrenocorticism should be considered in patients that present for signs of hypoglycemia (such as seizures) and hypercalcemia. Because most patients also have a specific gravity  $<1.030$ , azotemic patients can be incorrectly diagnosed with primary renal failure. In these cases, the patient’s history and rapid response to fluid therapy should increase suspicion of hypoadrenocorticism.

Patients exposed to cortisol often exhibit neutrophilia and lymphopenia (“stress leukogram”). In the absence of cortisol, such as with hypoadrenocorticism, patients may be predicted to have neutropenia, lymphocytosis, and eosinophilia. In fact, these specific changes don’t occur very frequently in Addisonian patients. However, a number of Addisonians do have a “lack of a stress leukogram,” meaning that they do not have neutrophilia or lymphopenia. (I have recently heard the “lack of a stress leukogram” referred to as a “relaxed leukogram” by clinical pathologists!) In a clinically ill patient, the findings of normal neutrophil and/or lymphocyte counts, with or without eosinophilia, are unexpected, and may raise suspicion of hypoadrenocorticism.

## **ADDITIONAL DIAGNOSTICS**

In cases of moderate to severe hyperkalemia, an ECG may reveal spiked T-waves, absent p-waves, increased P-R interval, and/or bradycardia. Other basic diagnostic findings in hypoadrenocortical dogs are non-specific. Thoracic radiographs may reveal microcardia (consistent with hypovolemia) or megaesophagus. Abdominal ultrasound may reveal small adrenal glands.

## **DEFINITIVE DIAGNOSIS**

Definitive diagnosis relies on results of an ACTH-stimulation test in both typical and atypical Addisonians. Post-stimulation cortisol samples of  $<2 \mu\text{g/dL}$  are consistent with hypoadrenocorticism, although rare patients may have stim results between 2 and  $3 \mu\text{g/dL}$ . Steroids given days prior to the test may blunt the response, and it is not uncommon for a dog with a history of recent glucocorticoid administration to have a post-stimulation cortisol of  $2.5 - 5.0 \mu\text{g/dL}$ . Most synthetic glucocorticoids (including prednisone and methylprednisolone) will interfere with the cortisol assay itself, and may cause a falsely elevated cortisol result. However, dexamethasone does not interfere with the cortisol assay and may be given prior to or during the ACTH stimulation test, if necessary.

## **BASELINE CORTISOL—FOR RULE-OUT PURPOSES ONLY!**

Although definitive diagnosis of Addison's requires an ACTH stimulation test, the disease can be RULED-OUT by checking baseline cortisol values. If the baseline cortisol is  $>2 \mu\text{g/dL}$ , the dog does not have hypoadrenocorticism (there are exceptionally RARE cases that could have a value from 2-3  $\mu\text{g/dL}$ ). If the baseline cortisol is  $<2 \mu\text{g/dL}$ , an ACTH stimulation test MUST be run to confirm the diagnosis. The baseline cortisol is most useful in patients without electrolyte abnormalities that may be suspected of atypical hypoadrenocorticism because of chronic GI signs. Since it does not require the purchase of synthetic ACTH, it is much less expensive than the ACTH stimulation test.

## **TREATMENT—TYPICAL HYPOADRENOCORTICISM**

Treatment of hypoadrenocorticism depends on the presentation of the patient. If they present in hypovolemic shock ("Addisonian crisis"), diagnosis is usually unknown initially, and treatment is generally similar to that for any patient in hypovolemic shock. The first priorities in stabilizing a patient in Addisonian crisis are to correct the hypovolemia and the hyperkalemia, since these conditions are most likely to be fatal if not treated immediately. Although 0.9% NaCl has been recommended because of its sodium content and lack of potassium, isotonic crystalloids such as Normosol-R and Lactated Ringer's Solution may also be used—they are generally more alkalinizing, they have minimal amounts of potassium, and their lower sodium contents are actually helpful in patients with severe hyponatremia ( $<120 \text{ mEq/L}$ ). Hypoglycemic patients should be treated with dextrose.

If the dog is moderately hyperkalemic, the hyperkalemia will likely be corrected with fluid therapy alone. However, if the hyperkalemia is severe ( $>8.5 \text{ mEq/L}$ ) or causing ECG changes, additional therapy may

be warranted. A 10% solution of calcium gluconate (0.5-1.5 mL/kg, or 2 to 10 mL/dog) may be administered intravenously over 10 to 15 minutes while monitoring for ECG changes associated with hypercalcemia. Although the effect is almost immediate, it lasts for only about 10 to 30 minutes. This treatment is cardioprotective and does NOT lower the potassium concentration. Simultaneous intravenous administration of dextrose (1 g/unit of insulin) and regular (R) insulin (0.1 U/kg) will decrease potassium levels within 15 to 30 minutes. A 5% dextrose solution in a balanced electrolyte solution (Norm R or LRS) should be administered after insulin treatment to alleviate hypoglycemia. Administration of a  $\beta$ 2-agonist such as albuterol also helps drive potassium into the cells.

Glucocorticoids should be given to a patient during the crisis. Dexamethasone, 0.2 mg/kg, may be given initially. Although this dose is lower than recommended in some drug resources, it is equivalent to approximately 1.5 mg/kg of prednisone and is more than adequate. This dose is often given twice the first day and then cut in half for the next two days. As soon as the patient is eating, she may be given oral prednisone. While in the hospital, the patient requires a dose above the normal physiologic dose (~0.2 mg/kg/day); approximately 1 mg/kg/day is commonly used. The dog may be started on an increased dose of 0.5 mg/kg/day for a couple of days, then tapered to around 0.1–0.3 mg/kg/day. This dose is adjusted based on the clinical signs of the dog (activity level, appetite, gastrointestinal signs), combined with the avoidance of side effects from the prednisone, such as PU/PD. The author frequently tapers to doses lower than 0.1 mg/kg (such as 0.03 mg/kg), especially in large dogs, based on clinical signs and side effects. Note that once an ACTH stimulation test confirms naturally occurring hypoadrenocorticism, it does not need to be repeated and is not used in monitoring prednisone dose.

Following confirmation of hypoadrenocorticism, the dog should also be started on a mineralocorticoid replacement. The author's preference is desoxycorticosterone pivalate (DOCP). The label dose is 2.2 mg/kg, q25-28d, but recent studies and experience show that lower doses may be acceptable, particularly in large dogs. I usually start no higher than 1.5 mg/kg, and often as low as 1 mg/kg, especially in bigger dogs (>25 kg). Although the first dose may be given IM in case dehydration impedes SQ absorption, subsequent doses can usually be given SQ. Electrolyte values should be checked 14 days after injection to assess the dose, and immediately prior the next injection (approximately 28d) to assess duration of activity. Dose and frequency should then be modified based on these electrolyte values. Electrolytes should be rechecked every 3-6 months following dose stabilization. This means that electrolytes assessment is not required prior to each injection after the dosage and optimal dosing interval has been determined (which usually takes 1-2 doses, but sometimes more).

Two FDA-approved DOCP formulations are available—Percorten-V® (Elanco) and Zycortal® (Dechra). The only differences between the two formulations are a different preservative is used in each, and that Zycortal® is labeled for SQ administration, while Percorten-V® is labeled for IM administration. In 1995, a study (McCaben, et al, *JAAHA*) established that Percorten-V® may be administered SQ, and there's no reason to believe that Zycortal® could not be administered IM, if necessary.

It is IMPERATIVE that owners be cautioned not to try to space out or skip DOCP injections without the advice of a veterinarian for financial reasons. This almost always leads to an Addisonian crisis eventually, which risks the patient's life and increases overall cost of treatment. Alternatively, fludrocortisone may be used as a mineralocorticoid supplement. It is oral and initially given at 0.02 mg/kg/d, divided. It also has some glucocorticoid activity. However, patients should be stabilized (ie, consistently normal electrolytes during rechecks) using a combination of fludrocortisone and prednisone. Then the prednisone dose can be tapered to the lowest effective dose. Approximately 50% of Addisonian dogs managed with fludrocortisone do not require long-term prednisone supplementation.

Management of a chronic Addisonian involves the administration of prednisone and a mineralocorticoid, as described above. Additional glucocorticoids, 2 times the normal dose, should be given when the dog is stressed, such as prior to veterinary visits (even for DOCP injections), or when there are visitors to the home. Owners should be empowered to determine when their dog will need a dose increase, as it varies significantly from one dog to another. Signs of inadequate dosing often occur the day AFTER the stressful event, so owners should journal when this occurs.

## **TREATMENT—ATYPICAL HYPOADRENOCORTICISM**

Treatment of atypical hypoadrenocorticism includes glucocorticoid replacement and supportive therapy. Depending on the presentation, patients with more chronic signs may be managed at home, whereas patients with more significant gastrointestinal signs will need hospitalization. The physiologic dose of prednisone is thought to be 0.1- 0.25 mg/kg, and stressed patients need approximately 2 times this dose. At diagnosis, I typically start these patients at about 1 mg/kg of prednisone per day to account for the stress of illness and hospitalization (or hospital visits). (If parenteral therapy is necessary, I use 0.10-0.15 mg/kg dexamethasone, as it has 7-8 times the glucocorticoid activity as prednisone.) This dose is slowly decreased so that the patient is receiving the physiologic dose of prednisone within a few days of returning home. Dose is adjusted based on the clinical signs. If the dog becomes PU/PD, the dose is decreased. If gastrointestinal signs increase, or the dog is lethargic overall, the dose is increased. Additionally, the prednisone dose must be increased if the patient experiences stress—such as a vet visit, houseguests, increased exercise (such as hunting), or unrelated illness. As with “typical” Addisonian dogs, some of these patients (especially larger dogs) may need less than 0.1 mg/kg/day of prednisone.

Supportive therapy may include intravenous fluids, gastroprotectants, blood transfusion (if GI blood loss is severe), dextrose administration, etc., depending on the clinical presentation of the patient.

As at least some patients with atypical Addison's have been shown to have aldosterone deficiency despite electrolyte concentrations within reference range, the use of mineralocorticoids in these patients is controversial. If an ACTH stimulation test shows that aldosterone concentrations are low, mineralocorticoid supplementation (potentially low dose DOCP) may be considered. Client factors, including finances, will play a role in this decision.

## **PROGNOSIS**

The prognosis for good quality of life is excellent with prompt treatment of typical hypoadrenocorticism. Even hunting dogs can return to normal activity (with adjustment of prednisone dose), and patients have a normal life expectancy. Dogs with atypical hypoadrenocorticism also have a great prognosis, and some (approximately 10%) develop electrolyte abnormalities following initial diagnosis (if not treated with mineralocorticoids). Thus, measurement of electrolytes one week, 1 month, and then every 3-6 months following diagnosis is recommended.