Canine Hypoadrenocorticism
Overview, Diagnosis, & Treatment

Maya Lottati DVM, PhD
VCA Veterinary Specialists of the Valley
Woodland Hills, California

David Bruyette, DVM, Diplomate ACVIM (Internal Medicine)
VCA West Los Angeles Animal Hospital
Veterinary Diagnostic Investigation and Consultation

Canine hypoadrenocorticism, or Addison's disease, results from adrenocortical hormone insufficiency. An overall low disease prevalence combined with vague clinical signs and nonspecific clinicopathologic abnormalities makes diagnosis challenging. Ultimately, specialized laboratory testing is required for definitive diagnosis.

Early identification and treatment can result in an overall excellent long-term prognosis; therefore, it is essential that clinicians be familiar with the various forms and potential presentations of canine hypoadrenocorticism.

ADRENAL CORTEX PHYSIOLOGY

The adrenal cortex is composed of 3 distinct functional layers (**Figure**):
- **Outer zona glomerulosa:** Primarily involved in production of mineralocorticoids (ie, aldosterone)
- **Middle zona fasciculata:** Responsible for production of glucocorticoids (ie, cortisol)
- **Inner zona reticularis:** Primarily involved in production of sex hormones (ie, androgens, estrogens).

Glucocorticoids

Glucocorticoids (cortisol) influence nearly every tissue in the body and are vital for metabolism, immunity, and stress counter–regulation.
- Production is regulated by an elaborate **hypothalamic–pituitary–adrenal axis**, which uses a series of positive and negative feedback loops for precise moment-to-moment control of cortisol production from the adrenal cortex.
- Pituitary-derived **adrenocorticotropic hormone** (ACTH) binds to ACTH receptors in the adrenal cortex, resulting in glucocorticoid synthesis and secretion.

- Glucocorticoids are subject to a feedback mechanism that stimulates or inhibits their production.

Aldosterone

Aldosterone is the primary mineralocorticoid that promotes sodium resorption and potassium excretion in the distal renal tubules.
- Water passively follows sodium, facilitating movement of fluid from the glomerular filtrate into the renal medullary interstitium.
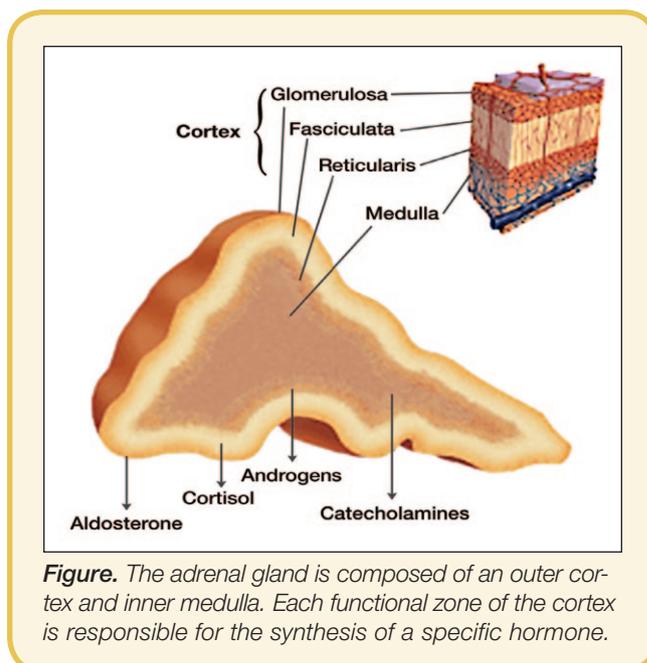- Synthesis and release of aldosterone are primarily regulated

Figure. *The adrenal gland is composed of an outer cortex and inner medulla. Each functional zone of the cortex is responsible for the synthesis of a specific hormone.*

by the **renin–angiotensin–aldosterone system**, which is upregulated in states of hypotension and hypovolemia.

- To a lesser extent, the release of aldosterone is regulated by elevated serum potassium concentrations.

FORMS OF HYPOADRENOCORTICISM

Primary Hypoadrenocorticism

Primary hypoadrenocorticism, the classic form of the disease, is characterized by a lack of glucocorticoids and mineralocorticoids.

Causes. Primary hypoadrenocorticism typically results from immune-mediated destruction of adrenal cortical tissue; nearly 85% to 90% of adrenal tissue must be destroyed before substantial biochemical and clinical manifestations occur. Less common causes of adrenocortical destruction include:[1,2]

- Iatrogenic administration of mitotane or trilostane for hyperadrenocorticism treatment
- Neoplasia, infection, or infarction of the adrenal glands.

Autoantibodies. Although the specific immunologic antigen is not yet known in dogs, the presence of 21-hydroxylase autoantibodies characterizes most human cases.[3,4] Recently, autoantibodies for a P450 side-chain cleavage enzyme were more commonly identified in canine patients with hypoadrenocorticism as compared to control patients.[5] However, further studies are required to elucidate the role of antibodies to this enzyme in the pathogenesis of hypoadrenocorticism.

Atypical Hypoadrenocorticism

In a small population of "atypical" dogs—approximately 5% to 10%—adrenal destruction is purported to spare the glomerulosa layer, resulting in an isolated glucocorticoid deficiency.[6] Most dogs with isolated glucocorticoid insufficiency do not progress to clinically significant mineralocorticoid deficiency,[6,7] although a recent paper showed that these dogs may have low or undetectable levels of aldosterone despite apparently normal electrolyte concentrations.[8]

Secondary Hypoadrenocorticism

Secondary hypoadrenocorticism refers to a central (anterior pituitary) deficiency of ACTH, resulting in isolated glucocorticoid insufficiency. Mineralocorticoids are spared because ACTH does not directly influence their release.

Causes. This condition most commonly results from abrupt discontinuation of long-term exogenous administration of corticosteroids or progesterone analogs. Rarely, congenital defects of the pituitary gland, such as a cystic Rathke's pouch, neoplasia, or trauma[9] affecting the hypothalamus or pituitary gland, result in secondary hypoadrenocorticism.

Critical Illness-Related Corticosteroid Insufficiency

Critical illness-related corticosteroid insufficiency (CIRCI) is also referred to as relative adrenal insufficiency and has been associated with severe illness, such as sepsis, septic shock, or trauma. The syndrome is typically transient, and adrenal function normalizes following correction of the underlying condition. Critically ill patients exhibiting refractory hypotension despite aggressive fluid therapy and the use of pressor agents should be evaluated for CIRCI.

SIGNALMENT

Age & Sex

Primary hypoadrenocorticism is most commonly reported in young to middle-aged female dogs,[10] while atypical hypoadrenocorticism generally occurs at older ages than those seen with primary hypoadrenocorticism.[7]

Breeds

Although dogs of any sex, age, or breed (including mixed breeds) can develop the disease, certain breeds are over-represented (**Table 1**),[10] and strong evidence suggests the disease is heritable in certain breeds.[11–13] A study underway at North Carolina State University is attempting to identify genetic factors involved in Addison's disease in standard poodles (ncstatevets.org/addisonsstudy).

TABLE 1: Common Breeds Affected by Hypoadrenocorticism

- Great Dane
- Poodle[12]
- Portuguese water dog[11]
- Rottweiler
- Wheaten terrier
- West Highland white terrier

DIAGNOSIS

Hypoadrenocorticism is diagnosed on the basis of a compatible history, clinical signs, laboratory abnormalities, imaging studies, and ACTH stimulation test results. With the exception of the ACTH stimulation test—which has narrow values that define hypoadrenocorticism—there is a vast continuum of potential findings on the initial screening tests.

History & Clinical Signs

The clinical presentation of hypoadrenocorticism can vary in severity (**Table 2,** page 34), with waxing and waning episodes of illness that classically worsen during times of stress. The *Addisonian crisis* is the life-threatening culmination of combined hormone deficiencies that can be fatal if not appropriately treated.

Based on the signs noted in **Table 2**, it is understandable that atypical hypoadrenocorticism is more challenging to diagnose because signs related to isolated glucocorticoid deficiency are more insidious.

Laboratory Abnormalities

Patients with hypoadrenocorticism may present with myriad laboratory abnormalities related to glucocorticoid and/or mineralocorticoid insufficiency (**Table 3,** page 34). The serum biochemical profile may reveal hypoglycemia,

TABLE 2. Clinical Signs of Mineralocorticoid & Glucocorticoid Insufficiency

MINERALOCORTICOID INSUFFICIENCY	GLUCOCORTICOID INSUFFICIENCY
Results in: • Low sodium concentrations • High potassium concentrations • These changes may manifest as: » Dehydration » Hypovolemic shock » Collapse	**Results in vague signs:** • Lethargy/weakness • Shaking • Polyuria/polydipsia • Vomiting/diarrhea • Abdominal pain • Inappetence/weight loss

eosinophilia, lymphocytosis, hypercalcemia, hypocholesterolemia, hyperphosphatemia, hypochloremia, and elevated liver enzymes.[10]

GI Abnormalities. Anorexia, vomiting, and diarrhea are common. Anemia—from chronic disease or gastrointestinal (GI) bleeding—may be identified, although relative polycythemia may also result from dehydration. Depending on the degree of vomiting and diarrhea, hypoalbuminemia, hypoglobulinemia, or acidemia may be identified.

Na/K Ratio. When hyponatremia, hyperkalemia, or both are noted, mineralocorticoid insufficiency is identified. A sodium/potassium (Na/K) ratio < 27:1 is strongly suggestive for hypoadrenocorticism, and lower ratios are associated with higher specificity.[14,15] However, low Na/K ratios as severe as < 20:1 can also occur with other disorders, such as acute kidney injury, diabetic hyperosmolar syndrome, gastroenteritis, and various causes of abdominal and thoracic effusions.

A recent study demonstrated that the combination of Na/K ratio *with* lymphocyte count is a better screening test for hypoadrenocorticism than either variable alone,[15] but this also can be subject to misinterpretation.

Renal Abnormalities. Azotemia in the presence of an inappropriately low specific gravity (typically < 1.030) can easily be confused with primary renal insufficiency, but hypoadrenocorticism can coexist with renal insufficiency.

Atypical Hypoadrenocorticism. Patients with atypical hypoadrenocorticism are more likely to exhibit hypoalbuminemia, hypocholesterolemia, and anemia on routine bloodwork (**Table 3**).[7]

Diagnostic Imaging
Thoracic radiographs may reveal a small heart and caudal vena cava, which signifies hypovolemia;[16] rarely, megaesophagus may be seen in association with hypoadrenocorticism.[17]

On **abdominal ultrasonography**, atrophy of the adrenal glands should result in a measurable reduction in adrenal size. In the hands of experienced ultrasonographers, the adrenal glands may appear thin and short when compared with adrenal glands in healthy dogs;[18] however, in a few cases of hypoadrenocorticism, normal size adrenal glands have been reported.[14]

An **electrocardiogram** may reveal a bradyarrhythmia with absent P waves, tented T waves, prolonged QRS complexes, and decreased R wave amplitude, depending on the degree of hyperkalemia.

ACTH Stimulation Test
A baseline serum cortisol level > 2 mcg/dL can be used to rule out hypoadrenocorticism, while a cortisol level ≤ 2 mcg/dL necessitates an ACTH stimulation test.[19] The ACTH stimulation test remains the gold standard for diagnosis of all forms of hypoadrenocorticism; it should be performed in *any* patient suspected of having the disease.

Cortisol is measured at baseline and then one hour following an IV or IM injection of synthetic ACTH (5 mcg/kg).[20] Typical and atypical hypoadrenocorticism are defined by a pre- and postcortisol concentration of ≤ 2 mcg/dL.[7]

Differentiation between primary and secondary hypoadrenocorticism requires demonstration of elevated or low/absent endogenous ACTH.

Currently, the diagnosis of CIRCI is controversial, and the following guidelines have all been used to evaluate adrenal function in critically ill patients:[21-23]
• A change in cortisol concentration (delta cortisol) of < 3 mcg/dL following exogenous ACTH administration
• A post ACTH cortisol concentration < the top end of the normal reference range, with a normal to high baseline cortisol concentration.
• A normal or elevated baseline cortisol concentration and < 5% increase in cortisol following ACTH administration.

TABLE 3. Comparison of Typical Versus Atypical Hypoadrenocorticism in Dogs

PARAMETER	HYPOADRENOCORTICISM	
	TYPICAL	**ATYPICAL**
Age	Young to middle age	Middle to older age
LABORATORY ANALYSIS		
Anemia	Present	Present*
Azotemia	Present*	Present
Eosinophilia/ lymphocytosis	Present	Present
Hypercalcemia	Present*	Absent
Hyperkalemia/ hyponatremia Na:K ratio < 27	Present*	Absent
Hypoalbuminemia	Present	Present*
Hypocholesterolemia	Absent	Present*
Hypoglycemia	Present	Present
Urine specific gravity < 1.030	Present	Present
THERAPY		
Glucocorticoid replacement	Required	Required
Mineralocorticoid replacement	Required	Not required

* Significant difference between typical and atypical groups[7]

TREATMENT

Addisonian Crisis

1. As soon as possible, collect samples for a minimum database (complete blood count, serum biochemical profile, urinalysis) and baseline cortisol level—*before* starting any therapy.
2. Initiate an ACTH stimulation test and begin aggressive IV fluid therapy with isotonic crystalloids (0.9% sodium chloride, Ringer's lactate solution).
3. Incrementally and rapidly administer shock fluid doses (up to 90 mL/kg) until perfusion parameters noticeably improve. Proceed cautiously if the serum sodium concentration is < 120 mEq/L to avoid demyelinating certain parts of the brain.
4. Once hemodynamic stability has been reached, correct dehydration and ongoing losses over the next 12 to 24 hours.
5. Monitor packed cell volume/total solids, serum electrolytes, and blood glucose every 6 to 8 hours until values have normalized and the patient is clinically stable.

If **hyperkalemia persists** despite fluid resuscitation and mineralocorticoid replacement therapy, suspect renal failure and monitor patient for oliguria or anuria. Additionally, to correct life-threatening hyperkalemia:

- Consider treatment with dextrose and regular insulin, addressing metabolic acidosis, *or*
- Treatment with a beta-adrenergic drug, such as terbutaline or albuterol.

> In the acute setting, IV fluids are lifesaving and—through dilution and renal excretion—restore blood volume, improve renal perfusion, and decrease potassium concentrations.

If **primary hypoadrenocorticism is highly suspected**, then replacement of glucocorticoids and mineralocorticoids in the acute setting can help improve clinical signs and clinicopathologic abnormalities.

- Administer IV dexamethasone after fluid resuscitation (**Table 4**) because it does *not* interfere with the ACTH stimulation test.
- After the ACTH stimulation test, if documented hyperkalemia is a concern, administer an IM injection of the synthetic mineralocorticoid desoxycorticosterone pivalate (DOCP) (2.2 mg/kg), which is safe in the emergency setting even if primary hypoadrenocorticism is not the final diagnosis. Studies have shown that DOCP administered to healthy dogs at these doses does not produce adverse effects.[24]

In the emergency setting, **avoid**:

- Administration of prednisone, prednisolone, and cortisone acetate because they interfere with the cortisol assay and artificially alter test results
- SC administration of DOCP or any other medication due to poor absorption in the dehydrated patient
- PO administration of any medication, including fludrocortisone, in patients exhibiting GI signs or poor GI tract perfusion.

Long-Term Maintenance

Patients with primary hypoadrenocorticism require lifelong glucocorticoid and mineralocorticoid replacement, while those with atypical or secondary hypoadrenocorticism require only glucocorticoid replacement.

Replace glucocorticoids daily at physiologic doses (**Table 4**).

- Prednisone, prednisolone, and cortisone acetate are all reasonable choices; titrate doses to the lowest effective dose that controls clinical signs and minimizes adverse effects.

TABLE 4. Recommended Starting Doses for Glucocorticoid & Mineralocorticoid Replacement

MEDICATION	MECHANISM OF ACTION	DOSE	SPECIAL CONSIDERATION
Acute (Addisonian Crisis)			
Dexamethasone *or* Dexamethasone sodium phosphate	Glucocorticoid	**0.1–0.2 mg/kg** IV Q 24 H	
Prednisone *or* Prednisolone	Glucocorticoid	**0.5–1 mg/kg** PO Q 24 H, *or* SC (prednisone only)	PO/SC steroids *not* recommended in dehydrated patients or those with GI signs
Desoxycorticosterone pivalate	Mineralocorticoid	**2.2 mg/kg** IM Q 28 D, *or* as necessary	SC administration *not* recommended in dehydrated patients
Maintenance Phase			
Prednisone *or* Prednisolone	Glucocorticoid	**0.25–0.5 mg/kg** PO Q 24 H	Titrate dose to effect
Cortisone acetate	Glucocorticoid	**0.25–0.5 mg/kg** PO Q 24 H	Titrate dose to effect
Fludrocortisone acetate	Mineralocorticoid & glucocorticoid	**0.02 mg/kg** PO Q 24 H, *or* divided	Titrate dose to effect
Desoxycorticosterone pivalate	Mineralocorticoid	**2.2 mg/kg** SC or IM Q 28 D, *or* as necessary	Frequency of administration/required dose vary among dogs

- Determine which steroid to use based largely on availability, cost, and adverse effects seen in a given patient.
- Consider increasing the initial dose if, during the course of treatment, GI signs, malaise, or weight loss continue.
- Conversely, consider decreasing the dose, or switching to another corticosteroid, if there are clinical signs of glucocorticoid excess, such as polyuria/polydipsia. **Note:** it might be difficult to distinguish these signs from the polydipsia/polyuria that can accompany DOCP treatment.
- The maintenance dose should be increased (2–3 times) during times of stress, such as illness, injury, or surgery, including elective procedures that require anesthesia.
- Parenteral steroid administration may be necessary in patients that cannot tolerate oral medications or are dehydrated (**Table 4**).

Clinical signs of secondary hypoadrenocorticism in veterinary patients on long-term steroid therapy are uncommon. Rarely, some patients may experience GI signs secondary to glucocorticoid withdrawal following abrupt cessation of steroid therapy. To avoid signs of adrenal insufficiency, it is recommended to taper steroids to physiologic replacement doses over several weeks.

Treatment of CIRCI

Glucocorticoid treatment of veterinary patients with CIRCI is controversial, and limited data is available to support use, dosage, or route of administration. In patients that meet the criteria of CIRCI and display refractory hypotension (despite aggressive medical management), we suggest the use of supplemental glucocorticoids at doses similar to those used in an Addisonian crisis (**Table 4**). Following resolution of critical illness, corticosteroid therapy may be tapered and discontinued depending on the patient's clinical response. A repeat ACTH stimulation test can be performed 4 to 6 weeks following discontinuation of steroid therapy to document adrenal recovery.

Replace mineralocorticoids in the form of IM or SC DOCP (2.2 mg/kg Q 25 days[25])—the most common form of replacement; these patients also require daily glucocorticoid replacement therapy.

- Check patient electrolyte levels at 2 and 3 weeks after initial DOCP administration; then every 3 to 4 days until abnormal shifts in Na or K are detected.
- The dosing interval lasts 28 days on average, but range varies widely among patients. It is not uncommon for veterinarians to successfully extend the dosing interval.
- See **Dosing & Financial Considerations for DOCP**.

Combined glucocorticoid and mineralocorticoid activity is provided by fludrocortisone acetate, a PO daily medication, which abolishes the requirement for a separate corticosteroid and can be substituted if DOCP is not available. However, compared with DOCP, disadvantages of fludrocortisone include increased cost (especially in larger dogs), more frequently recognized adverse effects (eg, polyuria/polydipsia), and less control of hyponatremia.[27]

Dosing & Financial Considerations for DOCP

A recent paper demonstrated that, in canine patients with hypoadrenocorticism, lower initial doses of DOCP are equally efficacious in controlling electrolytes and clinical signs compared with the recommended starting dose (**Table 4**).[26]

DOCP is relatively expensive, particularly in large breed dogs; thus, these findings have important financial implications for veterinarians and pet owners. If finances are of concern, after the first dose, it is reasonable to attempt incremental lowering of the subsequent DOCP doses by approximately 25%. Clients can also be taught to administer DOCP at home, which has potential cost savings.

When an attempt is made to reduce the dose or extend the interval between injections, more frequent monitoring of serum electrolytes is required, and clients should be informed that—in addition to the cost of DOCP—initial cost will increase accordingly.

PROGNOSIS

All patients with primary hypoadrenocorticism require life-long medical therapy. Once patients are well regulated, evaluate them at least 2 times each year, with a physical examination and routine bloodwork. Although canine hypoadrenocorticism is serious and, sometimes, life-threatening, early identification and proper treatment can result in an excellent long-term prognosis in most patients.[27] ■

ACTH = adrenocorticotropic hormone; CIRCI = critical illness-related corticosteroid insufficiency; DOCP = desoxycorticosterone pivalate; GI = gastrointestinal; K = potassium; Na = sodium

***Maya Lottati**, DVM, PhD, is a resident in internal medicine at VCA Veterinary Specialists of the Valley in Woodland Hills, California. She received her DVM from University of California–Davis and completed a small animal internship at VCA West Los Angeles Animal Hospital.*

***David Bruyette**, DVM, Diplomate ACVIM, is the medical director at West Los Angeles Animal Hospital and a clinical professor in the Department of Radiation Oncology at University of California—Los Angeles. He received his DVM from University of Missouri and completed an internship at Purdue University and residency in internal medicine at University of California—Davis. He then became a staff internist at West Los Angeles Veterinary Medical Group and member of the Department of Comparative Medicine at Stanford University.*

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