

Update on Managing Canine Hyperadrenocorticism

UNDERSTAND

Hyperadrenocorticism (HAC, Cushing's syndrome) describes the clinical manifestation of chronic exposure to excess levels of glucocorticoids, primarily cortisol. It is relatively common in older dogs, increasingly recognized in cats, and rare in other domestic animals. The symptoms of HAC are the results of chronic overproduction of circulating glucocorticoids by the adrenal glands. Left untreated, dogs experience a progressive decrease in overall quality of life and are predisposed to life-threatening conditions such as hypertension, chronic infections, glomerular disease and pulmonary thromboembolism.

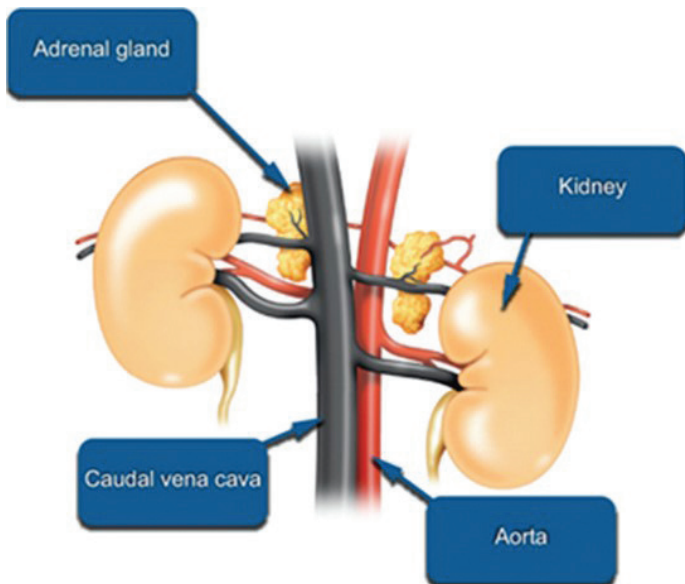


Figure 1: Location of adrenal glands.

Each adrenal gland is divided into two functionally distinct parts: the cortex and medulla. The adrenal cortex comprises 80 – 90% of the entire gland and produces glucocorticoids, mineralocorticoids, and androgens. The medulla comprises 10 – 20% of the adrenal gland and produces catecholamines.^{1,2} Cortisol is released by the adrenal gland in response to stress. A classical negative feedback loop operates to regulate endogenous production.

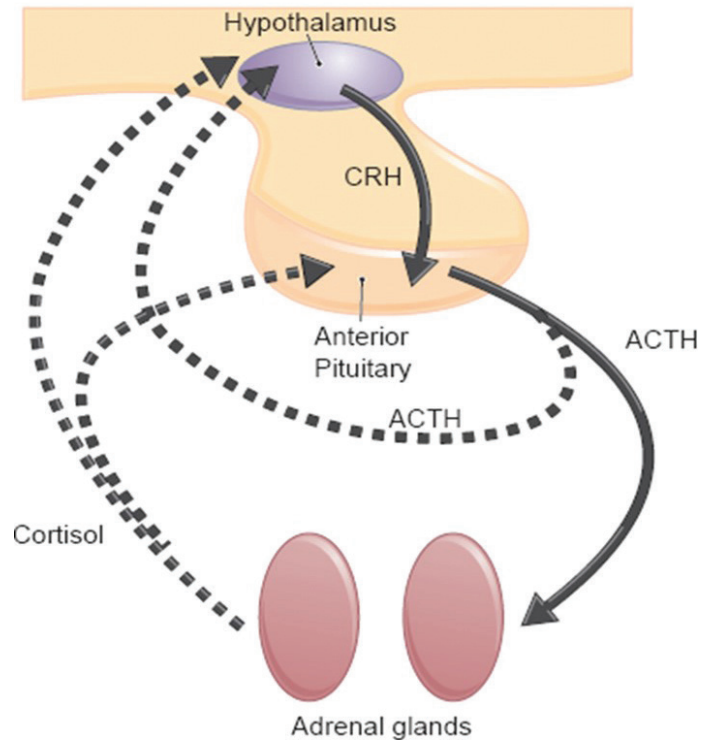


Figure 2: Hypothalamic-pituitary-adrenal (HPA) axis in a healthy dog. Note - the solid line is the positive feedback (direct release of hormones) and the dotted line represents the negative feedback (mechanism by which the hormone release is turned off).

The hypothalamus secretes corticotropin-releasing hormone (CRH) that travels to the anterior pituitary, regulating the secretion of adrenocorticotropic hormone (ACTH), which regulates the secretion of cortisol by the adrenal cortex. Both cortisol and ACTH have negative feedback effects on higher centers.

HAC can be spontaneous or iatrogenic. The spontaneous cases are associated with a tumor in either the pituitary or the adrenal gland. Pituitary tumors are responsible for 80 – 85% of HAC cases. The majority of pituitary tumors are microadenomas (< 1 cm), while 10 – 20% are macroadenomas (> 1 cm). Patients with macroadenomas are prone to neurologic signs. In pituitary-dependent hyperadrenocorticism (PDH), a tumor in the

anterior pituitary autonomously secretes ACTH in excess, which triggers excessive cortisol production. In adrenal-dependent hyperadrenocorticism (ADH), the adrenal tumor secretes cortisol autonomously. Adrenal tumors have a 50% chance of malignancy. Determining the tumor location (adrenal vs. pituitary) allows for: 1) determination of the proper treatment, 2) a more specific prognosis, and 3) greater prediction of additional clinical signs.^{1,2}

Atypical HAC is a controversial diagnosis with an unclear etiology/pathogenesis. These dogs have a history, physical exam findings, clinical pathology abnormalities, and adrenal imaging consistent with HAC, yet routine screening tests are inconclusive.^{3,4} The 2012 ACVIM consensus statement for diagnosing HAC suggests that the current reference ranges and cut-off values for HAC screening tests introduced in the 1970s and 1980s should be re-evaluated and possibly adjusted.⁵ If clinical suspicion of HAC is high and other disease processes have been ruled out, then re-evaluation/testing should be performed 30-90 days later.

IDENTIFY

Cortisol has diverse effects on the body that can lead to a wide variety of clinical signs. This can result in changes to bone, muscle, skin/hair coat, renal system, liver, CNS, blood production, and immune response. Clinical signs associated with HAC are described in the lists below.

Common clinical signs:

- Polyuria/polydipsia
- Depression/lethargy
- Polyphagia
- Panting
- Pot-bellied appearance
- Alopecia
- Secondary dermatologic conditions

Other clinical signs:

- Muscle wasting
- Hyperglycemia (insulin resistance)
- Neurologic signs
- Hypertension
- Redistribution of adipose tissue
- Proteinuria
- Calcinosis cutis
- Recurrent infection (UTI, pyoderma)

HAC is rarely seen in dogs less than 6 years of age. Males and females are equally represented. There are some breeds that appear to have an increased predilection, such as Boxers, Poodles, Dachshunds, various terrier breeds, German shepherd dogs, and Labradors.^{1,2}

Dogs often present with a vague history; clinical signs may be overlooked by the owner, or presented as “age related changes”. A thorough history and clinical examination are important to make a diagnosis of Cushing’s syndrome.



Figure 3: A dog with hyperadrenocorticism. Note the muscle wasting on hips and muscles of mastication, marked alopecia and secondary skin changes (including calcinosis cutis).



Figure 4: Close-up view of calcinosis cutis. Photo credit: Timothy Smaha, DVM

DIAGNOSE

HAC is a clinical diagnosis that starts in the exam room and is supported by laboratory data. Since clinical signs are sometimes subtle, a thorough history is necessary. It is important to perform endocrine testing only when clinical signs are present, as treatment is heavily based on response of clinical signs to medical management.

Findings on routine laboratory screening tests can be variable in HAC patients. The CBC can show increases in hematocrit and platelets (>600,000), which may contribute to hypercoagulability. Stress leukograms are common, but immunosuppression is possible in dogs with HAC, and the clinical pathology may differ. Routine biochemical profile findings may include hyperglycemia (likely due to gluconeogenesis and insulin resistance), increased alkaline phosphatase (ALKP), cholesterol and triglycerides.^{1,2} Occasionally, hyperphosphatemia can be seen, which has been associated with decreased survival times (statistically found to be a negative prognostic indicator).⁶ Urinalysis often reveals a low urine specific gravity (often less than 1.010). Glucosuria and proteinuria can be present. Occult urinary tract infections are common and often require urine culture and sensitivity for successful diagnosis and treatment.^{1,2}

Before proceeding with endocrine testing for HAC, ensure the patient has clinical signs consistent with HAC that cannot be explained by other disease conditions. For example, an elevated ALKP in isolation, with no clinical signs, is not sufficient to pursue endocrine testing. The 2012 ACVIM consensus states, “the primary indication for pursuing a diagnosis of HAC is the presence of one or more of the common clinical signs and physical examination findings.” It is important to keep in mind HAC is a clinical diagnosis.⁵

In the diagnosis of HAC, there are two questions to answer: 1) is HAC present? 2) what is the primary cause? To answer the first question, laboratory tests must demonstrate either an increased cortisol production, or a

decreased sensitivity of the HPA axis to negative glucocorticoid feedback. To avoid cross-reactivity with the assay antibodies, exogenous steroid use should be discontinued for at least 24 hours prior to any endocrine testing.

Screening tests for HAC include the following: the urinary cortisol:creatinine ratio (UCCR), the low-dose dexamethasone suppression test (LDDST), and ACTH stimulation test. All of these tests have negative and positive attributes; there is no perfect test.⁵

Any screening test may be negative in a patient with HAC. If a test is negative, but suspicion for HAC remains, another test should be performed. If more than one test is negative, the patient likely does not have HAC. Re-evaluate the patient in 3 – 6 months if clinical signs progress.

Test	Sensitivity (%)	Specificity (%)
ACTH stimulation	Less than ideal (80-95)	Good (86-91)
LDDST	Excellent (85-100)	Poor (44-73)
UCCR	Excellent (75-100)	Poor (24-77)
Poor Sensitivity → HAC may be missed Poor Specificity → HAC may be misdiagnosed		

Figure 5: Sensitivity and specificity of current tests used to diagnose HAC.^{1, 2, 5}

Urinary Cortisol:Creatinine Ratio

Creatinine is excreted in the urine at a constant rate; cortisol is not. The UCCR is a sensitive test to detect cortisol hypersecretion. It is imperative the dog is not stressed for the urine sample collection. To minimize stress, the owner should collect free-catch samples for 1-3 days at home and bring to the practice; first morning samples are ideal. Samples can be pooled to increase chances of observing an elevated cortisol due to daily variation. Stress and non-adrenal illness can cause increases in urine cortisol levels. False positives are common (specificity is as low as 20-25%), but a normal ratio is considered truly negative, and HAC can be ruled out.^{1, 2, 5}

Low-Dose Dexamethasone Suppression Test

The LDDST evaluates the negative feedback system. If the system is intact, there will be suppression of CRH, ACTH, and ultimately cortisol production at 4 & 8 hours. A normal dog will suppress cortisol production within 2 – 3 hours and remain suppressed for 16 – 24 hours or more. Collect a baseline sample, then immediately administer 0.01mg/kg of dexamethasone IV. Additional samples are taken at 4 hours and 8 hours. The LDDST is considered consistent with HAC if the 8 hour cortisol is > 1.4 ug/dL. An inverse pattern, where the 4 hour post-dexamethasone cortisol was increased, but the 8 hour post-dexamethasone cortisol was below the cut-off value, has also been seen in PDH and warrants further testing for HAC.^{1, 2, 5}

The LDDST has a high sensitivity (85 – 90%), so a negative result provides a high confidence the dog is normal. Unfortunately, it has a low specificity, so a positive result is not confirmatory for HAC. False positives will occur in 27 – 66% of dogs as a result of non-adrenal illness or stress. This test should not be used if a patient has a history of exogenous steroid administration.^{1, 2, 5}

A positive LDDST can help differentiate PDH from ADH if the 4 hour sample is < 1.4 ug/dL or if there is at least 50% suppression from baseline cortisol levels at the 4 hour or 8 hour time point.^{1, 2, 5}

ACTH Stimulation Test

The ACTH stimulation test evaluates the adrenocortical reserve. Dogs with hyperplastic adrenal tissue have exaggerated cortisol response to ACTH. Collect a baseline sample,

then administer 5 µg/kg (max dose 250 µg) synthetic ACTH IV or IM (IV is the preferred method). Peak cortisol excretion occurs 60 – 90 minutes after injection. A 2nd blood sample is collected at 1 hour after ACTH administration. A diagnosis of HAC is made when cortisol levels post stimulation are greater than 22 µg/dL.

A recently published study in dogs authenticated a 1 µg/kg dose for ACTH stimulation tests for monitoring patients receiving either mitotane or trilostane. This dose cannot be used for diagnosing HAC. Caveats to using the low dose for monitoring include the following: the dose has to be administered IV, and the post stimulation blood sample must be taken at the 60 minute mark.⁷

Differentiation

Once a diagnosis of HAC has been confirmed, determining the source (pituitary or adrenal tumor) is the next step. The LDDST may be useful in differentiation in approximately 60% of dogs with PDH.^{1, 2, 5} If this does not occur, then a secondary test is needed to differentiate PDH from ADH. The most common modality for differentiation is imaging, with ultrasound being used in the majority of cases. Endogenous ACTH may also be measured as it would only be present in dogs with PDH. Pre-emptive collection and freezing of an EDTA plasma sample at collection of LDDST baseline cortisol sample may spare additional exam appointments. Careful handling of the sample is necessary to get reliable results with the endogenous ACTH assay and warrants a call to your preferred reference laboratory for further instructions.



TREAT

Treatment of HAC may be achieved by surgery, pituitary irradiation, or medical management. Transsphenoidal hypophysectomy can be offered to dogs with PDH and in good clinical condition. The surgery is effective with a median survival rate of 86% and remission for up to seven years.^{8,22} It is not widely available and can be cost prohibitive for many clients. Inoperable pituitary tumors can be treated by radiotherapy. Radiotherapy is effective in reducing the size of such pituitary tumors, but with a variable delay, from 1 to 16 months. The reduction in size is gradual in onset, but can continue for a year or more after completion of therapy. The improvement in clinical signs of HAC is associated with the reduced pituitary ACTH secretion.⁸ The treatment of choice of unilateral ADH is adrenalectomy. Successful removal eliminates both the tumor and the associated clinical signs of glucocorticoid excess without the need for lifelong medication. The median survival time after adrenalectomy is about 2 years, although some dogs survive more than 4 years.⁸

Surgery and radiotherapy are complicated procedures and only available at a few specialty centers; therefore, medical management is often the most practical and approachable treatment choice. Four options for medical management of HAC include mitotane, selegiline, ketoconazole, and trilostane.

Mitotane (Lysodren[®], Bristol Myers Squibb) is not approved for use in dogs, but for many years was the only available choice for managing HAC in dogs. It is a human cytotoxic/anti-neoplastic drug that works by causing cellular death in the adrenal gland. Through this dose-related adrenal necrosis, cortisol secretion is decreased.

Selegiline Hydrochloride, L-Deprenyl Hydrochloride (Anipryl[®], Zoetis) is FDA approved for uncomplicated PDH. It increases dopamine concentration, which in turn down-regulates ACTH concentration. Efficacy is fairly low, with only about 10 -15% of patients showing improvement in clinical signs.¹

Ketoconazole is a fungistatic drug that blocks several enzymes in the P-450 enzyme system, thus effectively blocking the synthesis of glucocorticoids and androgens with negligible effects on mineralocorticoids. There is no FDA-approved formulation of ketoconazole for use in the dog. For the treatment of HAC, it takes higher doses than for most yeast/fungal infections, and side effects can be significant. It is effective in about 50% of HAC cases at controlling clinical signs.¹

VETORYL[®] CAPSULES (trilostane), Dechra Veterinary Products, is the only FDA-approved drug for the treatment of both PDH and ADH in dogs. It is a short-acting, reversible enzyme inhibitor. It preferentially inhibits 3 β -hydroxysteroid dehydrogenase enzyme in the adrenal cortex, thus blocking the production of cortisol, and to a lesser extent (typically at higher doses), aldosterone and the sex hormones.^{9,10} The effect on aldosterone production is usually clinically insignificant at the doses required to control cortisol production in dogs. Effects only last as long as the half-life of the drug, so if over-suppression occurs at a particular dose, the drug can be discontinued, and hormone production usually returns to normal. The clinician can then decide to restart VETORYL Capsules at a lower dose or discontinue use if clinical symptoms of HAC do not return.

COMPLIANCE

When treated with trilostane, median or mean survival times ranged from 662-930 days for PDH and 353 days for ADH.^{11,12,13,14} The most recent study to look at this was published in 2017. In this study, 52.2% of dogs treated with trilostane were still alive at 2 years post-diagnosis compared to just 8.5% of untreated dogs. Furthermore, the publication found there was no significant difference in the number of visits to the hospital or the total cost of treatments between the two groups. The investigators also found a higher risk of death in untreated dogs.²²

Occasionally, the post-ACTH stimulation cortisol result is above 9.1 µg/dL, but the dog is clinically doing well. In these cases, do not increase the dose to chase the number – the goal is resolution and/or control of clinical signs, not an absolute number on blood work.

Clinical improvement should be evident within the first two weeks of starting VETORYL® CAPSULES (trilostane). Owners should notice the dog is drinking and urinating less, and is less ravenous. Excessive panting and lethargy should be reduced (usually a 40 – 50% improvement of these common clinical signs will occur in the first two weeks). The two clinical signs that take longer to improve are abdominal girth (3-4 months for improvement) and alopecia (hair regrowth can take up to 6-9 months). A 6-month clinical efficacy trial in 60 dogs had no more than 15% of dogs exhibiting any of the clinical signs associated with HAC.⁹ Do not expect ALKP to return to normal. Most dogs will have some level of persistent hepatic vacuolar changes driven by cortisol. Monitoring ALT activity is a better indicator of hepatocellular injury, and modest increases are much more important. As these are usually older patients, consider ultrasonography of the abdomen in patients where hepatic enzymes are of concern. Rule out liver masses and gallbladder

mucoceles with ultrasound. Hypercortisolism is a predisposing factor for the development of gallbladder mucoceles, and dogs with HAC are 29 times more likely to develop one than dogs who do not have HAC.¹⁶

If PU/PD does not improve with control of cortisol levels, perform a urine culture to rule out a urinary tract infection.

Patients with macroadenomas rarely have neurological signs at the time of presentation, but can develop them during the initial treatment of PDH with either trilostane or mitotane. Clinical signs are likely due to the removal of the negative feedback inhibition of cortisol on the pituitary and hypothalamus. Corticosteroids are often used to shrink the size of brain tumors and the removal of the endogenous cortisol can contribute to swelling or enlargement of the tumor.

Continued elevation of cortisol levels on an ACTH stimulation test can be due to many causes. Timing of VETORYL Capsule administration can affect the test. The ACTH stimulation test needs to be performed during VETORYL Capsules' peak effect. Absorption of VETORYL Capsules is greatly enhanced by food; if the dog was fasted the morning of the ACTH stimulation test, cortisol levels will be affected. In addition, consider if the client is actually giving the medication consistently and following the administration instructions.

Once client factors have been ruled out, ensure the ACTH stimulation test itself is being performed appropriately. Many internists discourage the use of compounded ACTH gels, as these gels have inconsistent activity and often lead to confusing data.

Cosyntropin can be frozen into 50 µg aliquots in plastic syringes and placed in a deep freezer without an auto-defrost mode. Do not store for longer than 4 months. If the cosyntropin is stored in glass vials, or is allowed to defrost during storage, its potency can be variable.¹⁷

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KEY POINTS

- **Hyperadrenocorticism is a clinical diagnosis.**
Do not treat if the patient is asymptomatic.
Remember, your best monitoring tool is improvement and/or control of clinical signs; if the patient is asymptomatic, then it is difficult to monitor therapy appropriately.
- **When using VETORYL Capsules (trilostane), start at the low end of the dose range.**
 - Round down when choosing a capsule size.
 - Majority of patients will do well with once-daily dosing.
 - Always give VETORYL Capsules with food.
- **Early monitoring, 10 – 14 days after starting VETORYL Capsules, can help identify patients who are becoming over-suppressed.**
 - Early signs include lethargy, weakness, anorexia, vomiting, and diarrhea.
 - If an owner sees these clinical signs, they should stop the medication ASAP.
 - Evaluation includes electrolytes and an ACTH stimulation test.
- **Typically, dose increases are not made until the 30 day mark.**
Dose changes are made based on clinical signs, electrolytes, and ACTH stimulation results.
- **Beware of the potential need for changes in dose requirements, even when a patient has been well-managed for a long time.**
- **Continue monitoring patients at regular intervals to ensure patients continue to do well.**
- **Client communication and compliance is key to treatment success.**
All members of your veterinary team should work together to empathize, educate, engage, and empower the client.

Written, Edited, and Presented by Dechra Veterinary Services Team



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