



Canine Hyperadrenocorticism (HAC, Cushing's disease)

What are the adrenal and pituitary glands?

The pituitary and adrenal glands are part of the *endocrine system* that controls hormones in the body. The pituitary gland is a small gland located at the base of the brain that helps to regulate many hormones and other endocrine organs throughout the body. The adrenal glands are two small organs near the kidneys that produce a number of different hormones. The pituitary produces *ACTH*, a hormone that tells the adrenal glands to release the hormone *cortisol*. There is a normal *feedback loop* that keeps these hormone levels in balance and from being produced in excess.

- *Cortisol* is a hormone made by the adrenal glands to deal with day to day stress and normal cellular and organ function
- *Mineralocorticoids* are hormones made by the adrenal glands to regulate electrolyte and fluid balance in the body
- *Androgens* are hormones made by the adrenal glands and reproductive system that are important for reproduction, development and certain cell functions

What is hyperadrenocorticism (HAC, Cushing's disease)?

HAC is the overproduction of hormones normally made by the adrenal glands. This usually involves cortisol, but much less frequently can also include androgens. The excess in hormone production causes a multitude of clinical signs and laboratory changes. Without treatment, HAC can cause progressive conditions that can be fatal. HAC commonly affects the liver, kidneys, and the immune, musculoskeletal, respiratory, vascular, and nervous systems.

What causes HAC?

HAC can result from a pituitary tumor (85%) or from an adrenal tumor (15%). Adrenal tumors can be benign or malignant. Pituitary tumors are usually benign and microscopic, although a small percentage can be actual space-occupying masses that cause neurological signs in addition to the HAC signs.

- *Pituitary dependent HAC (PDH)* is HAC of pituitary origin
- *Microadenoma* is a microscopic tumor of the pituitary (90%)
- *Macroadenoma* is a macroscopic (space-occupying) tumor of the pituitary (10%)



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What clinical signs does HAC cause?

HAC may cause no clinical signs at all and simply be a laboratory diagnosis very early on. Typically, however, HAC causes a number of clinical signs that will progress without treatment.

Common signs include:

- Hair loss
- Panting
- Muscle wasting
- Polyphagia
- Exercise intolerance
- Thin skin
- Abdominal distension
- Polydipsia
- Polyuria

Less common clinical signs include:

- Blindness
- Seizures
- Restlessness
- Decreased appetite
- Malaise
- Breathing difficulty
- Behavioral change

- ❁ *Polyuria (PU)* is the increased urination that results from direct effects of cortisol on the kidney's ability to concentrate urine
- ❁ *Polydipsia (PD)* is the increased drinking that results from the polyuria of HAC
- ❁ *Polyphagia (PP)* is the increased appetite commonly seen in HAC

What laboratory changes does HAC cause?

HAC can potentially cause many changes on laboratory tests. Depending on the severity and duration of disease, the changes may be mild or extreme. Ultimately, laboratory tests are required to confirm the diagnosis and differentiate what type of HAC is present.

Common laboratory changes include:

- Dilute urine
- Increased lipids
- Increased liver enzymes
- Increased platelets
- Urinary infection
- Increased white blood cells

- ❁ *Alkaline phosphatase* is the most common liver enzyme to be elevated in HAC. It is usually disproportionately elevated over *ALT*, another liver enzyme



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- *Lipemia* is the gross increase of fats in the blood, making the serum look milky or white
- *Cholesterol* elevation is the most common lipid abnormality, although *triglycerides* are also commonly elevated

What testing is recommended for HAC patients?

In evaluating patients with HAC, there are many things that need to be considered. First, there are baseline tests that are important in evaluating for severity of disease and secondary internal changes; secondly, there are tests that are used to confirm the diagnosis itself; finally, there are differentiating tests that may be required to differentiate the type of HAC present. Depending on presentation, history, previous labwork, and timing of the visit, a combination of diagnostic and differentiating tests may be required. This is often a multi-step process. If a pituitary macroadenoma is suspected, MRI is required to confirm the diagnosis.

Most patients evaluated for HAC will need the following tests:

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|---------------------|------------------------------|------------------------|
| ■ Chemistry profile | ■ Complete Blood Count (CBC) | ■ Blood pressure |
| ■ Urine culture | ■ Urinalysis | ■ Abdominal ultrasound |

- *Abdominal ultrasound* is a non-invasive test that uses sound waves to create images of internal organs and structures
- *Diagnostic* tests for HAC are tests that help confirm the diagnosis of HAC; these include urine cortisol: creatine ratio, low-dose dexamethasone suppression test, and ACTH stimulation tests
- *Differentiating* tests are tests that differentiate between adrenal tumors and pituitary tumors; these include low-dose dexamethasone suppression test, high-dose dexamethasone suppression tests, endogenous ACTH levels, ultrasound, and MRI
- By evaluating a selection of these tests *together*, we can confirm the diagnosis, type of HAC present, and help develop a treatment and monitoring plan

What treatment options are available for adrenal tumors?

Adrenal tumors are most commonly treated with surgery. The ability to remove these tumors depends on whether the right or left adrenal is affected, and whether the adrenal



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tumor is invasive into surrounding structures. In unique cases where surgery is not elected, medical therapy can be considered (see below).

What treatment options are available for pituitary dependent HAC?

Lysodren and Trilostane are the two primary drug options for treating HAC. Both medications have pros and cons that need to be considered when opting for therapy.

Lysodren has been used for years to treat HAC in dogs. It works by killing off part of the adrenal gland (*adrenocorticolytic*). The drug is given at high doses initially (*loading phase*), and then used every 2-4 days to maintain adrenal status (*maintenance phase*). Side effects can include GI upset and immune-mediated reactions (rare). Because this drug is adrenocorticolytic, if it destroys too much of the adrenal gland, you can create hypoadrenocorticism (*Addison's disease*), a condition wherein the body makes too *little* cortisol. Signs of this include nausea, vomiting, diarrhea, weakness, and lethargy. It is not uncommon for signs of HAC to recur after months of therapy, requiring a repeat of the loading phase and higher maintenance dosages. Rechecks include one to three ACTH stimulation tests during the loading phase, followed by periodic tests thereafter (usually once every 4 months or so).

Trilostane is a newer drug that has been used in Europe in recent years to treat HAC. It is not approved for use in the United States, but is becoming very popular in the treatment of HAC. Rather than destroy the adrenal gland tissue, it simply decreases the hormone production. This seems to reduce side effects and minimize the creation of Addison's disease. Because we are just gaining experience with this medication there is a risk of unexpected side effects. Based on the European experience, however, it seems that side effects are very rare. There is no loading phase, with the medication being given on a daily basis. Likewise, monitoring overall seems to be simpler, less frequent, and less costly.

If a macroadenoma is present, radiation therapy is the treatment of choice.

What sort of long-term monitoring is recommended for HAC patients?

General recommendations for patients with HAC will depend on the type of HAC diagnosed and what other secondary conditions may be present. Follow-up for medical management after establishing drug dosages includes ACTH stimulation testing every 3-6 months. CBC and chemistry values will likely also be monitored on an every 6-12 month basis. Urinalysis and urine culture may need to be repeated in certain cases. Monitoring is often patient-specific and unique recommendations may be made.



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What is the prognosis with HAC?

With adrenal tumors that can be surgically removed, the prognosis is good. Invasive or metastatic adrenal cancer carries a more guarded prognosis. With pituitary dependent disease and medical management animals can live for long periods with resolution of clinical signs and excellent quality of life. Severity and duration of disease as well as whether secondary conditions are present may affect the prognosis in rare cases.