Cushing’s Syndrome (HAC, CCS)

Most Common in dogs, rare in cats

Most dogs middle aged or older (rare < 6 yrs), slight female predisposition

Most common clinical signs in Dogs

Pu/pd, polyphagia, pendulous abdomen, excessive bruising, panting, alopecia, weakness/lethargy, exercise intolerance, muscle atrophy and truncal obesity

Clinical signs that Dogs with HAC DO NOT Have
Poor Appetite/anorexia, vomiting/diarrhea, icterus, pain, pruritis, renal/liver failure and pancreatitis (controversial)

Non adrenal illness (NDI) will give rise to false positive test results

The most sensitive and specific screening tests for HAC is the history and physical exam findings. Treatment recommendations, therefore, should be based on the history, physical findings and the results of the initial database (serum chem, CBC, urinalysis) as well as the results of the endocrine screening tests.

The decision to treat a dog for Cushing’s syndrome should never be based solely on laboratory information.

_Cushing’s syndrome is a clinical disorder with clinical signs. If a dog does not have clinical signs do not treat!_

_From Feldman Endo_
Testing for HAC occurs in two steps. First, a screening test is done to determine the diagnosis of HAC. Once HAC is diagnosed, discriminatory testing is done to determine if the HAC is PDH or ADH because the treatments vary for these two forms of HAC.

Disease description:
Hyperadrenocorticicism (HAC) or Cushing's syndrome refers to all cases whereby excessive glucocorticoid exposure results in clinical signs. There are 3 forms of Cushing's syndrome.

ACTH-dependent or pituitary dependent hyperadrenocorticism (PDH)
This form occurs when there is hypersecretion of ACTH, usually caused by uncontrolled proliferation (tumor) of the basophilic or chromophobie cells of the pars intermedia and the pars distalis of the pituitary. This form of HAC constitutes about 85-90% of the cases of Cushing's syndrome and is more commonly called Cushing's disease. The excessive secretion of ACTH by these tumors results in bilateral adrenal hyperplasia and excessive cortisol production by the adrenal glands. Most pituitary tumors are small to microscopic, < 1 cm in diameter, and are called microadenomas. But up to 15% are > 1 cm in diameter and are called macroadenomas. With both tumor types, clinical signs are due to excessive ACTH production. However with macroadenomas, central nervous system (CNS) signs can also occur and are associated with the mass effects of the macroadenoma.
Ectopic ACTH production has not been completely documented in dogs or cats, but in humans, non-pituitary tumors may secrete ACTH to result in bilateral adrenal hyperplasia.

ACTH-independent or adrenal dependent hyperadrenocorticism (ADH)
This form occurs when a cortical adenoma or carcinoma causes increased secretion of cortisol. The opposite normal adrenal gland atrophies because of the excessive secretion of cortisol by the adrenal tumor. This form of HAC constitutes about 10-15% of the cases of Cushing's syndrome.

Iatrogenic HAC or Cushing's syndrome
This form occurs when the patient is exposed to excessive or prolonged administration of glucocorticoids which causes adrenal atrophy and suppressed ACTH levels. Clinically, it is indistinguishable from natural disease.

CLINICAL SIGNS
**General signs**

Polyphagia is a common sign because glucocorticoids have a direct stimulatory effect on the appetite.
Polydipsia and polyuria occur in 85 to 95% of dogs with HAC. It is suspected that glucocorticoids interfere with antidiuretic hormone (ADH) release and activity, resulting in polyuria. Polydipsia is compensatory. Pendulous, "pot-bellied abdomen" or abdominal distension occurs due to the redistribution of fat to the abdomen, muscle wasting of the abdominal muscles (less ability to contain abdominal contents), and hepatomegaly (which occurs due to the accumulation of glycogen). Muscle weakness and atrophy are due to excessive protein catabolism and muscle wasting. Cruciate ruptures can occur. High levels of cortisol may induce myotonia characterized by stiff extensor muscles and bizarre, high frequency spontaneous motor unit potentials detected with electromyography.

Hypertension is seen in 50% of patients with HAC. Treatment for hypertension is not required unless treatment for HAC does not resolve the hypertension.

**Clinical signs that Dogs with HAC DO NOT Have**
Poor Appetite/anorexia
Vomiting/Diarrhea
Sneezing/Coughing
Icterus
Pruritis
Pain
Lameness due to inflammation
Seizures
Bleeding
Renal Failure
Pancreatitis
Liver Failure
Immune mediated diseases

**LABORATORY AND RADIOGRAPHIC FINDINGS**

*Hemogram:* Results can be normal or show a neutrophilic leukocytosis, monocytosis, lymphopenia and eosinophilia. Some cases have thrombocytosis and a high normal red blood cell count.

*Chemistry profile:* In dogs, alkaline phosphatase may be normal or greatly increased; a cortisol-specific isoenzyme of alkaline phosphatase can be measured. An increase in serum alkaline phosphatase due to HAC is not accompanied by an increase in bilirubinemia. Serum ALT may be mildly to moderately increased. Hypercholesterolemia
is often present. The most common finding in cats is hyperglycemia. In 5-10 % of the dogs with Cushing's disease, diabetes mellitus may be concurrently present.

**Urinalysis:** There can be a great variation in specific gravity in dogs but if the patient is polyuric and polydipsic, the urine specific gravity is usually decreased. Pyuria and bacteriuria may be detected and occur because of the immunosuppression associated with excessive corticosteroids. Proteinuria may occur in dogs secondary to glomerulopathy. The cause of the glomerular sclerosis is unknown but may result from arterial hypertension. Some cases of proteinuria are reversible with proper control of cortisol concentrations.

**Urine culture:** In one study, urinary tract infection was found in nearly 50% of the dogs with HAC. Clinical signs of urinary tract infection are usually absent and pyuria and bacteriuria are absent in 40% and 30% of cases with infection, respectively.

**Urine cortisol creatinine ratio (UCC):** Although the ratio is increased above the normal level in most dogs with HAC, the ratio is also increased in many dogs with non-adrenal illness. Therefore while this simple test appears highly sensitive in detecting HAC in dogs, it is not that specific. The UCC ratio should not be used in dogs that have moderate to severe nonadrenal disease because of false positive results.

**Radiographs:** Thoracic cavity radiographs may show bronchial calcification or metastases from an adrenal adenocarcinoma. Osteopenia may be identified. Abdominal radiographs often show hepatomegaly. About one-half of the adrenal tumors are calcified and may be visible on radiographs. Subcutaneous calcification has also been noted.

**Abdominal ultrasound:** PDH usually results in symmetrically slightly enlarged adrenal glands or normal sized adrenal glands in contrast to adrenal tumors which cause one adrenal gland to be much larger than the other on ultrasound. Ultrasound should be used to identify the affected adrenal gland before surgical removal is attempted.

**DIAGNOSIS**

**Testing for HAC occurs in two steps.** First, a screening test is done to determine the diagnosis of HAC. Once HAC is diagnosed, discriminatory testing is done to determine if the HAC is PDH or ADH because the treatments vary for these two forms of HAC.

**SCREENING TESTS TO DIAGNOSE HAC**

SPINS and SNOUTS

SPinS = Specificity - a positive test rules it in

SNoutS = Sensitivity - a negative test rules it out
The most sensitive and specific screening tests for HAC is the history and physical exam findings. Treatment recommendations, therefore, should be based on the history, physical findings and the results of the initial database (serum chem, CBC, urinalysis) as well as the results of the endocrine screening tests.

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Out patient testing

Urine Cortisol: Creatinine Ratio (UC: CR)

Have owner collect urine at home. The test is used for its negative predictive value. That is if the UC: CR is within reference range the diagnosis of HAC is unlikely.

In Hospital Testing

In general, the low-dose dexamethasone suppression test (LDDST) is more sensitive (95 %) but less specific (44-73 % depending on the study) than the ACTH stimulation test (sensitivity of 80 % and specificity of 85 %). In other words, the LDDST is more likely to be positive in dogs with HAC, but it is also more likely to give a false-positive test result in sick patients or those with non-adrenal illness (NAI). Therefore, the following general recommendations can be made:

If the dog has no known NAI and moderate to severe clinical signs of HAC, do the LDDST.
If clinical signs are mild or only laboratory abnormalities are present (e.g., increased ALP), do the ACTH stimulation test.
If NAI is present, if the dog has received any form of exogenous glucocorticoids including topicals, or if the dog is receiving Phenobarbital, do the ACTH stimulation test.
If there is any doubt about the accuracy of the results of whichever test you chose, perform the other test for confirmation.

*Low dose dexamethasone suppression test (LDDST)* is both a screening and discriminating test. In normal dogs, a low dose of dexamethasone inhibits ACTH release from the pituitary via negative feedback; this decreases plasma cortisol concentrations. Dogs with HAC are more resistant to dexamethasone suppression. Therefore, lack of suppression following a dexamethasone injection suggests HAC.

*How to perform:* Obtain plasma samples for cortisol measurement before and at 4 and 8 hours after I.V. administration of 0.01 or 0.015 mg/kg of the active ingredient
Dexamethasone. Either dexamethasone sodium phosphate or dexamethasone in propylene glycol can be used, but note that dexamethasone in propylene glycol contains all dexamethasone whereas in dexamethasone sodium phosphate, the sodium phosphate accounts for about 25% of the weight. Calculate the dose of dexamethasone sodium phosphate on the basis of the dexamethasone concentration, not the dexamethasone sodium phosphate concentration.

Dexamethasone may have to be diluted with sterile saline (1:10) for sufficiently accurate dosing.

**How to interpret the results.**
1. First look at the 8 hour value. The actual cut-off value for suppression will depend on your lab. If the 8 hour value is above the normal cut-off value, the diagnosis of HAC is made. If the value is below your lab's normal value, the test is either a false negative or the dog does not have HAC; in either case, there is no need to look at the rest of the results.
2. If the 8 hour plasma cortisol is greater than your lab's normal values, then the rest of the results may allow you to differentiate between PDH and ADH using one of these 3 criteria:
   a. If the 8 hour plasma cortisol is greater than your lab's normal value, but less than 50% of the basal value, the diagnosis is PDH.
   b. If the 8 hour plasma cortisol is greater than your lab's normal value and the 4 hour plasma cortisol concentration is less than 1.0 mg/dl, the diagnosis is PDH.
   c. If the 8 hour plasma cortisol is greater than your lab's normal value and the 4 hour plasma cortisol concentration is less than 50% of the baseline value, the diagnosis is PDH.
3. If the 8 hour plasma cortisol is greater than your lab's normal value, but none of the criteria in point 2 were met, the dog could have either PDH or ADH at which time abdominal ultrasound, endogenous ACTH testing, or a high dose dexamethasone suppression test can be done.

**Advantages of LDDST:**
1. The LDDST is more reliable than the ACTH stimulation test in confirming HAC, since the results are diagnostic in all ADH cases and in 90 to 95 per cent of dogs with PDH.
2. There are fewer false negatives compared to the ACTH test.
3. It is less expensive than the ACTH test.
4. The results of a LDDST can sometimes aid in discriminating PDH from ADH, as described earlier.

**Disadvantages of LDDST:**
1. LDDST is affected by more variables than the ACTH stimulation test and therefore has more false positives than the ACTH stimulation test. For example, recent administration of corticosteroids can interfere with the test. Hydrocortisone and prednisolone will be directly measured on the cortisol assay, so they should not be used within 24 hours before the test. Dexamethasone and betamethasone aren't directly measured on the cortisol assay but still affect the endocrine tests, especially if they have been administered for days to
months. Dexamethasone has been shown to have a duration of activity of 24-48 hours in healthy dogs, while in a dog with PDH; the duration is only 3-6 hours. So dexamethasone administered a week prior to the LDDST will not affect it, but betamethasone, a longer acting corticosteroid, could affect the test. In cases that have had corticosteroids administered within the last month, it is probably best to run ACTH test.

2. It takes 8 hours to complete.
3. There are more false positives.
4. The patient can not be stressed during the test e.g. no ultrasound, radiographs, etc should be done.

ACTH stimulation test is only a screening test; it cannot discriminate PDH from ADH. By giving a supra-physiological dose of ACTH, the adrenal gland will be maximally stimulated. This gives us an estimation of the "size" or functional capacity of the adrenal cortex. The theory is that with PDH the adrenals are hyperplastic and have an increased secretory ability. However, this hyperplasia and increased secretory ability can also occur with chronic illness or stress which helps to explain the false positive results that are sometimes obtained.

How to perform: Take a baseline blood sample for resting cortisol and then administer 5 micrograms/kg IV of synthetic ACTH (Cortosyn is preferred). Take a second blood sample one hour post-injection. Since you may not use the entire vial on one patient, you can save the left over portion and use it later.

How to interpret the results.
1. While the baseline cortisol level can vary from normal to above normal, the post ACTH stimulation cortisol value is above normal in dogs with HAC; the actual cut-off value for "normals" will depend on your lab.
2. If the post ACTH stimulation cortisol value is within the normal range, the dog could still have HAC as about 20 % of cases will have a false negative ACTH stimulation test.
3. If the post ACTH stimulation cortisol value is suppressed (value may be similar to the resting value or only a few points higher), then this "blunted response to ACTH" could be caused by one of the following:
   a. The ACTH was not administered properly.
   b. The form of ACTH that was used was not reliable. Unfortunately this has been seen with some of the ACTH gels.
   c. The patient has received iatrogenic steroids. A suppressed response to ACTH in animals with clinical signs of HAC suggests iatrogenic HAC.

Advantages of ACTH test:
1. Takes only one hour to perform.
2. Fewer false positives than with LDDS.
3. Can run other tests at the same time e.g. bile acids.
4. Can also rule-out Addison's disease.
5. This is the only test for iatrogenic Cushing's.
6. This is the only test for monitoring response to therapy for HAC.
**Disadvantages of ACTH test:**
1. It is more expensive (due to cost of synthetic ACTH) than LDDST.
2. There are more false negatives.
3. It is more likely to miss adrenal tumor.
4. It cannot discriminate between PDH and ADH.

**DISCRIMINATING TESTS TO DIFFERENTIATE PDH FROM ADH**

If the LDDS test did not differentiate PDH from ADH, one of the following tests can be done: high dose dexamethasone suppression test (HDDST), endogenous ACTH level, and abdominal ultrasound. None of these tests are perfect since all have grey zones.

**Abdominal ultrasound** is often more convenient and can give you information about adrenal size (normal width should be less than ~ 7mm), symmetry, invasion of adjacent structures if adrenal tumor is present, liver changes, etc. The presence of unilateral adrenomegaly or distortion of adrenal architecture in an animal with signs of HAC is strong evidence of ADH. However a focal mass on one adrenal can be difficult to identify as a tumor vs. nodular hyperplasia. Some HAC dogs have uroliths, either struvite or calcium oxalate. Some adrenal tumors are mineralized and therefore easily visualized on abdominal radiographs. One study showed that endogenous ACTH level and abdominal ultrasound are similarly accurate and have better sensibility and specificity for detecting PDH than the HDDST.

**Endogenous ACTH** is very accurate but is highly susceptible to sample mishandling causing the ACTH to be falsely low, leaving you with the false impression that the dog has ADH. But if you handle the sample meticulously, you can trust the results, especially if they indicate PDH. Dogs with PDH have normal or high levels of ACTH, while those with ADH have low to undetectable levels of endogenous ACTH (because the adrenal tumor produces high levels of cortisol which suppresses ACTH production by the pituitary gland). If results suggest ADH, it is good idea to follow up with adrenal ultrasound to be sure. Contact the lab before you submit the test and get specific directions; use of a preservative (Aprotinin XE "Aprotinin") in EDTA tubes may result in fewer handling errors.

**HDDST** can be used to differentiate PDH from ADH because if there is suppression, the diagnosis is PDH. However, about 25% of dogs with PDH do not suppress on the HDDST and virtually 100% of dogs with ADH do not suppress. **So if there is no suppression on the HDDST, you can't tell if it is ADH or PDH.** With PDH, a high dose of corticosteroids results in a decrease in ACTH release from the pituitary and a decrease in plasma cortisol. With ADH, the tumor secretes cortisol autonomously thereby suppressing ACTH production. With low ACTH concentrations already present, dexamethasone has no effect on plasma cortisol.

**How to perform HDDST:** Take a 0 hour or pre-dexamethasone blood sample for cortisol measurement. Then give 0.1 mg/kg of dexamethasone IV and resample at 4 and 8 hours. If you have suppression at 4 or 8 hours, then you have PDH. Suppression is defined as
cortisol less than your lab's normal values (usually somewhere between 1.0 and 1.4 ug/dl) at 4 or 8 hours or cortisol result less than 50% of baseline at 4 or 8 hours.