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Overview of Hyperadrenocorticism

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Key Points

- Of dogs with naturally occurring hyperadrenocorticism (HAC), 85% have pituitary gland tumors and 15% have adrenal gland tumors.
- A diagnosis of HAC is based on clinical signs, laboratory tests, and diagnostic imaging.
- Treatment for HAC depends on the etiology and clinical signs.

Hyperadrenocorticism (HAC), also known as Cushing's disease, is a common endocrine syndrome that affects middle-aged and geriatric dogs and, occasionally, cats. HAC is generally caused by tumors of either the pituitary or adrenal glands; however, long-term administration of exogenous glucocorticoids can also cause HAC. Regardless of the etiology, the cause of the clinical signs typically seen in this syndrome is an abnormally elevated serum cortisol level.

Etiology

Normally, the amount of cortisol in the blood is controlled by interaction between the adrenal glands, the pituitary gland, and the hypothalamus. When cortisol is needed (e.g., to respond to a stressful situation), the hypothalamus signals the pituitary gland to release adrenocorticotropic hormone (ACTH), which prompts the adrenal glands to produce cortisol. In turn, high levels of cortisol in the blood cause the hypothalamus to decrease its signal to the pituitary gland, which in turn produces less ACTH, thereby reducing the demand for cortisol. This relationship is known as a negative feedback loop.[1]

When a pituitary or adrenal gland is affected by a tumor, it stops responding to the signals of the feedback loop. Pituitary tumors cause the pituitary gland to produce ACTH regardless of cortisol levels, leading to increased production of cortisol, and adrenal tumors continue to secrete excessive amounts of cortisol despite diminished quantities of plasma ACTH.[1] Pituitary gland tumors account for 85% of naturally occurring cases (pituitary-dependent hyperadrenocorticism [PDH]); the remaining 15% of cases are caused by adrenal gland tumors.[2] Secondary, or iatrogenic, HAC caused by administration of high doses of exogenous cortisol creates a physiologic situation similar to that of an adrenal tumor. The exogenous cortisol has a negative feedback effect on the hypothalamus and suppresses the release of ACTH from the pituitary gland. The diminished ACTH level can lead to atrophy of the adrenal glands. However, continued administration of cortisol perpetuates HAC.

Necropsy of canine patients with PDH commonly reveals adenomas of the pars distalis.[1] These pituitary tumors usually have complications limited to the clinical signs of HAC (e.g., polyuria, polydipsia). Large pituitary adenomas can result in neurologic signs, such as stupor or confusion.[2]

Tumors affecting the adrenal glands tend to be unilateral, with benign adenomas comprising half of all cases and the other half being malignant carcinomas.[2] The resulting persistent negative feedback of diminished ACTH on the nonneoplastic adrenal gland leads to its atrophy.[1]

Other than problems caused by the size and location of the tumor, the clinical signs of PDH and adrenal tumor are identical.[2] Patients with iatrogenic HAC share the same clinical signs as patients with naturally occurring disease. A definitive diagnosis of HAC is contingent on laboratory and radiographic tests. Technicians familiar with the diagnostic procedures, current therapies, and monitoring protocols for canine patients with HAC can play a vital role in the management of this disease.

Signalment

The median age of dogs with PDH is 10 years. Dogs with adrenal tumors tend to be older, with a median age of 11.3 years at the time of diagnosis. Females are slightly more predisposed than males and account for approximately 60% of all dogs with HAC.[1] Poodles, dachshunds, beagles, German shepherds, and many terrier breeds are commonly affected. Although there are no established correlations between weight and adrenal tumor development, 75% of dogs with diagnosed PDH weigh less than 9 lb (20 kg).[1]

Clinical Signs

Physical Abnormalities

The most frequently reported and recognized clinical signs of canine HAC are polyuria and polydipsia. These signs are reported in 80% to 85% of cases.[1] Owners often bring affected dogs to their veterinarian because of increased urination or the loss of housetraining habits.

Other common clinical signs include lethargy, increased appetite, and a "potbellied" appearance. Although a patient with HAC can gain weight as a result of a hearty appetite, abdominal enlargement is attributable to cortisol's promotion of muscle weakness, hepatomegaly, and increased abdominal fat stores.[1]

High cortisol levels also induce hair follicle atrophy and cause several dermatologic problems.[1] Patients with HAC often develop alopecia, which can be limited to pressure points, such as elbows and hocks, or can be bilaterally symmetric and of variable severity.[1] HAC should be suspected in geriatric canine patients with poor hair regrowth after clipping. Additional dermatologic changes associated with hypercortisolemia include thin, transparent skin; seborrhea; and pyoderma.[1]

Respiratory effects of HAC can be mild, such as panting or tachypnea, or severe, such as pulmonary thromboembolism. Several factors contribute to the development of these problems. Panting and tachypnea at rest are attributable to increased abdominal fat, weakened respiratory muscles, and hepatomegaly.[1] The formation of pulmonary thromboemboli is thought to be the result of a hypercoagulable state caused by diminished levels of antithrombin III and increased levels of several clotting factors, fibrinogen, and plasminogen.[1] The predisposition to develop pulmonary thromboemboli poses the greatest threat to patients with HAC.

Technicians presented with an older canine patient with a history of urinary accidents should inquire about the dog's water consumption, appetite, and breathing pattern. Changes in a dog's appearance can be subtle; therefore, it is important to ask the owner if he or she has noticed a change in the pet's coat or general appearance.

Hematologic Abnormalities

Cortisol is associated with the "fight or flight" stress response; therefore, it is logical that patients with HAC exhibit hematologic changes consistent with a stress leukogram. These changes include neutrophilia, monocytosis, lymphopenia, and eosinopenia. Hematocrit values tend to be normal or slightly elevated.[1]

Serum Biochemistry Abnormalities

HAC can cause several changes in serum biochemistry. Excessive cortisol induces lipolysis, which increases levels of serum cholesterol and triglycerides.[1] Cortisol also plays a role in promoting glucose production and has antagonizing effects on insulin, which may lead to a mild increase in serum blood glucose.[1] The diuresis that is a frequent reason for presentation can result in loss of blood urea nitrogen and phosphorus.

An elevation in serum alkaline phosphatase (ALP) is the most common abnormality that can raise suspicion for HAC. Cortisol's direct effect on hepatocytes results in ALP and alanine aminotransferase production.[1] Despite the large percentage of dogs with HAC and elevated ALP, the finding of elevated ALP lacks specificity and is not diagnostic for HAC.

Urine Abnormalities

In addition to a complete blood count and serum biochemical profile, a urinalysis should be conducted for all dogs suspected of having HAC. Urinalysis is useful as a screening test and helps to diagnose secondary problems, such as diabetes mellitus and urinary tract infections. Dogs with HAC are predisposed to urinary tract infections because of the immunosuppressive effects of cortisol. The most common urine abnormality seen in dogs with HAC is a reduced urine specific gravity. The exact cause of dilute urine is uncertain, but it is speculated to be related to cortisol's effects on antidiuretic hormone.[1]

Screening Tests for HAC

Urine Cortisol: Creatinine Ratio

Although developed for use in humans, the urine cortisol:creatinine ratio (UC:CR) has been found to be useful as a screening test for dogs suspected of having HAC. The test is convenient because it requires only a free-catch urine sample and does not involve hospitalization or venipuncture. Because stress has been speculated to cause false elevations in urine cortisol levels, it is recommended that the sample be collected at home in a stress-free environment.[2]

A study to assess the diagnostic value of the UC:CR was conducted using healthy dogs, dogs that had a history of polyuria/polydipsia, and dogs with a confirmed diagnosis of HAC.[3] The sensitivity, or probability that a dog with HAC would have a positive test result, was 100%. However, many dogs with polyuria/polydipsia caused by conditions other than HAC also had elevated UC:CR results. Therefore, the specificity of the test (i.e., the probability that a dog without HAC would have a negative test result) was low (22%).[3] Because of the high sensitivity and low specificity of the UC:CR, a negative result is very helpful in ruling out HAC, but an elevated UC:CR result requires further testing to confirm a diagnosis.

Low-Dose Dexamethasone Suppression Test

The low-dose dexamethasone suppression test (LDDST) is based on the negative feedback system between the pituitary and adrenal glands. In a dog without HAC, the administration of exogenous dexamethasone causes the pituitary gland to decrease its secretion of ACTH, which, in turn, decreases the adrenal glands' release of cortisol. However, canine patients with pituitary-dependent HAC (PDH) are minimally affected by the administration of a low dose of exogenous dexamethasone. The diseased pituitary gland continues to secrete ACTH, thus maintaining excessive release of cortisol from the typically hypertrophied adrenal glands. Analysis of blood samples taken before and 4 and 8 hours after dexamethasone administration reveals whether cortisol levels are affected by this test.

Adenomas and adenocarcinomas of the adrenal glands also function autonomously despite the administration of exogenous dexamethasone. During an LDDST, ACTH levels drop in patients with a normal pituitary gland and a diseased adrenal gland, but the abnormal adrenal gland continues its excessive production of cortisol.

The sensitivity of the LDDST is estimated to be between 85% and 100%. Because illnesses other than HAC can contribute to false-positive results, the specificity of the LDDST has been estimated to be between 44% and 73%.[2]

ACTH Stimulation Test

The ACTH stimulation test relies on the fact that dogs with HAC have an increased capacity to produce cortisol from either PDH-induced adrenal hypertrophy or a functioning adrenal tumor. In this test, exogenous ACTH is administered and the patient's cortisol response measured. Dogs with naturally occurring HAC are expected to have exaggerated cortisol production.[4] Because the adrenal glands are atrophied in dogs with iatrogenic HAC, increased cortisol production is not seen in these patients. The advantages of this test are the short time it requires and its ability to distinguish naturally occurring HAC from iatrogenic HAC.[5]

Studies including dogs with either PDH or adrenal tumor revealed the sensitivity of the ACTH stimulation test to be between 73% and 95%.[2] Sensitivity levels decrease when the two individual forms of HAC are evaluated separately.[2]

Dogs with early-onset PDH may not have adrenal hypertrophy and therefore may fail to have an exaggerated response to ACTH administration. Also, not all adrenal tumor cells produce excessive cortisol when challenged with ACTH.

Diagnostic Test Protocols[1]

ACTH stimulation test

This test can be conducted using either ACTH gel or a synthetic aqueous solution.

If ACTH gel is used:

- Obtain a preadministration blood sample.
- Administer 2.2 U/kg of gel IM.
- Collect a second blood sample 2 hours later.

If synthetic ACTH is used:

- Obtain a preadministration blood sample.
- Administer 5 µg/kg of synthetic ACTH IV.
- Collect a second blood sample 1 hour later.

LDDST

- Obtain a preadministration blood sample.
- Administer dexamethasone (0.01 to 0.015 mg/kg) IV.
- Collect blood samples 4 and 8 hours after injection.

UC:CR

- Ask the client to collect a free-catch urine sample at home.
- Centrifuge the urine.
- Submit at least 1 ml of supernatant to the laboratory for testing.

HDDST

The protocol for this test is the same as that for the LDDST except that the dose of dexamethasone is 0.1 mg/kg.

Endogenous ACTH

Because this test has very specific handling requirements, technicians should consult their testing laboratory for its preferred protocol.

Differentiating Tests for PDH versus Adrenal Tumor

Following the confirmation of naturally occurring HAC via screening tests, it is important to differentiate pituitary disease from adrenal disease. Determining the cause of disease enables the veterinarian to formulate the most appropriate treatment protocol and determine an accurate prognosis. The LDDST is sometimes useful in differentiating PDH from adrenal tumor; however, the ACTH stimulation test is not.

High-Dose Dexamethasone Suppression Test

The high-dose dexamethasone suppression test (HDDST), similar to the LDDST, is based on the feedback system between the pituitary and adrenal glands. Using a higher dose of dexamethasone can overcome a pituitary tumor's resistance to negative feedback and cause a decrease in serum cortisol. In contrast, adrenal tumors tend to be immune to the administration of high doses of exogenous dexamethasone and continue to produce excessive amounts of cortisol.[2] Unfortunately, the HDDST is not very sensitive. Approximately 25% to 30% of dogs with PDH do not show suppressed cortisol levels during the HDDST.[2,4]

Endogenous ACTH Concentration

The measurement of endogenous ACTH concentration cannot be used as a screening test because many dogs with HAC have values within the normal range. However, this test does have merit in differentiating patients with PDH from those with adrenal tumor or iatrogenic HAC. Dogs with iatrogenic HAC or adrenal tumor have diminished levels of endogenous ACTH compared with dogs with PDH.[1]

The endogenous ACTH concentration test has significant drawbacks. Results can fall into a nondiagnostic range, and the sample requires very careful and specific handling by veterinary technicians and laboratory personnel.

Diagnostic Imaging

Abdominal ultrasonography can be useful in differentiating PDH from adrenal tumor, but it has limitations. For optimal accuracy, the test should be conducted by an experienced veterinary radiologist. Even well-trained radiologists cannot always discern changes in the size, shape, and architecture of the adrenal glands. In general, bilaterally enlarged adrenal glands are suggestive of PDH, and unilateral changes are suggestive of adrenal tumor.[2] In a study that evaluated 71 dogs with adrenal tumor, 86% of cases were correctly diagnosed.[2] Ultrasonography is not useful for distinguishing adrenal adenomas from carcinomas.

Abdominal computed tomography is a better differentiating test than abdominal ultrasonography.[2] False-negative results are possible because not all dogs with HAC have enlarged adrenal glands. Dogs with unilateral adrenal hyperplasia can have computed tomography results identical to those of dogs with adrenal tumor.[2]

Pituitary tumors can also be elusive. These masses are often less than 1 cm in diameter and are not always detected on imaging studies.[2] Magnetic resonance imaging is more commonly used to evaluate diagnosed pituitary tumors than to differentiate pituitary disease from adrenal disease.[2]

Treatment

The course of treatment for HAC is contingent on the diagnosis of PDH, adrenal tumor, or iatrogenic HAC. If pharmaceutical therapy is instituted, the goal is to ameliorate the clinical problems of HAC by indirectly suppressing the pituitary gland's release of ACTH or directly suppressing the adrenal glands' production of cortisol. Unless a tumor is deemed nonresectable, the preferred treatment for adrenal tumor is adrenalectomy. Dogs with PDH are more commonly treated with drug therapy than with radiation or surgery.[6] If a pituitary mass results in neurologic problems, then surgical removal should be considered. Dogs with iatrogenic HAC should be slowly weaned off of exogenous steroids to allow the adrenal glands to resume normal production of glucocorticoids.

Medical Therapy

Mitotane

Mitotane, a derivative of the insecticide dichlorodiphenyldichloroethane, causes cell necrosis in two of the three layers of the adrenal glands — the zona fasciculata and zona reticularis.[7] The areas affected are responsible for the production of glucocorticoids. The zona glomerulosa is typically spared from necrosis; therefore, it continues to produce the mineralocorticoid aldosterone.[7] Maintenance of aldosterone production is important because this hormone regulates the body's sodium and potassium balance. Mitotane can be used to treat PDH or adrenal tumor. The initial induction phase of therapy involves a daily mitotane dose of 40 to 50 mg/kg PO with food. This "knockdown" dose is typically given for 7 to 10 days to promote necrosis and atrophy of the adrenal zona fasciculata and zona reticularis.[6]

Concurrent prednisone or prednisolone (0.15 to 0.25 mg/kg/day PO) can help alleviate the potential side effects following mitotane administration.[8] The development of anorexia, vomiting, diarrhea, lethargy, and weakness is not directly caused by mitotane but rather is the result of a rapid drop in the serum cortisol level, known as an addisonian (hypoadrenocorticism) crisis. Technicians should carefully advise owners about these potential problems associated with mitotane dosing.

At the end of the induction phase, an ACTH stimulation test is conducted to assess the success of therapy. It is important to instruct owners to discontinue oral steroid supplementation on the day of the ACTH stimulation test. Owners should also be instructed to give mitotane with a meal for enhanced absorption and to wear gloves when handing fragments of the pills.

Once clinical signs have improved and desired results of an ACTH stimulation test are reported, maintenance mitotane therapy is started. The dose is usually 25 to 50 mg/kg PO divided over 2 or 3 days of the week indefinitely.[8] Technicians must stress the importance of conducting ACTH stimulation tests every few months to ensure control of HAC and the avoidance of iatrogenic hypoadrenocorticism.

Ketoconazole

Ketoconazole is an antifungal agent that decreases cortisol production by inhibiting the enzymes necessary for glucocorticoid synthesis.[7] Its side effects are similar to those of mitotane and are the result of rapidly diminished serum cortisol levels. Unlike mitotane, ketoconazole has the potential to cause a change in coat color, elevated liver enzymes, and hepatotoxicity.[7,8]

Further studies are needed to establish the efficacy of ketoconazole in treating HAC. Current estimates, based on a survey of veterinary internists and dermatologists, indicate that at least 20% to 25% of dogs with PDH will not respond to ketoconazole.[7] Ketoconazole is dosed at 5 to 30 mg/kg/day PO.[8] Because of its expense, requirement for twice-daily dosing, and lower efficacy rating in the survey, it is not the primary choice for treatment of PDH. It is most useful in patients with mitotane intolerance or a mitotane-resistant adrenal tumor.[8] An ACTH stimulation test should be conducted after 3 weeks of therapy. The test should commence 3 to 6 hours after the administration of ketoconazole on the day of the test.[8] Unless adverse effects are observed, or ketoconazole is deemed ineffective, it is administered indefinitely.

Trilostane

Trilostane is a synthetic, hormonally inactive steroid that inhibits the production of cortisol, aldosterone, and sex hormones.[7,8] Trilostane has not been associated with severe side effects. As it resolves hypercortisolemia, patients may experience lethargy and a decrease in appetite.[8]

The efficacy of trilostane is comparable to that of mitotane. Because trilostane does not induce adrenal necrosis, its effects are largely reversible,[8] and it poses less risk than mitotane for causing permanent hypoadrenocorticism (Addison's disease). The greatest drawbacks of trilostane are its cost and requirement for daily dosing. Trilostane was previously only available to international pharmacies. It has become more accessible in the United States, but only through compounding pharmacies. Many patients require higher dosages to remain in remission. Gradual dose increases are recommended to help minimize adverse effects. Patients should be monitored with an ACTH stimulation test 2 weeks, 1 month, and then every 3 months after beginning trilostane therapy. This test, along with measurement of serum electrolyte concentrations, should be conducted 4 to 6 hours after the administration of trilostane on the day of testing.[8] If well tolerated and effective, trilostane is administered indefinitely.

l-Deprenyl

l-Deprenyl increases central dopamine concentration by selectively and irreversibly inhibiting monoamine oxidase type B. The benefits of elevated dopamine levels are postulated to be a decrease in ACTH secretion and the inhibition of pituitary adenoma growth.[8] The drug's efficacy in the treatment of HAC is limited. Because of l-deprenyl's wide margin of safety, its use can be considered for patients intolerant of mitotane, trilostane, or ketoconazole or for patients with mild clinical signs of PDH. l-Deprenyl has been found to help alleviate problems associated with canine cognitive dysfunction.[8]

Surgical Therapy

In the absence of predetermined complicating factors (e.g., uncontrolled diabetes mellitus, hypercoagulability), patients with adrenal tumors are usually managed with adrenalectomy. All canine candidates for adrenalectomy should have a preoperative workup that includes a complete blood count, chemistry profile, urinalysis, and chest radiography. Abdominal ultrasonography can be helpful in identifying complicating circumstances, such as tumor invasion of the caudal vena cava or the renal vein. Medical therapy with ketoconazole or mitotane can be used before surgery to help control the signs of HAC.[9] For dogs undergoing unilateral adrenalectomy, corticosteroids should be administered before and after surgery. If bilateral adrenalectomy is to be performed, glucocorticoids and mineralocorticoids should be given before surgery, and both will need to be continued indefinitely.[9]

Postoperatively, technicians must closely monitor respiratory rate, heart rate, blood pressure, mucous membrane color, and capillary refill time. Electrolyte levels should be checked with close attention to decreasing sodium and increasing potassium levels.[9]

Adrenal adenomas tend to be well delineated and less invasive than adenocarcinomas.[10] Dogs with invasive tumors that cannot be resected completely require medical therapy following surgery. The long-term prognosis for adrenalectomy patients is good; however, several serious perioperative complications, such as thromboembolism, hypoadrenocorticism, pancreatitis, and cardiac arrest, can occur. Veterinary technicians play a vital role in patient monitoring following surgery.

Role of the Technician

HAC is a complex syndrome, but its successful management is rewarding for the pet, the client, and the veterinary team. Familiarity with the hypothalamus-pituitary-adrenal axis is important for veterinary technicians to gain an understanding of the tests and treatments associated with HAC. Technicians play an important role in diagnosing HAC and are crucial in maintaining the correct protocol for screening tests. Technicians also can help in differentiating PDH from adrenal tumor

by assisting with imaging tests, conducting the HDDST, and overseeing the proper handling of endogenous ACTH samples.

The numerous steps involved in diagnosing HAC and the potential for serious adverse complications of therapy make client communication a priority. Technicians must be familiar with the requirements of the ACTH stimulation test in particular. Clients must be properly instructed on when to discontinue medications (e.g., prednisone) before testing as well as the appropriate time frame for testing during medical treatment (e.g., 4 to 6 hours following ketaconazole or trilostane administration).

REFERENCE:

1. FELDMAN EC, NELSON RW: HYPERADRENOCORTICISM (CUSHING'S SYNDROME), IN *CANINE AND FELINE ENDOCRINOLOGY AND REPRODUCTION,* ED. 2. PHILADELPHIA, SAUNDERS, 1996, PP 187-265.

2. BEHREND EN, KEMPPAINEN RJ: DIAGNOSIS OF CANINE HYPERADRENOCORTICISM. *VET CLIN NORTH AM SMALL ANIM PRACT* 31(5): 985-1003, 2001.

3. FELDMAN EC, MACK RE: URINE CORTISOL:CREATININE RATIO AS A SCREENING TEST FOR HYPERADRENOCORTICISM IN DOGS. *JAVMA* 200(11):1637-1641, 1992.

4. BRADDOCK JA: DIAGNOSIS OF HYPERADRENOCORTICISM IN THE DOG. *AUST VET J* 81(1-2):25-27, 2003.

5. MACK RE: SCREENING TESTS USED IN THE DIAGNOSIS OF CANINE HYPERADRENOCORTICISM. *SEMIN VET MED SURG (SMALL ANIM)* 9(3):118-122, 1994.

6. PETERSON ME, KINTZER PP: MEDICAL TREATMENT OF PITUITARY-DEPENDENT HYPERADRENOCORTICISM IN DOGS. *SEMIN VET MED SURG (SMALL ANIM)* 9(3):127-131, 1994.

7. BRADDOCK JA: MEDICAL TREATMENT OF HYPERADRENOCORTICISM IN THE DOG. *AUST VET J* 81(1-2):31-33, 2003.

8. DECLUE AE, COHN LA, KERL ME: MEDICAL THERAPIES FOR CANINE PITUITARY-DEPENDENT HYPERADRENOCORTICISM. *VET MED* 99(6): 519-527, 2004.

9. AXLUND TW, BEHREND EN, WINKLER JT: SURGICAL TREATMENT OF CANINE HYPERADRENOCORTICISM. *COMPEND CONTIN EDUC PRACT VET* 25(5):334-346, 2003.

10. ANDERSON CR, BIRCHARD SA, POWERS BE: SURGICAL TREATMENT OF ADRENOCORTICAL TUMORS: 21 CASES (1990-1996). *JAAHA* 37:93-97, 2001.

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Consensus Statement

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Diagnosis of Spontaneous Canine Hyperadrenocorticism: 2012 ACVIM Consensus Statement (Small Animal)

E.N. Behrend, H.S. Kooistra, R. Nelson, C.E. Reusch, and J.C. Scott-Moncrieff

This report offers a consensus opinion on the diagnosis of spontaneous canine hyperadrenocorticism. The possibility that a patient has hyperadrenocorticism is based on the history and physical examination. Endocrine tests should be performed only when clinical signs consistent with HAC are present. None of the biochemical screening or differentiating tests for hyperadrenocorticism are perfect. Imaging can also play a role. Awareness of hyperadrenocorticism has heightened over time. Thus, case presentation is more subtle. Due to the changes in manifestations as well as test technology the Panel believes that references ranges should be reestablished. The role of cortisol precursors and sex hormones in causing a syndrome of occult hyperadrenocorticism remains unclear.

Key words: Adrenal cortex; Cushing's syndrome; Dog; Pituitary.

Clinical Presentation: Indications For Diagnostic Testing

The possibility that a patient has hyperadrenocorticism (HAC) is based on the history and physical examination. Endocrine tests should be performed only when clinical signs consistent with HAC are present. The Panel believes that because of heightened awareness of HAC, dogs are currently evaluated at much earlier stages of disease development. Consequently, clinical manifestations are more subtle, and the prevalence of clinical signs and physical examination findings in individual dogs is less than that published several decades ago.

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 (Table 1).[1–10] If only 1 clinical sign is present, it is usually polyuria and polydipsia, or alopecia and skin changes suggestive of an endocrine disease.[11] Cases seen by dermatologists may have a different constellation of findings than those seen by internists. Failure

Abbreviations:

ACTH	adrenocorticotrophic hormone
ALP	alkaline phosphatase
AT	adrenal tumor
cACTH	canine ACTH
CBC	complete blood count
CT	computed tomography
ELISA	enzyme-linked immunosorbent assay
EQUAS	External Quality Assurance Specimens
HAC	hyperadrenocorticism
HDDST	high-dose dexamethasone suppression test
HPAA	hypothalamic/pituitary/adrenal axis
IRMA	immunoradiometric assay
LDDST	low-dose dexamethasone suppression test
MRI	magnetic resonance imaging
PDH	pituitary-dependent hyperadrenocorticism
RIA	radioimmunoassay
UCCR	urinary corticoid : creatinine ratio

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Table 1. Clinical manifestations of canine HAC.[1–11,111–113] Categorization of frequency is based on identification at the time of initial presentation.

Common	Less Common	Uncommon
Polydipsia	Lethargy	Thromboembolism
Polyuria	Hyperpigmentation	Ligament rupture
Polyphagia	Comedones	Facial nerve palsy
Panting	Thin skin	Pseudomyotonia
Abdominal distention	Poor hair regrowth	Testicular atrophy
Endocrine alopecia	Urine leakage	Persistent anestrus
Hepatomegaly	Insulin-resistant diabetes mellitus	
Muscle weakness		
Systemic hypertension		

HAC, hyperadrenocorticism.

Table 2. Common laboratory abnormalities in dogs with HAC.[1–11,111,113]

CBC	Serum Biochemistry Panel	Urinalysis
Neutrophilic leukocytosis	Increased alkaline phosphatase	Specific gravity ≤1.018–1.020
Lymphopenia	Increased alanine aminotransferase	Proteinuria
Eosinopenia	Hypercholesterolemia	Indicators of urinary tract infection
Thrombocytosis	Hypertriglyceridemia	
Mild erythrocytosis	Hyperglycemia	

HAC, hyperadrenocorticism; CBC, complete blood count.

to identify multiple indicators for HAC does not rule out the disease. However, the more abnormalities identified, the stronger the indication to pursue testing. Less common clinical signs and physical examination findings add further support for diagnostic testing.

Less common clinical presentations of HAC include anestrus and testicular atrophy; ligament laxity that may lead to tearing and lameness[12]; facial palsy; and pseudomyotonia.[13,14] Severe polyuria, urinary tract infection or both may lead to urine leaking, especially when the dog is asleep, and owner-perceived urinary incontinence. Hypercoagulability may result in spontaneous thromboembolism, typically involving pulmonary vessels and causing acute respiratory distress.[15,16] Cortisol-induced insulin resistance may promote diabetes mellitus and impair exogenous insulin response.[17,18] If less common clinical presentations are identified first, a thorough review of the history, physical examination findings, and routine laboratory test results often provides additional evidence for the disease. Failure to identify abnormalities listed in Tables 1 and 2 is a major negative indicator for the presence of HAC.

Clinical manifestations may develop secondary to mass-occupying effects of a pituitary or adrenal tumor (AT). A large pituitary tumor may cause neurologic signs (pituitary macrotumor syndrome), including inappetence, anorexia, stupor, circling, aimless wandering, pacing, ataxia, and behavioral alterations. Although pituitary macrotumor syndrome develops in 10–25% of dogs months to years after HAC diagnosis, some have pituitary macrotumor syndrome, albeit subtle, at initial presentation. Documenting a large pituitary mass on computed tomography (CT) or magnetic resonance imaging (MRI) during the evaluation of neurologic signs supports testing for HAC. Adrenocortical carcinomas may invade the phrenicoabdominal vein, caudal vena cava, or both, causing retroperitoneal hemorrhage, blood-loss anemia and abdominal pain, or incite formation of a tumor thrombus that leads to ascites or rear limb paresis.[19,20]

Testing for HAC is recommended after unexpected identification of an adrenal mass on imaging performed for another problem such as vomiting. A review of the history, physical examination findings, and results of routine blood and urine tests will usually, but not always, provide evidence for HAC, if present, and prompt additional testing. Because the presence of an AT dictates perioperative management, testing for HAC should be recommended before adrenalectomy.

Results of a complete blood count (CBC), biochemistry panel, urinalysis, urine protein : creatinine ratio, and blood pressure measurement may further support HAC (Table 2). No abnormality listed in Table 2 is pathognomonic for HAC. Laboratory test results and a blood pressure measurement must be interpreted within the context of the history and physical examination findings. An absence of common abnormalities noted in Table 1 should strongly decrease the suspicion of HAC. Conversely, failure to identify abnormalities listed in Table 2 does not, by itself, rule out HAC. If measured, bile acid concentrations may be mildly increased. A cause and effect relationship between HAC and formation of gall bladder mucoceles has yet to be clarified. Identification of bilateral adrenomegaly or an AT on abdominal ultrasound examination provides additional evidence to pursue the diagnosis of HAC in dogs with common abnormalities listed in Table 1. However, the presence of ultrasonographically normal-sized adrenal glands does not rule out HAC.

Ideally, testing for HAC should be avoided if serious illness exists. Many illnesses affect results of HAC screening tests.[21,22] Testing for HAC is not mandatory at the time suspicion arises. Postponing testing until concurrent illness is resolved or controlled is recommended, but the concurrent illness must be considered.

In summary, indicators for performing diagnostic tests for HAC are:

- Compatible history and physical examination findings. The greater the number of findings, the stronger the suspicion. Biochemical panel, CBC, urinalysis, and urine protein : creatinine ratio

results and blood pressure measurement by themselves are not indications to test.
- A pituitary macrotumor.
- A diabetic dog with persistently poor response to high dosages of insulin not attributed to another cause, including owner issues.
- An adrenal mass.
- Persistent hypertension. (The Panel did not reach consensus on this point. Some would not test if hypertension was the only abnormality present.)

Screening Tests

No test has 100% diagnostic accuracy. Positive and negative predictive values are dependent upon disease prevalence. In a population appropriately screened so that disease prevalence is high, all diagnostic tests will be more accurate.

Diagnosis of HAC depends on demonstration of either: (1) increased cortisol production or (2) decreased sensitivity of the hypothalamic-pituitary-adrenal axis (HPAA) to negative glucocorticoid feedback. Measurement of a single basal cortisol concentration has no diagnostic value. Pulsatile adrenocorticotrophic hormone (ACTH) secretion results in variable cortisol concentrations[23,24] which may at times be within the reference range. Dogs with nonadrenal illness (NAI) can have increased baseline cortisol concentrations.[22,25]

The tests used most often include the low-dose dexamethasone suppression test (LDDST), urinary corticoid : creatinine ratio (UCCR), and ACTH stimulation test. Because all were introduced into veterinary medicine in the 1970s and 1980s, the Panel believes current reference ranges and cut-off values should be re-evaluated. First, measured cortisol concentrations differ among assays. Thus, values generally cannot be used interchangeably. Second, methods and assays have changed over previous decades, but new reference ranges were not usually generated. Third, studies from which reference ranges were derived had various shortcomings, namely comparison of dogs with HAC to healthy dogs rather than those suspected of having HAC; inclusion of groups with small numbers of dogs; and, use of controls with NAI that were not suspected of having HAC. Furthermore, trials to evaluate screening tests were performed in referral settings with a high disease prevalence, but the tests often are now used in primary care settings with a low disease prevalence. Fourth, the incidence of mild cases of HAC has appeared to increase over time, possibly because of heightened awareness and earlier patient presentation. Milder cases will have a lower degree of cortisol hypersecretion, and cut-off values previously established may not apply.

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 1 test is negative, the possibility that the patient does not have HAC must be considered. Alternatively, the patient may have mild HAC and the tests have not yet become positive. It may be worthwhile to retest in 3–6 months if clinical signs progress.

Technical Aspects

Cortisol Assays. In serum or plasma, total cortisol (bound and free) is measured; in urine and saliva, only free cortisol is measured. Various techniques are available (eg, RIA, ELISA, chemiluminescence). To the Panel's knowledge, data regarding in-house cortisol measurements have not been published in the peer-reviewed literature; therefore, such methods were not considered.

Circulating cortisol concentrations differ depending on the assay. The EQUAS program run by Michigan State University provides data comparing measurements among laboratories. Consistent differences are reported. For example, cortisol measured by Immulite is higher than that measured by RIA (Dr R. Nachreiner, personal communication). Differences exist among laboratories using the same methodology. From the EQUAS XXXV report (July 2010), 27 laboratories using the Immulite assay found cortisol concentrations from 3.7 to 7.2 μg/dL (101–199 nmol/L) in the same sample. Eleven laboratories used the same RIA; cortisol concentrations in the same sample ranged from 3.0 to 5.0 μg/dL (83–137 nmol/L).

Tube Type, Sample Type, Time of Centrifugation, and Stability. Cortisol concentrations were the same whether measured on samples stored in glass or plastic,[26] serum or plasma,[26,27] and centrifuged 10 minutes or 40 hours after blood collection.[27] Cortisol is stable in plasma and urine at 4 and 25°C for 5 days, but decreases in serum at 4, 25, and 37°C (compared to −20°C).[26] However, to ensure adequate sample integrity, the Panel recommends that after centrifugation samples either be refrigerated for up to 24 hours or frozen for longer at −20°C. Urine can be stored at 4°C for up to 4 days or at −20°C for >5 days. Samples should be sent to the laboratory overnight; sample type will not matter and no special packaging is needed.

Cross-Reactivity. Because of assay-dependent cross-reactivity among various steroids (prednisolone, prednisone, methylprednisolone, fludrocortisone, cortisone, hydrocortisone), the Panel recommends a 24 hour interval between the last steroid administration and cortisol measurement. However, the 24 hour time period will not eliminate the risk of adrenal suppression secondary to glucocorticoid administration.

Influence of Hemolysis and Lipema. The effect of lipemia and hemolysis may differ among assays. The Panel recommends contacting the individual laboratory for information related to the assay used.

Hypothalamic-Pituitary-Adrenal Axis and Drugs. Many drugs affect human HPAA activity.[27] A number of these drugs are not used in veterinary medicine, but metoclopramide, clonidine, buprenorphine, codeine, clomipramine, ceruletide, and desmopressin are used in veterinary medicine. Except for desmopressin,[28] studies are lacking in veterinary medicine.

Exogenous progestins[29] and glucocorticoids can suppress the HPAA. The duration of suppression reflects duration of use, dose, administration route, form of

synthetic steroid (short- or long-acting), and individual sensitivity and cannot be predicted.[30]

Conclusions

- No particular assay is recommended.
- Cortisol concentrations vary by assay and among laboratories using the same method. Reference ranges and cut-off values must be established by each laboratory; therefore, the Panel does not recommend specific reference ranges and cut-off values.
- Samples for cortisol measurement should be centrifuged within 1 hour after collection, immediately refrigerated or frozen for longer storage, and shipped overnight to a reference laboratory.

Low-Dose Dexamethasone Suppression Test

Test Principles. The LDDST can demonstrate decreased HPAA sensitivity to negative glucocorticoid feedback, 1 of the 2 characteristics of HAC diagnosis. Additionally, dexamethasone may be metabolized quicker in dogs with HAC than in healthy dogs.[31] Resistance to dexamethasone suppression is not "all or nothing" but a continuum; slight resistance may be present in early or mild cases and more severe resistance may be present in advanced cases of HAC.[32]

The LDDST as a Screening Test. A diagnosis of HAC is determined by the cortisol concentration 8 hours after dexamethasone administration. In human medicine, because patients with mild HAC may have greater sensitivity to dexamethasone suppression, cut-off values have decreased over time.[33] As stated above, the Panel suggests that updated cut-off values be established by each laboratory. However, no cut-off correctly identifies all patients with HAC.[34] In veterinary medicine, the reported sensitivity and specificity of the LDDST range from 85 to 100% and from 44 to 73%, respectively.[6,21,22,35–43]

An "inverse" pattern, in which the cortisol concentration 8 hours after dexamethasone was below the cut-off value, but the cortisol concentration 4 hours post-dexamethasone was increased was described in 5 dogs with PDH.[41] Because this pattern is highly suspicious for HAC, further testing should be pursued.

Dexamethasone Form, Dosage, and Time of Testing. In the 1st LDDST study, the best separation between healthy dogs and dogs with HAC was achieved by cortisol concentrations 8 hours after 0.01 mg/kg dexamethasone IV.[37] Intravenous dosages of 0.01 mg/kg dexamethasone sodium phosphate and 0.015 mg/kg dexamethasone polyethylene glycol yielded similar cortisol concentrations in dogs with HAC after 2, 4, 6, and 8 hours.[39] When comparing dexamethasone in the polyethylene glycol or sodium phosphate form, no differences were detected after 0.01 and 0.1 mg/kg dosages.[44] Dexamethasone sodium phosphate dosage should be calculated based on the active compound. According to Plumb's Veterinary Drug Handbook (7th ed), 1.3 mg dexamethasone sodium phosphate is equivalent to 1 mg dexamethasone.

Effect of Timing and Feeding. Dogs do not exhibit a circadian cortisol secretion.[23] Therefore, the Panel assumes that time of day does not affect LDDST results. The effect of feeding on LDDST results is unknown. The Panel recommends not feeding during the test. Fasting before testing is not necessary unless lipemia affects results of the cortisol assay used.

Influence of Drugs. Dexamethasone is metabolized primarily by cytochrome P450 3A4. Agents that increase the enzyme's activity accelerate dexamethasone clearance and could cause false positive results. In humans, such agents include carbamazepine, phenytoin, rifampicin, barbiturates, and St. John's wort. In veterinary medicine, only phenobarbital has been studied. Available evidence suggests no effect of phenobarbital on LDDST results, although occasionally phenobarbital-treated dogs may not show suppression.[45–47]

Conclusions

- The Panel considers the LDDST the screening test of choice unless iatrogenic HAC is suspected.
- The LDDST should be performed using 0.01–0.015 mg/kg dexamethasone sodium phosphate or polyethylene glycol IV; calculate dose using the parent compound and not the salt.
- The LDDST can be started any time of the day; avoid feeding during the test.
- Obtain blood samples before and 4 and 8 hours after dexamethasone administration.
- The cortisol concentration 8 hours after dexamethasone administration is used to diagnose HAC. It is the clinical experience of the Panel that in normal dogs cortisol concentrations 4 and 8 hours after 0.01 mg/kg dexamethasone are below or very close to the detection limit of current assays. New cut-off values should be established.
- An "inverse pattern" should prompt further testing for HAC.
- Because clinical signs and biochemical abnormalities in dogs on phenobarbital may be similar to those in dogs with HAC, confirmation of HAC in phenobarbital-treated dogs is challenging. If clinical and laboratory abnormalities persist after switching to another anticonvulsant (substantiating the suspicion of HAC), an LDDST then may be performed. If discontinuation of phenobarbital is impossible, LDDST results should be interpreted cautiously and further diagnostic testing considered.

ACTH Stimulation Test

Test Principles and Diagnostic Accuracy. The ACTH stimulation test assesses adrenocortical reserve and is the gold standard for diagnosis of iatrogenic HAC.

Because of its low sensitivity, its diagnostic usefulness as a screening test for spontaneous HAC is inferior to the LDDST.

The sensitivity of the ACTH stimulation test for all forms of spontaneous canine HAC ranges between 57 and 95%. It has been determined that for dogs with HAC because of an AT, sensitivity is 57–63%; for dogs with PDH it is 80-83%. Specificity ranges between 59 and 93%.[6,21,36,43,48–51]

Form, Dosage, and Route of ACTH. Synthetic polypeptides containing the biologically active first 24 amino acids of ACTH are available, eg, Cortrosyn (cosyntropin) or Synacthen (tetracosactrin). The potency of the preparations has not been compared. Recently, Cosyntropin Injection was introduced for IV use only. No differences in cortisol concentrations were found in response to 250 μg Cortrosyn IM or Cosyntropin Injection IV in 18 healthy dogs.[52] In some countries, compounded ACTH preparations are available. In 1 study, cortisol concentrations 60 minutes after administration of compounded ACTH (2.2 U/kg IM) were no different than after Cortrosyn (5 μg/kg IV).[53]

No difference in mean peak cortisol concentration was detected when comparing IV and IM administration of 250 μg Cortrosyn in healthy dogs[54]; IV and IM administration of 5 μg/kg Cortrosyn in healthy dogs and dogs with HAC[55]; or IV administration of 250 μg/dog and 5 μg/kg Cortrosyn in dogs with HAC.[56,57] When comparing various cosyntropin dosages (10, 5, 1, 0.5, 0.1, 0.05, 0.01 μg/kg) on cortisol concentrations in healthy dogs[56–58], the lowest dosage that stimulated maximal cortisol secretion was 0.5 μg/kg IV.[58] Depot tetracosactide (250 μg/kg IM) and cosyntropin (5 μg/kg IV) produced similar cortisol responses at 60 minutes after administration in healthy dogs.[59] However, neither cosyntropin dosages below 5 μg/kg nor tetracosactide depot have been assessed in dogs with HAC.

Sample Timing. After administration of Cortrosyn at 5 μg/kg or 250 μg/dog IV or IM, peak cortisol secretion occurs at 60–90 minutes.[53–57] After 5 μg/kg IV, no difference was detected between 60- and 90-minute cortisol concentrations.[53,55,56] Using 4 compounded products (2.2 U/kg IM) in healthy dogs, cortisol concentrations at 60 minutes were similar to each other as well as to concentrations after Cortrosyn (5 μg/kg IV). However, at later times cortisol concentrations varied considerably.[53]

Effect of Timing and Feeding. Dogs do not exhibit circadian cortisol secretion.[23] Similar to the LDDST, the Panel assumes that time of day does not affect test results. Fasting before testing is not necessary unless lipemia affects results of the cortisol assay used.

Cosyntropin Storage. Cosyntropin can be reconstituted and frozen in aliquots at −20°C in plastic syringes for 6 months.[60] Whether Synacthen can be frozen has not been investigated; according to the manufacturer, it should be stored at 2–8°C.

Influence of Drugs. In people, cortisol response to ACTH may be decreased by serotonin receptor agonists, progestagens, ketoconazole, and fluconazole and may be enhanced by propranolol.[27] In veterinary medicine, the ability of glucocorticoids of any form,[30] progestagens[29] and ketoconazole[61] to suppress cortisol secretion is known. No effect on the ACTH stimulation test was documented overall or individually in healthy dogs treated with phenobarbital for 8[62] (n = 12) or 29 weeks[46] (n = 12) or in epileptic dogs treated for 1 year[45] (n = 5) or >2 years[62] (n = 5).

Conclusions

- The ACTH stimulation test is the gold standard for diagnosis of iatrogenic HAC. It is of less use for the diagnosis of spontaneous HAC.
- The ACTH stimulation test can be performed at any time of day.
- The effect of feeding on ACTH stimulation test results is unknown. The Panel recommends not feeding during the test.
- Because of greater purity and quality control, only use of synthetic ACTH is recommended and utilization of compounded ACTH is discouraged.
- Cortrosyn, Cosyntropin Injection, and Synacthen can be used interchangeably.
- Perform the test using 5 μg/kg of the preferred compound with blood samples drawn before and 60 minutes after administration. The Panel prefers IV administration.
- Depot tetracosactide needs to be given IM, but the Panel does not recommend its use until it has been tested in dogs with HAC.
- Progestagens, glucocorticoids, and ketoconazole suppress the HPAA and decrease responses to ACTH. Phenobarbital does not appear to affect results.

Combined Dexamethasone Suppression/ACTH Stimulation Test

The combined test merges an ACTH stimulation test for screening with a high-dose dexamethasone suppression test for differentiating. As the diagnosis of HAC is based on ACTH stimulation test results, the combination test has a lower sensitivity than the LDDST.

Urinary Corticoid : Creatinine Ratio

Test Principles and Diagnostic Accuracy. The UCCR provides an integrated reflection of corticoid production, adjusting for fluctuations in blood concentrations.

Determination of basal UCCRs can be performed in tandem with a high-dose dexamethasone suppression test (see below). The combination has the advantage of potentially demonstrating both increased cortisol production and decreased sensitivity to glucocorticoid feedback.

When a single, random urine sample is collected in veterinary hospitals, the reported sensitivity and specificity of the UCCR for diagnosis of HAC ranges from

75–100%[21,63–66] and 20–25%, respectively.[21,63,64] However, using the protocol below, in dogs with physical and biochemical changes consistent with HAC, the sensitivity of finding 2 basal UCCRs above the cut-off level was 99% (95% confidence interval [CI], 94–100%) and the specificity was 77% (95% CI, 64–87%).[42] In some dogs, considerable day-to-day variation exists in the UCCR. In mild cases, a UCCR may be just within the reference range 1 day and increased another day.

Protocol. To avoid the influence of stress,[67] urine for UCCR should be collected at home at least 2 days after a visit to a veterinary clinic. Although a UCCR sample can be collected at any time of day,[68] morning urine may be preferred because it usually represents several hours of urine production.

Influence of Drugs and Concurrent Disease. Glucocorticoids and other drugs that suppress cortisol secretion, such as progestagens,[29] can decrease a UCCR by suppressing endogenous cortisol secretion. Phenobarbital treatment does not affect UCCR.[47] Nonadrenal disease may cause endogenous stress and increased cortisol secretion. Therefore, high UCCRs in dogs without a high degree of clinical suspicion of HAC should be interpreted cautiously.

Conclusions

- The UCCR is a sensitive test to detect cortisol hypersecretion.
- To avoid false-positive results, urine should be collected at home minimally 2 days after a visit to a veterinary clinic.

Differentiating Tests

It is important to differentiate PDH and AT because treatment and prognosis differ. Spontaneous HAC from ectopic ACTH secretion[69] and food-stimulated cortisol secretion[69] are rare. Biochemical tests (canine ACTH or cACTH, LDDST, HDDST, dexamethasone suppression of the UCCR) can distinguish PDH and AT, but no test is 100% accurate. Differentiating tests should not be done unless a positive result has been obtained on a screening test.

Endogenous ACTH Concentration

Test Principles. Canine ACTH is secreted from the pituitary gland in an episodic, pulsatile fashion in healthy dogs and those with PDH.[23,71] A circadian rhythm has not been convincingly demonstrated, although 1 study reported higher plasma cACTH concentrations in late afternoon than in the morning.[72] Concentrations of cACTH do not differ between healthy dogs and those with PDH, and its measurement is not useful to screen for HAC.[73] Measurement of cACTH is the most accurate stand-alone biochemical test for differentiating PDH from AT.

cACTH Assays. Immunoradiometric assay (IRMA) and chemiluminescent assays have been validated for cACTH measurement.[74–77] Measured cACTH concentrations are lower using chemiluminescent technology than RIA.[76]

The accuracy for differentiation of PDH from AT depends upon analytical sensitivity and the working range of the assay (Table 3). The most common problem with the cACTH assay is poor sensitivity. Some dogs with PDH have cACTH concentrations at or below the sensitivity of the assay, particularly with the Immulite 1000 analyzer. The largest study of cACTH in dogs with HAC used a 2-site solid-phase chemiluminescent immunometric assay (Immulite ACTH kit and Immulite 2000 analyzer) and showed excellent discrimination between PDH and AT.[75] No dogs with PDH had undetectable cACTH concentrations, likely because of the analytical sensitivity (5 pg/mL), but the range of cACTH concentrations for dogs with PDH was 6–1,250 pg/mL, with many dogs falling close to the lower end of the range. Thus, less sensitive assay systems (eg, Immulite 1000) would likely have poorer discrimination. Intra-assay and interassay variability (increased at lower cACTH concentrations), pulsatile

Table 3. Results of cACTH assays for dogs with HAC (last 10 years with currently available assays only).

Study	Assay	PDH	AT	Number Incorrect
Zeugswetter[77]	Immulite 1000	49 dogs <10–101 pg/mL	10 dogs <10 pg/mL	9/59
Rodriguez Pineiro[75]	Immulite 2000	91 dogs 6–1,250 pg/mL	18 dogs <5 pg/mL	0/109
Castillo[72]	Nichols IRMA	5 dogs 40–135 pg/mL	NA	NA
Scott-Moncrieff[76]		11 dogs	4 dogs	
	Immulite ACTH	<10–50 pg/mL	<10 pg/mL	4/15 (Immulite)
	Nichols IRMA	9–99 pg/mL	<10 pg/mL	3/15 (IRMA)
Gould[114]	Nichols IRMA	21 dogs 28–1,132 pg/mL 1 dog <5 pg/mL	6 dogs <5 pg/ml 1 dog 76 pg/mL	2/29

ACTH, adrenocorticotrophic hormone; cACTH, canine ACTH; HAC, hyperadrenocorticism; IRMA, immunoradiometric assay; PDH, pituitary-dependent hyperadrenocorticism; AT, adrenal tumor.

ACTH secretion, and inappropriate sample handling allowing ACTH degradation increase the likelihood of a falsely low value in dogs with PDH.

Timing of Sample Collection. No clear evidence exists that the specific time of sample collection affects results or discriminatory power of the test.

Sample Handling. Plasma proteases degrade cACTH rapidly if samples are not cooled appropriately. Blood should be collected into chilled, silicon-coated glass or plastic tubes containing EDTA, centrifuged within 15 minutes (ideally in a cooled centrifuge), and the plasma transferred to plastic tubes and frozen immediately.[74,76,78] Samples must stay frozen until analysis; if a courier is used for quick transport to a reference laboratory, ice may be sufficient. If samples are shipped, they should be sent overnight packed in dry ice.

Addition of the protease inhibitor aprotinin (Trasylol) prevents ACTH degradation by plasma proteases.[74] With the Immulite assay, aprotinin introduces an artifactual decrease[76] and is not recommended.

Discordant Test Results. Discordance between cACTH concentration and results of other differentiating tests sometimes occurs. Episodic cACTH secretion, poor assay sensitivity, and sample degradation are potential explanations. Stress and the presence of multiple adrenal disorders (ie, cortisol-secreting AT or PDH with pheochromocytoma; cortisol-secreting AT and PDH) also may influence ACTH concentrations. Ectopic ACTH secretion and food-stimulated cortisol secretion could also cause discordance.[69,70]

Conclusions

- cACTH measurement is the most accurate standalone biochemical differentiating test.
- Reference ranges vary by technique; each laboratory much establish its own reference ranges.
- Sensitivity is a concern with some assays.
- Proper sample handling is critical.

Dexamethasone Suppression Testing

Test Principles. In normal dogs, dexamethasone administration causes rapid and prolonged suppression of cortisol secretion. In patients with an AT, dexamethasone at any dosage does not suppress cortisol secretion. In dogs with PDH, ACTH secretion is not appropriately suppressed by administration of a low dose of dexamethasone (0.01 mg/kg), but in 75% of dogs with PDH, cortisol concentrations decrease after administration of 0.1 mg/kg dexamethasone used in the high-dose dexamethasone suppression test. The other 25% of dogs with PDH do not demonstrate suppression even after receiving higher dexamethasone dosages.[35] In dogs with PDH that do not suppress, a large pituitary tumor is more likely.[32,79]

Dexamethasone Form, Dosage, and Time of Testing. The HDDST should be performed as the LDDST except that the dosage of dexamethasone is 0.1 mg/kg IV. The free alcohol form should be avoided.

LDDST and HDDST as Differentiating Tests. The largest study evaluating both suppression tests included 181 dogs with PDH and 35 with AT.[35] Procedures used to classify dogs were fairly rigorous; however, some dogs with mitotane-responsive AT may have been included in the PDH group. The criteria proposed for identification of dogs with PDH using an LDDST were a 4-hour postdexamethasone cortisol concentration below the laboratory cut-off or <50% of the basal cortisol concentration or an 8-hour cortisol concentration <50% of the basal cortisol concentration, but greater than the laboratory cut-off. The criteria for suppression on the HDDST were a 4- or 8-hour cortisol concentration or both below the laboratory cut-off or <50% of the basal cortisol concentration. Approximately 75% of dogs with PDH met at least 1 criterion for suppression on either the LDDST or HDDST. Of dogs with PDH, 12% did not suppress on an LDDST but did on the HDDST. Dexamethasone resistance (ie, no criteria were met) occurred in all dogs with AT and the remainder of the dogs with PDH. The criteria proposed in this study still are well accepted, although no follow-up studies have been performed for confirmation. In 41 dogs with AT in another study, 28 LDDST and 30 HDDST were performed.[6] No suppression was seen on any test.

Based on clinical experience, the Panel agrees that suppression in response to dexamethasone supports a diagnosis of PDH, and a dog with dexamethasone resistance can have either AT or PDH. However, cut-off values need to be re-evaluated.

Dexamethasone Suppression with UCCR. Decreased blood cortisol concentration after dexamethasone administration is reflected in decreased UCCR. After collection of a morning urine sample on 2 consecutive days at home, 3 doses of dexamethasone (0.1 mg/kg) are administered PO at 6- to 8-hour intervals, and a 3rd urine sample is collected the next morning. A decrease in the 3rd UCCR to <50% of the mean of the basal values is consistent with PDH.[80] Lack of suppression does not confirm AT. In 160 dogs with HAC (49 AT and 111 PDH), the UCCR in 72% of dogs with PDH suppressed to <50% of the basal UCCR.[81] The other 28% of dogs with PDH were dexamethasone-resistant. In dogs with AT, the maximum suppression was 44% of the baseline sample.

Discordant Test Results. Discordance between results of suppression tests and other differentiating tests may occur for the same reasons as for cACTH measurement. Changes in dexamethasone metabolism also may influence results of suppression tests.[31,82]

Conclusions

- Dexamethasone suppression can help distinguish PDH from AT. If suppression occurs, the patient likely has PDH. However, cut-off values should be reevaluated.

- Lack of suppression after dexamethasone administration on either the LDDST or HDDST does not confirm an AT because approximately 25% of dogs with PDH fail to suppress.
- Suppression to < 50% of baseline on an LDDST (using criteria outlined above) in a dog with HAC confirms the disease as pituitary-dependent.
- If there is no suppression on an LDDST, measurement of cACTH or abdominal ultrasound is recommended. If these tests are not available, the HDDST is an alternative but it will only provide differentiation in approximately 12% additional PDH cases.
- Results of either the LDDST or HDDST cannot be considered 100% absolute.

Diagnostic Imaging

Diagnosis of HAC cannot be performed solely with imaging (ultrasonography, CT, MRI) and must rely on hormone tests. Moreover, finding normal adrenal glands on imaging studies does not rule out HAC.

Radiography. Abdominal distension, good contrast because of abdominal fat deposition, hepatomegaly, and bladder distension may be seen as well as mineralization of the bronchi and pulmonary interstitium[82] and of dermal and subcutaneous tissues in areas predisposed to calcinosis cutis. A small liver makes HAC unlikely.[83] An AT may be visualized either because of mass effect or tumoral calcification.

Ultrasonographic Imaging. Adrenal gland width is the most informative parameter. Because the long axis of an adrenal gland often is misaligned with either the medial or dorsal plane of the body, cross-sectional images may lead to oblique views and miscalculation of glandular dimensions. Breed and body size-related differences also must be considered.

Ultrasonography can estimate AT size and possibly vascular or local soft tissue invasion.[85,86] Symmetrical, normal sized, or enlarged adrenal glands are found in dogs with PDH,[87] but mild asymmetry also may occur.[88,89] Moderate asymmetry, contralateral adrenocortical atrophy (adrenal width <4 to 5 mm), destruction of normal tissue architecture, or some combination of these is consistent with an AT. Distinguishing macronodular hyperplasia from AT can be difficult with ultrasonography. Although most AT are unilateral, bilateral tumors may occur.[86,90,91]

When an AT has been confirmed, certain findings suggest malignancy. Possible metastases may be identified by thoracic radiography and abdominal ultrasonography. Metastasis can be confirmed by ultrasound-guided biopsy. Adrenal gland width >4 cm is highly correlated with malignancy. Invasion into the vena cava or adjacent tissues can be detected by ultrasonography, but CT[92] and MRI are more sensitive techniques to identify vascular invasion and detect metastases. Therefore, abdominal ultrasonography ideally should be followed by CT or MRI before adrenalectomy. Differentiating benign from malignant AT often is difficult, even with histopathological examination. No dog should be sent to surgery for adrenalectomy without confirmation of the presence of an AT (and atrophy of contralateral adrenal gland) by abdominal ultrasound examination, CT, MRI, or some combination of these.

Pituitary Imaging. Pituitary imaging provides valuable information regarding treatment options and prognosis. Pituitary lesions range from small nests of hyperplastic cells to large tumors.[5] The absence of neurological abnormalities does not exclude a pituitary macrotumor (ie, a tumor that is either >1 cm diameter, extends above the sella turcica, or has a pituitary/brain ratio of >0.31).[32,92]

Because pituitary lesions may be quite small, contrast-enhanced CT and MRI may identify a normal-sized pituitary gland in dogs with PDH.[32,88,94–96] The blood supply of the posterior pituitary gland is direct (arterial), whereas that of the anterior pituitary gland is mainly indirect via the pituitary portal system; dynamic contrast-enhanced CT takes advantage of this difference. In a dog with a normal pituitary gland, after IV administration of contrast medium, the posterior pituitary gland can be identified first. This phase is called the "pituitary flush," and its absence indicates atrophy of the posterior pituitary gland because of compression by a pituitary tumor. Displacement or distortion of the flush can be used to identify and localize anterior pituitary microtumors.[97] Dorsal displacement and decreased signal intensity of the posterior lobe on T1-weighted MRI also indicates the presence of a microtumor.[98]

The Panel does not recommend a specific pituitary imaging technique; choice reflects availability and the type of information sought. Over time, some pituitary tumors become macrotumors. Because radiation therapy or hypophysectomy is required for their treatment and both are more effective with smaller tumors and in the absence of neurological abnormalities, the Panel recommends that pituitary imaging be considered for all dogs at the time of PDH diagnosis. If clinical features suggest a pituitary macrotumor, confirmation requires imaging. Imaging also is essential for treatment planning before either hypophysectomy or pituitary irradiation.

A cortisol-secreting AT and pituitary tumor may occur simultaneously.[99] Thus, 2 Panel members advise pituitary imaging in dogs with AT. All Panel members recommend pituitary imaging when discordant results of previous tests exist (eg, an AT is visualized but cACTH concentration is not low, the contralateral adrenal gland is not atrophied, [>4 to 5 mm], or part of the affected adrenal gland appears normal).

Conclusions

- Diagnostic images should be carefully interpreted and always in conjunction with hormonal studies.
- No dog should undergo adrenalectomy without confirmation of the presence of an AT (and atro-

phy of contralateral adrenal gland) by abdominal imaging.
- Metastases, vena caval invasion by tumor mass, adrenal width >4 cm, or some combination of these findings strongly suggests malignancy.
- Pituitary imaging is recommended in all cases of PDH and considered essential in some.

Measurement of Cortisol Precursors and Adrenal Sex Hormones

The syndrome of atypical or occult HAC is defined as "a syndrome in which a dog appears to have HAC based on history, physical examination, and clinicopathologic findings, but the LDDST, UCCR, *and* ACTH stimulation test fall into currently accepted reference ranges." The Panel prefers the term "occult" over atypical, but also notes that in the human literature, occult HAC refers to individuals not showing typical signs of HAC, ie, those with subclinical or inapparent disease. Because the term is known, the Panel chose to continue to refer to the syndrome as "occult HAC."

Current theory, which possibly is incorrect, is that "occult HAC" is because of the abnormal adrenocortical secretion of sex hormones. The Panel does not believe that sex hormones cause "occult HAC." Readers are referred elsewhere[100] for a discussion of the evidence for or against the theory.

The diagnosis of standard HAC is never based solely on basal cortisol concentration. No evidence exists that measurement of basal serum sex hormone concentrations are any more reliable for diagnosis of adrenal dysfunction. Thus, the following discussion will focus on ACTH-stimulated concentrations, which are a measure of adrenal reserve.

Clinical Picture

Only 14 cases in the veterinary literature meet the definition.[101–104] No specific phenotype for "occult HAC" is apparent.

Although sudden acquired retinal degeneration syndrome and hyperphosphatasemia in Scottish Terriers[105] have been linked with "occult HAC," causative evidence is lacking. If only post-ACTH sex hormone concentrations were considered, no single sex hormone was increased in more than 62% of dogs with retinal degeneration, and no single hormone was consistently increased. Similarly, in Scottish Terriers with hyperphosphatasemia, no single hormone was consistently increased. Furthermore, more Scottish Terriers without hyperphosphatasemia had increased sex hormones than did those with increased enzyme activity. Correlation is not causation.

Indications for Diagnostic Testing. Testing for "occult HAC" should not be undertaken if no clinical indication for testing for classic HAC exists. If the clinical picture fits, the primary indication for measuring cortisol precursors and adrenal sex hormones is when a dog is tested for HAC with an ACTH stimulation test or LDDST and all cortisol concentrations, including basal, are below the reference range. If administration of exogenous glucocorticoids of any form or of medications that alter cortisol synthesis (eg, ketoconazole) is ruled out, a sex hormone-secreting AT may be present. The ultrasonographic finding of an AT in such patients would further support the diagnosis, but the lack of visualizing an AT does not rule it out. Secretion of progesterone and 17-α-hydroxy-progesterone (17OHP) or other sex hormone or cortisol precursor[103,106] may suppress pituitary ACTH secretion and cause atrophy of normal adrenocortical tissue. A cause and effect relationship between AT sex hormone secretion and clinical signs has been documented,[103,104,107] whereas a causative relationship with PDH and sex hormones has not. Furthermore, AT cells can dedifferentiate, losing ability to synthesize enzymes in the hormone synthesis pathways. Thus, a sex hormone or cortisol precursor may be the end-product of hormone synthesis, not cortisol. If pituitary-dependent "occult HAC" exists, how or why adrenocortical tissue should have altered steroid synthesis is unexplained.

Therefore, if clinical signs are mild, the Panel recommends waiting and retesting for classical HAC when progression is noted. If clinical signs are moderate to severe, abdominal ultrasound examination should be performed. If the adrenal glands are normal, the differential diagnoses for the patient should be reconsidered. If bilateral adrenomegaly is present, pituitary CT or MRI should be considered to identify a pituitary tumor causing early HAC. Lastly, food-stimulated HAC should be considered as a diagnosis, as in these patients fasting cortisol concentration may be low.

Sex Hormone Testing. Measurement of serum sex hormone concentrations has been advocated for diagnosis of "occult HAC." Use of a sex hormone panel has been proposed to increase sensitivity and specificity over measurement of a single hormone alone. Increased concentrations of any of the sex hormones are common, with increases in estradiol noted in approximately 40% of panels submitted to a reference laboratory.[108]

On the other hand, dogs with NAI might have increased sex hormone concentrations compared to healthy dogs because of adaptation of adrenocortical function to the stresses of chronic illness. Dogs with chronic NAI had a 14%[21]or 36%[22] chance of having post-ACTH stimulation cortisol concentrations consistent with HAC. Dogs without adrenal disease also can have increased sex hormone concentrations, and sex hormones may be more likely to be falsely increased by NAI than cortisol. In 1 study, post-ACTH serum cortisol, 17OHP, and corticosterone concentrations were significantly correlated both in dogs with neoplasia and in those suspected of having HAC, suggesting that as adrenal function is increased either by adrenal disease or by NAI, production of all hormones increases proportionately.[48] Test specificity for 17OHP may be as low as 59–70%.[48,51,109] The specificity of progesterone measurement in a single study was 55%.[51] In 6 dogs with either pheochromocytoma or a nonfunctional AT, serum concentrations of androstenedione, progesterone, 17OHP, testosterone, estradiol, or some combination of these were increased.[107]

Alternate Theories. The Panel recognizes cases that fulfill criteria for "occult HAC." Three Panel members will test for "occult HAC" by measuring sex hormones in specific cases after all other differential diagnoses have been excluded.

A few explanations exist for the existence of such cases. First, as discussed above, the reference ranges and cut-off values for the LDDST need to be reestablished; the Panel believes they should be lower than they currently are, resulting in some dogs with "occult HAC" actually having typical HAC. If so, dogs with mild or early HAC that are "normal" on tests using current cut-off values may not be with revised (lower) values. Second, variable cortisol sensitivity exists in humans[110] and may occur in dogs. Dogs with high sensitivity may show clinical signs of HAC at cortisol concentrations considered "normal" for the general population. Accordingly, the appropriate name for the syndrome may be "suspected HAC." Third, dogs that meet the definition for "occult HAC" may have rare forms such as food-dependent HAC. Other explanations also may exist.

Conclusions

- Sex hormones have not been proven to cause "occult HAC."
- In general, if the clinical picture does not fit testing for classic HAC, it does not fit testing for "occult HAC."
- One indication for testing of "occult HAC" is inappropriately low cortisol concentrations on HAC screening tests.
- The specificity of adrenal sex hormone panel testing is low.
- Finding an AT does not mean HAC is present. Given the specificity of sex hormone testing, a sex hormone panel must be interpreted cautiously if clinical signs of HAC are lacking.

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References

1. Capen CC, Martin SL, Koestner A. Neoplasms in the adenohypophysis of dogs. Path Vet 1967;4:301–325.

2. Ling GV, Stabenfeldt GH, Comer KM, et al. Canine hyperadrenocorticism: Pretreatment clinical and laboratory evaluation of 117 cases. J Am Vet Med Assoc 1979;174:1211–1215.

3. Neiger R, Ramsey IK, O'Conner J, et al. Trilostane treatment of 78 dogs with pituitary-dependent hyperadrenocorticism. Vet Rec 2002;150:799–804.

4. Owens JM, Drucker WD. Hyperadrenocorticism in the dog: Canine Cushing's syndrome. Vet Clin North Am 1977;7:583–602.

5. Peterson ME, Krieger DT, Drucker WD. Immunocytochemical study of the hypophysis in 25 dogs with pituitary-dependent hyperadrenocorticism. Acta Endocrinol 1982;101:15–24.

6. Reusch CE, Feldman EC. Canine hyperadrenocorticism due to adrenocortical neoplasia. Pretreatment evaluation of 41 dogs. J Vet Int Med 1991;5:3–10.

7. Ruckstuhl NS, Nett CS, Reusch C. Results of clinical examinations, laboratory tests, and ultrasonography in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane. Am J Vet Res 2002;63:506–512.

8. Scavelli TD, Peterson ME, Matthiesen DT. Results of surgical treatment for hyperadrenocorticism caused by adrenocortical neoplasia in the dog: 25 cases (1980–1984). J Am Vet Med Assoc 1986;189:1360–1364.

9. Schechter RD, Stabenfeldt GH, Gribble DH, Ling GV. Treatment of Cushing's syndrome in the dog with an adrenocorticolytic agent (o, p'DDD). J Am Vet Med Assoc 1973;162:629–639.

10. Reusch C, Steffen T, Hoerauf A. The efficacy of L-deprenyl in dogs with pituitary-dependent hyperadrenocorticism. J Vet Intern Med 1999;13:291–301.

11. Zur G, White SD. Hyperadrenocorticism in 10 dogs with skin lesions as the only presenting clinical signs. J Am Anim Hosp Assoc 2011;47:419–427.

12. Rewarts JM, Grooters AM, Payne JT, Kornegay JN. A traumatic rupture of the gastrocnemius muscle after corticosteroid administration in a dog. J Am Vet Med Assoc 1997; 210:655–657.

13. Swinney GR, Foster SF, Church DB, Malik R. Myotonia associated with hyperadrenocorticism in two dogs. Aust Vet J 1998;76:722–724.

14. Greene CE, Lorenz MD, Munnell JF, et al. Myopathy associated with hyperadrenocorticism in the dog. J Am Vet Med Assoc 1979;174:1310–1315.

15. Feldman BF, Rasedee A, Feldman EC. Haemostatic abnormalities in canine Cushing's syndrome. Res Vet Sci 1986;41:228–230.

16. Burns MG, Kelly AB, Hornof WJ, Howerth EW. Pulmonary artery thrombosis in three dogs with hyperadrenocorticism. J Am Vet Med Assoc 1981;178:388–393.

17. Blaxter AC, Gruffydd-Jones TJ. Concurrent diabetes mellitus and hyperadrenocorticism in the dog: Diagnosis and management of eight cases. J Small Anim Pract 1990;31:117–122.

18. Peterson ME, Nesbitt GH, Schaer M. Diagnosis and management of concurrent diabetes mellitus and hyperadrenocorticism in 30 dogs. J Am Vet Med Assoc 1981;178:66–69.

19. Lang JM, Schertel E, Kennedy S, et al. Elective and emergency surgical management of adrenal gland tumors: 60 cases (1999–2006). J Am Anim Hosp Assoc 2011;47:428–435.

20. Vandenbergh AGGD, Voorhout G, van Sluijs FJ, et al. Haemorrhage from a canine adrenocortical tumour: A clinical emergency. Vet Rec 1992;131:539–540.

21. Kaplan AJ, Peterson ME, Kemppainen RJ. Effects of disease on the results of diagnostic tests for use in detecting hyperadrenocorticism in dogs. J Am Vet Med Assoc 1995;207:445–451.

22. Chastain CB, Franklin RT, Ganjam VK, Madsen RW. Evaluation of the hypothalamic pituitary-adrenal axis in clinically stressed dogs. J Am Anim Hosp Assoc 1986;22:435–442.

23. Kemppainen RJ, Sartin JL. Evidence for episodic but not circadian activity in plasma concentrations of adrenocorticotrophin, cortisol and thyroxine in dogs. J Endocrinol 1984;103:219–226.

24. Eiler H, Oliver JW, Legendre AM. Stages of hyperadrenocorticism: Response of hyperadrenocorticoid dogs to the combined dexamethasone suppression/ACTH stimulation test. J Am Vet Med Assoc 1984;185:289–294.

25. Church DB, Nicholson AI, Ilkiw JE, Emslie DR. Effect of non-adrenal illness, anasthesia and surgery on plasma cortisol concentrations in dogs. Res Vet Sci 1994;56:129–131.

26. Behrend EN, Kemppainen RJ, Young DW. Effect of storage conditions on cortisol, total thyroxine and free thyroxine concentrations in serum and plasma of dogs. J Am Vet Med Assoc 1995;212:1564–1568.

27. Ambrogio AG, Pecori GF, Cavagnini F. Drugs and HPA axis. Pituitary 2008;11:219–229.

28. Zeugswetter F, Hoyer MT, Pagitz M, et al. The desmopressin stimulation test in dogs with Cushing's syndrome. Domest Anim Endocrinol 2008;34:254–260.

29. Selman PJ, Mol JA, Rutteman GR, et al. Effects of progestin administration on the hypothalamic-pituitary-adrenal axis and glucose homeostasis in dogs. J Reprod Fertil Supp 1997;51:345–354.

30. Feldman EC, Nelson RW. Glucocorticoid therapy. In: Feldman EC, Nelson RW, eds. Canine and Feline Endocrinology and Reproduction. St. Louis, MO: Saunders; 2004:465–538.

31. Lothrop CD, Oliver J. Diagnosis of canine Cushing's syndrome based on multiple steroid analyses and dexamethasone turnover kinetics. Am J Vet Res 1984;45:2304–2309.

32. Kooistra HS, Voorhout G, Mol JA, Rijnberk A. Correlation between impairment of glucocorticoid feedback and the size of the pituitary gland in dogs with pituitary-dependent hyperadrenocorticism. J Endocrinol 1997;152:387–394.

33. Findling JW, Raff H, Aron DC. The low-dose dexamethasone suppression test: A re-evaluation in patients with Cushing's syndrome. J Clin Endocrinol Metab 2004;89:1222–1226.

34. Boscaro M, Arnaldi G. Approach to the patient with possible Cushing's syndrome. J Clin Endocrinol Metab 2009;94:3121–3131.

35. Feldman EC, Feldman MS, Nelson RW. Use of low- and high-dose dexamethasone tests for distinguishing pituitary-dependent from adrenal tumor hyperadrenocorticism in dogs. J Am Vet Med Assoc 1996;209:772–775.

36. Feldman EC. Comparison of ACTH response and dexamethasone suppression as screening tests in canine hyperadrenocorticism. J Am Vet Med Assoc 1983;182:506–510.

37. Meijer JC, de Bruijne JJ, Rijnberk A, Croughs RJM. Biochemical characterization of pituitary-dependent hyperadrenocorticism in the dog. J Endocrinol 1978;77:111–118.

38. Meijer JC, Lubberink AAME, Rijnberk A, Croughs JM. Adrenocortical function tests in dogs with hyperfunctioning adrenocortical tumors. J Endocrinol 1979;80:315–319.

39. Mack RE, Feldman EC. Comparison of two low-dose dexamethasone suppression protocols as screening and discrimination tests in dogs with hyperadrenocorticism. J Am Vet Med Assoc 1990;197:1603–1606.

40. May ER, Frank LA, Hnilica KA, Lane IF. Effects of a mock ultrasonographic procedure on cortisol concentrations during low-dose dexamethasone suppression testing in clinically normal adult dogs. Am J Vet Res 2004;65:267–270.

41. Mueller C, Sieber-Ruckstuhl N, Wenger M, et al. Low-dose dexamethasone test with "inverse" results: A possible new pattern of cortisol response. Vet Rec 2006;159:489–491.

42. Rijnberk A, van Wees A, Mol JA. Assessment of two tests for the diagnosis of canine hyperadrenocorticism. Vet Rec 1988;122:178–180.

43. van Liew CH, Greco DS, Salman MD. Comparison of results of adrenocorticotropic hormone stimulation and low-dose dexamethasone suppression test with necropsy findings in dogs: 81 cases (1985–1995). J Am Vet Med Assoc 1997;211:322–325.

44. Kemppainen RJ, Sartin JL. Effects of single intravenous doses of dexamethasone on baseline plasma cortisol concentrations and response to synthetic ACTH in healthy dogs. Am J Vet Res 1984;45:742–746.

45. Chauvet AE, Feldman EC, Kass PS. Effects of phenobarbital administration on results of serum biochemical analyses and adrenocortical function tests in epileptic dogs. J Am Vet Med Assoc 1995;207:1305–1307.

46. Muller PB, Wolfsheimer KJ, Taboada J, et al. Effects of long-term phenobarbital treatment on the thyroid and adrenal axis and adrenal function tests in dogs. J Vet Intern Med 2000;14:157–164.

47. Foster SF, Church DB, Watson ADJ. Effect of phenobarbitone on the low-dose dexamethasone suppression test and the urinary corticoid:creatinine ratio in dogs. Aust Vet J 2000;78:19–23.

48. Behrend EN, Kemppainen RJ, Boozer AL, et al. Serum 17-α-hydroxyprogesterone and corticosterone concentrations in dogs with non-adrenal neoplasia and dogs with suspected hyperadrenocorticism. J Am Vet Med Assoc 2005;227:1762–1767.

49. Gieger TL, Feldman EC, Wallack ST, Dank G. Lymphoma as a model for chronic illness: Effects on adrenocortical function testing. J Vet Intern Med 2003;17:154–157.

50. Peterson ME, Gilbertson SR, Drucker WD. Plasma cortisol response to exogenous ACTH in 22 dogs with hyperadrenocorticism caused by adrenocortical neoplasia. J Am Vet Med Assoc 1982;180:542–544.

51. Monroe WE, Panciera DL, Zimmerman KL. Concentrations of noncortisol adrenal steroids in response to ACTH in dogs with adrenal-dependent hyperadrenocorticism, pituitary-dependent hyperadrenocorticism, and nonadrenal illness. J Vet Intern Med 2012;26:945–952.

52. Cohen TA, Feldman EC. Comparison of IV and IM formulations of synthetic ACTH for ACTH stimulation tests in healthy dogs. J Vet Intern Med 2012;26:412–414.

53. Kemppainen RJ, Behrend EN, Busch KA. Use of compounded adrenocorticotropic hormone (ACTH) for adrenal function testing in dogs. J Am Anim Hosp Assoc 2005;41:368–372.

54. Hansen BL, Kemppainen RJ, MacDonald JM. Synthetic ACTH (Cosyntropin) stimulation tests in normal dogs: Comparison of intravenous and intramuscular administration. J Am Anim Hosp Assoc 1994;30:38–41.

55. Behrend EN, Kemppainen RJ, Bruyette DS, et al. Intramuscular administration of a low dose of ACTH for ACTH stimulation testing in dogs. J Am Vet Med Assoc 2006;229:528–530.

56. Kerl ME, Peterson ME, Wallace MS, et al. Evaluation of a low-dose synthetic adrenocorticotropic hormone stimulation test in clinically normal dogs and dogs with naturally developing hyperadrenocorticism. J Am Vet Med Assoc 1999;214:1497–1501.

57. Frank LA, DeNovo RC, Kraje AC, Oliver J. Cortisol concentrations following stimulation of healthy and adrenopathic dogs with two doses of tetracosactrin. J Small Anim Pract 2000;41:308–311.

58. Martin LG, Behrend EN, Mealey KL, et al. Effect of low doses of cosyntropin on serum cortisol concentrations in clinically normal dogs. Am J Vet Res 2007;68:555–560.

59. Ginel PJ, Sileo PJ, Blanco B, et al. Evaluation of serum concentrations of cortisol and sex hormones of adrenal gland origin after stimulation with two synthetic ACTH preparations in clinically normal dogs. Am J Vet Res 2012;73:237–241.

60. Frank LA, Oliver J. Comparison of serum cortisol concentrations in clinically normal dogs after administration of freshly reconstituted versus reconstituted and stored frozen cosyntropin. J Am Vet Med Assoc 1998;212:1569–1571.

61. Willard MD, Nachreiner R, McDonald R, Roudebush P. Ketoconazole-induced changes in selected canine hormone concentrations. Am J Vet Res 1986;47:2504–2509.

62. Dyer KR, Monroe WE, Forrester SD. Effects of short- and long-term administration of phenobarbital on endogenous ACTH concentration and the results of ACTH stimulation tests in dogs. J Am Vet Med Assoc 1994;205:315–318.

63. Smiley LE, Peterson ME. Evaluation of a urine cortisol: creatinine ratio as a screening test for hyperadrenocorticism in dogs. J Vet Int Med 1993;7:163–168.

64. Feldman EC, Mack RE. Urine cortisol:creatinine ratio as a screening test for hyperadrenocorticism in dogs. J Am Vet Med Assoc 1992;200:1637–1641.

65. Stolp R, Rijnberk A, Meijer JC, Croughs JM. Urinary corticoids in the diagnosis of canine hyperadrenocorticism. Res Vet Sci 1983;34:141–144.

66. Jensen AL, Iverson L, Koch J, et al. Evaluation of the urinary cortisol:creatinine ratio in the diagnosis of hyperadrenocorticism in dogs. J Small Anim Pract 1997;38:99–102.

67. van Vonderen IK, Kooistra HS, Rijnberk A. Influence of veterinary care on the urinary corticoid:creatinine ratio in dogs. J Vet Intern Med 1998;12:431–435.

68. Zeugswetter F, Bydzovsky N, Kampner D, Schwendenwein I. Tailored reference limits for urine corticoid:creatinine ratio in dogs to answer distinct clinical questions. Vet Rec 2010;167:997–1001.

69. Galac S, Kooistra HS, Voorhout G, et al. Hyperadrenocorticism in a dog due to ectopic secretion of adrenocorticotropic hormone. Domest Anim Endocrinol 2005;28:338–348.

70. Galac S, Kars VJ, Voorhout G, et al. ACTH-independent hyperadrenocorticism due to food-dependent hypercortisolemia in a dog: A case report. Vet J 2007;177:141–143.

71. Kooistra HS, Greven SH, Mol JA, Rijnberk A. Pulsatile secretion of alpha-MSH and the differential effects of dexamethasone and haloperidol on the secretion of alpha-MSH and ACTH in dogs. J Endocrinol 1997;152:113–121.

72. Castillo V, Blatter C, Gomez NV, et al. Diurnal ACTH and plasma cortisol variations in healthy dogs and in those with pituitary-dependent Cushing's syndrome before and after treatment with retinoic acid. Res Vet Sci 2009;86:223–229.

73. Hanson JM, Kooistra HS, Mol JA, et al. Plasma profiles of adenocorticotropic hormone, cortisol, alpha-melanocyte-stimulating hormone, and growth hormone in dogs with pituitary-dependent hyperadrenocorticism before and after hypophysectomy. J Endocrinol 2006;190:601–609.

74. Kemppainen RJ, Clark TP, Peterson ME. Preservative effect of aprotinin on canine plasma immunoreactive adrenocorticotropin concentrations. Domest Anim Endocrinol 1993;11:355–362.

75. Rodriguez Pineiro MI, Benchekroun G, de Fornel-Thibaud P, et al. Accuracy of an adrenocorticotropic hormone (ACTH) immunoluminometric assay for differentiating ACTH-dependent from ACTH-independent hyperadrenocorticism in dogs. J Vet Intern Med 2009;23:850–855.

76. Scott-Moncrieff JCR, Koshko M, Brown JA, et al. Validation of chemiluminescent enzyme immunometric assay for plasma adrenocorticotropic hormone in the dog. Vet Clin Pathol 2003;32:180–187.

77. Zeugswetter F, Pagitz M, Hittmair K, Schwendenwein I. Diagnostic efficacy of plasma ACTH-measurement by a chemiluminometric assay in canine hyperadrenocorticism. Schweiz Arch Tierheilkd 2011;153:111–116.

78. Hegstad RL, Johnston SD, Pasternak DM. Effects of sample handling on adrenocorticotropin concentration measured in canine plasma, using a commercially available radioimmunoassay kit. Am J Vet Res 1990;51:1941–1947.

79. Bosje JT, Rijnberk A, Mol JA, et al. Plasma concentrations of ACTH precursors correlate with pituitary size and resistance to dexamethasone in dogs with pituitary-dependent hyperadrenocorticism. Domest Anim Endocrinol 2002;22:201–210.

80. Galac S, Kooistra HS, Teske E, Rijnberk A. Urinary corticoid/creatinine ratios in the differentiation between pituitary-dependent hyperadrenocorticism and hyperadrenocorticism due to adrenocortical tumor in the dog. Vet Quart 1997;19:17–20.

81. Galac S, Buijtels JJCWM, Kooistra HS. Urinary corticoid: creatinine ratios in dogs with pituitary-dependent hypercortisolism during trilostane treatment. J Vet Intern Med 2009;23:1214–1219.

82. Kemppainen RJ, Peterson ME. Circulating concentration of dexamethasone in healthy dogs, dogs with hyperadrenocorticism, and dogs with nonadrenal illness during dexamethasone suppression testing. Am J Vet Res 1993;54:1765–1769.

83. Berry CR, Hawkins EC, Hurley KJ, Monce K. Frequency of pulmonary mineralization and hypoxemia in 21 dogs with pituitary-dependent hyperadrenocorticism. J Vet Intern Med 2000;14:151–156.

84. Schwarz T, Stork CK, Mellor D, Sullivan M. Osteopenia and other radiographic signs in canine hyperadrenocorticism. J Small Anim Pract 2000;41:491–495.

85. Voorhout G, Rijnberk A, Sjollema BE, van den Ingh TSGAM. Nephrotomography and ultrasonography for the localization of hyperfunctioning adrenocortical tumors in dogs. Am J Vet Res 1990;51:1280–1285.

86. Hoerauf A, Reusch C. Ultrasonographic characteristics of both adrenal glands in 15 dogs with funtional adrenocortical tumors. J Am Anim Hosp Assoc 1999;35:193–199.

87. Grooters AM, Biller DS, Theisen SK, Miyabayashi T. Ultrasonographic characteristics of the adrenal glands in dogs with pituitary-dependent hyperadrenocorticism: Comparison with normal dogs. J Vet Intern Med 1996;10:110–115.

88. Rodriguez Pineiro MI, de Fornel-Thibaud P, Benchekroun G, et al. Use of computed tomography adrenal gland measurement for differentiating ACTH dependence from ACTH independence in 64 dogs with hyperadenocorticism. J Vet Intern Med 2011;25:1066–1074.

89. Benchekroun G. Ultrasonography criteria for differentiating ACTH dependency from ACTH independency in 47 dogs with hyperadrenocorticism and equivocal adrenal asymmetry. J Vet Intern Med 2010;24:1077–1085.

90. Ford SL, Feldman EC, Nelson RW. Hyperadrenocorticism caused by bilateral adrenocortical neoplasia in dogs: Four cases (1983–1988). J Am Vet Med Assoc 1993;202:789–792.

91. van Sluijs FJ, Sjollema BE, Voorhout G, et al. Results of adrenalectomy in 36 dogs with hyperadrenocorticism caused by adrenocortical tumor. Vet Quart 1995;17:113–116.

92. Schultz RM, Wisner ER, Johnson EG, MacLeod JS. Contrast-enhanced computed tomography as a preoperative indicator of vascular invasion from adrenal masses in dogs. Vet Radiol Ultrasound 2009;50:625–629.

93. Kipperman BS, Feldman EC, Dybdal NO, Nelson RW. Pituitary tumor size, neurologic signs, and relation to endocrine test results in dogs with pituitary-dependent hyperadrenocorticism: 43 cases (1980–1990). J Am Vet Med Assoc 1992;201:762–767.

94. Bertoy EH, Feldman EC, Nelson RW, et al. Magnetic resonance imaging of the brain in dogs with recently diagnosed but untreated pituitary-dependent hyperadrenocorticism. J Am Vet Med Assoc 1995;206:651–656.

95. van der Vlugt-Meijer RH, Voorhout G, Meij BP. Imaging of the pituitary gland in dogs with pituitary-dependent hyperadrenocorticism. Mol Cell Endocrinol 2002;197:81–87.

96. Auriemma E, Barthez PY, van der Vlugt-Meijer RH, et al. Computed tomography and low-magnetic resonance imaging of the pituitary gland in dogs with pituitary-dependent hyperadrenocorticism: 11 cases (2001–2003). J Am Vet Med Assoc 2009;235:409–414.

97. van der Vlugt-Meijer RH, Meij BP, van den Ingh TSGAM, et al. Dynamic computed tomography of the pituitary gland in dogs with pituitary-dependent hyperadrenocorticism. J Vet Intern Med 2003;17:773–780.

98. Taoda T, Hara Y, Masuda H, et al. Magnetic resonance imaging assessment of pituitary posterior lobe displacement in dogs with pituitary-dependent hyperadrenocorticism. J Vet Med Sci 2011;73:725–731.

99. Greco DS, Peterson ME, Davidson AP, et al. Concurrent pituitary and adrenal tumors in dogs with hyperadrenocorticism: 17 cases (1978–1995). J Am Vet Med Assoc 1999;214:1349–1353.

100. Behrend EN, Kennis RA. Atypical Cushing's syndrome in dogs: Arguments for and against. Vet Clin North Am Small Anim Pract 2010;40:285–296.

101. Ristic JME, Ramsey IK, Heath FM, et al. The use of 17-hydroxyprogesterone in the diagnosis of canine hyperadrenocorticism. J Vet Intern Med 2002;16:433–439.

102. Benitah N, Feldman EC, Kass PH, Nelson RW. Evaluation of serum 17-hydroxyprogesterone concentration after administration of ACTH in dogs with hyperadrenocorticism. J Am Vet Med Assoc 2005;227:1095–1101.

103. Syme HM, Scott-Moncrieff JCR, Treadwell NG, et al. Hyperadrenocorticism associated with excessive sex hormone production by an adrenocortical tumor in two dogs. J Am Vet Med Assoc 2001;219:1725–1728.

104. Norman EJ, Thompson H, Mooney CT. Dynamic adrenal function testing in eight dogs with hyperadrenocorticism associated with adrenocortical neoplasia. Vet Rec 1999;144:551–554.

105. Zimmerman KL, Panciera DL, Panciera RJ, et al. Hyperphosphatasemia and concurrent adrenal gland dysfunction in apparently healthy Scottish Terriers. J Am Vet Med Assoc 2010;237:178–186.

106. Reine NJ, Hohenhaus AE, Peterson ME, Patnaik AK. Deoxycorticosterone-secreting adrenocortical carcinoma in a dog. J Vet Intern Med 1999;13:386–390.

107. Hill KE, Scott-Moncrieff JCR, Koshko M, et al. Secretion of sex hormones in dogs with adrenal dysfunction. J Am Vet Med Assoc 2005;226:556–561.

108. Oliver J. Steroid profiles in the diagnosis of canine adrenal disorders. Proc 25th Ann Vet Med Forum 2007:471–473.

109. Chapman PS, Mooney CT, Ede J, et al. Evaluation of the basal and post-adrenocorticotrophic hormone serum concentrations of 17-hydroxyprogesterone for the diagnosis of hyperadrenocorticism in dogs. Vet Rec 2003;153:771–775.

110. Huizenga NA, Koper JW, De Lange P, et al. A polymorphism in the glucocorticoid receptor gene may be associated with an increased sensitivity to glucocorticoids in vivo. J Clin Endocrinol Metab 1998;83:144–151.

111. Ortega TM, Feldman EC, Nelson RW, et al. Systemic arterial blood pressure and urine protein/creatinine ratio in dogs with hyperadrenocorticism. J Am Vet Med Assoc 1996;209:1724–1729.

112. Goy-Thollot I, Pechereau D, Keroack S, et al. Investigation of the role of aldosterone in hypertension associated with spontaneous pituitary-dependent hyperadrenocorticism in dogs. J Small Anim Pract 2002;43:489–492.

113. Lien YH, Hsiang TY, Huang HP. Associations among systemic blood pressure, microalbuminuria and albuminuria in dogs affected with pituitary- and adrenal-dependent hyperadrenocorticism. Acta Vet Scand 2010;52:61.

114. Gould SM, Baines EA, Mannion PA, et al. Use of endogenous ACTH concentration and adrenal ultrasonography to distinguish the cause of canine hyperadrenocorticism. J Small Anim Pract 2001;42:113–121.

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Diagnosing and treating Cushing's disease (Proceedings)

Hyperadrenocorticism (HAC) (commonly called Cushing’s disease) is a commonly diagnosed endocrinopathy in dogs which is caused by persistently high cortisol levels in circulation.

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Hyperadrenocorticism (HAC) (commonly called Cushing’s disease) is a commonly diagnosed endocrinopathy in dogs which is caused by persistently high cortisol levels in circulation. Diagnosis and treatment may not be straightforward, and successful management depends upon evaluation of clinical signs, performance of diagnostic tests, and administration and monitoring of therapy.

Cortisol is a hormone produced by the adrenal glands, which are paired glands located near each kidney. The anterior pituitary gland in the brain produces a hormone called adrenocorticotropic hormone (ACTH) that is released into circulation in response to the body’s need for cortisol. ACTH stimulates release of cortisol, and cortisol, in turn, shuts off release of ACTH. Cortisol has a variety of beneficial functions in the body that are mainly centered around helping cells and tissues remain healthy, maintaining blood glucose, and helping the body to combat stress. Excessive amounts of cortisol can cause muscle weakness, panting, increased urination and drinking, thinning of skin, loss of hair, and increased susceptibility to infections and to diabetes mellitus. Too little cortisol causes weakness, low blood sugar, loss of appetite, vomiting, diarrhea, and shaking.

The adrenal glands also make aldosterone, a hormone that helps the kidneys maintain sodium and excrete potassium. Without aldosterone, low sodium and high potassium can cause severe dehydration, mental dullness, shock, and cardiac arrhythmias.

Cushing’s disease occurs commonly in older dogs, has symptoms that occur slowly and gradually over time, and affects quality and length of life. A series of tests is required to diagnose, and a coordinated long-term treatment effort is important for treatment success. The most common disorder causing hyperadrenocorticism is a malfunctioning pituitary gland that releases ACTH despite elevated cortisol levels in circulation. A few dogs (up to 15% of those diagnosed) may have an adrenal gland tumor that hyper-functions and does not respond to signals from the pituitary gland. As a result of these changes, too much cortisol is released from the adrenal glands and has harmful effects within the body.

Dogs are usually middle-aged to geriatric (>7 years) at diagnosis, may be any breed or mixed breed, and either sex. Cats are rarely affected, and always have concurrent diabetes mellitus at the time of diagnosis. The most common client observations include increased appetite, drinking and urinating, weight gain with a pot-bellied appearance, and loss of hair, especially on the abdomen and sides, but not on the head or legs. Hyperadrenocorticism should not cause the animal to act “sick” unless there is another disease process going on at the same time.

Testing for Hyperadrenocorticism:

In addition to routine blood testing for patients with illness (CBC, serum chemistry profile, urinalysis), the veterinarian may order tests that specifically evaluate function of the pituitary-adrenal axis. These tests must be performed following specific protocol,

and may be adversely affected by stress or nervousness. Patients should be maintained in a stress-free environment for that reason. In the diabetic patient, blood glucose must not become below normal throughout testing since low blood sugar is a form of stress. When hyperadrenocorticism is suspected, the disease must first be diagnosed with one or more tests. If diagnosis is confirmed, then additional tests are necessary to identify the cause of hyperadrenocorticism prior to starting treatment.

Common tests to diagnose hyperadrenocorticism:

Urine cortisol: creatinine ratio (UCCR)

Rationale: Cortisol is excreted in the urine. Diagnosis of hyperadrenocorticism in people involves calculating urine cortisol excretion over a 24-hour period. Evaluating ratio of creatinine to cortisol in veterinary patients eliminates need to do timed urine collection since cortisol should be present in urine in proportion to creatinine at steady state
Protocol:

- Obtain a free-catch urine sample from a dog in a relaxed environment (best plan: have the owner collect urine at home)
- Submit for laboratory measure of urine cortisol and creatinine

UCCR < 20 x 10-6 is normal
Bottom line: Good choice for a one-time test to exclude diagnosis of hyperadrenocorticism. False positive tests common.

ACTH stimulation test

Rationale: ACTH is released from the pituitary gland, stimulates release of cortisol from adrenal gland. Injectable ACTH hormone is administered in excess of the body's need to maximally stimulate cortisol release. With hyperadrenocorticism, cortisol is released at greater than normal levels.

Protocol:

- Paired serum cortisol samples at 0 and 1-hour post synthetic ACTH
- Administer synthetic ACTH at 250ug/dog IV or IM, or at a dose of 5ug/kg IV or IM. ACTH can be reconstituted, diluted, and frozen: maintains potency when frozen for 4 months.

Interpretation of post-sample

- 550 mmol/L, consistent with hyperadrenocorticism
- 200-550 mmol/L, normal
- 60-200 mmol/L, goal for post-treatment with trilostane
- < 60 mmol/L = hypoadrenocorticism

Bottom line: Extremely useful test for pituitary-dependent hyperadrenocorticism, iatrogenic hyperadrenocorticism, and hypoadrenocorticism. May be normal if an adrenal tumor is causing the disease.

Low dose dexamethasone suppression test

Rationale: Normal pituitary will stay suppressed for at least 8 hours following dexamethasone administration, and dexamethasone will not be measured on the cortisol assay
Protocol:

- Measure cortisol before dexamethasone administration
- Administer 0.015mg/kg dexamethasone IV or IM
- Measure cortisol at 4 and 8-hours post dexamethasone

Interpretation:

- Suppression by 8 hours < 40 mmol/L, normal
- No suppression by 8 hours, hyperadrenocorticism
- Suppression by 4 hours, escape by 8 hours, consistent with pituitary-dependent hyperadrenocorticism

Bottom line: Mainstay of diagnosing hyperadrenocorticism if stress can be minimized. Can diagnose and localize disease with one test in 30% of dogs.

Tests to localize hyperadrenocorticism:

High dose dexamethasone suppression test (HDDST)

Rationale: With enough cortisol, any pituitary disease should suppress for > 8 hours, but adrenal disease should not

Protocol: Measure cortisol at 0, 4, and 8 hours. Administer dexamethasone at 0.15mg/kg IV or IM (modified high dose) or 1mg/kg/hr (true high dose). Suppression of < 45 mmol/l is consistent with pituitary disease or a normal dog. No suppression is consistent with adrenal-dependent disease 60% of the time. True high dose can cause more pituitary-dependent dogs to suppress.
Bottom line: Is the right test to localize, but may not localize in all cases

ACTH level

Rationale: In hyperadrenocorticism, adrenal-dependent dogs should have minimal circulating ACTH, while pituitary dependent dogs should have excessive ACTH
Protocol: Discuss protocol with your diagnostic lab – procedures vary. Typically just a one-time blood draw.
Bottom line: Very useful test, but not particularly easy to locate a lab doing clinical testing. Must have diagnosed dog with hyperadrenocorticism first.

Imaging studies: Radiographs, ultrasound, CT scan

Rationale: With pituitary-dependent hyperadrenocorticism, adrenal glands should be bilaterally symmetrical and non-calcified. Asymmetry or calcification is seen with adrenal dependent disease.
Protocol: Take imaging studies and look for unilateral or bilateral adrenal enlargement, as well as screening for other disease
Bottom line: Evaluate all studies for presence of adrenal glands, even if you were taking imaging studies to look for other disease

Treatments for hyperadrenocorticism:

Pituitary-dependent hyperadrenocorticism is usually treated with oral medications. Two oral medications are used in the United States: mitotaine (Lysodren) and Trilostane. Mitotaine treats hyperadrenocorticism by causing necrosis of the section of the adrenal gland that produces cortisol. When using this medication, a higher dose is used initially to cause adrenal gland necrosis, and then reduced to a maintenance dose to maintain the gland function at a limited level. The biggest side effect of this medication is that necrosis can also occur in the section of the adrenal gland that produces aldosterone which controls sodium and potassium levels. Regular ACTH stimulation testing is used to monitor response to mitotaine. Clients should be instructed to plan on post-treatment ACTH stimulation testing 3 days after the high dose phase of mitotaine, and every 3 months thereafter. Testing must occur at 4 hours post-pill administration.

Trilostane limits enzyme function in the adrenal glands so that less cortisol is produced. The biggest side effect of this medication is excessive reduction of cortisol causing weakness, loss of appetite, and intestinal upset from excessively rapid reduction of cortisol (iatrogenic hypoadrenocorticism). Any complaint of these symptoms in dogs receiving treatment deserves to be evaluated. Symptoms may happen at any time during a course of treatment. Pituitary-dependent hypoadrenocorticism is not cured, but is merely treated and controlled. Regular ACTH stimulation testing is used to monitor response to trilostane. Clients should be instructed to plan on post-treatment ACTH stimulation testing 10 days after initiation of the medication, and every 3 months thereafter. Testing must occur at 4 hours post-pill administration.

Adrenal dependent hyperadrenocorticism is best treated and may be cured with surgery. Removing the abnormal adrenal gland may resolve symptoms. Removal may not be possible since adrenal tumors sometimes grow into nearby vital structures like the caudal vena cava. 50% of adrenal tumors are malignant and may re-grow after removal, and 50% are benign. Postoperative care following adrenal removal requires particular attention to monitor for sudden hypoadrenocorticism since the adrenal tumor that was removed will have caused suppression of the opposite adrenal gland. Prednisone will need to be administered to cover maintenance needs of the body for the weeks following surgery until the remaining adrenal gland function returns.

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Canine Hyperadrenocorticism (HAC; Cushing's Syndrome)

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Pathophysiology

- Syndrome characterized by chronic excess of systemic cortisol
    - Pituitary tumor making excess ACTH (most common)*
    - Pituitary hyperplasia due to excess CRH (not dogs and cats)
    - Autonomous adrenocortical tumor*
    - Iatrogenic
        - Excess ACTH (rare)
        - Excess glucocorticoids (common)*
    - (ACTH from non-pituitary sources – very rare in dogs and cats)

*3 most clinically important causes in dogs and cats

- Pituitary-Dependent Hyperadrenocorticism (PDH)
    - 80-85% dogs with HAC
    - Most have pituitary adenoma in pars distalis
    - Most microadenomas (< 1 cm)
    - 10-20% macroadenomas (> 1 cm)

    - Frequency and amplitude of ACTH "bursts" are chronically excessive
    - Chronic excess cortisol secretion
    - Adrenocortical hyperplasia
    - Relatively ineffective feedback on pituitary adenoma
    - Suppression of hypothalamic function and CRH
        - Loss of hypothalamic control of ACTH
    - ACTH and cortisol levels usually within reference ranges on single blood samples
        - Have to look at "area under the curve"

- Adrenal Tumor (AT)
    - Adenoma or carcinoma (carcinomas larger) (50:50 distribution)
    - Cortisol secretion independent of pituitary control
    - Suppression of CRH and ACTH
    - Atrophy of contralateral adrenal and normal cells in affected adrenal
    - Episodic random cortisol secretion
    - Can respond to ACTH

        - (Non-Cortisol Secreting Adrenal Tumors
            - Carcinomas
            - Secrete adrenal steroids other than cortisol
            - Mutation in neoplastic tissue

- Typical Cushing's signs
- Low cortisol levels
- High levels of other steroid hormones)

- Iatrogenic Hyperadrenocorticism
  - Good medical history is essential!
  - Excessive administration of glucocorticoids
    - Allergic or immune-mediated disease
    - Oral, eye, ear, or skin medications
    - Suppression of endogenous ACTH
    - Bilateral adrenocortical atrophy

Signalment

Middle-aged and older dogs
- PDH: 55-60% female
  - 75% > 9 yrs
  - Median 11.4 yr
- AT: 60-65% female
  - 90% > 9yrs
  - Median 11.6 yr

Any breed can be affected
- PDH:
  - Poodles, dachshund, terriers, beagles, German shepherd dogs (GSD)
  - 75% < 20 kg
- AT:
  - Poodles, GSD, dachshund, labs, terriers
  - 50% > 20 kg

Clinical Signs, History, Physical Examination

- Polyphagia (> 90%)
- PUPD (80-85%)
- Abdominal enlargement (>80%) – "pot-bellied"
  - Hepatomegaly
  - Redistribution of fat
  - Abdominal muscle weakness
- Muscle weakness (75-85%)
- Panting
- Lethargy
- Obesity
- Heat intolerance
- Alopecia
  - Truncal
  - Bilaterally symmetrical
- Calcinosis cutis

- Thin skin, bruising, striae
- Seborrhea, pyoderma
- Comedones
- Hyperpigmentation
- Anestrus
- Testicular atrophy
- Facial paralysis
- Pseudomyotonia

Neurological Signs Associated with Pituitary Macroadenoma

- Dull, listless
- Decreased appetite
- Aimless wandering
- Pacing, circling
- Behavioral changes
  - Seizures rare

NOT *Clinical Signs of Hyperadrenocorticism*

- Anorexia/hyporexia
- Vomiting
- Diarrhea
- Sneezing
- Coughing
- Icterus
- Pruritus
- Pain
- Lameness due to inflammation
- Seizures
- Bleeding
- Renal failure
- Pancreatitis
- Liver failure
- Immune-mediated diseases

Hyperadrenocorticism

- Most patients are not critically ill
- Rarely an emergency
- Slowly progressing illness
- Not all dogs have all the signs
- Most dogs have one or a few signs
- This is a CLINICAL syndrome:
- DON'T TRY TO DIAGNOSE IT WITHOUT THE CLINICAL SIGNS!!

Clinicopathological Findings

CBC

- "Stress leukogram"
  - Neutrophilia
  - Monocytosis
  - Lymphopenia
  - Eosinopenia
- Thrombocytosis
- nRBCS
- Mild erythrocytosis (females - androgens)

Serum Biochemistry

- ⇑ ⇑ AP (90-95%) (can be > 1000)
  - (SIAP is of little value - sensitive, but not specific)
- ⇑ ALT (< 400)
- Mildly ⇑ fasting BG
- Normal to ⇓ BUN
- ⇑ cholesterol and triglycerides
- Mildly ⇑ bile acids
- Mild ⇑ Na
- Mild ⇓ K

Urinalysis

- SG < 1.015, often < 1.008
- Mild increase in UP:C (less than 5)
- Urinary Tract Infection (UTI) in 40-50%
- UTI often "silent"
  - Inactive sediment
  - No clinical signs
  - Low USG
  - Cystocentesis sample and culture is MANDATORY!

Diagnostic Imaging

Abdominal Radiographs

- Excellent detail
- Hepatomegaly
- Distended urinary bladder
- Urolithiasis
- Dystrophic calcification of soft tissues
- Osteoporosis of vertebrae
- Calcified adrenal gland
  - Rare
  - Consistent with adrenal adenoma or carcinoma

Thoracic Radiographs

- Calcification of airways
- Osteoporosis of vertebrae
- Pulmonary metastases
    - Rare
- Evidence of pulmonary thromboembolism

Abdominal Ultrasound Examination

- Adrenomegaly (PDH)
- Adrenal mass with small contralateral adrenal (AT)
- Calcified adrenal gland (AT)
- Tumor thrombus or metastasis
- Hepatomegaly
- Hyperechoic liver
- Distended urinary bladder
- Urolithiasis
- Dystrophic calcification of soft tissues

Advanced Imaging

- Brain CT or MRI may reveal pituitary tumor
    - Recommended to confirm cause of neurological signs
    - Recommended if considering radiation therapy or surgery
- Abdominal CT recommended prior to adrenalectomy

Complications of Hyperadrenocorticism

- Hypertension (> 50%)
- Urinary tract infection (UTI)
    - Pyelonephritis
    - Cystitis (clinically silent)
- Urolithiasis
    - Calcium-containing
    - Struvite, related to UTI
- Congestive heart failure
- Pancreatitis???
- Diabetes mellitus
- Poor wound healing
- Recurrent infections
- Joint laxity
- Hypercoagulability
    - Pulmonary thromboembolism
    - Aortic thromboembolism

Diagnosis of Canine Hyperadrenocorticism

- Screening tests
- Differentiation tests
- Need to understand sensitivity and specificity
    - False positives and false negatives
- Can improve predictive value of tests by only testing the appropriate population
    - Consistent clinical signs
    - No concurrent illnesses

Screening Test: Basal Cortisol

Just say NO for Cushing's diagnosis

- Wide fluctuations throughout the day
- Normal dogs can be out of the reference range
- Basal levels higher with stress or other illnesses
- Cushing's dogs usually in reference range
- Typical reference range: 1-5 ug/dl

NOTE: Can be used to RULE OUT hypoadrenocorticism

Screening Test: Urine Cortisol: Creatinine Ratio

UCCR: screening test

- High sensitivity
    - But not 100%
- Few false negatives - but how few?
    - Depends on study:
    - one study: 75% sensitive
    - earlier study: 99% sensitive
    - May have 1/100 - 25/100 false negatives
- Low specificity
    - Many false positives
    - ↑UCCR in 75 - 85% dogs with NON-adrenal disease

Good screening test for the "healthy" Cushing's suspect
Quick, easy, outpatient test

Screening Test: ACTH Stimulation Test

Screening test – measures maximum secretory capacity of the adrenal cortex.

- *How to do it:*

Obtain baseline cortisol sample

- Inject Cortrosyn IV
    - 5 ug/kg (up to 250 ug max)
    - 1 vial if >25 kg

- 1/2 vial if < 25 kg

Obtain 1-hour post ACTH cortisol sample

Wise Use of Cortrosyn

- If Cortrosyn in limited supply
- Reserve Cortrosyn for hypoadrenocorticism diagnosis and Cushing's monitoring
- Use the 5 µg/kg dose
  - Reconstitute one vial (250 µg)
  - Store in freezer in aliquots in syringes
  - e.g. 5 x 50 µg doses - one per 10 kg
  - Will dry out in a frost-free freezer

➢ *ACTH Stimulation Test and Steroids:*

Two Separate Problems:

1. Cross-Reaction with the Cortisol Assay
2. Suppression of pituitary-adrenal axis

1. Cross-Reaction with Cortisol Assay:

- Prednisone
- Prednisolone
- Hydrocortisone
  - Should be off prednisone for 12-24 hours

2. All glucocorticoids can suppress pituitary-adrenal axis

- Depends on dose
- Depends on duration of therapy
- Depends on route
- Depends on type of glucocorticoid

➢ *How to interpret it:*

ACTH Stimulation Test Results

- Pre-ACTH cortisol: normal: 0.5 - 6.0 µg/dl
- Post-ACTH cortisol:
  - Normal: <18 µg/dl
  - Exaggerated: >22 µg/dl
  - Grey zone: 18 - 22 µg/dl
- Hypoadrenocorticism: both values < 2 µg/dl
- Usually < 0.2 µg/dl

➢ *Pros and Cons of the ACTH Stimulation Test*

- More false negatives than LDDST
  - Lower sensitivity

- Fewer false positives than LDDST
    - Higher specificity
- Does not distinguish between PDH and AT
- One hour test
- Can combine with other procedures (e.g. ultrasound)
- Useful in a referral setting
- Only test for:
    - Iatrogenic Cushing's
    - Hypoadrenocorticism
    - Monitoring mitotane or trilostane therapy
    - Monitoring post-adrenalectomy

Screening Test: Low-Dose Dexamethasone Suppression Test (LDDST)

- More sensitive (95%) than ACTH stimulation test
- Less specific (more false positives)
- CAN distinguish between PDH and AT
- Not useful for iatrogenic Cushing's or hypoadrenocorticism

➢ *How to do it*

- Blood sample at 0 (pre), 4, and 8 hours
- Give 0.01 mg/kg dexamethasone IV (0.015?)

- Less expensive than ACTH stimulation test (at current price of Cortrosyn)
- Takes 8 hours
- Avoid stress, excitement, handling, other tests

➢ *How to interpret it*

LDDST Results
Normal patient:
- 0 hr: Cortisol = 1 - 5 mg/dl
- 4 hr: Cortisol < 1.4 mg/dl
- 8 hr: Cortisol < 1.4 mg/dl

Cushing's patient:
- 8 hr: Cortisol > 1.5 mg/dl

Discrimination Test: LDDST

- Discriminatory test in some cases
    - Cannot confirm AT
- "Decrease" occurs in 60 - 65% of dogs with PDH:
    - 4 hr: Cortisol < 1.4 μg/dl, or

    - 4 hr or 8 hr: Cortisol < 50% baseline
    - Confirms PDH

- BUT - 35-40% of PDH do NOT suppress
    - 4 hr cortisol > 1.5 µg/dl
    - and both > 50% baseline:
        - Adrenal tumor
        - PDH (35 - 40%)
- High Dose Dexamethasone Suppression Test (HDDST)
- Endogenous ACTH
- Abdominal Ultrasound
    - Not a good discriminating test in all cases
    - Results can be misleading
    - Is indicated if you suspect adrenal tumor

Discrimination Test: High Dose Dexamethasone Suppression test (HDDST)

- *How to do it*

- Give 0.1 mg/kg dexamethasone iv
- Blood sample at 0 (pre), 4, and 8 hours
- AT: no suppression at 4 or 8 hours
- PDH:
    - Cortisol < 1.4 mg/dl at 4 or 8 hours
    - Cortisol < 50% baseline at 4 or 8 hours
    - 25% PDH cases do NOT suppress

- Pituitary-Dependent Hyperadrenocorticism:
    - 35-40% do not suppress on LDDST
    - 25% do not suppress on HDDST
    - If no suppression on LDDST, will only pick up another 10-15% on the HDDST, so probably better to choose another test
    - Can NEVER DIAGNOSE adrenal tumor on LDDST or HDDST

Discrimination Test: Endogenous ACTH

- Specific for discrimination of PDH vs. AT

- Important to remember:
    - Must have diagnosis of Cushing's
    - ACTH very labile
    - Special handling precautions (plastic, freezing)
    - Repeat measurement may be necessary
- Hospitalize dog overnight and sample at 8-9 am?

Normal range: 10 - 80 pg/ml

Adrenal tumor: < 20 pg/ml
PDH: > 45 pg/ml

20 < ACTH < 45

- Non-diagnostic
- Repeat test

Discrimination Test: Abdominal Ultrasound Examination

- Not a good discriminating test in all cases
- Results can be misleading
- Is indicated if you suspect adrenal tumor

➢ *Sources of ultrasound confusion*

- Adrenocortical nodular hyperplasia
  - 5-10% of HAC
  - Form of PDH
- Bilateral adrenocortical tumors
- Adrenocortical tumor AND pheochromocytoma
- Simultaneous PDH and AT

Treatment of Hyperadrenocorticism

Before commencing treatment

- Be confident of the diagnosis
- Patient must have consistent clinical signs, clinicopathological findings, and positive diagnostic testing

➢ *What to do if HAC strongly suspected but tests do not confirm?*

- Wait and retest
- Consider ACTH stimulation with sex hormone panel (controversial)

➢ *What to do if tests confirm HAC but patient has minimal signs?*

- Ensure that test results are not false positive
  - Stress
  - Concurrent non-adrenal illness
- No evidence that early treatment is beneficial
- Treat when
  - Signs affecting quality of life of dog, or
  - Signs affecting quality of life of owner, or
  - Signs concerning to veterinarian
    - Monitor for occult complications of HAC
      - Hypertension

- UTI
- Proteinuria

➢ *Client Education*

Medical therapy is indicated for PDH and for adrenal tumors in which surgery is not an option. Medical therapy for HAC is life long, requires diligent monitoring and follow-up, and is potentially expensive. Serious side effects are possible with all forms of medical therapy.

Surgical Therapy

- Surgery is indicated for functional adrenocortical tumors
    - Adenoma – good prognosis
    - Carcinoma with no metastases
        - Ultrasound
        - CT
        - Radiographs
- Recommend referral to specialists
    - Experienced surgeon
    - Good anesthetic support
    - Internist for management pre- and post-surgery
        - Hypertension
        - Hypercoagulability
        - Post-operative hypoadrenocorticism

- Surgery for pituitary tumors
    - Hypophysectomy
    - Routinely performed in Europe
    - Not currently widely available in the US

Medical Therapy: Mitotane

- o,p'-DDD
- Derived from DDT
- Lysodren®
- Adrenocorticolytic
    - Fasciculata
    - Reticularis
    - Glomerulosa?
        - Zona glomerulosa makes NEW adrenocortical cells

- Previous treatment of choice for PDH – replaced by trilostane?
- Occasionally used for AT:
    - Pre-surgical stabilization
    - Surgery not an option
- Effective

- Safe, if used carefully

- Normal dogs are relatively resistant
    - Reduced GI absorption in normal dogs compared to dogs with hyperadrenocorticism
    - Cortex is damaged but dogs not clinically affected
    - (HAC dogs more sensitive to loss of cortical function)

- Some Cushing's dogs appear "resistant"
    - Not getting drug
    - Drug not absorbed (give with food, crush or make suspension)
    - Bad batch of medication
    - Other medications interfering
    - Adrenal tumor
    - Resistant form of PDH (need a higher dose)
    - Incorrect diagnosis

- 2 phases of therapy:
    - Loading/induction
    - Maintenance
- Monitoring is key:
    - ACTH stimulation test
        - Determine end-point of induction
        - Confirm ongoing successful maintenance

Mitotane Induction:

- Dose: 50 mg/kg (500 mg tablets)
    - Divide daily dose
    - Give with food
- Talk to owner daily
- YOU (or nurse) call the owner
    - Pick up subtle signs of induction
    - Reinforces importance of close monitoring

- Stop therapy and do ACTH stimulation test when see:
    - Subtle decrease in appetite (usually happens first), or
    - Decrease in PUPD, or
    - Vomiting, anorexia, diarrhea, or
- ACTH stimulation test at 7 days even if no change in signs

- Concurrent prednisone: NO
- Owner has prednisone on hand - call first

- Successful induction is achieved when basal and post-ACTH cortisol:
    - both < 4 (5) mg/dl (40 ng/ml) and > 1 mg/dl

- Most cases take 5 - 15 days

Mitotane Maintenance:

- Give daily induction dose weekly (divided)

- Example:
  - 10 kg dog required 250 mg BID for induction (7 days)
  - Maintenance dose would be 250 mg twice weekly
  - Divide dose (125 mg BID)

- Continue to monitor with ACTH stimulation tests

Mitotane Monitoring:

- ACTH stimulation test:
  - At end of induction
  - 1 month later
  - 3 months later
  - every 6 months
  - 1 - 2 months after every dosage change
  - If problems arise
- POST ACTH cortisol is the most important
- CANNOT monitor with basal cortisol!

Pre and Post ACTH Cortisol (µg/dl)	**ACTION**
0.2 and 0.2 (goal is both values 1- 4 µg/dl)	Stop mitotane, give prednisone, check electrolytes, monitor ACTH stimulation tests
1 and 3	Continue maintenance dose
0.2 and 2	Continue maintenance dose
1 and 6	Increase weekly maintenance dose
3 and 9	Re-induce

Mitotane Side Effects

- Vomiting, diarrhea, loss of appetite
  - Not uncommon, often transient
- Lethargy

    - Not uncommon, often transient
- Neurological signs (DDx: pituitary tumor)
    - Very uncommon, usually transient
        - Blindness, ataxia, obtundation, circling, head-pressing
        - Reduce dose, give smaller increments

- Always do ACTH stimulation test
- Induction of hypoadrenocorticism
    - Uncommon, but manageable
- Check/monitor electrolytes

Iatrogenic Hypoadrenocorticism

- Cortisol deficiency alone:
    - Pre- and post-ACTH cortisols both < 0.2 mg/dl
    - Supplement with prednisone (0.1 - 0.2 mg/kg)
    - Follow ACTH stimulation tests
    - Usually recover (may take days, weeks, or months)

- Cortisol and aldosterone deficiency (< 5%):
    - Pre- and post-ACTH cortisols both < 0.2 mg/dl
    - Abnormal electrolytes
    - Usually do not usually recover
    - Manage as Addisonian
    - Damage to zona glomerulosa

Prognosis with Mitotane

- Dogs with PDH on mitotane:
    - Feldman and Nelson
    - 1500 dogs
    - Dogs that have died - mean survival 31.6 m
    - (range: few days to several years)
    - >35% relapse
    - 5% mildly overdosed during induction
    - Dogs that died:
        - 37% related to HAC
        - 20-30% due to pituitary tumor
        - <1% due to mitotane overdose

Planned Medical Adrenalectomy

- Induction of permanent addisonian state
- “not recommended” in literature
- Consider for selected cases?
    - Dogs that relapse frequently on maintenance mitotane
    - Dogs with diabetes and Cushing’s
    - Financial concerns
        - Expensive initially, then costs are fixed

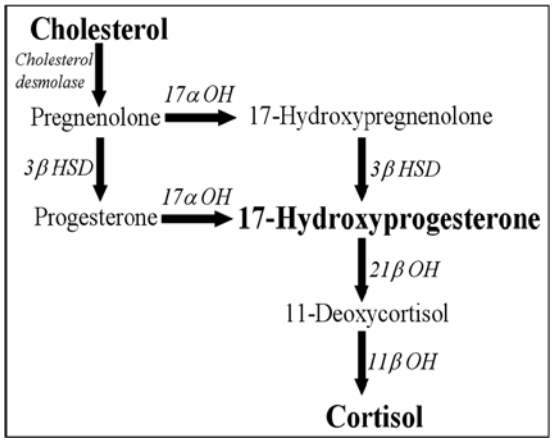
"Utrecht Protocol"

- **Day 1:** start mitotane (usual dose - ?higher dose for smaller dog)
    - Continue for 25 days
- **Day 3:** start usual medications for Addison's disease (DOCP or fludrocortisone, and prednisone)
    - Fludrocortisone 0.1 mg/5kg (divide BID)
    - Prednisone
        - 0.5 mg/kg initially
        - Gradually reduce to 0.1 mg/kg/day

- ACTH stimulation test at end of the 25 days
    - (Stop prednisone for at least 12 hours)
- Goal is pre and post cortisol < 1mg/dl
    - Continue Addison's therapy as for other cases
- During induction:
    - Stop mitotane if dog is anorexic
    - Do NOT stop Addison's therapy
    - Monitor electrolytes weekly

Medical Therapy: Trilostane

- Vetoryl® (Dechra)
    - Tested and licensed in Europe and USA for canine Cushing's
    - Competitively inhibits steroid synthesis
        - Inhibits 3-β-hydroxysteroid dehydrogenase
        - Converts pregnenolone to progesterone
        - Converts 17-OH pregnenolone to 17-OH progesterone



    - Appears safe and effective
    - Monitor with ACTH stimulation tests
    - Adrenals keep getting bigger
    - Some reports of adrenal necrosis

- Reports of successful therapy of adrenal tumors (median survival 14 months)
- One case series of 3 dogs with adrenal metastasis (survived 11m, 16m, and 10 m)
- Has been used in cats

Using Trilostane

- Start with lower dose
  - 1 mg/kg BID (or less)
- ACTH stimulation tests
  - Start 3-4 hours post-pill
  - 10-14 days
    - Ensure not over-dosing
  - Monthly
  - Whenever clinical signs change
  - Aim for pre and post values between 2 and 6 ug/dl
  - ACTH response may decrease over time
  - Do not be too quick to increase dose

- SID or BID?
  - Use BID if ACTH stim results are good on SID, but clinical signs persist
    - Interpret ACTH stim results and clinical signs together
  - Use BID if significant co-morbidities or complications of HAC
    - Diabetes mellitus
    - Calcinosis cutis
    - Thromboembolic disease
    - Proteinuria?
    - Hypertension?

- Just use Vetoryl®!
  - Compounded trilostane?
    - No!
    - JAAHA study (Cook)
      - Marked variability within batches of medication
      - Marked variability between batches of medication
      - Several pharmacies evaluated

Mitotane or Trilostane: Which to Use?

- Effectiveness?
  - Similar
- Frequency of adverse effects?
  - Similar
- Cost comparison (assuming no dose increase):
  - Small dog

        - Mitotane and trilostane equivalent in first month (mitotane induction is expensive)
        - Mitotane much less expensive in maintenance phase
    - Medium to large dog
        - Mitotane more expensive in first month
        - Differential is greater for larger dogs
        - Mitotane less expensive in maintenance phase

- Mitotane preferred for:
    - Adrenal tumor?
    - Require more consistent control of cortisol levels
        - Diabetic
        - Serious complications of HAC
        - Thromboembolic disease
        - Pseudomyotonia
        - Calcinosis cutis

- Transitioning between mitotane and trilostane
    - Stop first medication
        - Monitor clinical signs and ACTH stimulation tests
        - Start second medication when have clinical signs and exaggerated response to ACTH (high normal or above normal post-ACTH cortisol)
            - Probably happens more quickly with trilostane

STUDY!

Contact Dr. Lunn if you have a newly diagnosed (or strongly suspected) dog with pituitary-dependent Cushing's NOT yet on therapy. We have a study that will provide about $300 of work-up, in return for allowing ophthalmology to perform some non-invasive tests on the patient. The purpose of the study is to compare a variety of endocrine and other tests in dogs with SARDS, dogs with advanced progressive retinal atrophy, and dogs with Cushing's.

Contact Details for Study:

Dr. Freya Mowat (ophthalmologist and principal investigator): fmmowat@ncsu.edu
Dr. Kathy Lunn (internal medicine and co-investigator): kflunn@ncsu.edu
Melanie Foster (research associate): melanie_foster@ncsu.edu