Disorders of the Pituitary and Adrenal Cortex

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Hyperadrenocorticism in Cats

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Hyperadrenocorticism (HAC) is relatively rare in cats. HAC is characterized by persistent hypercortisolemia and can be either primary (adrenal tumor) or secondary (pituitary adenoma) in origin. Approximately 80% of cats with HAC have pituitary dependent (PDH) disease. The vast majority of cats with PDH have autonomous section of ACTH synthesized by a pituitary adenoma, although carcinomas have been reported. Excessive secretion of ACTH leads to hyperstimulation of the adrenal glands, adrenal gland hyperplasia and the development of HAC. For cats with adrenal tumors (AT) approximately 50% will be carcinomas.

Signalment and Clinical Features: HAC typically effects middle aged to older, female cats. The vast majority (>75%) present for diabetes mellitus and therefore, polydipsia, polyuria, polyphagia and weight loss are common clinical signs. A pot-bellied appearance, hepatomegaly, muscle wasting, increased skin fragility, alopecia and an unkempt hair coat are frequent findings.

Clinicopathologic abnormalities: Hyperglycemia and hypercholesterolemia are the most common laboratory abnormalities. High serum ALP activity is uncommon. Urine SG is typically greater than 1.020 and glucosuria is common.

Diagnostic Testing

Screening test: Urine cortisol to creatinine ratio (UCC) is a screening test for HAC in cats. However, UCC is not specific and therefore, should not be used to make a definitive diagnosis. In general UCC is used to rule out hyperadrenocorticism only.

Diagnosing tests: ACTH stimulation test is not recommended because it has a low sensitivity for HAC in cats, with up to 50% of cats with HAC having a normal result. This test differs in cats in that pre, 30 and 60 min post cortisol concentrations should be evaluated and the dose of ACTH (cosyntropin) is typically given at 125 ug/cat, IM. The low dose dexamethasone (LDDS) test has excellent sensitivity for HAC in cats, but false positives are possible. It is important to note that the dose of dexamethasone (0.1 mg/kg, IV) used for the LDDS in cats is higher than what is traditionally used in dogs.

Differentiating tests: High dose dexamethasone suppression test is performed by administering dexamethasone (1.0 mg/kg, IV). Pre, 4 hour and 8 hour post dexamethasone cortisol concentrations should be evaluated. Suppression at 4 or 8 hours is specific for PDH. Since 50% of cats with PDH and all cats with AT will fail to suppress, a lack of response is inconclusive. Endogenous ACTH concentrations which are high or low are consistent with PDH or AT, respectively. Unfortunately, there is considerable overlap between cats with PDH and AT so results within the reference range are not diagnostic. Imaging of the adrenal glands (radiographs, US, CT, MRI) or pituitary (CT, MRI) can be helpful as differentiating tests as well. Bilateral adrenomegaly is most consistent with PDH and unilateral adrenomegaly with atrophy of the contralateral gland is most consistent with AT. Approximately 50% of cats with PDH will have pituitary enlargement on CT or MRI.
Treatment

PDH: Treatment focuses on managing the hormonal consequences of pituitary corticotroph tumors. Medically, both mitotane and trilostane have been used to decrease cortisol production. Mitotane, although safe, has provided little success as most cats appear to be resistant to the effects of the drug. Trilostane is the preferred drug for medical management of pituitary dependent HAC in cats. Approximately 85% of cats will have improvement in their clinical signs and post-ACTH cortisol concentrations. Median survival time is 617 days for cats treated with trilostane.

Bilateral adrenalectomy and subsequent management for hypoadrenocorticism has been recommended in the past as the treatment of choice to control the hormonal effects of pituitary dependent hyperadrenocorticism. However, successful definitive therapy via hypophysectomy, radiation therapy or medical management with trilostane have minimized the need for bilateral adrenalectomy. Survival time with radiation therapy range from 5.5-20.5 months. Approximately 70% of cats treated with hypophysectomy achieve clinical remission and long-term survival.

AT: Adrenalectomy is the recommended treatment for adrenal tumors in cats. There are reports of successful medical management with trilostane in cats with cortisol secreting adrenal tumors. Mitotane is generally ineffective. Prognosis is guarded for cats with functional adrenal tumors producing cortisol or androgens unless they are trilostane responsive.

Prognosis

See treatment section for specific information about prognosis based on the location of the lesion and the selected treatment modality.
Primary Hyperaldosteronism in Cats
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Aldosterone is the major mineralocorticoid secreted by the adrenal cortex in response to the renin-angiotensin-aldosterone system. Aldosterone exerts its primary effects on the distal renal tubules, colon and salivary glands causing sodium reabsorption, and potassium and hydrogen excretion. Sodium retention results in volume expansion. Primary hyperaldosteronism is most commonly due to either an adenoma or carcinoma of the adrenal cortex.

History/clinical signs: Sudden blindness and hypokalemic polymyopathy are the two most common clinical findings in cats with hyperaldosteronism. Sudden blindness is caused by intraocular hemorrhage and retinal detachment secondary to hypertension. Polymyopathy secondary to hyperaldosteronism usually manifests as weakness, cervical ventroflexion, forelimb stiffness, dysphagia and/or ataxia. Polyuria, polydipsia, hyporexia, weight loss, nocturia, abdominal distension, mydriasis and abdominal distension may also be noted.

Clinicopathologic abnormalities: Hypokalemia is the most common clinicopathologic abnormality found in cats with hyperaldosteronism. Although total body sodium is increased, serum sodium concentrations are typically maintained within the reference interval since aldosterone causes retention of both sodium and water. Metabolic alkalosis, hypophosphatemia, hypomagnesemia and azotemia may be noted. Cats with hypokalemic polymyopathy will have an increase in CK as well. CBC changes are typically nonspecific.

Diagnostic Testing

Hyeraldsteronism should be suspected in any cat with unexplained hypokalemia, metabolic alkalosis or hypertension. Suppressed renin secretion and markedly increased plasma aldosterone concentrations are the classic criteria used to diagnose primary hyperaldosteronism. Unfortunately, commercial assays for feline renin are often not available. Plasma aldosterone concentrations in cats with clinical signs of primary hyperaldosteronism are typically markedly increased. However, this marked increase may represent the late stage at which the disease is typically diagnosed, not true criteria for diagnosis. Further study is indicated to determine the most appropriate diagnostic criteria in cats. It is important to note that samples for plasma aldosterone analysis must be collected prior to administration of potassium, fluids or antihypertensive medications as they could alter aldosterone secretion. Blood pressure, electrolyte and acid/base status should be closely monitored in any patient suspected of having primary hyperaldosteronism. Since primary hyperaldosteronism is caused by either an adenoma or carcinoma of the adrenal cortex, imaging of adrenal glands via ultrasound or CT should be performed in all cases. It is important to remember that other diseases, most commonly renal or cardiovascular, can cause increased aldosterone. An effort should be made to rule out causes of secondary hyperaldosteronism prior to any invasive procedures.
Treatment

Hypertension or hypokalemia should be corrected prior to invasive therapy. When indicated, potassium supplementation and amlodipine are most commonly used to treat hypokalemia and hypertension, respectively. Almost all cats with primary hyperaldosteronism will require potassium supplementation. Spironolactone, an aldosterone antagonist, can be used to stabilize patient pre-operatively or as long-term medical management.

Prognosis

Long-term (1-3 years) survival with medical management has been reported. Nevertheless, adrenalectomy is definitive therapy. For cats surviving the immediate post-operative period, survival times of 1-8 years have been reported.
Acromegaly in Cats
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Acromegaly is caused by excessive release of growth hormone by the pituitary gland. Growth hormone (GH) has both anabolic and catabolic effects. Catabolic actions include stimulation of hepatic glucose production, promotion of lipolysis and induction of lipid oxidation. GH has direct insulin-antagonizing and diabetogenic properties. Anabolic activities of GH are mediated by somatomedin C (insulin like growth factor-1 (IGF-1)). Somatomedin C stimulates growth, especially of the visceral, tongue, cartilage and bone. While the incidence of acromegaly is relatively low, it is still an important consideration for cats with insulin-resistant diabetes mellitus. Recent evidence suggests that acromegaly may be more common than previously suspected. In a clinical study that screened 184 diabetic cats for acromegaly, 59 (32%) had markedly increased serum IGF-1 concentrations. Of these 59 cats with markedly increased IGF-1 concentrations 18 were revaluated and the diagnosis of acromegaly was confirmed in 17/18 or approximately 9% of the original diabetic population. Other studies have documented acromegaly in up to 26% of diabetic cats.

History/Clinical signs: Acromegaly most commonly affects neutered male cats over 8 years of age. It is characterized by the overgrowth of bone, connective tissue and viscera. All patients will present for uncontrolled diabetes mellitus, with polyphagia, polydipsia and polyuria being the most common clinical signs. These patients rarely become ketotic and often gain weight despite poor diabetes regulation. Secondary hypertrophic cardiomyopathy and arthropathies are common. Occasionally, cats will present for neurologic signs due to tumor expansion.

Clinicopathologic abnormalities: Hyperglycemia, hypercholesterolemia, mildly increased ALT and ALP, hyperphosphatemia and hypochloridemia are common findings.

Diagnostic Testing
Documentation of increased serum IGF-1 or GH concentrations in a cat with appropriate clinical signs is consistent with acromegaly. Growth hormone secretion is pulsatile in nature so false negative results are possible. False negative test results are also possible with IGF-1 testing since insulin is required for production of IGF-1. Therefore, it is advisable to insure that insulin therapy has been administered in a diabetic cat during for at least 8 weeks preceding IGF-1 measurement to avoid a false negative test result. A pituitary tumor is identified on CT or MRI in most cats with acromegaly. Serum type III procollagen propeptide (PIIP), serum ghrelin and glucose suppression testing (measuring GH before and after administration of glucose) are additional tests that might be helpful for the diagnosis of acromegaly.

Treatment
L-deprenyl, lanreotide and octreotide have been used in a few cases with no success. Pegvisomant (GH receptor antagonist) has been used successfully to treat acromegaly in human medicine, but have not been evaluated in cats. Pasireotide is a promising medical therapy for acromegaly. In a clinical trial
involving 12 cats with acromegaly, serum IGF-1 concentrations and insulin requirements improved with pasireotide therapy. Nevertheless, currently, radiation therapy or hypophysectomy are the most effective treatment modalities for cats with acromegaly.

**Prognosis**

Cats without neurologic signs and with reasonable control of their diabetes mellitus may have a fair to good short-term prognosis. 75-90% of cats that are treated with radiation therapy have improved glycemic control. Diabetic remission is achieved within 3 months of completion of radiation therapy in about 32-62% of cats. Survival times with radiation therapy range from 1.2-3 years.
Hypoadrenocorticism in Dogs

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Dogs with hypoadrenocorticism can have glucocorticoid (GC) and mineralocorticoid (MC) deficiency (primary only), GC deficiency only (primary or secondary) or very, very rarely MC deficiency only (primary only). Dogs with primary GC deficiency occasional progress to develop MC deficiency as well. For dogs with GC deficiency only, it is important to differentiate primary (ie adrenal dysfunction) from secondary (ie pituitary dysfunction) disease. Because mineralocorticoids facilitate resorption of sodium, volume expansion and excretion of potassium, deficiency leads to hyponatremia, hyperkalemia, and volume depletion. Glucocorticoid affects are ubiquitous throughout the body. Since they are the major stress-coping mechanism, any stress may have more severe consequences in glucocorticoid deficient animal. GI signs (V & D, anorexia), mental changes (lethargy, dullness), and hypoglycemia frequently accompany glucocorticoid deficiency.

Primary hypoadrenocorticism (Addison’s disease)

Destruction of 85-90% of the adrenal cortex will result in signs of both mineralocorticoid and glucocorticoid deficiency. There are many potential causes for adrenocortical destruction, including infection (TB, fungus), iatrogenic (lytic drugs, surgical adrenalectomy), infiltration (lymphoma, metastasis, amyloidosis), trauma, immune mediated, and idiopathic. Most cases in dogs are considered idiopathic although because middle aged to young females are affected most often, and because there is often more than one endocrinopathy in affected dogs, it is likely often immune mediated.

Secondary hypoadrenocorticism

The result of deficient ACTH secretion from the pituitary. Signs are due to glucocorticoid deficiency alone since ACTH is not required for mineralocorticoid secretion. This is most often either iatrogenic, or due to brain disease such as neoplasia.

History/Clinical Findings: Most affected dogs are female (~68%), and young to middle aged are affected most often (mean 4.6 years). While many reports suggest over represented breeds, most are mixed breeds. Standard poodles, Portuguese Water Dogs and bearded collies (and others) have a genetic predisposition. Large dogs are more frequently affected.

Immune mediated destruction is a gradual process, so many dogs have a waxing and waning history of illness prior to diagnosis, often precipitated by stressful events. Severity of signs ranges from mild to life threatening. Common complaints include anorexia and weight loss, lethargy, vomiting, diarrhea, weakness, collapse, and PU/PD. Dogs may not be presented until they experience a “crisis”, but usually have had clinical signs for a while. Physical examination findings are typically non-specific and range from “normal” to collapse and severe weakness. Bradycardia, hypotension and severe dehydration/hypovolemia may be evident in dogs with crisis.
Clinicopathologic abnormalities: Most animals with hypoadrenocorticism will have an absence of a stress leukogram and could have a normocytic, normochromic anemia, lymphocytosis and eosinophilia. Hyponatremia, hyperkalemia, hypochloremia, azotemia, hypoglycemia, hypoalbuminemia, mild hypercalcemia, acidemia are common biochemical findings. Microcardia from hypovolemia and small adrenal glands are common imaging findings. Electrocardiographic abnormalities relate to hyperkalemia and include bradycardia, peaked T waves, P-R interval prolongation, P wave diminution, QRS widening, and irregular R-R intervals.

**Diagnostic Testing**

Resting cortisol concentrations: Resting cortisol concentrations can be used as a rule out test for hypoadrenocorticism. Dogs with basal cortisol >1µg/dl were significantly less likely to have hypoadrenocorticism compared to dogs with basal cortisol ≤ 1 µg/dl. The sensitivity and specificity of a basal cortisol >1 µg/dl to rule out hypoadrenocorticism are 98.4% and 100%, respectively.

CAR and ARR: Cortisol to ACTH and aldosterone to renin ratios have also been used to evaluate hypoadrenocorticism in dogs. Dogs with primary hypoadrenocorticism should have a low cortisol:ACTH (hypocortisolemia with increased ACTH secretion) and/or low aldosterone:renin ratio (hyperreninemic hypoaldosteronism).

ACTH stimulation test: ACTH stimulation test is the gold standard for diagnosis of cortisol deficiency. The ACTH stimulation test is performed by collecting an initial blood sample for cortisol concentration. Then, 0.25 mg/dog or 0.005 mg/kg of cosyntropin is given IM or IV, and a post cortisol sample is collected at 60 or 90 minutes. A post-ACTH plasma cortisol concentration <2.0 µg/dl indicates the lack of an appropriate response and is diagnostic for hypoadrenocorticism. ACTH stimulation testing does not distinguish between primary and secondary, or between iatrogenic suppression and deficiency. Reconstituted cosyntropin can be stored frozen (-20 ̊C) in plastic syringes for up to 6 months.

Ideally, an ACTH stimulation test should be performed prior to administration of glucocorticoids. However, glucocorticoids should not be withheld pending the results of the ACTH stimulation test. If an ACTH stimulation test cannot be performed immediately, glucocorticoids should be administered until hypoadrenocorticism is confirmed. Dexamethasone is an ideal glucocorticoid in this situation since it is rapid acting and, unlike other glucocorticoids, will not directly interfere with the cortisol assay. Therapeutic dexamethasone will not alter ACTH stimulation test results if administered for fewer than 3-4 days (probably even longer).

Aldosterone: Serum aldosterone concentrations are not frequently used, and affected by many variables. Aldosterone release is only mildly “stimulated” by ACTH administration. Evaluation of serum/plasma concentrations of sodium and potassium are the best tests for aldosterone deficiency. Normonatremia and normokalemia prior to therapy indicates adequate aldosterone production. Some veterinarians use the Na⁺ to K⁺ ratio as a marker of hypoaldosteronism. A ratio of <27/1 is suggestive, but not diagnostic for MC deficiency. Other things that might cause similar electrolyte changes include severe GI disease (whipworms), pleural or peritoneal effusions, ARF or urinary tract rupture, severe acidosis and diabetes mellitus. Remember that secondary hypoadrenocorticism does NOT typically cause electrolyte alterations (with the possible exception of mild hyponatremia without concurrent hyperkalemia).
Endogenous plasma ACTH: Endogenous ACTH should be high if primary hypoadrenocorticism, and low in secondary hypoadrenocorticism. This is the predominate test to differentiate between primary and secondary once the diagnosis of hypoadrenocorticism has been made. It is a good idea to collect a sample for eACTH with the baseline sample for your ACTH stimulation test in animals without sodium or potassium abnormalities for differentiation between primary and secondary. The reason it is important to differentiate is that dogs with primary disease may progress from GC only deficiency to GC and MC deficiency. Identification of primary hypoadrenocorticism will necessitate more frequent electrolyte monitoring.

**Treatment**

Depends on clinical condition of the dog: adrenal crisis or poor doer. Crisis management involves 1.) correction of hypovolemia and 2.) protection of the heart from the effects of hyperkalemia and 3.) administration of glucocorticoids

- Aggressive 0.9% saline IV (or any balanced electrolyte solution)
- Managing hyperkalemia (see chart)
- Dexamethasone sodium phosphate (0.05-0.1 mg/kg), or prednisolone sodium succinate (4-30 mg/kg), or hydrocortisone hemisuccinate or phosphate (5mg/kg IV, repeat 1 mg/kg q 6 hr).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
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<tbody>
<tr>
<td>10% Calcium gluconate</td>
<td>0.5-1.5 ml/kg, IV over 2-5 minutes</td>
</tr>
<tr>
<td>0.9% NaCl</td>
<td>15-25 ml/kg, IV bolus initially, then as needed based on evaluation of physiologic end points</td>
</tr>
<tr>
<td>Dextrose</td>
<td>1-2g/kg, IV in a non-diabetic patient</td>
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<tr>
<td>Dextrose and regular insulin</td>
<td>Dextrose 1-2 g/unit of insulin planned, regular insulin 0.1-0.25 U/kg, IV. Always give dextrose first!</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>1-2 mEq/kg, IV over 20 minutes</td>
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Maintenace therapy for dogs with hypoadrenocorticism includes life-long supplementation of glucocorticoids, mineralocorticoids or both. Since mineralocorticoid deficiency alone is rare, almost all dogs with hypoadrenocorticism require glucocorticoid supplementation. Prednisone or prednisolone is used for maintenance glucocorticoid replacement and is initially started at 0.2 mg/kg daily and the dose adjusted based on clinical signs. Pet owners should be instructed to double the dose of GC any time there is an environmental change, day of excitement or perceived stressful event (visitors, holidays, grooming, vet visit etc.). Owners often don’t understand what constitutes a “stressful” event (oh, my dog LOVES going to the groomer, my dog LOVES when the grandkids chase him around the house…), so emphasizing the importance of increasing the dose in times of excitement or any environmental
change is important. There is a misconception that some dogs will do fine with no GC supplementation. This is likely true right up until the dog needs GCs, doesn’t have them and then dies. Long-acting steroid injections are no substitution for daily administered GCs because of unpredictable pharmacokinetics and an inability to fine tune the dose to the patient’s needs.

If mineralocorticoid deficiency causing hyperkalemia and hyponatremia is present, treatment with desoxycorticosterone pivalate (DOCP) or fludrocortisone acetate should be instituted. Desoxycorticosterone pivalate is a long-acting, injectable mineralocorticoid given at 2.0 mg/kg intramuscularly or subcutaneously approximately every 25 days. However, the duration of action can vary from 14 days to more than 55 days. Therefore, the dose and frequency of dosing should be adjusted as needed. Serum electrolytes are monitored at approximately day 14, 21 and 28 post-injection then as needed to determine duration of action and efficacy of the drug. DOCP has negligible glucocorticoid activity and should always be administered in conjunction with glucocorticoid therapy. Fludrocortisone acetate is a short-acting, oral mineralocorticoid and is administered at a daily dose of 0.01 to 0.02 mg/kg. Similarly to DOCP, the dose should be adjusted based on serum electrolyte concentrations. Fludrocortisone has some glucocorticoid activity, however about 50% of dogs need additional glucocorticoid supplementation while the other half often have signs of glucocorticoid excess. DOCP is preferred over fludrocortisones because it is long-acting, there are fewer issues with bioavailability and you can more effectively titrate the GC dose since it is given independently.

**Prognosis**

Excellent with appropriate therapy.
Hyperadrenocorticism (HAC) refers to a disease state involving persistent hypercortisolemia. Hyperadrenocorticism can be due to excess production of ACTH by the pituitary gland resulting in excess cortisol production from the adrenal gland (pituitary dependent HAC, secondary HAC) or from an adrenal tumor (primary HAC). 80-85% of dogs with HAC have PDH. The majority of dogs with PDH have pituitary adenomas and the adenoma will be located in the pars distalis (80-90%). Pituitary hypertrophy and pituitary carcinomas are less common causes of PDH. The remaining 15-20% of dogs with HAC have a tumor of the adrenal cortex. Tumors of the adrenal glands occur with equal frequency in the left and right gland with 14-30% of dogs having bilateral tumors. Approximately 56-83% of adrenal cortical tumors are carcinomas. Tumor size greater than 2 cm in diameter, peripheral fibrosis, capsular invasion, trabecular growth pattern, hemorrhage and necrosis are morphologic features that are associated with adrenal cortical carcinomas. Metastatic lesions are recognized in 14-28% of dogs with adrenal neoplasia with the lungs, liver and lymph nodes being the most common sites.

History/Clinical findings: HAC is more common in middle to older aged (>6 years), female dogs. The majority (75%) of dogs with pituitary dependent HAC (PDH) weigh less than 20 kg while 50% of dogs with adrenal tumors (AT) weight more than 20 kg.

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Clinicopathologic abnormalities</th>
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<tbody>
<tr>
<td>Polyuria/polydipsia*</td>
<td>Stress leukogram*</td>
</tr>
<tr>
<td>Polyphagia*</td>
<td>Mild to severely &gt; ALP*</td>
</tr>
<tr>
<td>Panting*</td>
<td>Hypercholesterolemia</td>
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<tr>
<td>Pendulous abdomen*</td>
<td>Mildly &gt;ALT</td>
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<tr>
<td>Hepatomegaly</td>
<td>Thrombocytosis</td>
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<tr>
<td>Alopecia</td>
<td>Proteinuria</td>
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<tr>
<td>Thin skin</td>
<td>Subclinical UTI</td>
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<tr>
<td>Hyperpigmentation</td>
<td></td>
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<tr>
<td>Calcinosis cutis</td>
<td></td>
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<tr>
<td>Hypertension</td>
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Diagnostic Testing

Diagnostic evaluation for HAC should include a complete blood count, serum and urine biochemical evaluation, endocrine assessment, urine culture, and blood pressure. Endocrine assessment for HAC includes screening tests, diagnosing tests, and differentiating tests.

Screening tests (generally not useful)

- Urine cortisol to creatinine ratio
- Cortisol-induced ALP

Diagnosing tests

- ACTH stimulation tests (rule in test only)
- Low dose dexamethasone suppression test (rule in or rule out test) (8 hour)
- ACTH stimulation test with androgen panel (if androgen excess is suspected)

Differentiating tests (differentiate PDH from AT after the diagnosis of HAC is confirmed)

- Low dose dexamethasone suppression test (4 hour)
- High dose dexamethasone suppression test
- Endogenous ACTH concentration
- Imaging (can be confusing!)

Screening tests for HAC: UCC and CALP

_Urine cortisol/creatinine ratio (UCC)_ - Single random urine sample needed. Poor sensitivity and specificity. Generally not used.

_Cortisol induced ALP (CALP) –_ Poorer sensitivity and specificity. Generally not used.

Diagnosing tests for HAC: ACTH stimulation test and LDDST

_ACTH stimulation test_ - Administer exogenous ACTH and measure cortisol response before and after ACTH is administered. You can use an empirical dose of 250 ug/dog or 5 ug/kg with equal efficacy. The post ACTH cortisol will increase above reference range in dogs with HAC. The ratio of pre to post cortisol means nothing, only the absolute cortisol values. ~80-85% of dogs with PDH have an exaggerated response, while only ~50-60% of dogs with adrenal disease do. This means there are a number of false negatives, and ill animals with lots of stress may have false positives (up to 15-20%). It is important to note that you can NOT rule out HAC with an ACTH stimulation test. This test can NOT distinguish between PDH and AT. However, ACTH stimulation testing will allow differentiation of iatrogenic from naturally developing HAC. This test is generally not recommended any more since the sensitivity is relatively poor and the specificity is no better than the LDDST.
**Low-dose dexamethasone suppression test (LDDST)** – This is the recommended test for HAC in dogs. Dexamethasone is a synthetic glucocorticoid that does not cross react with cortisol on routine laboratory cortisol assays. Small quantities of dexamethasone in a normal dog suppress ACTH and therefore suppress cortisol within 2-3 hours, and keep suppressing it for 24-48 hours. In PDH, there is both rapid clearance of dexamethasone and relative resistance to dexamethasone, meaning that after giving the dexamethasone, cortisol either fails to suppress or suppresses but then “escapes” suppression. Adrenal tumors produce cortisol without ACTH stimulation, therefore there is no negative feedback when exogenous glucocorticoids like dexamethasone are administered. This test has about a 97% sensitivity for PDH and about 100% sensitivity for AT. Specificity is approximately 70-85%. Therefore, LDDST is more sensitive, and if used appropriately about as specific as the ACTH stimulation test. The disadvantage is that it takes 8 hours to run the test. Despite this limitation, in appropriately selected patients (ie dogs with a clinical picture consistent with HAC lacking concurrent disease), LDDST is the diagnostic test of choice for HAC in dogs. This test is performed by evaluating serum cortisol concentrations before, 4 and 8 hours after administration of dexamethasone. To interpret this test, you should first look at the 8 hour cortisol concentration. Normal dogs should have suppression of serum cortisol at 8 hours. The 4 hour sample is used to differentiate PDH from AT (see below).

Tests to differentiate between PDH and AT: LDDST, HDDST, eACTH, Imaging

To differentiate between PDH and AT you MUST diagnose a cortisol excess using an ACTH stimulation test or LDDST first. Then, pick one of the following tests to differentiate, if that doesn’t get you an answer, continue to do testing until you know for sure. It doesn’t matter which tests you choose first, they all have advantages and disadvantages. Differentiation between PDH and AT is not always necessary. In general, most dogs will be managed in a similar fashion regardless of the primary lesion, UNLESS surgery or radiation therapy is pursued. For pet owners unable or unwilling to pursue these treatment options or for animals with co-morbid risk factors that would make them poor surgical/radiation therapy candidates, differentiation is unnecessary.

**Low-dose dexamethasone suppression (LDDST)**– After the diagnosis of HAC has been confirmed based on failure to suppress at 8 hours, the 4 hour cortisol concentration is evaluated. If there is greater than 50% suppression from baseline (pre-dex sample) or complete suppression at 4 hours, the test result is consistent with PDH. If there is failure to suppress at 4 hours, you cannot differentiate between PDH or AT.

**High dose dexamethasone suppression (HDDST)** – This test is similar to a LDDST with the exception that a higher dose of dexamethasone is used. This higher dose should theoretically suppress ACTH and keep it suppressed, so that PDH dogs will suppress at 8 hours, while autonomous adrenal tumors will continue to produce cortisol. Although 100% of dogs with adrenal hyperadrenocorticism fail to suppress on the HDDST, 20-25% of dogs with PDH also fail to suppress. Suppression of cortisol synthesis at 8 hours post high dose dexamethasone indicates it is PDH. Failure to suppress does not allow for differentiation, thus you need to do further testing to determine if it is PDH or AT.

**Endogenous ACTH (eACTH)** - ACTH in plasma is fragile and has to be handled in a special manner to get accurate results. Plasma ACTH concentrations help with discrimination between PDH and adrenal
disease, but they can’t be used as the lone test for HAC. ACTH should be low in adrenal and iatrogenic disease, high in PDH. Up to 40% of dogs with adrenal disease had normal range ACTH in one study. In another study, while 85-90% of dogs with PDH had increased ACTH, 10-15% had normal ACTH. It is probably true that high or low concentrations are useful but concentrations within the reference interval do not differentiate. Newer analytical methods have improved the sensitivity and specificity of this test. The use of an Immulite 2000 assay system provides approximately 100% accuracy for eACTH. When this analytical method is used, eACTH is likely the best test for differentiating PDH and AT.

**POMC/pro-ACTH concentrations** - POMC/pro-ACTH, precursors for the production of ACTH, have been shown to increase in PDH. They are correlated with pituitary size in humans. A recent investigation evaluated the association between large pituitary size and POMC/pro-ACTH. The test is sensitive (93%) and fairly specific (86%) test for identifying the presence of macroadenomas in dogs with PDH. This test is likely best used to rule out a macroadenoma. If the test is positive (i.e., increased concentrations of POMC/pro-ACTH), imaging of the pituitary is indicated to confirm the diagnosis.

**Abdominal radiographs** - Radiographic evidence of adrenal calcification is present in about half of patients with adrenal tumors but calcification does not differentiate benign from malignant lesions.

**Abdominal ultrasonography** – Theoretically speaking, both adrenals should be normal to large and symmetrical with PDH and dogs with adrenal tumors should have one large adrenal gland and one small (atrophied) adrenal gland. In reality, there is a great deal of overlap with some dogs with PDH having asymmetrical adrenal glands and some dogs with AT having symmetrical adrenal glands. Therefore, differentiating between PDH and AT is not always possible with ultrasound and ideally, endocrine testing like LDDST, HDDST or eACTH should be used. If ultrasound is used, the only clinically useful finding is identification of contralateral adrenal gland atrophy for the diagnosis of ACTH-independent HAC (ie AT). Atrophy (<5mm at the maximal DV thickness of the smaller gland) has a sensitivity of 82-100% and specificity of 82-99% (95% CI) for the diagnosis of ACTH-independent HAC. However, a lack of contralateral adrenal gland atrophy does not necessarily rule out an AT so care should be taken in interpreting a lack of atrophy. An adrenal gland that is greater than 2 cm in diameter is more likely to be an adrenal cortical carcinoma. Metastatic lesions are recognized in 14-28% of dogs with adrenal neoplasia with the lungs, liver and lymph nodes being the most common sites. Therefore, abdominal (and thoracic) evaluation for metastatic disease is indicated in any patient with an adrenal tumor.

**CT or MRI of the pituitary or adrenals** – You may see a pituitary tumor >3 mm (~ half of all PDH, but that means you see nothing in the other 50%). Computed tomography (CT) is a more sensitive imaging modality for the detection of adrenal tumors and metastases than radiographs or possibly ultrasound.

**Treatment**

Pituitary dependent hyperadrenocorticism

In general, treatment for pituitary dependent hyperadrenocorticism (PDH) is initiated to maintain a good quality of life. Treatment has little impact on survival in dogs lacking co-morbid diseases. Therefore, treatment should only be considered in dogs with clinical signs unless they have other conditions that could alter their prognosis if the PDH was left untreated (e.g., diabetes mellitus, PLN, thromboembolic
disease, GB mucocele, hyperlipidemia, hypertension, possibly CHF). Caution should be used when treating dogs with poor appetites medically for PDH (may be a sign of a macroadenoma). With any treatment, some signs respond rapidly (PU/PD, polyphagia) and others take weeks-months to improve (skin and coat changes, pot belly). This is because some are direct effects of circulating cortisol, and some are due to long term cortisol exposure changing tissues (ie, atrophy of hair follicles, calcium deposition, muscle atrophy and wasting, etc). It is important to note that all of the standard medical therapies for PDH have the potential to promote pituitary adenoma growth. Tumor expansion occurs because of a lack of negative feedback from cortisol (any cortisol lowering therapy has the potential to cause this). This phenomenon is called Nelson’s syndrome; named after Dr. Don Nelson who documented this effect in 1960. The two medical treatments used for PDH in dogs are mitotane and trilostane; levodeprenyl is no longer recommended.

Mitotane (a.k.a., O,P’-DDD)

In the late 1940s, it was noted that dogs given the insecticide DDD developed severe adrenocortical necrosis and atrophy. The therapeutic use of mitotane to treat hyperadrenocorticism was described in 1973 and gained widespread acceptance. A recent survey of over 200 veterinary internists and dermatologists revealed that 95.6 % routinely utilized mitotane for the treatment of PDH in dogs. Or at least this is the way it was about 10 years ago, now trilostane has become a more commonly used treatment.

Mechanism of Action - Mitotane exerts its cortisol lowering effects through progressive, selective necrosis of the adrenal zona fasciculata and reticularis. The zona glomerulosa is relatively resistant to the cytotoxic effects and, therefore, normal secretion of aldosterone is usually maintained. Mitotane also interferes with steroid biosynthesis, primarily through inhibition of the 11-hydroxylase and cholesterol side-cleavage enzymes.

Mitotane is a fat-soluble drug and is distributed to virtually all tissues with primary storage in adipose tissue. It is converted to its active form by mitochondrial P-450 mono-oxygenases. Although the metabolic disposition of mitotane is not known in dogs, it likely undergoes oxidative metabolism in the liver as it does in humans. This pathway may be clinically important since induction of hepatic microsomal enzymes by drugs like phenobarbital may increase mitotane metabolism and, concurrently, diminish the adrenocorticolytic effect.

Safety - Most adverse effects of mitotane are related to a rapid decrease in serum cortisol or hypocortisolemia (Table 1). Lethargy, ataxia, weakness, anorexia, vomiting or diarrhea occurs in approximately 25 % of patients. These effects are usually mild and resolve with administration of glucocorticoids. Permanent hypoadrenocorticism (Addison’s disease) develops in approximately 2-5 % of dogs with PDH treated with mitotane. Despite the relative resistance of the zona glomerulosa, hypoadrenocorticism may include hypoaldosteronism with resultant hyponatremia and hyperkalemia as well as hypocortisolemia. Rarely, delayed drug-induced central nervous system (CNS) signs occur including wandering, circling, and head pressing. Typically, these CNS signs are transient and are abolished by giving lower doses of mitotane more frequently. Hepatic changes including congestion, centrilobular atrophy, and moderate to severe fatty degeneration have been noted.
Efficacy - Mitotane is an effective treatment in 85-90% of dogs with PDH. Despite initial efficacy, approximately 50% of dogs treated with mitotane will relapse within the first year of therapy. Typically, patients that relapse will respond to a re-induction and an increased maintenance dosage.

Administration - Most clinicians still utilize the protocol originally suggested by Schechter, et al in 1973. This protocol includes an induction period followed by long-term maintenance therapy. The induction dosage of mitotane is 30-50 mg/kg per day for 8 to 10 days or until signs suggestive of hypoadrenocorticism develop. When possible, the daily dosage should be divided into two equal doses and administered with food (fat) to increase absorption. Concurrent glucocorticoid supplementation with prednisone or prednisolone (0.15-0.25 mg/kg/day) can be used to mitigate the possible adverse effects associated with rapid serum cortisol reduction. However, glucocorticoid supplementation during induction makes recognition of therapeutic end points difficult. If glucocorticoids are not concurrently administered, it is imperative that clients are provided with glucocorticoids in case signs of potentially life-threatening hypoadrenocorticism develop. Dexamethasone is preferred over prednisolone since it does not cross react with cortisol assays.

At-home monitoring is crucial, especially during the induction period. Vomiting, weakness, anorexia, dullness or ataxia may be signs of mitotane over-dosage or alternatively may be due to stomach upset associated with the drug. Owners should be educated to recognize these warning signs, instructed to discontinue mitotane, give steroids and seek immediate veterinary care. In the absence of these adverse reactions, mitotane should be discontinued when water consumption in a previously polydipsic dog decreases, when appetite wanes, or after the initial 8 to 10 days of therapy. Remember, most dogs with HAC will have medullary washout, therefore decreased water intake is an unreliable clinical sign for cortisol control. Some veterinarians will decrease food rations by 25% at the initiation of mitotane to encourage a “strong” appetite. Clients should be well educated to monitor for decreased appetite and/or decreased water intake as signs to stop mitotane. When signs of decreased cortisol production are noted (decreased appetite, decreased water intake, GI signs, lethargy, ataxia), ACTH stimulation test and serum electrolyte concentrations should be evaluated. Glucocorticoid therapy (if using a glucocorticoid other than dexamethasone) should not be given the morning of the ACTH stimulation test to avoid cross-reaction with the cortisol assay and falsely increased cortisol concentrations.

The goal of treatment with mitotane is to achieve an ACTH stimulation test result with a basal cortisol concentration of 1-4 ug/dL with little increase in cortisol post stimulation. If cortisol is suppressed excessively, discontinuation of mitotane for a period of 2-6 weeks typically results in return of serum cortisol into the normal range. Once cortisol concentrations, both pre- and post ACTH stimulation, are between 1 and 5 µg/dL, maintenance therapy is initiated. Maintenance therapy involves dividing the daily mitotane induction dose (25-50 mg/kg) over two to three days of the week (e.g., Monday, Wednesday, Friday or Wednesday, Saturday). Serum electrolyte measurement and ACTH stimulation testing should be repeated at 3 and 6 months and then every 6 months thereafter. If ACTH stimulation test results are above the desired ranges, the dosage of mitotane should be increased. If a conservative increase in the mitotane dosage does not alleviate clinical signs and decrease cortisol appropriately, mitotane induction should be repeated.
Trilostane

Trilostane is FDA approved for the treatment of HAC in dogs. It is used throughout the world as a management tool for HAC in the dog.

**Mechanism of Action** - Trilostane is a synthetic, orally active steroid analog. It acts as a competitive inhibitor of the 3 beta-hydroxysteroid dehydrogenase enzyme system and possibly 11β-hydroxylase. The effects of trilostane are largely reversible and dose dependent.

**Safety** - Trilostane seems to be well tolerated by dogs. Mild lethargy and decreased appetite are occasionally seen 2-4 days after initiation of therapy, and are likely due to steroid withdrawal syndrome (this can happen with any cortisol lowering medication). Mild hyperkalemia, azotemia, hyperbilirubinemia, and hypercalcemia have been reported, but were usually not associated with clinical illness and spontaneously resolve within a few weeks. Bilateral enlargement of the adrenal glands has been reported, but was not clinically important. Permanent hypoadrenocorticism develops in dogs treated with trilostane and mitotane with an equal frequency (~2-6%). In general, trilostane is no safer nor is it more efficacious than mitotane. Dogs with PDH treated with trilostane have an average survival of ~3 years (ie they die from something other than HAC) which is similar to that of mitotane. Given that this is the only efficacious FDA approved treatment for PDH in dogs, trilostane is considered the medical treatment of choice for PDH.

**Efficacy** - Trilostane is highly effective at resolving the signs of PDH with a reported 82-97% efficacy based on resolution of clinical signs and normalization of ACTH stimulation tests.

**Administration** - Typical starting dose range for dogs with PDH is 1-6.7 mg/kg once daily, although some dogs respond better to twice daily dosing. However, whenever possible the low range of the dosing scheme (1-3 mg/kg/day) should be used to avoid potential side effects. A reasonable starting dose for trilostane is 2 mg/kg q 24 hours or 1 mg/kg q 12 hours. The dose can be adjusted based on response over time. In the author’s experience, many dogs will experience better hormonal control with fewer side effects if trilostane is used twice daily (1 mg/kg q 12h). A key clinical clue that twice daily therapy is needed is the persistence of Cushing’s syndrome despite achieving optimal pre and post-ACTH cortisol concentrations. Similarly to mitotane, trilostane should be given with food to increase absorption.

An ACTH stimulation test and serum electrolyte concentrations should be evaluated 7-14 days, 30 days and 90 days after the initiation of therapy. It is important to perform these tests 3-6 hours after trilostane administration (timing of peak effect) since the duration of action of the drug is only about 8-12 hours. If the post ACTH cortisol concentration is less than 1.0 ug /dL, trilostane should be stopped for 48 hours and then re-introduced at a lower dosage. If the post ACTH cortisol concentration is greater than 4 ug/dL, then the dose of trilostane should be increased. The dose remains unaltered if post ACTH cortisol concentration is between 1.0 ug /dL and 4 ug /dL, serum electrolytes are within reference range, and the patient appears clinically normal (ie no signs of hypoadrenocorticism or hyperadrenocorticism). To confuse matters, many internists (including the author) believe that post-ACTH cortisol concentrations as high as 8 ug/dl may still result in clinical remission from HAC. Thus, if the patient has a post-ACTH stimulation cortisol concentration between 1-8 ug/dl and good clinical control of Cushing’s syndrome,
dose adjustment may not be necessary. After the dosage has been stabilized and the animal is free of clinical signs, ACTH stimulation testing and serum electrolytes should be monitored every 3-6 months.

Surgical/Radiation Therapy for PDH

Since metastases are rare, local tumor growth has the greatest effect on morbidity and mortality in most patients with PDH. Over 75% of dogs with pituitary dependent HAC will have a visible pituitary mass on MRI within the first year after diagnosis. Furthermore, about 50% of dogs will have enlargement of their pituitary mass after a year of medical management. Macroadenomas are identified in about 50% of dogs with pituitary dependent HAC.

Surgical Therapy for PDH - Hypophysectomy is the treatment of choice for humans with pituitary tumors and has also been used for the treatment of dogs with pituitary adenomas with good success. In one study, the estimated 2 year survival and relapse-free rates for 150 dogs with pituitary adenomas treated with hypophysectomy were 76% and 75%, respectively. Procedure related mortality occurred in 12/150 dogs. Post-operative complications included decreased tear production, hypothyroidism, mild transient hypernatremia and central diabetes insipidus. Dogs with smaller pituitary adenomas had longer survivals and a decreased risk for development of central diabetes insipidus. Currently, the availability of neurosurgeons to perform this complicated procedure and the high mortality rate has limited the routine use of surgical intervention for PDH.

Radiation therapy for PDH - Treatment for pituitary corticotroph macroadenomas relies on radiation therapy (RT). Mean survival for dogs with macroadenomas treated with RT (1405 days), significantly longer than in untreated dogs (551 days). Radiation therapy is associated with a 1-, 2-, and 3-year estimated survival of 93, 87, and 55%, respectively for dogs with macroadenomas. For dogs with neurologic signs at the time of RT, about 50% will have partial or complete resolution of those signs. Some dogs will go on to have recurrence of neurologic signs months to years after RT, however. Increased tumor size and endocrine activity were associated with a poorer prognosis in dogs undergoing radiation therapy for pituitary macroadenomas with neurologic signs. While radiation therapy is successful at decreasing pituitary size, aberrant ACTH secretion is not controlled in many cases and 35-70% of dogs will continue to have clinical evidence of hormone excess despite RT. Therefore, medical management of HAC is still warranted in many dogs. Additionally, controlling hormonal effects before and during RT may reduce the risk of HAC associated complications.

Surgical Therapy for Adrenal Tumors

Adrenalectomy is the treatment of choice for any hormonally functional adrenal cortical tumor or any adrenal cortical tumor greater than 2 cm. Although reported post-operative mortality has been reported to be 6-60%, patients that survive 2 weeks post adrenalectomy, have a good long term prognosis. The median survival is 778 days for cortisol secreting adrenal cortical carcinomas treated with surgery alone. It is important to note that tumor size, patient age, histopathologic diagnosis, presence of tumor thrombi of the vena cava are not prognostic. Noting the vast difference in post-op mortality, one should consider strategies to minimize complicating factors that often lead to death. Specifically, care should be taken to minimize hormonal effects and co-morbid disease pre-operatively and monitor patients for hypoadrenocorticism post-adrenalectomy. The importance of pre-op and post-op management cannot be overstated!!
Pre-surgical preparation should include reduction of circulating cortisol concentrations via mitotane, trilostane or maybe ketoconazole, management of co-morbid disease (e.g., PLN, hypertension, DM), TE prophylaxis and treatment of secondary infections. Ideally, the hormonal effects of HAC should be controlled (ie the dog is in complete remission) for a minimum of 1 month (hopefully a little longer; optimum duration is unknown) prior to surgery. Appropriate TE prophylaxis should be discussed with the surgeon performing the procedure. It is always wise to assume that any suspected adrenal mass may be a pheochromocytoma (regardless of endocrine testing suggesting otherwise) and adrenergic and anesthetic management should be adjusted accordingly. Post-op, care should be taken to avoid risk factors for TE and TE prophylaxis should be continued for 2-4 weeks. For some patients with moderate to poor cortisol control pre-op, glucocorticoids should be supplemented, tapering over 2 weeks. Hypoadrenocorticism is a rare, but life-threatening complication of unilateral adrenalectomy. Electrolytes should be monitored as well as signs of glucocorticoid deficiency (e.g., hypotension, GI signs, anorexia) post-op. Some internists recommend post-op ACTH stimulation testing to assess adrenal cortical reserve in the remaining gland. Aggressive medical management pre and post-op is just as important as exceptional surgical and anesthetic expertise for these patients.

Medical Therapy for Adrenal Tumors

For patients that are poor anesthetic candidates or owners that are not amendable to surgery, medical management is possible. Trilostane or mitotane can be used as medical treatment for adrenocortical tumors secreting cortisol and/or androgens. Overall median survival for dogs with AT treated with either trilostane or mitotane is 277 days (95% CI, 102–473 days). Trilostane has no effect on tumor growth or metastases so there is some theoretical preference for mitotane. Also, mitotane may be administered to control cortisol or androgen related clinical signs associated with metastatic disease. However, there very little information comparing survival between dogs with AT treated with trilostane and mitotane. In one retrospective study that was considered somewhat controversial, median survival times for dogs on mitotane (n = 13; 102 days; 95% CI, 43–277 days) was not significantly different than trilostane (n = 22; 353 days; 95% CI, 95–528 days). The 1-year survival fraction for dogs on mitotane was 23% (95% CI, 5.6–47.5%), whereas the 1-year survival fraction for dogs on trilostane was 50% (95% CI, 28.2–68.4%). Previously, median survival for dogs with adrenal cortical tumors treated with mitotane alone has been reported to be 11.5 months. In dogs with AT and evidence of metastatic lesions, median survival is ~2 months with mitotane or trilostane therapy.

Prognosis

See treatment section for specific information about prognosis based on the location of the lesion and the selected treatment modality.
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