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

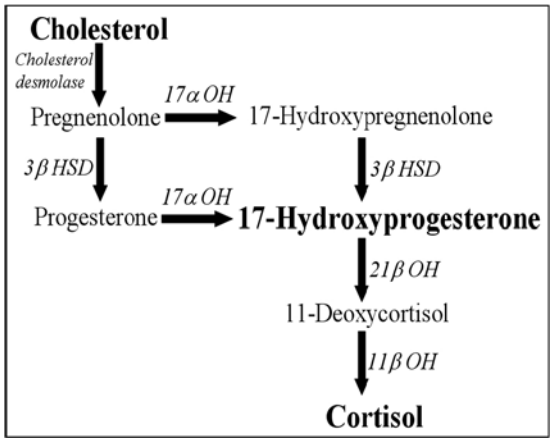
"Utrecht Protocol"

- **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