

# Hyperadrenocorticism

Diagnosis, Treatment, & Monitoring



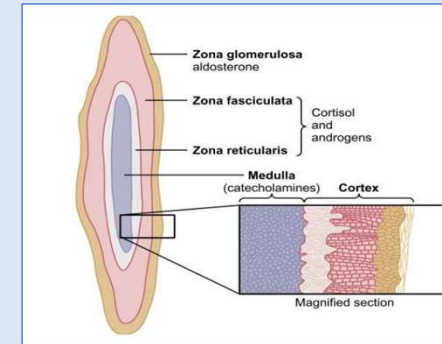
Kelly Monaghan, DVM, DACVIM (SAIM)  
Consultant to Heska  
May 4, 2023



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## Background

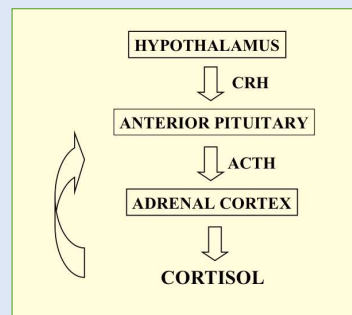
- Clinical syndrome
- Results from excessive cortisol production



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## Outline

- Background & pathophysiology
- Clinical signs
- Diagnostics
- Therapies
- Monitoring
- Prognosis



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## Pathophysiology

- ACTH-Dependent Hyperadrenocorticism (HAC)
  - Pituitary Dependent HAC (PDH)
    - 75-85% of cases
    - Pituitary (micro)adenoma most common
      - Macroadenomas or carcinomas are rare
  - Ectopic ACTH hypersecretion
    - Case report of pancreatic neuroendocrine tumor



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## Pathophysiology

- ACTH-Independent HAC
  - Functional adrenal tumor (FAT, ADH)
    - 15-25% of cases
    - Adrenocortical tumor (adenoma, adenocarcinoma)
- Food-dependent hypercortisolism
  - Normally, Glucagon Inhibitory Peptide (GIP) is produced by stomach after every meal and binds to pancreas to stimulate insulin production
  - In these patients, GIP binds to aberrant receptors on the adrenal triggering release of cortisol



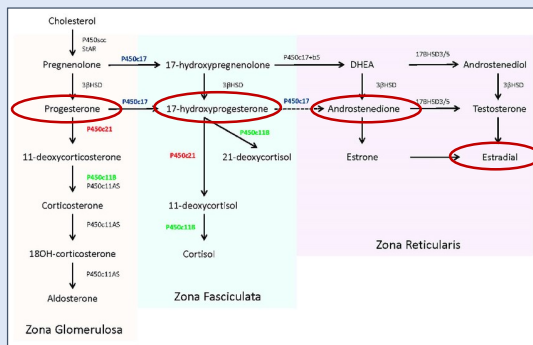
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## Diagnosis



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## Atypical Cushing's?



- Clinical signs of HAC with negative LDDST and ACTH stimulation test
- Excessive adrenal hormones other than cortisol
  - 17-OHP, progesterone, androstenedione, estradiol
- Wide overlap between non-adrenal illness & HAC



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## Clinical Signs

- PU/PD
- Polyphagia
- Panting
- "Pot belly"
- Muscle atrophy/weakness
- Decreased exercise tolerance
- Symmetric non-pruritic truncal alopecia
- Calcinosis cutis



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## Labwork

- Elevated ALP (95%)
- Elevated ALT (90-95%)
- Hypercholesterolemia (80%)
- Hypertriglyceridemia
- Hyperglycemia (~10% DM)
- Thrombocytosis
- Dilute urine (85%)
- Proteinuria (75%)
- UTI (6.6%)
- Elevated lipase (48%)



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## Testing

- Screening
  - UC:CR
  - LDDST
  - ACTH stimulation test
- Differentiating
  - LDDST
  - HDDST
  - Endogenous ACTH
  - Imaging



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## Other Exam Findings

- Hepatomegaly
- Hypertension
- Thin skin
- Evidence of hypercoagulability



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## Urine Cortisol:Creatinine

- Single sample collected in hospital
  - 75-100% sensitive
  - 20-25% specific
- 2 samples collected at home  $\geq 2$ d after vet visit
  - 94-100% sensitive
  - 64-87% specific



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## Urine Cortisol:Creatinine

- Interpretation
  - Normal result
    - HAC unlikely
    - Mild cases may be negative due to day-to-day variation
  - High
    - HAC or anything else
    - More tests needed



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## LDDST

- Screening test of choice
- Sensitivity 85-100%, specificity 44-73%
  - Not recommended in sick dogs
  - Don't use when on steroids



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## Low Dose Dexamethasone Suppression Test (LDDST)

- Principles
  - Shows decreased HPAA sensitivity to negative feedback
  - Dexamethasone may be metabolized faster in HAC dogs
- In normal dogs– cortisol decreases 2-3 hours after dex and stays down for 24-48 hrs



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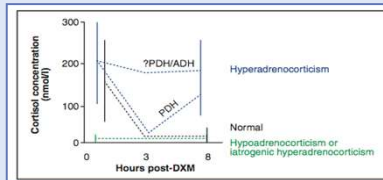
## LDDST: Interpretation

- Diagnosis is based on cortisol 8 hrs after 0.01mg/kg IV dexamethasone
  - $\geq 1.4$  @ 8hrs= HAC
  - Normal dogs have a cortisol  $< 1.4$  ug/dl at 4 & 8 hours post
  - Should new cutoffs be established?
- Can be differentiating too

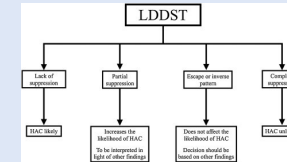


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## LDDST: Interpretation



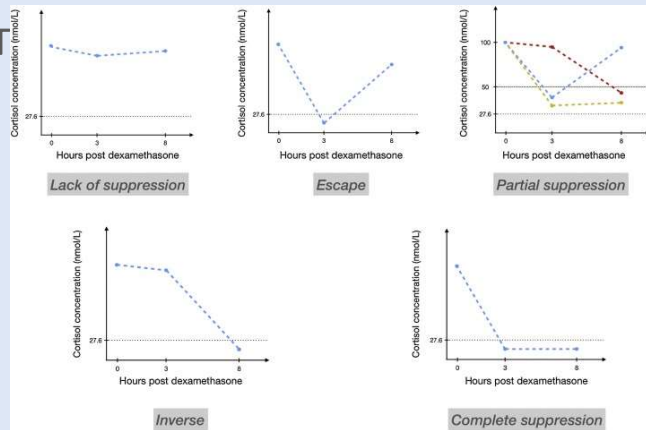
- ADH's don't suppress at all
- PDH
  - ~60% suppress and escape
  - ~40% don't suppress



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## LDDST



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## ACTH Stimulation Test

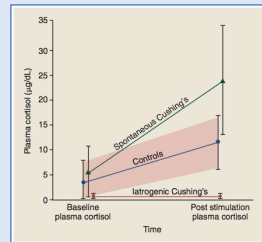
- Principle: Assesses adrenocortical reserve
- Sensitivity
  - All forms of spontaneous HAC= 57-95%
  - ADH= 57-63%
  - PDH= 80-92%
- Specificity: 59-93%
  - Gold standard for iatrogenic



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## ACTH Stimulation Test

- Performed with 5ug/kg Cortrosyn, Cosyntropin, or Synacthen
  - Avoid compounded products
  - IV preferred, IM ok
- Interpretation
  - Normal
    - Pre: 0.5-6.0
    - Post: 6-18
  - HAC: >22.0



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## Abdominal Ultrasound

- In adrenal tumors
  - Look for metastases, tumor size, location, presence of vascular invasion/tumor thrombi
- Evaluate for co-morbidities (e.g. mucoceles, uroliths)



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## Abdominal Ultrasound

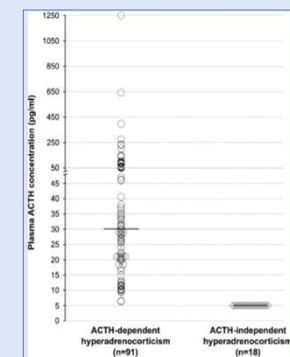
- Evaluate for adrenal mass vs enlargement
  - Adrenals can be normal in PDH
  - Adrenal masses are usually unilateral; <10% bilateral
- *Benckroun et al. JVIM 2010.*
  - In equivocal adrenal asymmetry, if the smaller adrenal is <5.0mm thick, the other is likely a functional tumor
    - 100% sensitive, 96% specific



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## Endogenous ACTH

- *Rodriguez et al. JVIM 2009*
  - Low/undetectable in dogs with ADH
  - If <5pg/ml, sensitivity 100%, specificity 100%
    - No overlap in [ACTH] in ADH v PDH
  - ACTH is unstable and must be centrifuged and frozen immediately after collection to prevent falsely low readings



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## High Dose Dexamethasone Suppression Test

- Similar to LDDST but with 0.1mg/kg dexamethasone IV
- ADH won't suppress at all
  - Only ~75% of PDH's suppress
- Not very helpful



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## Sex Hormone Panel

- Advocated for diagnosis of "atypical HAC"
- Dogs with non-adrenal disease may have elevations in sex hormones
  - These may be more likely to be increased in non-adrenal illness than cortisol = poor specificity
  - Elevated estradiol reported in ~40% of samples submitted
  - Several elevations reported in pheos
- Sex hormones have not been proven to cause occult HAC



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## Pituitary Imaging

- Pituitary lesions range from small nests of hyperplastic cells to large tumors
- Absence of neuro signs does not exclude a macrotumor
- Over time, microadenomas can become macrotumors
  - Radiation or hypophysectomy indicated for these



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## Treatment



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## Mitotane

- o,p'-DDD (Lysodren) is a DDT (insecticide) derivative with cytotoxic effects on the adrenal cortex
- Adrenocorticolytic drug



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## Trilostane

- Synthetic non-hormonal steroid
- Competitive reversible inhibitor of 3- $\beta$ -hydroxysteroid dehydrogenase
- Adrenocorticostatic drug
- Only drug with FDA approval to treat PDH and ADH in dogs
  - Approved by the FDA in 2009



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## Mitotane

- Previously thought this may have advantage over trilostane in adrenal tumors due to destruction of cortex (e.g. the tumor)– not substantiated
  - Some suggested that higher doses are needed in ADH but this has not been shown in the literature either



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## Trilostane: Dosing

- Label: 2.2-6.7mg/kg SID
- Since FDA approval, concern for short duration of action
- Several studies evaluating low dose (~1mg/kg) BID use
  - Longer time to achieve control with low dose BID but possibly fewer crises
  - High doses SID up to 25% adverse effects vs <10% in low BID dose




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## Trilostane: Monitoring (USA)

- Clinical signs
- ACTH stimulation test 10-14 days after starting treatment or after dose change
  - @ 1 mo, then q3-6 months thereafter
  - Start test 2-4 hours after dosing
- Electrolytes as appropriate



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### CushQoL-pet: Cushing's Quality-of-life Questionnaire

Completing this questionnaire will help your vet understand how your dog is progressing and how Vetoryl® is working to bring back health and restore life.

Please choose the category that best describes how your dog is doing today for each question.

	Never	Occasionally	Often	All the time
<b>CLINICAL IMPACT</b>				
My dog is excessively thirsty	0	1	2	3
My dog urinates in the house				
My dog is excessively hungry				
My dog pants excessively				
<b>DOG'S DEMEANOUR</b>				
My dog is depressed and sad	0	1	2	3
My dog has no energy				
My dog doesn't want to interact with other people/dogs				
My dog is reluctant to play with me				
My dog seems disoriented/confused				
<b>PHYSICAL IMPACT</b>				
I struggle with my dog's weight	0	1	2	3
My dog's hair sheds in a poor condition				
My dog's skin appears to be uncomfortable (e.g. dry/itchy)				
My dog appears to be in a poor physical condition (e.g. muscle wastage/loss)				
My dog struggles to walk with me				
<b>OWNER IMPACT</b>				
I worry about the future health of my dog	0	1	2	3
Me and my dog's daily routine is disrupted				
I find it challenging to interact my dog in public				
I find the bond between me and my dog is lacking				
I find my dog's independence affects my personal commitments				
<b>TOTAL SCORE</b>				

To find out more visit [www.canine-cushings.co.uk/monitoring](http://www.canine-cushings.co.uk/monitoring)

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### Cushing's Clinical Score

There are five categories. Score 0-10 to record a response. Cushing's Clinical Score is a composite score used to help you and your vet monitor your dog's progress. Please choose the number that best describes how your dog is doing in each category.


Category	Score	Your Rating
<b>Drinking &amp; Urination</b>	0-3	
<b>Appetite</b>	0-3	
<b>Appearance</b>	0-3	
<b>Attitude/activity</b>	0-3	

Any other clinical signs observed (e.g. vomiting, diarrhoea, UTI) \_\_\_\_\_

To find out more visit [www.canine-cushings.co.uk/monitoring](http://www.canine-cushings.co.uk/monitoring)

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<https://www.canine-cushings.co.uk/treatment>



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## Trilostane: Monitoring (UK)

- Clinical signs
- Pre-Vetoryl cortisol
  - 2 studies have shown poor correlation between clinical status of patient and ACTH stim results
  - Pre-Vetoryl cortisols have shown improved correlation and may reflect clinical status better
  - Less expensive
- Best for clinically well dogs




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### How to monitor Cushing's

Developed by Ian Ramsay BVSc, PhD, DSAM, Dip. ECVM-CA, FHEA, MRCVS, Federico Fracassi DVM, PhD, Dip. ECVM-CA, Nadja Stöber-Rückert PhD, Dr. med. vet. Dip. ACVM, Dip. ECVM-CA

**Clinical signs of HAC<sup>1</sup>**



**Pre-Vetoryl Cortisol\***

40 nmol/l result      138 ± 15% result

**If Pre-Vetoryl Cortisol values do not match the clinical picture contact Dechra Technical Services**


Increase dose frequency<sup>2</sup> or Increase dose<sup>3</sup> → **Re-check in 1 month**

Re-evaluate case<sup>2</sup> Consider lower dose<sup>4</sup> → **Re-check in 3 months**

Continue Vetoryl treatment at current dose → **Re-check in 3 months**

Re-evaluate and consider either dividing SID dose equally into BID doses, if already dosing BID then consider small dose increase<sup>5</sup> → **Re-check in 3 months**

**No clinical signs of HAC**




**Pre-Vetoryl Cortisol\***

0 nmol/l result      40 nmol/l result      138 ± 15% result

Continue Vetoryl treatment at current dose → **Re-check in 3 months**

**Clinically unwell**



**Stop Vetoryl treatment**

Pre- and Post-ACTH Stimulation Test cortisols & analysis of serum electrolytes (in particular Na and K) immediately

Pre- and Post-ACTH Stimulation cortisols < 40 nmol/l → **Clinical signs probably due to over-suppression. Treat symptomatically as required<sup>6</sup>** → **Restart Vetoryl at lower dose when signs of HAC recur or post-ACTH cortisol > 140 nmol/l** → **Re-check in 1 month**

Pre- or Post-ACTH Stimulation cortisols ≥ 40 nmol/l → **Unlikely to be hypocortisolemia. Investigate other causes** → **Restart Vetoryl when well** → **Re-check in 1 month**

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## Mitotane vs Trilostane

- No difference in long-term outcomes
  - MST mitotane 102-702 days
  - MST trilostane 353-662 days
- Adverse effects more common with mitotane
  - 57.1% with mitotane
  - <10-33.3% with trilostane



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## Melatonin, Lignans

- Shown to decrease steroid hormone secretion in human adrenocortical carcinomas in vitro
- Melatonin shown to affect sex hormone levels in dogs and decrease signs in ferrets with adrenal tumors
- No published data on efficacy



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## Ketoconazole

- Inhibits synthesis of steroid hormones by interfering with activities of CYP450 dependent enzymes in the adrenal cortex
- *Lien, et al. JAVMA 2008.*
  - 90% of dogs had clinical improvement
  - Recheck ACTH stim was normal in 69% but they used a high range (<10.0ug/dl)



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## Selegeline (L-Deprenyl)

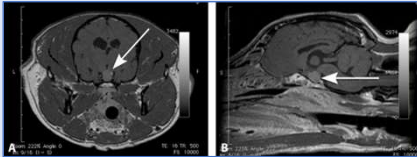
- Inhibits degradation of dopamine which potentially inhibits ACTH secretion from the pars intermedia
  - Only 20% of canine PDH comes from here
- Poor efficacy
- Expensive
- Difficult to monitor



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## Surgery: PDH

- 84-92% remission rate
- MST reported to be 781 days
- Larger tumors don't do as well
  - 2x the chance of early death
- Post-operative mortality 0-50% (~10% most recent)



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## Surgery: ADH

- No studies, but many feel that managing these patients medically prior to surgery may help
  - 3-4 weeks of pre-op treatment can reverse metabolic derangements and may minimize the complications associated with HAC
- Cortisol-induced immunosuppression, impaired wound healing, systemic hypertension, hypercoagulation



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## Surgery: ADH

- Surgery is treatment of choice but morbidity/mortality is high
  - Short-term mortality 8-24%
  - Perioperative complications up to 50%
  - Outcomes are good if they survive peri-op period
  - Carcinoma 778-1440 days
  - Adenomas- most alive at end of study so MST not determined



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## Prognosis: Untreated

- *Nagata et al. JVIM 2017.*
  - Retrospective on dogs with PDH either treated with trilostane (n=17) or untreated (n=26) for 2 years
  - Hazard ratio 5.01 higher risk of death in untreated dogs

	MST	2y survival fraction
Trilostane	Not reached	52.2%
Untreated	506 days	8.5%



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## Cats?

- Many similarities to dogs
- Most are diabetic
- Up to 1/3 have skin fragility
- Secondary infections common
- Different methods for testing
- Trilostane treatment of choice



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## Questions?

Remember to **download the CE certificate** in the handouts panel of the webinar control panel.

NOTE: CE certificate not available for watching the recording.

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Questions about topic?  
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## Summary

- Clinical diagnosis
  - LDDST test of choice
- Trilostane fewer side effects but similar MST vs mitotane
  - Lower dose BID may be better
- Evolving monitoring options
- Surgery?



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