# Hyperadrenocorticism

Diagnosis, Treatment, & Monitoring

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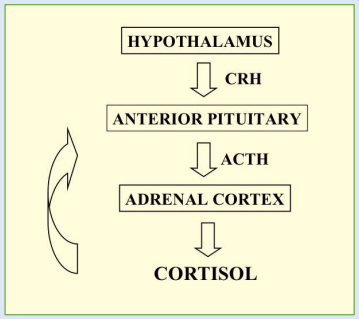
## Outline

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

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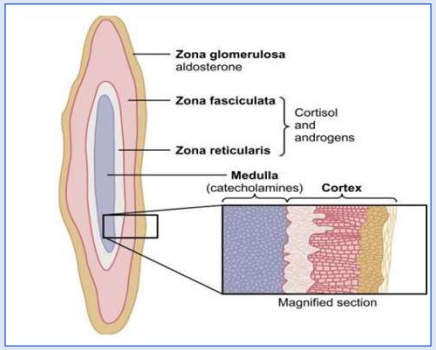
## Background

- Clinical syndrome
- Results from excessive cortisol production

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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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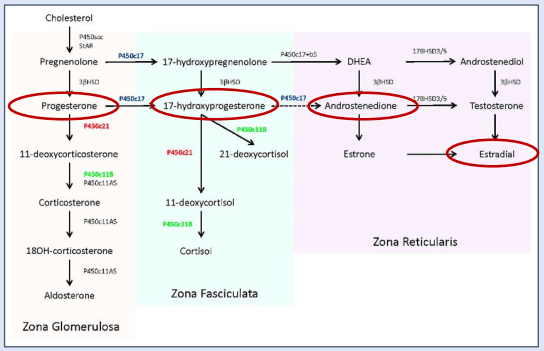
## Atypical Cushing's?




- 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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## Diagnosis

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## Clinical Signs

- PU/PD
- Polyphagia
- Panting
- "Pot belly"
- Muscle atropy/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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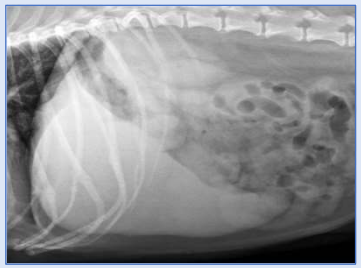
## Other Exam Findings

- Hepatomegaly
- Hypertension
- Thin skin
- Evidence of hypercoaguability



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## Testing

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



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## Urine Cortisol:Creatinine

- Single sample collected in hospital
  - 75-100% sensitive
  - 20-25% specific
- 2 samples collected at home ≥2d 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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## 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

- 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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## LDDST: Interpretation

- Diagnosis is based on cortisol 8 hrs after 0.01mg/kg IV dexamethasone
  - ≥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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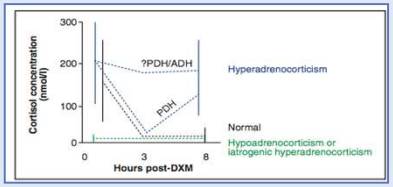
## LDDST: Interpretation




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

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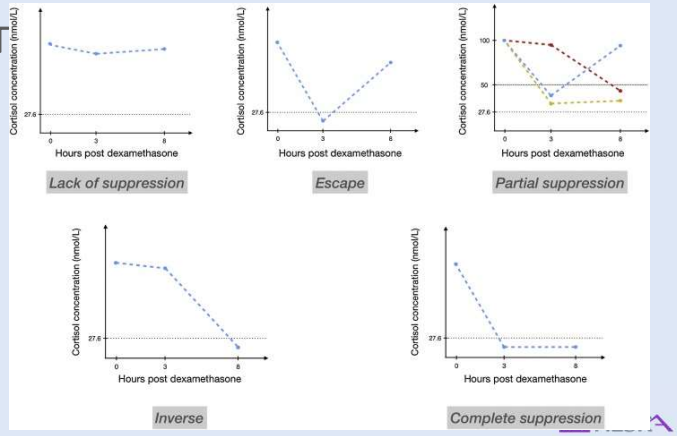
## LDDST

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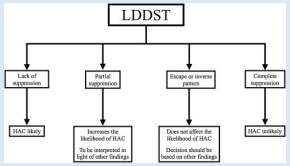


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## ACTH Stimulation Test

- 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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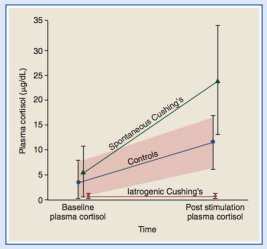
## ACTH Stimulation Test

- 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

- Evaluate for adrenal mass vs enlargement
  - Adrenals can be normal in PDH
  - Adrenal masses are usually unilateral; <10% bilateral
- *Benchekroun 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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## 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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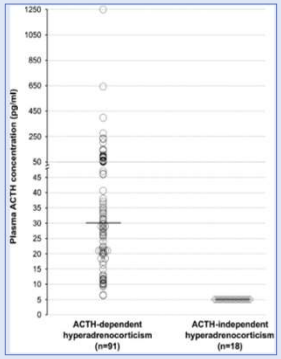
## Endogenous ACTH

- *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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## 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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## 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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## 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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## 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

- Synthetic non-hormonal steroid
- Competitive reversible inhibitor of 3-β-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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## 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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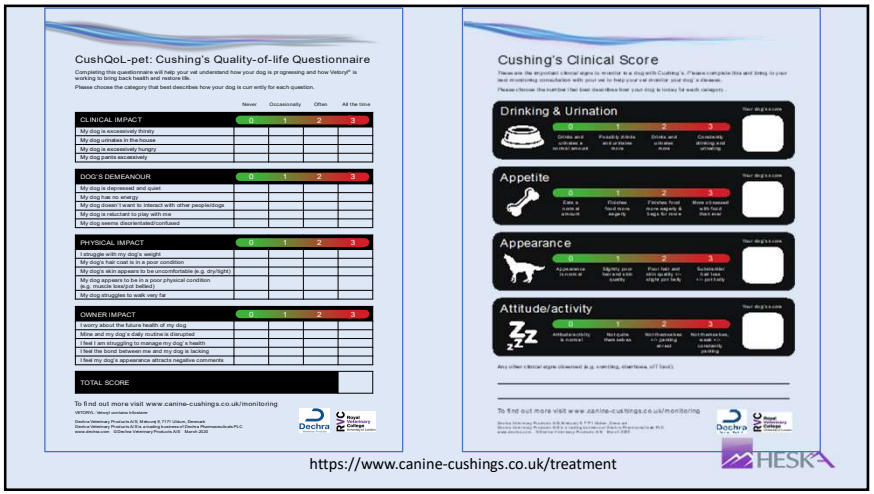


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## Trilostane: Monitoring (UK)

- 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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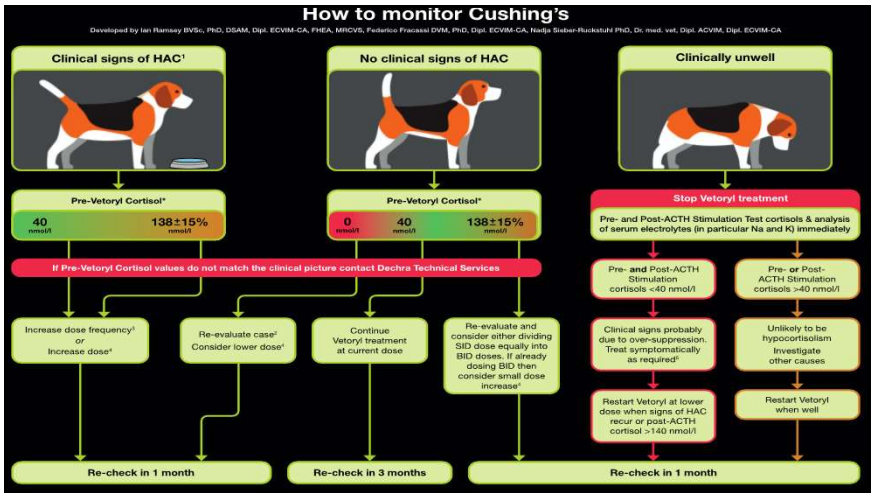


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## Mitotane vs Trilostane

- 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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## 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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## 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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## 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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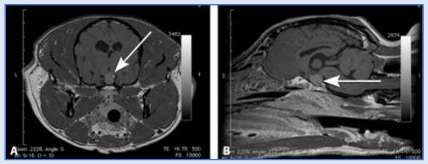
## Surgery: PDH

- 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

- 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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## 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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## 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

JFMS 2021

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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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## Questions?

Remember to
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the webinar control panel.
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Questions about CE?
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Questions about topic?
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Thank you for joining us!



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