Hypoadrenocorticism

Don’t Make A Drama Out Of a Crisis

Yvonne McGrotty

BVMS CertSAM DipECVIM-CA MRCVS

European & RCVS Specialist In Small Animal Internal Medicine

IM Consultant for IDEXX UK

Conflicts of Interest & Disclaimer

- Yvonne McGrotty is an employee of IDEXX Laboratories UK and also an employee of Anicura France.

- *The information contained herein is intended to provide general guidance only. As with any diagnosis or treatment, you should use clinical discretion with each patient based on a complete evaluation of the patient, including history, physical presentation, and complete laboratory data. With respect to any drug therapy or monitoring program, you should refer to product inserts for a complete description of dosages, indications, interactions, and cautions. Diagnosis and treatment decisions are the ultimate responsibility of the primary care veterinarian.*

Hypoadrenocorticism

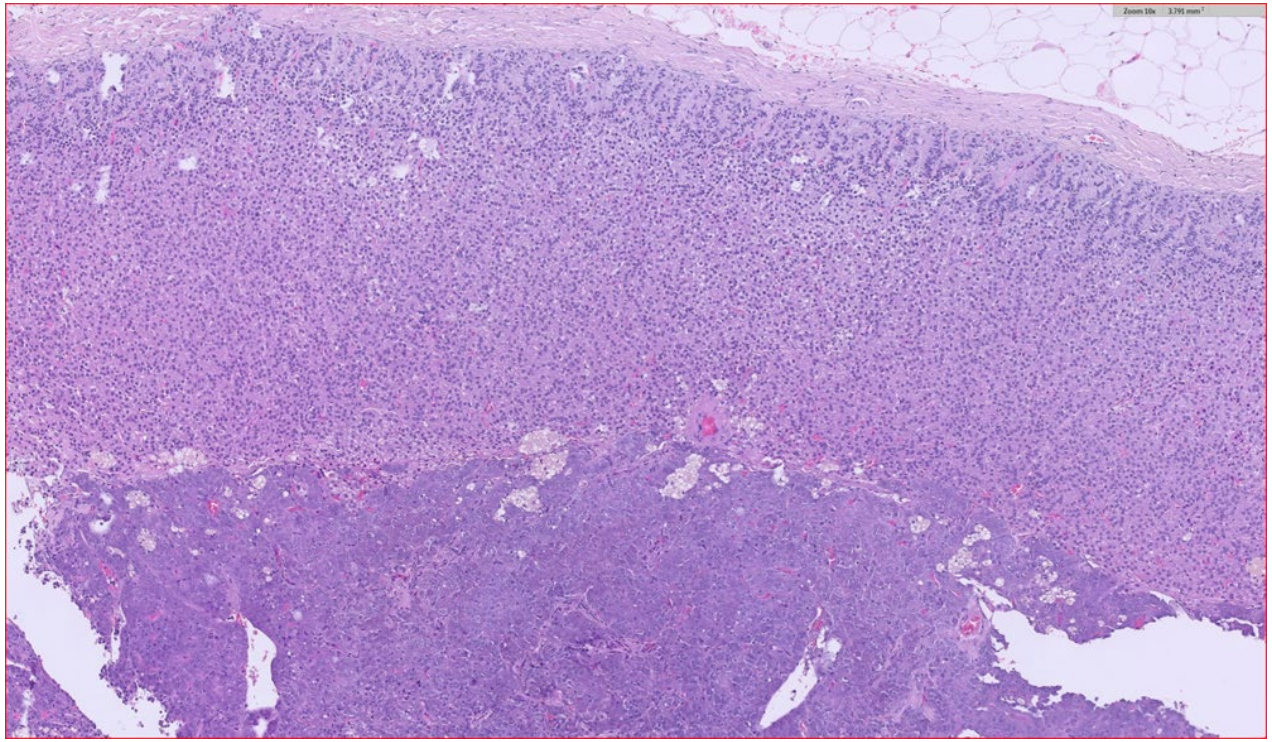
- Uncommon canine endocrinopathy
  - 0.06-0.28%
- Very rare in cats!

- Failure of adrenal glands to secrete
  - Glucocorticoids
  - +/- Mineralocorticoids

Keich W, Lynn R, Smith C, New J., Jr Canine hypoadrenocorticism (Addison's disease) *Compend Cont Educ Pract Vet.* 1998;20:8

Adrenal Glands

- Cortex
  - Zona glomerulosa
    - Mineralocorticoids
  - Zona fasciculata
    - Glucocorticoids
  - Zona reticularis
    - Sex hormones
- Medulla
  - Catecholamines

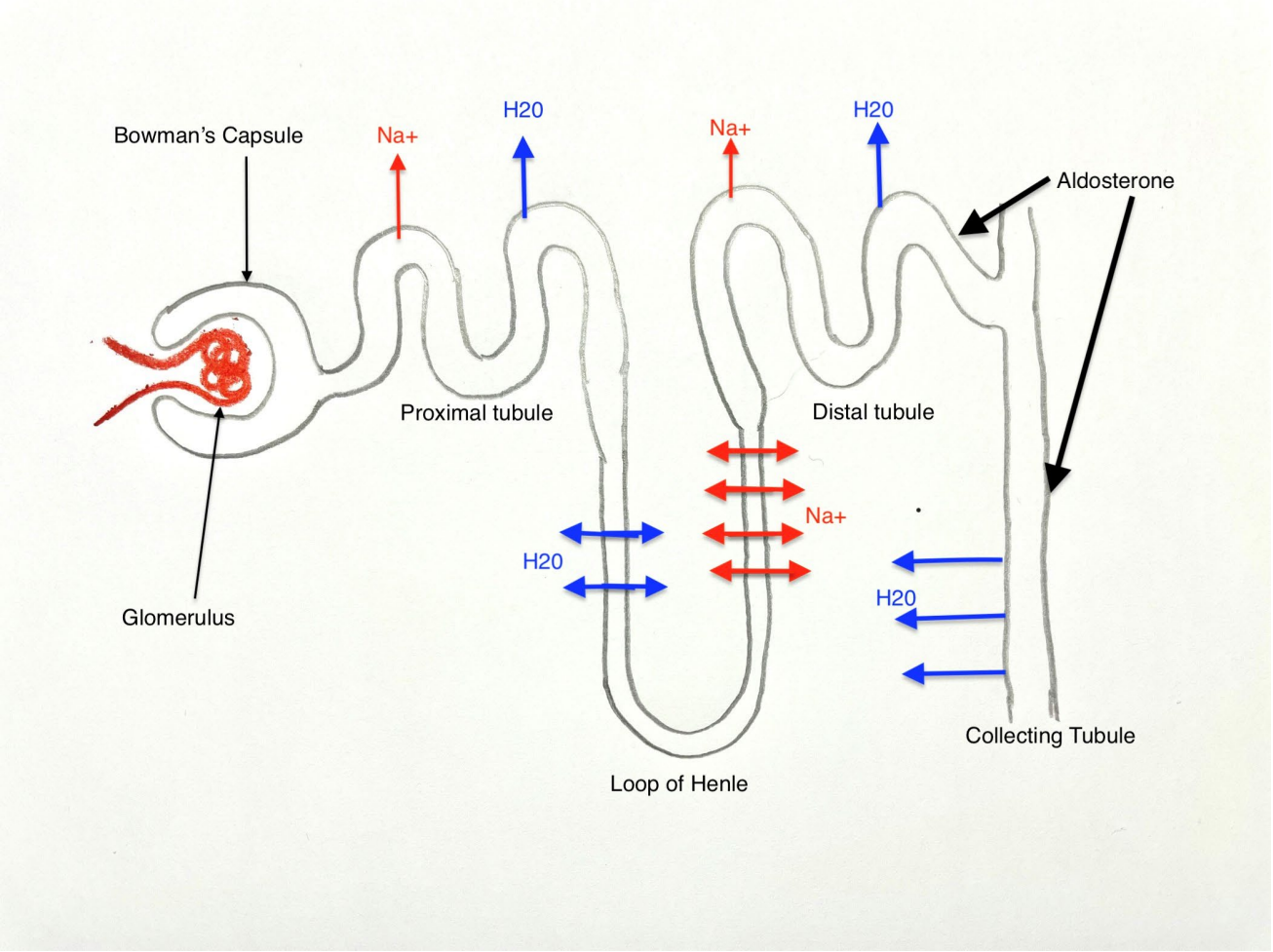


Addison's Disease/Hypoadrenocorticism

- Primary hypoadrenocorticism (hAC)
  - Destruction of adrenal cortex
- Secondary hAC
  - Deficient ACTH production
- Leads to aldosterone and cortisol deficiencies

Aldosterone

- Mineralocorticoid
- Zona glomerulosa of adrenal cortex
- Promotes Na, Cl & water resorption from renal tubules

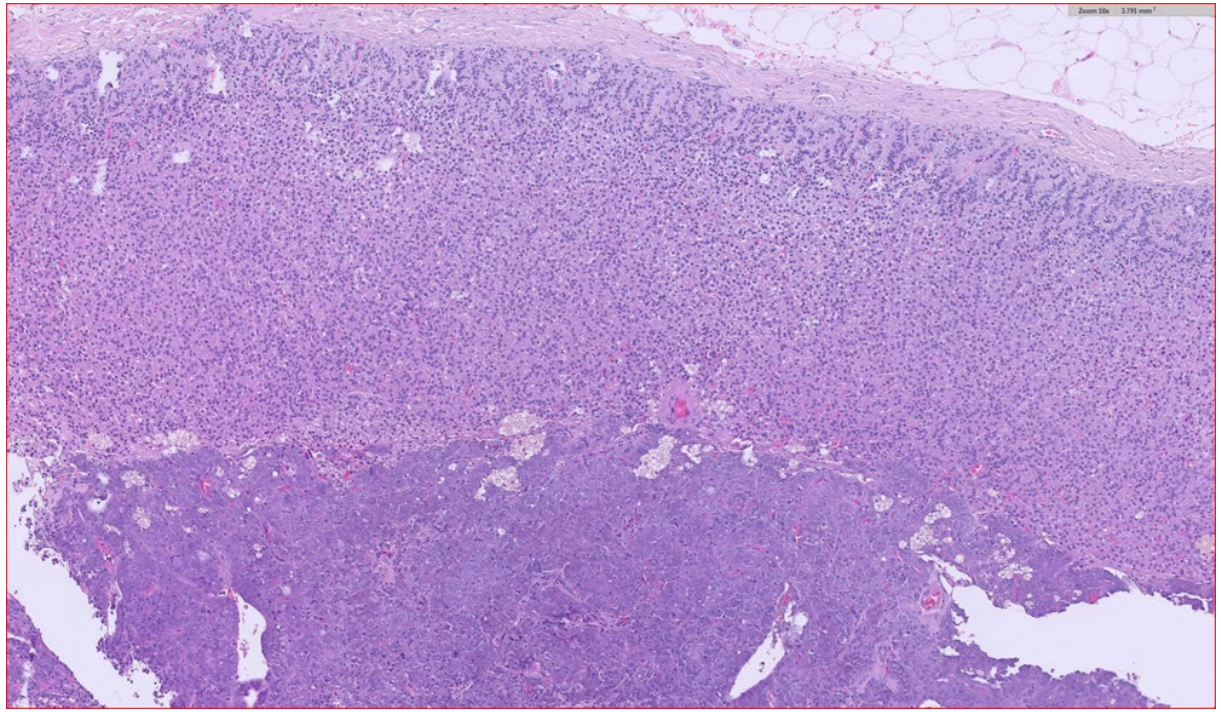


Aldosterone Deficiency

- Sodium wasting (hyponatraemia)
  - Hypotension
  - ↓GFR
  - ↓ cardiac output
- Decreased potassium excretion (hyperkalaemia)
  - Cardiac arrhythmias
  - Bradycardia

Cortisol

- Glucocorticoid
- Zona fasciculata & reticularis of adrenal cortex
- Promotes gluconeogenesis
- Important for integrity of GI tract

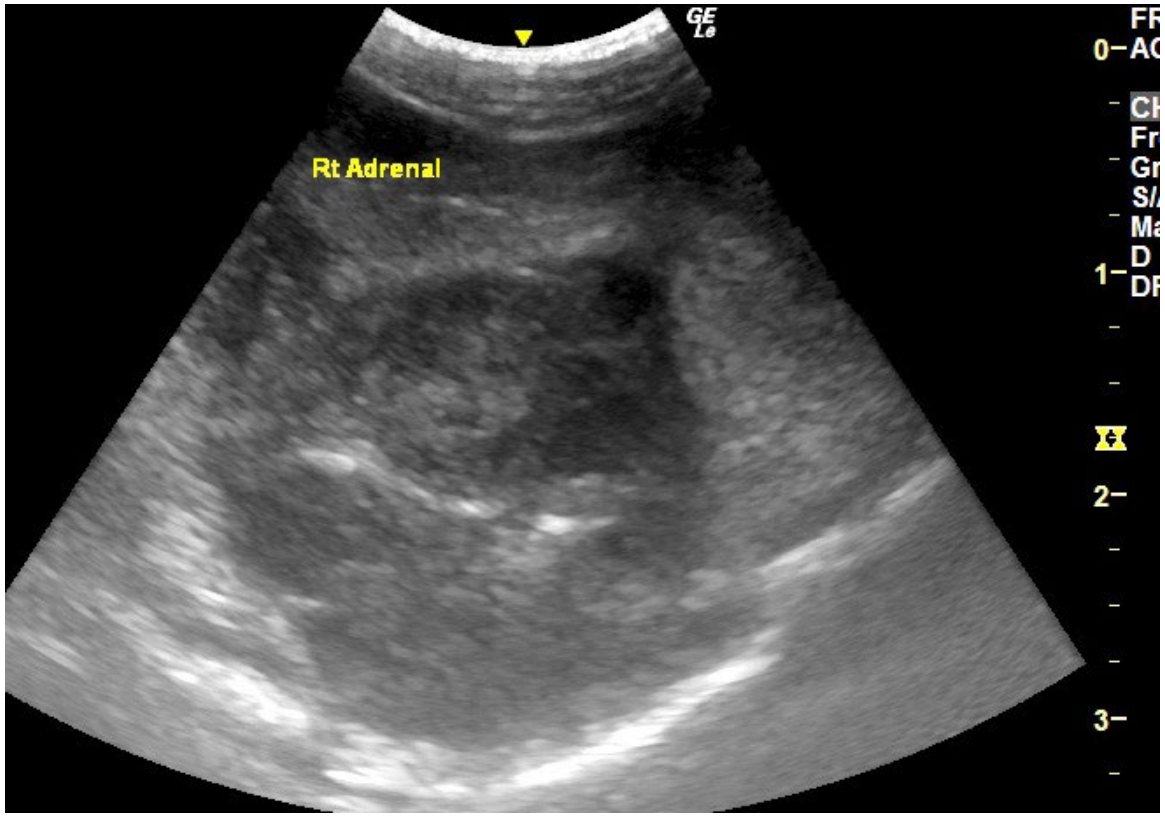


Cortisol Deficiency

- Gastrointestinal signs
  - Anorexia
  - Vomiting
  - Abdominal pain
- Non-regenerative anaemia
- Hypoglycaemia

Primary Hypoadrenocorticism

- Immune-mediated adrenal destruction
- Adrenal neoplasia
- Adrenal haemorrhage
- Adrenal necrosis
- Iatrogenic
  - Mitotane
  - Trilostane



Eunatraemic, eukalaemic (Atypical) Hypoadrenocorticism

- <10% cases
- Initially electrolytes within reference range
- May reflect gradual/selective destruction
  - Corticosteroid-secreting layer affected first
  - Electrolyte changes may develop over time

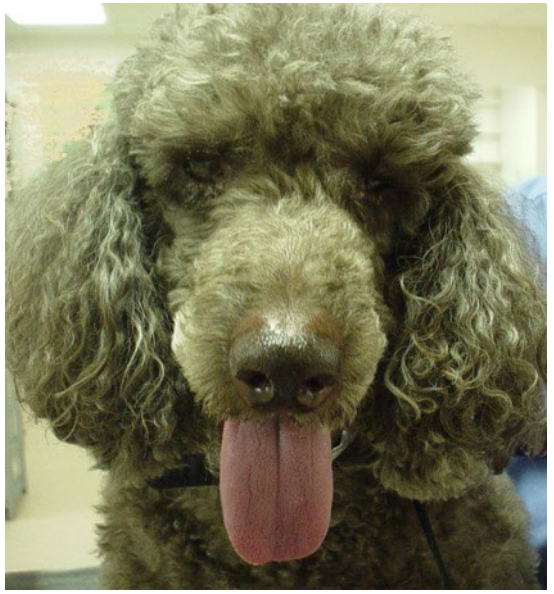
Klein SC, Peterson ME. Canine hypoadrenocorticism: part I. Can Vet J. 2010 Jan;51(1):63-9. PMID: 20357943; PMCID: PMC2797351.

Secondary Hypoadrenocorticism

- Failure of ACTH secretion from the pituitary gland
  - Head trauma
  - Neoplasia
  - Only causes glucocorticoid deficiency
- Iatrogenic
  - Abrupt cessation of chronic steroid therapy
    - Adrenal glands atrophied
  - Bilateral adrenalectomy

Signalment

- Can affect any age group
  - Young to middle-aged dogs most affected
  - Reported in dogs from 2 months – 14 years
  - Average age 3-4yrs
  - Dogs with glucocorticoid deficiency alone sl. older (6-8yrs)
- Standard Poodles, Portuguese water dogs, Nova Scotia Retrievers, Soft Coated Wheaten Terrier, Beardies
  - WHWT, Great Dane, Rottweiler
- Females most commonly affected??
- Very rare in cats (<50 reported)



Chronic Presentation

- Lethargy
- Anorexia
- Vomiting
- Diarrhoea
- Weight loss

- PUPD
  - Due to mineralocorticoid deficiency

Acute Presentation

- Collapse
- Weak pulses
- Hypotension
- Inappropriate bradycardia
- Muscle weakness
- Abdominal pain
- Hypovolaemic shock

First Steps

- Wide bore IV cannula
- Minimum database
  - PCV/TS
  - Glucose
- Electrolytes
- CBC & biochemisty
- ECG?

Haematological Changes

+ Eosinophilia/lack of eosinopenia
+ Lymphocytosis/ lack of lymphopenia
+ Mild non-regenerative anaemia

+ Lack of a stress leukogram in a sick animal should be considered suspicious!

Biochemical Changes #1

- Hyperkalaemia (in >80% of primary cases)
  - Doesn't occur in secondary hypoadrenocorticism
  - Doesn't occur in atypical cases
- Hyponatraemia (in >80% of primary cases)
  - Na:K usually <23
- Hypochloraemia (40-60% cases)
- Increased creatininine (up to 66%)
  - Usually pre-renal but urine specific gravity may not reflect this

Melian C, Peterson ME. Diagnosis and treatment of naturally occurring hypoadrenocorticism in 42 dogs. *J Small Anim Pract.* 1996;37(6):268–275. doi: 10.1111/j.1748-5827.1996.tb02377.x. Klein SC, Peterson ME. Canine hypoadrenocorticism: part I. *Can Vet J.* 2010;51(1):63–69.

Electrolyte Abnormalities

Sodium	132	144 - 160 mmol/L	
Potassium	9.8	3.5 - 5.8 mmol/L	
Na:K Ratio	13		
Chloride	101	109 - 122 mmol/L	

Biochemical Changes #2

- Hyperphosphataemia (up to 58%)
- Hypercalcaemia (up to 30%)
  - Total calcium, but less commonly iCa
- Hypoglycaemia (up to 33% cases)
  - Decreased gluconeogenesis
- Metabolic acidosis (60% cases)
- Hypoalbuminaemia
  - More common with glucocorticoid deficiency alone
  - GI losses, haemorrhage

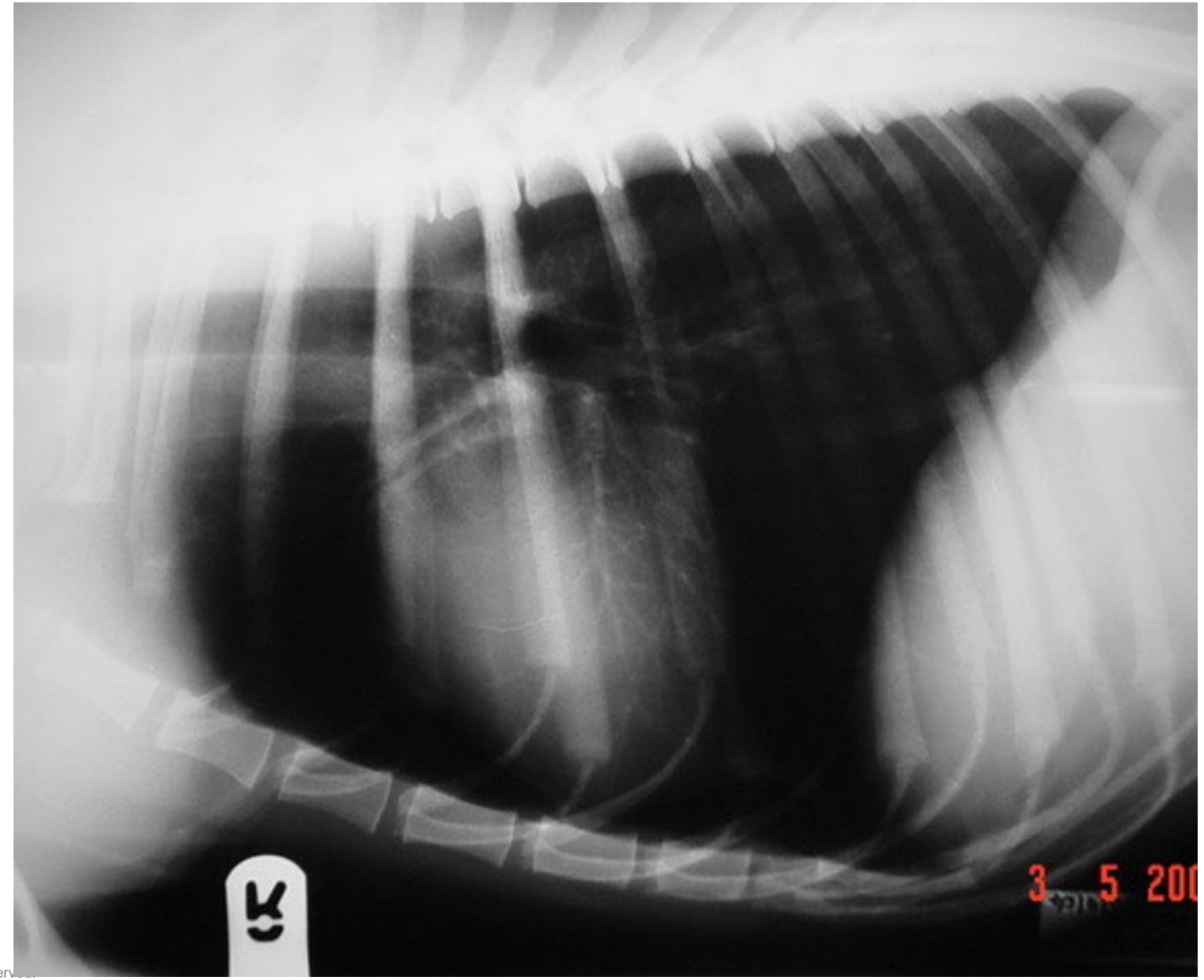
IDEXX SDMA Learn More	18	1 - 14 µg/dL
Creatinine	194	20 - 144.5 µmol/L
Urea	30.2	3.1 - 10.1 mmol/L
Phosphorus	2.51	0.80 - 1.60 mmol/L
Calcium	2.96	2.36 - 2.84 mmol/L

Klein SC, Peterson ME. Canine hypoadrenocorticism: part I. *Can Vet J.* 2010;51(1):63–69.

Differential Diagnoses

+ Hypoadrenocorticism (Addison's disease)
+ Renal failure
+ Severe haemorrhagic gastroenteritis
+ Obstructive uropathy
+ Uroabdomen
+ *Trichuris* infection

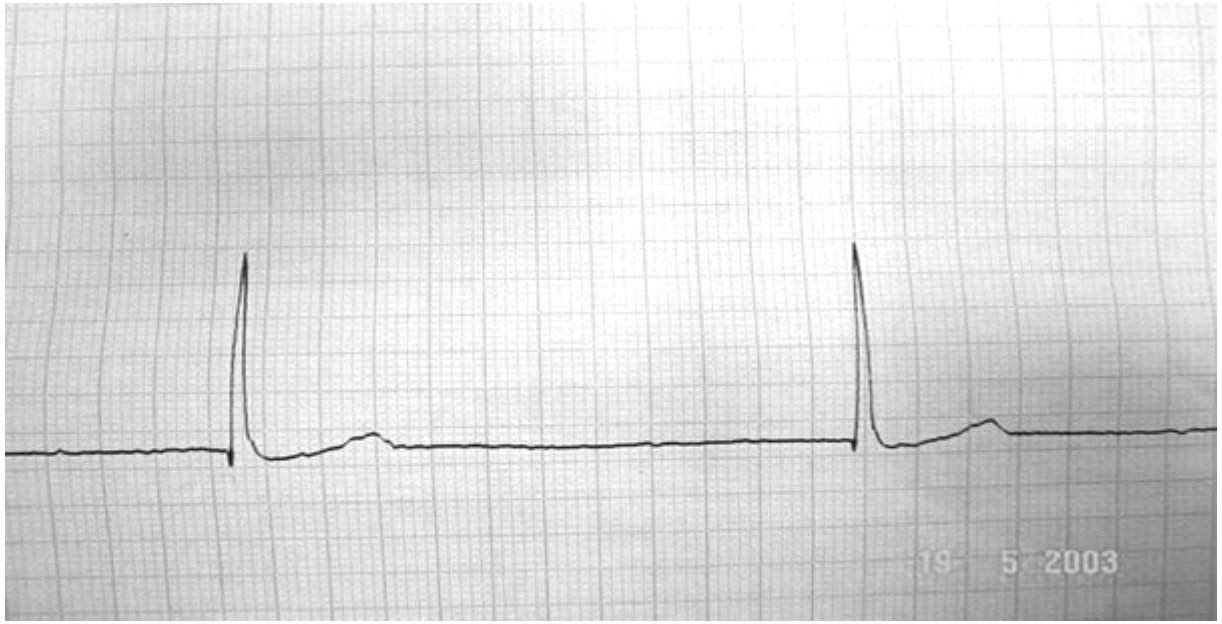
Radiographic Changes



ECG Abnormalities

- Due to hyperkalaemia

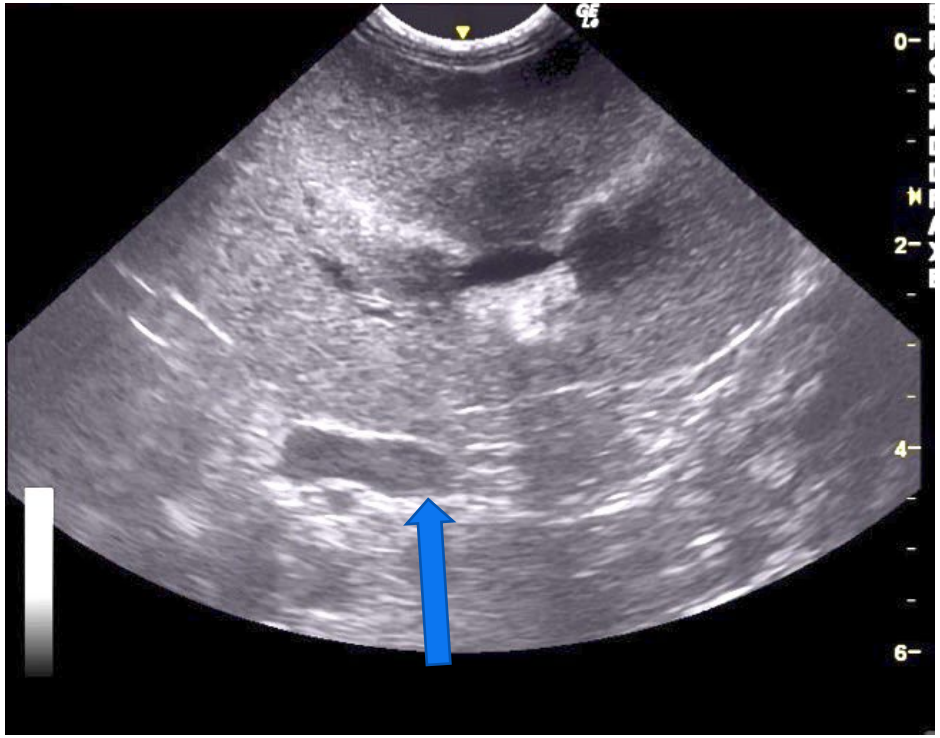
- >5.5mmol/l
- spiked T waves, shortened QT
- >6.5mmol/l
  - increased QRS duration
- >7.0mmol/l
  - decreased P wave amplitude
- >8.0mmol/l
  - atrial standstill



Atkins CE. Cardiac manifestations of systemic and metabolic disease. In: Fox PR, Sisson D, Moise NS, editors. *Textbook of Canine and Feline Cardiology.* 2nd ed. Philadelphia: WB Saunders; 1999. pp. 757–780.

Ultrasound Changes

- Thinner adrenal glands than healthy controls
- L adrenal <2.8mm thick is suggestive
- Left adrenal significantly shorter than those of healthy dogs



Vet Record

Paper

Ultrasonographic evaluation of adrenal glands in dogs with primary hypoadrenocorticism or mimicking diseases

M. Wenger MedVet, DipACVIM, C. Mueller MedVet, DipACVIM, P. H. Kook MedVet, DipACVIM, C. E. Reusch MedVet, DipECVIM-CA

First published: 07 August 2010 | https://doi.org/10.1136/vr.c4235 | Citations: 40

IDEXX

Basal Cortisol

- Basal cortisol > 55nmol/L generally excludes hypoadrenocorticism
  - Good screening test but low specificity

- Basal cortisol <55nmol/L still requires ACTH stim test to confirm or exclude

J Vet Intern Med. 2014 Sep-Oct; 28(5): 1541–1545.
Published online 2014 Jul 28. doi: 10.1111/jvim.12415
PMC

Basal Serum Cortisol Concentration as a Screening Test for Hypoadrenocorticism in Dogs

C. Bovens,[1,2,4] K. Tennant,[3] J. Reeve,[1,2] and K.F. Murphy[1,2,5]

ACTH Stimulation Test

- Perform BEFORE steroid administration!
  - Dexamethasone does not cross react at laboratory (single dose)

- Collect basal serum sample
- Tetracosactide IV (5µg/kg)
- Collect further sample 1hr later
- Measure cortisol on both samples

ENDOCRINOLOGY

ALERT	TEST	RESULT	UNITS	REF.INTERVAL
Low	*Cortisol - Baseline	<10.0	nmol/L	25.0 - 125.0
Low	*Cortisol - Post ACTH	<10.0	nmol/L	125.0 - 520.0

Pre- and Post ACTH Aldosterone

- ACTH stim
  - Measure aldosterone on both pre- and post samples
- Differentiates primary from secondary hypoadrenocorticism
- Differentiates glucocorticoid deficient hAC from mineralocorticoid deficient hAC
- Aldosterone levels low in dogs with mineralocorticoid deficiency
  - Minority of dogs had ref level aldosterone where electrolyte abnormalities present
- Indicates the need for mineralocorticoid supplementation
  - Even in those cases with no electrolyte abnormalities

Primary versus Secondary Hypoadrenorticism

- Endogenous ACTH (eACTH) measurement
  - Primary hAC = high levels of eACTH
  - Atypical hAC = high levels of eACTH
  - Secondary hAC = low levels of eACTH
- NB: Strict sample handling requirements!
- Samples must be collected before steroids
- Relevance?

What if I've already given steroids?

	Cortisol (nmol/L)	Aldosterone (pmol/L)
Pre ACTH	<10	<20
Post ACTH	<10	<20

Consistent with primary hypoadrenocorticism (even after steroid administration) and indicates need for mineralocorticoid administration

	Cortisol (nmol/L)	Aldosterone (pmol/L)
Pre ACTH	<10	Normal
Post ACTH	<10	Normal

Consistent with steroid administration (including topicals) or secondary (pituitary) hypoadrenocorticism

Acute Therapy

1. Restore circulating volume
2. Treat hyperkalaemia
3. Glucocorticoid supplementation
4. Mineralocorticoid supplementation
5. Treat GI haemorrhage & other problems

1. Fluids

- 0.9 % NaCl
  - Fluid of choice ?
  - Highest Na content
- Care in patients with cardiovascular disease
- Monitor sodium levels
  - Rapid correction can cause neuro signs
  - Don’t increase Na by >10mEq/L in 24hrs

Fluid Requirements

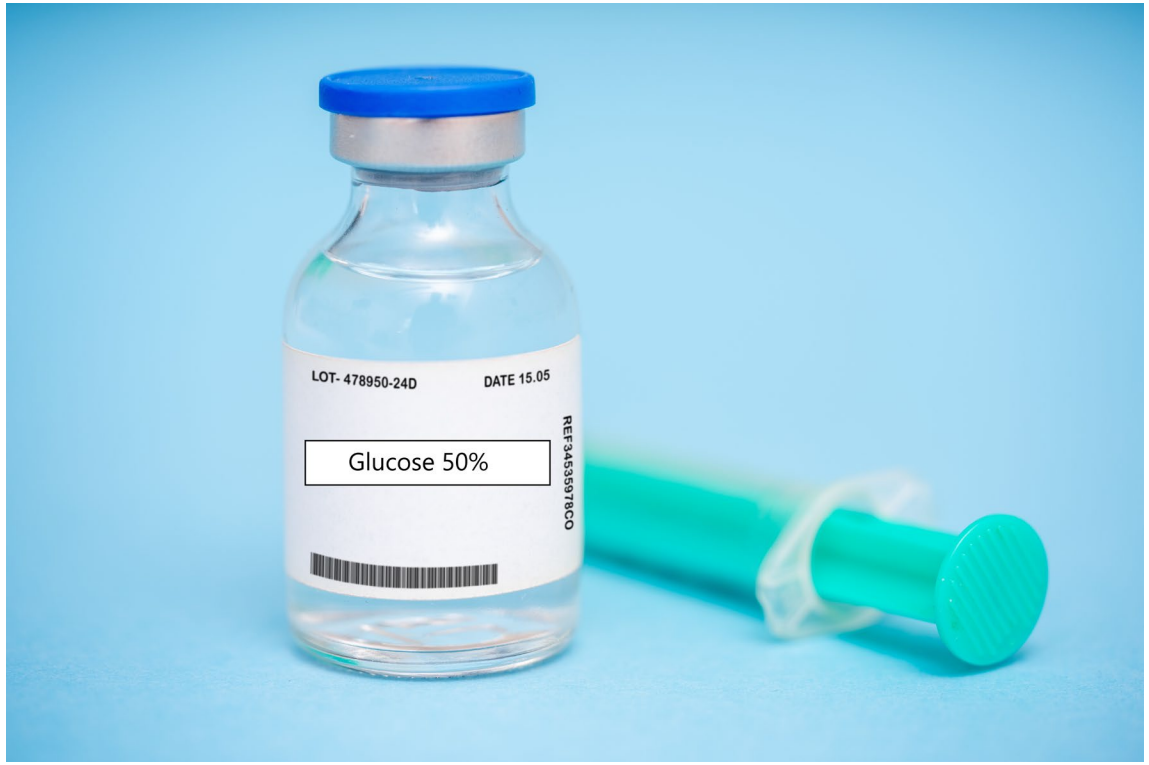
+ Fluid deficit = % dehydration x Bwt (kg) x 1000
+ Replace deficits over 2-6hrs
+ Use fluid boluses then reassess- preferred option!

+ Continue IVFT at 4-6ml/kg/hr until azotaemia has resolved & electrolytes normalised

2. Hyperkalaemia

+ Fluid therapy
    + Increases glomerular filtration rate
    + Promotes potassium excretion
    + May be all that's required to reduce K

+ 50% glucose
    + 0.5-1ml/kg diluted in the same volume of NaCL
    + Drives potassium intracellularly
    + Corrects hypoglycaemia if this is also present



Koenig A. Hypoglycemia. In: Hopper KH, Silverstein DC, editors. *Small Animal Critical Care Medicine.* 1st ed. St Louis, Missouri: Saunders Elsevier; 2009. pp. 295–298

Hyperkalaemia

- 10% Calcium gluconate
  - 0.5-1.5ml/kg iv over 20mins*
  - Antagonises myocardial effects of hyperK
  - Monitor ECG
  - **Does not lower potassium**

*BSAVA Small Animal Formulary 11th Edition

Hyperkalaemia

- Insulin
  - Soluble/Neutral insulin
  - 0.5 units/kg IV
  - Give glucose bolus
    - 2-3 g/U of insulin divided into 2 aliquots, the first given at the time of insulin injection and the rest over 6-8hrs
  - Monitor glucose hourly
  - Dogs with hAC v sensitive to insulin

3. Glucocorticoids

- Dexamethasone
  - 0.2 mg/kg i/v*
- Inject slowly!
- Continue 12-24hr until oral steroids can be given
- Single dose doesn't cross-react with cortisol assay at IDEXX ref lab (NB: will cross react on SNAP Cortisol)

*BSAVA Small Animal Formulary 11th Edition

4. Mineralocorticoids

- Desoxycortone pivalate (DOCP)
- 1.5- 2.2mg/kg s/c q28d
- NOT rapid-acting
- Only use once rehydrated

*BSAVA Small Animal Formulary 11th Edition

5. Treat additional problems

- Hypoglycaemia
  - Dextrose 2.5%
    - Add 50mls to 1 litre NaCl
    - (Remove 50mls NaCl before adding)
  - Dextrose 5%
    - Add 100mls to 1 litre NaCl
    - (Remove 100mls NaCl before adding)
- GI haemorrhage
  - Proton pump inhibitors?
  - Gut protectants

Chronic Therapy

- DOCP
- Inject s/c q 25-30 days
  - Starting dose 1.5- 2.2mg/kg
  - Titrate to effect
  - Dose range can be between 1.0-2.7mg/kg
- Try to maintain dosing interval at q25-30 days
- Adjust dose accordingly

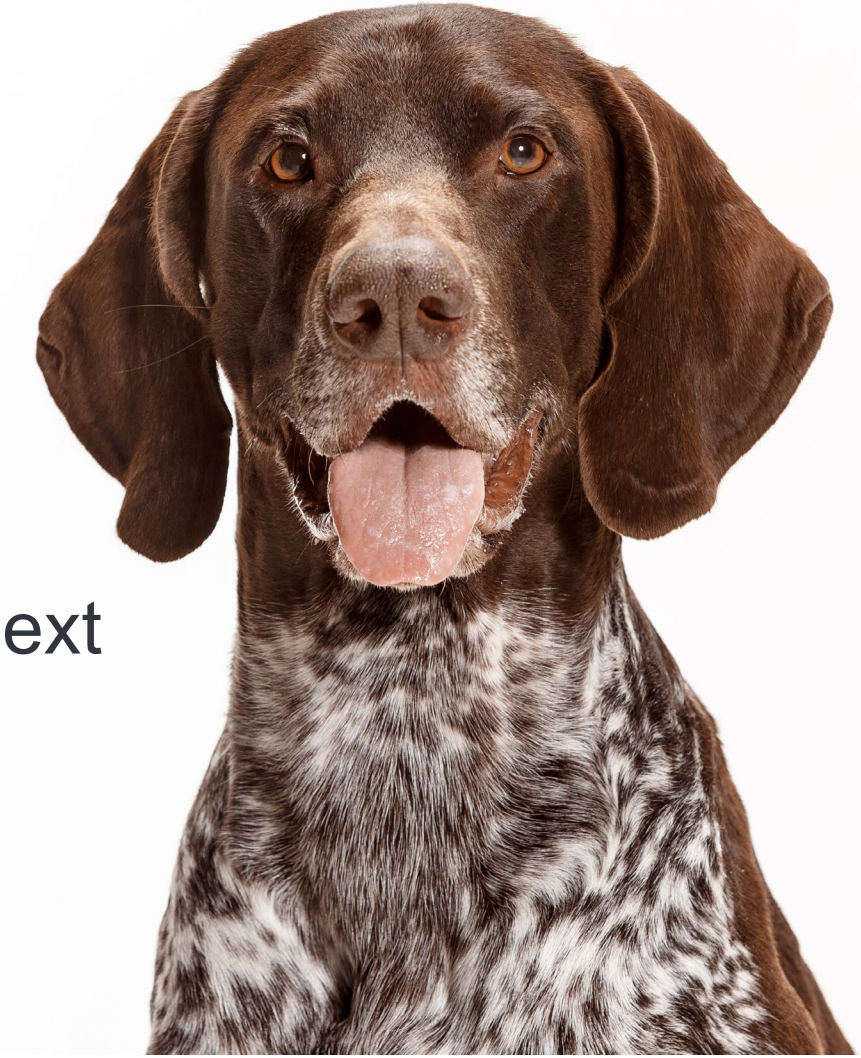
BSAVA Small Animal Formulary 11th Edition

Goals of Therapy

- Day 10 : K^+ in lower third of ref interval
- Pre-injection: K^+ in upper third of ref interval
- If pre-injection the dog has K levels in the lower end of the ref interval, then the dose can be prolonged
  - Check electrolytes q 5-9days until Na/K ratio is <32

Monitoring Response

- Day 10: check electrolytes
  - Time of peak effect
  - Assesses if dose is adequate
- Day 25-30: Check electrolytes before next injection
  - Assesses duration of drug effect



Adjusting the Dose

SMALL ANIMALS

Lower initial dose desoxycorticosterone pivalate for treatment of canine primary hypoadrenocorticism

JA Bates, S Shott ✉, WD Schall

First published: 26 February 2013 Full publication history

If the Day 10 Na^+/K^+ ratio is:		25 days after the first dose, administer Zycortal, as follows:
≥ 34	Do not administer Dose 2 on Day 10.	Decrease dose to: 2.0 mg/kg body weight
32 to < 34		Decrease dose to: 2.1 mg/kg body weight
27 to < 32		Continue 2.2 mg/kg body weight
≥ 24 to < 27		Increase dose to: 2.3 mg/kg body weight
< 24		Increase dose to: 2.4 mg/kg body weight

IDEXX

Chronic Therapy #2

- Fludrocortisone
  - 0.01mg/kg PO q12h*
- Mineralocorticoid & glucocorticoid activity
- Tolerance may develop after several months
- Lifelong therapy

*BSAVA Small Animal Formulary 11th Edition

Adverse Reactions to Zycortal

+ Polyuria (15%)
+ Polydipsia (13.3%)
+ Lethargy (9.7%)
+ Inappropriate urination (8.0%)
+ Alopecia (5.3%)
+ Decreased appetite (4.4%)
+ Panting (3.5%)
+ Vomiting (3.5%)

+ Injection site reactions also reported

https://www.dechra-us.com/Files/Files/SupportMaterialDownloads/US/01TB-ZYC21008-0421-Zycortal-Technical-Detailer_FINAL.pdf.
Downloaded 26/9/23

Chronic Therapy #2

- Prednisolone
  - 0.2-0.5mg/kg/day
- Daily pred required if receiving DOCP
- Only Tx required in secondary hAC

BSAVA Small Animal Formulary 11th Edition

Monitoring

- ACTH stimulation can NOT be used
  - Drugs cross react with assay!
  - Results not expected to improve with treatment!
- Electrolytes
- Renal parameters
- Clinical signs

Prognosis

- Very good assuming quick diagnosis and treatment initiated rapidly

- Lifelong therapy
- Risk of further crises at times of stress/illness