

Common Mistakes in Endocrine Disease - and how to avoid them!

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November 2026

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- 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.*

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Common mistakes #1:

- Running tests for Cushing’s syndrome on a dog without supportive clinical signs

The First Rule of ~~Fight~~ Endocrine Club

Endocrine tests should ONLY be performed when clinical signs are supportive!

Testing a sick dog for HAC is inappropriate

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Cushing's Syndrome -Signalment

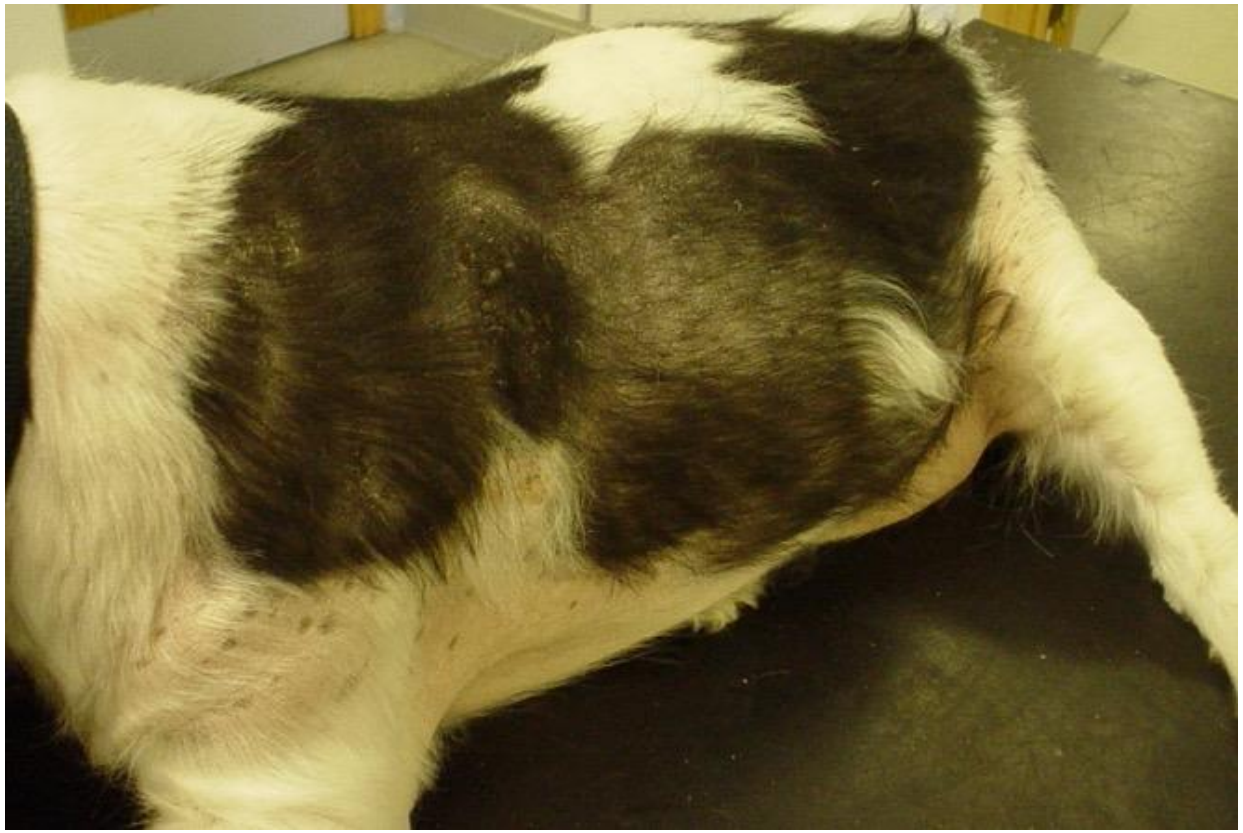
- Any breed
  - Border Terriers, Bichon Frise, Std. Schnauzer, Min. poodle, Boxer, Dachshund
  - Adrenal tumours more common in large breed dogs
  - PDH more common in smaller dogs <20kg
- Middle-aged to old
  - Median age is 10 years
  - Almost all dogs >6yrs
  - Dogs with ADH tend to be older (11.3yrs)
- Female neutered slightly more predisposed



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Clinical Signs

- PUPD (80-90% cases)
  - Interferes with ADH action
  - Acquired nephrogenic DI
- Polyphagia
- Panting
- Pot belly
- Symmetrical truncal alopecia
- Comedones
- Hepatomegaly



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Polydipsia/Polydipsia

- Normal H_2O intake
  - 40-60mls/kg/day
- Polydipsia
  - >100 mls/kg/day in dogs
- Don’t test for hypercortisolism in patients that aren’t PUPD
- Urine SG <1.020



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Common mistakes #2:

Running endocrine tests without having performed baseline haematology, biochemistry and urinalysis

What do you need to confirm Cushing's syndrome?

- Clinical signs!
  - PUPD
- Supportive clin path results
- Urinalysis confirming dilute urine
- Only then can you choose a more specific confirmatory test



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Diagnostic Approach

- History (including drug therapies)
- Quantify water intake accurately
  - Confirm PUPD

- Physical examination
- Urinalysis
- Haematology/biochemistry
- Specific endocrine tests
- Imaging

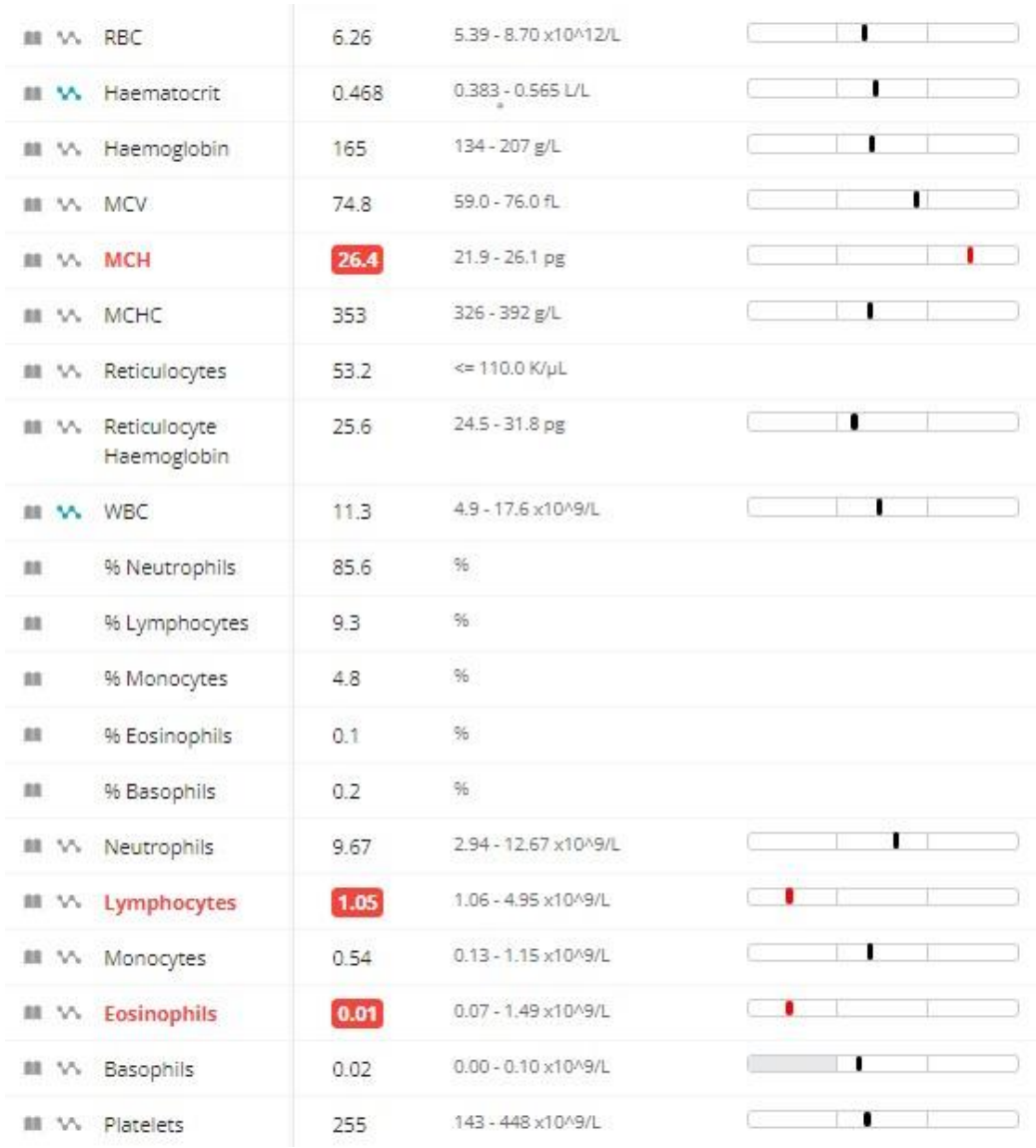


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Common Haematological Changes

+ Most cases have
  + Eosinopenia
  + Lymphopenia
  + Neutrophilia

+ Less common changes
  + Erythrocytosis
  + Thrombocytosis



RBC	6.26	5.39 - 8.70 x10^12/L
Haematocrit	0.468	0.383 - 0.565 L/L
Haemoglobin	165	134 - 207 g/L
MCV	74.8	59.0 - 76.0 fL
MCH	26.4	21.9 - 26.1 pg
MCHC	353	326 - 392 g/L
Reticulocytes	53.2	<= 110.0 K/µL
Reticulocyte Haemoglobin	25.6	24.5 - 31.8 pg
WBC	11.3	4.9 - 17.6 x10^9/L
% Neutrophils	85.6	%
% Lymphocytes	9.3	%
% Monocytes	4.8	%
% Eosinophils	0.1	%
% Basophils	0.2	%
Neutrophils	9.67	2.94 - 12.67 x10^9/L
Lymphocytes	1.05	1.06 - 4.95 x10^9/L
Monocytes	0.54	0.13 - 1.15 x10^9/L
Eosinophils	0.01	0.07 - 1.49 x10^9/L
Basophils	0.02	0.00 - 0.10 x10^9/L
Platelets	255	143 - 448 x10^9/L

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Biochemical Changes

- Increased ALT
  - Swollen hepatocytes, glycogen accumulation
  - Mild to moderate increase
- Disproportionate increase in ALP
  - >90% of cases
- Increased albumin?
- Increased lipids
  - Noted in >50% dogs with HAC

Glucose	5.6	3.6 - 7.0 mmol/L
IDEXX SDMA	10	1 - 14 µg/dL
Creatinine	46.0	44.0 - 133.0 µmol/L
Sodium	152.8	135.0 - 155.0 mmol/L
Potassium	4.41	3.60 - 5.60 mmol/L
Na: K Ratio	34.65	28.80 - 40.00
Chloride	105.8	100.0 - 116.0 mmol/L
ALT	374.7	19.8 - 124.0 U/L
ALP	730.0	<= 130.0 U/L



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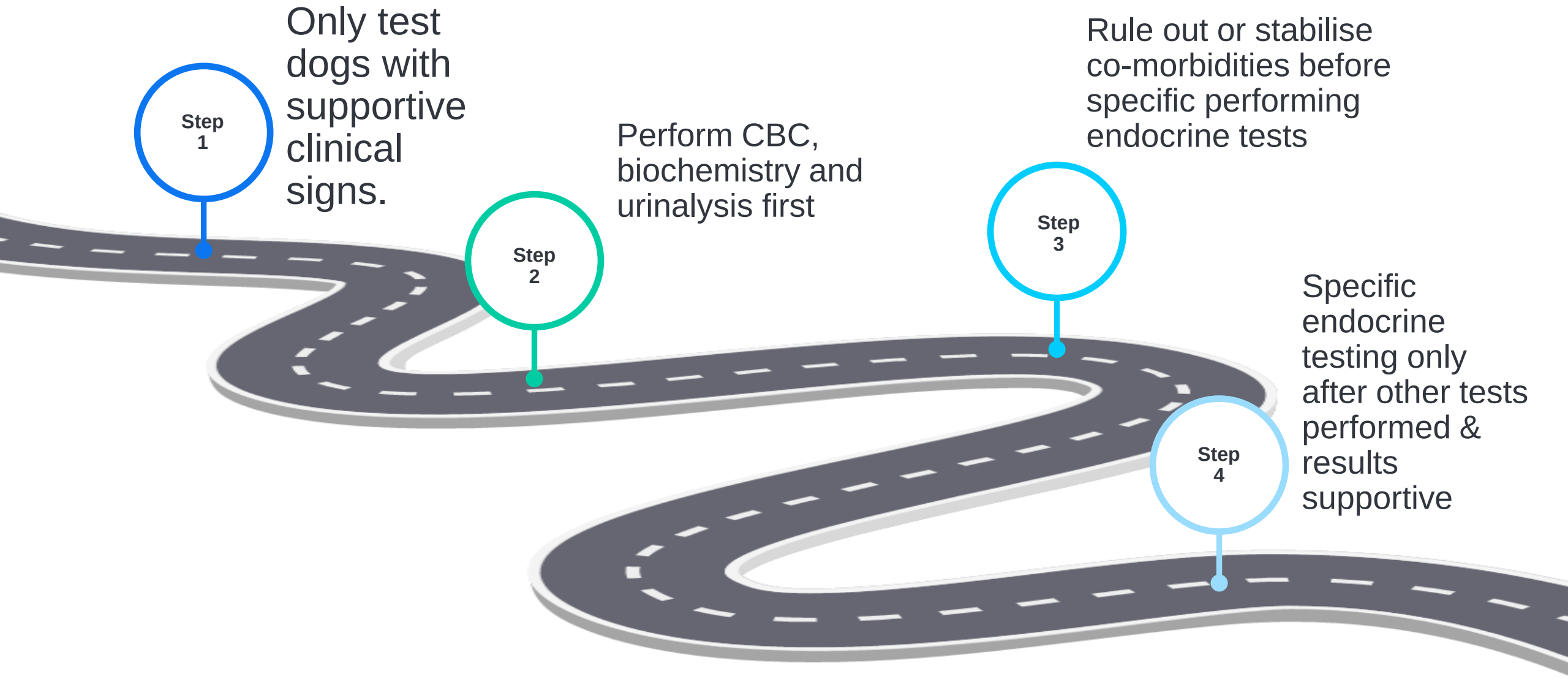
Urinary Changes



- SG <1.020
- UTIs common
  - 50% cases at time of Dx
  - Incomplete voiding
  - Inactive sediment
- UPCR increased
  - 45% cases
  - Usually <3.0
  - May persist despite treatement

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Cushing’s Syndrome- Testing Pathway



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Key Point

+

+Further tests for HAC only indicated once these tests have been performed!

+

And only if **Cx** are supportive

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Common mistakes #3:

- Using basal cortisol to diagnose Cushing’s syndrome?



Basal Cortisol- No!

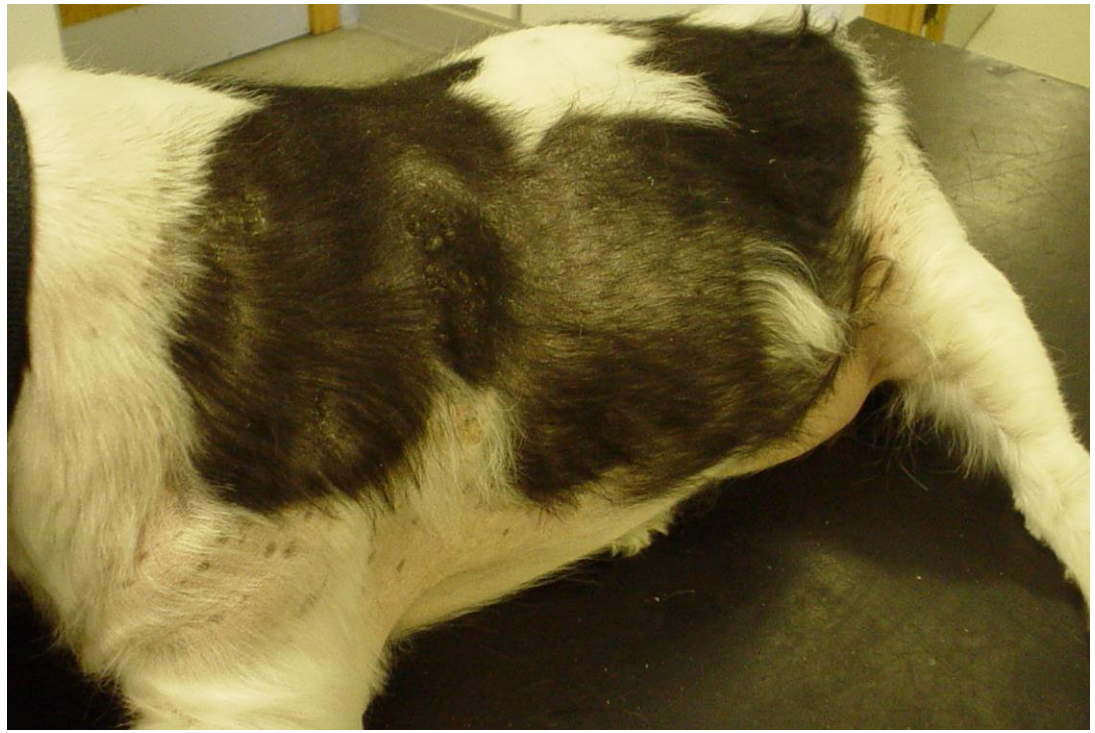
- Not useful for the diagnosis of Cushing’s syndrome!
- Episodic secretion
- Fluctuates widely
- Significant overlap with normal animals

Common mistakes #4:

- Using an ACTH stim test to ‘rule out’ Cushing’s syndrome

Does a normal ACTH stim rule out Cushing's syndrome?- No

- Clinical history!
  - Signalment
  - If PUPD is **not** present, then very unlikely to be Cushing's syndrome
- 'Screening' Tests
  - UCCR
  - Low dose dexamethasone suppression test



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ACTH Stimulation Test

- Not all dogs with hypercortisolism will test positive on ACTH stim
  - Only around 50% of dogs with ADH test positive
  - Around 80% of dogs with PDH test positive
- False negatives
  - Follow up with LDDST if HC still seems clinically likely
- False positives
  - Stress of non-adrenal illness (up to 14%)

Cortisol - Baseline	149.0	25.0 - 125.0 nmol/L	
Cortisol - Post ACTH	803.0	125.0 - 520.0 nmol/L	

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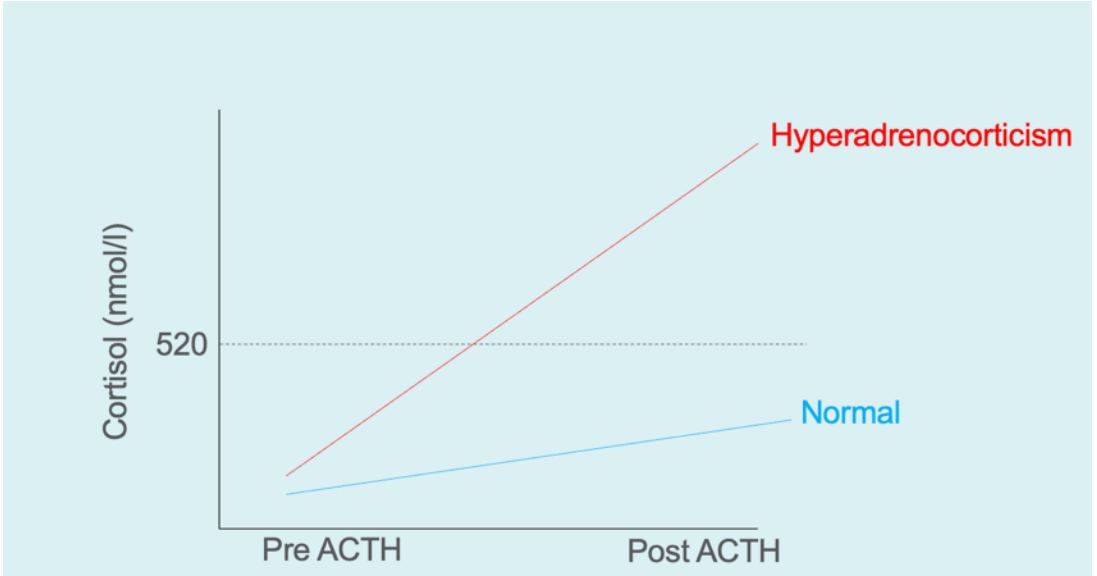
ACTH Stimulation Test Protocol

- Fast for 12hrs
- Sample for basal cortisol
- Inject tetracosactide (Cosacthen)
  - 5ug/kg IV
- Obtain 2nd sample 1hr later
- Measure cortisol on both samples



How Does ACTH Stimulation Test work?

- Indirectly gauges degree of adrenocortical thickness
- Dogs with hypercortisolism have increased thickness of adrenal cortex and have an exaggerated response to ACTH
- Dogs with iatrogenic hypercortisolism have blunted response



Courtesy of Stephen Jordan

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Advantages & Disadvantages of ACTH Stim Test

Advantages

- Quick and simple to perform
- Differentiates spontaneous from iatrogenic hypercortisolism
- Baseline information for therapeutic monitoring (trilostane/mitotane)

Disadvantages

- Poor sensitivity
- False negatives (especially with ADH)
- False positives (non-adrenal illness)
- Doesn’t discriminate between PDH and ADH

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Common mistake #5:

-Testing UCCR on sample collected at practice



Urine Cortisol:Creatinine (UCCR)

- Good screening test (rules out HC)
- Urine MUST be collected by owner at home
- False positives common
- Non-specific
- Positive result MUST be followed up by more specific testing

Common mistakes #6:

-Thinking there is there a ‘best’ test for Cushing’s syndrome?

Advantages & Disadvantages of LDDS

Advantages

- Good screening test
  - 90-95% dogs with PDH test positive
  - Almost 100% ADH
- May confirm PDH
  - Suppression at 3-4hrs

Disadvantages

- Low specificity
  - Especially in sick dogs (40-50%)
  - More likely to produce false positives
- Takes longer to perform (8hrs)

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Comparison of Tests- Neither test is perfect!

ACTH Stim

- Quick test (1hr)
- Low sensitivity
  - High rate of false negatives
- Moderate risk of false positives
  - Especially diabetes mellitus
- Tests for iatrogenic hypercortisolism

LDDS Test

- Long test (8hrs)
- High sensitivity
  - Low rate of false negatives
- Lower specificity
  - Risk of false positives
- Does not test for iatrogenic hypercortisolism

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Common mistake #7:

-Testing for Cushing’s syndrome just because pre-anaesthetic blood tests for routine dental work show increased ALP

Screening blood tests show increased ALP

- No dog has ever died of an increased ALP
- Only perform tests for hypercortisolism if there are supportive clinical signs
- Consider also
  - Benign nodular regeneration of the liver
    - Very common in older dogs
  - Gall bladder disease/mucocoele



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Common mistakes #8:

-Sedating a dog during testing for Cushing’s syndrome

Can I sedate a dog before running an ACTH stim or LDDS test?

+ Best to avoid sedation

+ Trazodone decreases cortisol levels in healthy dogs



J Vet Intern Med. 2024 Jan-Feb; 38(1): 130–134.
Published online 2023 Nov 15. doi: 10.1111/jvim.16935
PMCID: PMC10800203
PMID: 37965773

The impact of single-dose trazodone administration on plasma endogenous adrenocorticotropic hormone and serum cortisol concentrations in healthy dogs

Morgan Brown,[1] Tekla Lee-Fowler,[1] Ellen N. Behrend,[1] and Megan Grobman[1,2]

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Common mistake #9:

-Performing multiple other tests during LDDS test

Low Dose Dexamethasone (LDDS) Test Protocol

- Fast the patient for 12 hours
- Sample for basal cortisol (T=0)
- Inject dexamethasone (0.015mg/kg) IV
- Sample for cortisol at 4hrs and 8hrs after dexamethasone injection
- Avoid stress for the duration of the test
  - No other procedures



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Common mistakes #10:

-Testing for Cushing’s syndrome in a newly diagnosed or unstable diabetic patient

Can I test for Cushing's in a diabetic dog?

- Step away from the tetracosactide!
- Clinical signs and biochemical changes very similar
  - ALP, ALT, chol
- Wait until diabetes stabilised before considering testing for hypercortisolism
  - Usually takes at least 3mths to stabilise a diabetic
  - High risk of false positive if testing performed on an unstable diabetic
  - Need for high dose insulin to achieve stability should raise suspicion of concurrent hypercortisolism



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Common mistake #11 :

- Performing an ACTH stim on a dog receiving steroids?

Can I run an ACTH stim on a dog receiving steroids?

- Yes……but what would be the point?



- It confirms the dog is taking steroids!
- Adrenal suppression expected- flatline response
- May also cross react with assay

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Common mistake #12:

Using pre-pill cortisol to monitor trilostane response in a sick or stressed dog

Pre-Pill Cortisol

+ Sample collected immediately before trilostane Tx is due
+ Only useful for well animals
+ Do not use in animals that are very stressed
+ Must send to reference laboratory for analysis



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Common mistake #13:
‘Monitoring’ trilostane therapy with the LDDS test

Can I monitor trilostane therapy with LDDS test?

- No



- Trilostane is already suppressing the adrenal axis
- Our goal is to monitor the adrenals' ability to respond to stress, so a stimulation test is needed

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Common mistake #14:

-Confusing ‘reference ranges’ with ‘therapeutic ranges’

Therapeutic Goals- Cushing's Syndrome

- Post-ACTH cortisol >40nmol/L but <200nmol/L
- Resolution of clinical signs
  - PUPD resolves first
  - May take months for skin changes to improve



†Cortisol - Resting	17.3	nmol/L	25.0 - 125.0
†Cortisol - Post ACTH	84.1	nmol/L	125.0 - 520.0



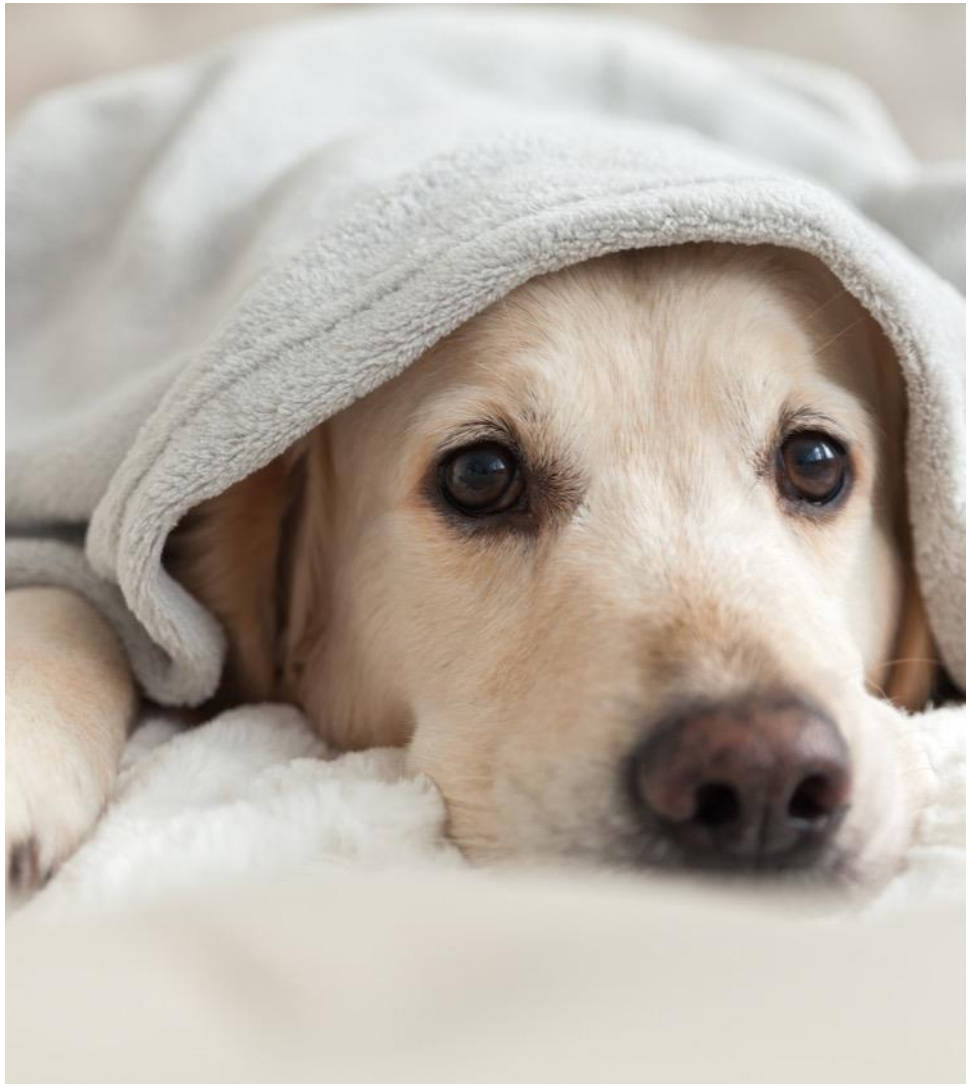
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Common mistake #15:

-Using ACTH stimulation test to monitor hypoadrenocorticism

Monitoring Hypoadrenocorticism

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



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Common mistake #16:

-Testing TT4 in patients as part of ‘screening’

Factors Associated With Decreased TT4

- Non thyroidal illness (NTI)
  - Any severe concurrent disease
  - Cushing’s syndrome
  - Neoplasia
  - Kidney disease
- Exercise e.g. Sled dogs
- Breed
  - Greyhound/Sighthound breeds
- Medications
  - Glucocorticoids
  - Potentiated sulphonamides
  - Phenobarbital
  - Clomipramine



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Using TT4 As A Screening Test?

- Poor specificity
- Don’t test in sick dogs
- Only test in dogs with supportive clinical signs
- Suggestive clinical/clinpath signs:
  - Truncal alopecia
  - Rat tail
  - Hypercholesterolaemia



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Primary Hypothyroidism

- Metabolic signs
  - Lethargy
  - Weakness
  - Weight gain
  - Exercise intolerance
- Skin changes
  - Non pruritic bilateral alopecia
  - Rat tail
- Does not cause PUPD



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Expected Clinpath Changes in Primary Hypothyroid Patients

+ Mild non regenerative anaemia

+ Increased cholesterol and triglycerides
  + Decreased lipid degradation

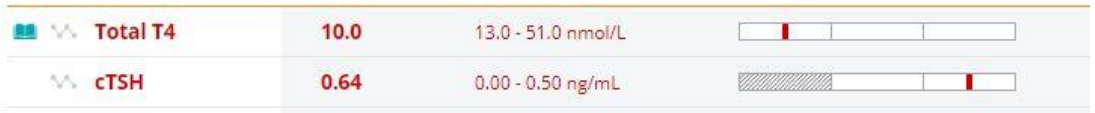


***RBC**	**4.87**	**10^12/L**	**5.80 - 9.00**	
***Haematocrit**	**0.379**	**l/L**	**0.410 - 0.600**	
***Haemoglobin**	**11.6**	**g/dL**	**14.6 - 21.7**	
***MCV**	**77.8**	**fL**	**62.0 - 76.0**	
*MCH	23.8	pg	22.0 - 27.0	
***MCHC**	**30.6**	**g/dL**	**32.3 - 38.0**	
*Reticulocytes	26.3	10^9/L	21.0 - 140.0	

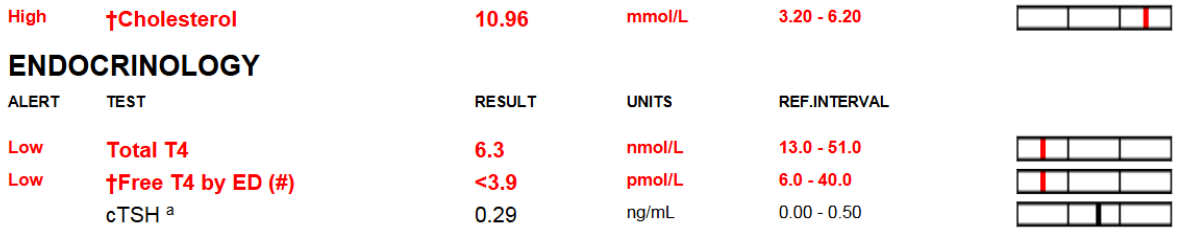
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How Do I Diagnose Primary Hypothyrodism In A Dog With Clinical Signs?

+ Measure both TT4 and TSH
  + Low TT4 and increased TSH
  + Diagnostic



+ T4 decreased but TSH WRI?
  + Measure FT4ED
    + Low FT4ED = diagnostic



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How To Interpret Thyroid Results

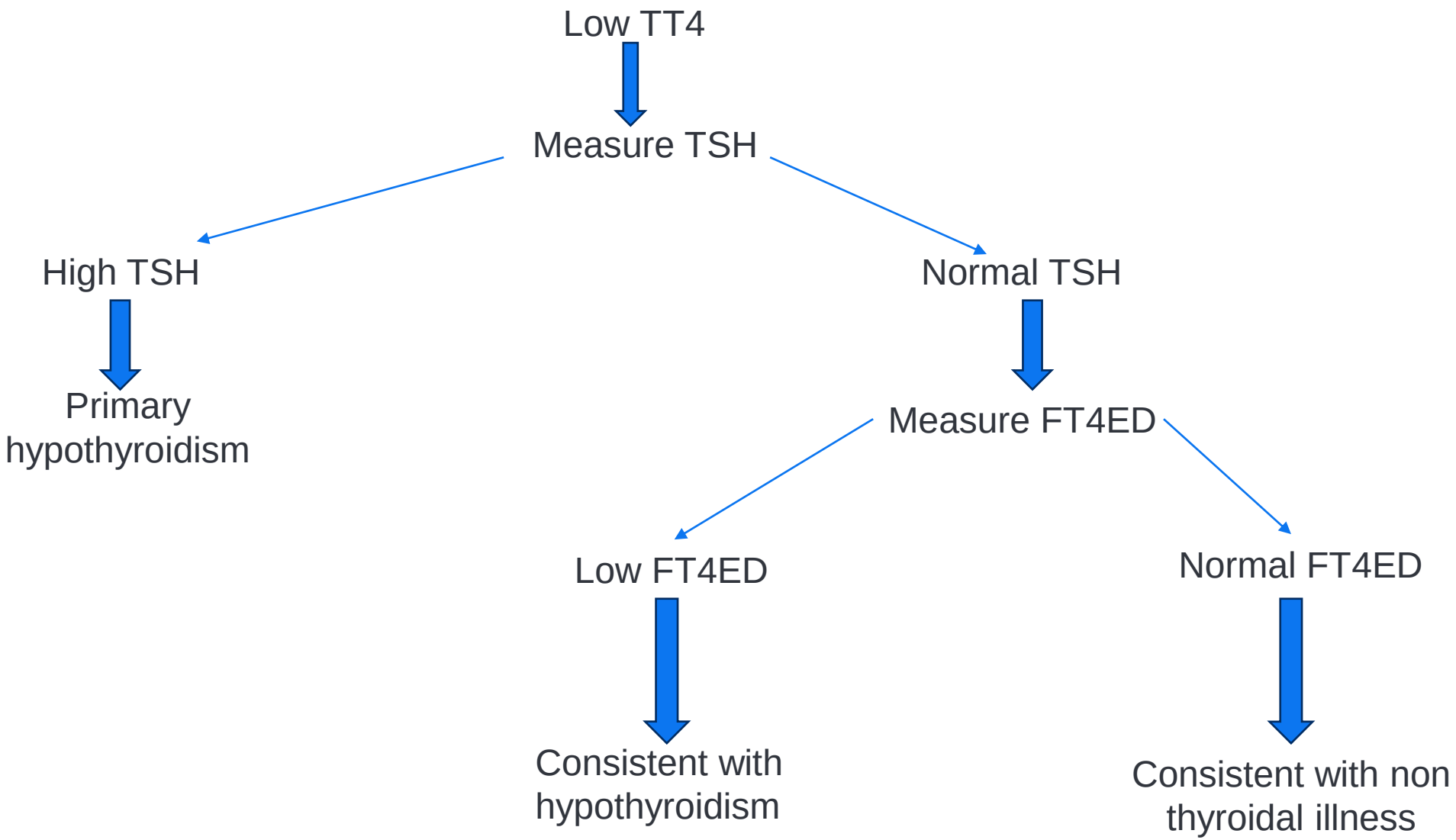
+ Low TT4 and high TSH → + Highly suggestive of hypothyroidism

+ Low TT4 and ref range TSH
  - → + Non thyroidal illness
  - → + Hypothyroidism still possible
    + (if Cx present)
    + Measure FT4ED

+ Ref range TT4 and increased TSH → Recovery from non thyroidal illness

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How To Interpret Thyroid Results (in dog with supportive Cx)



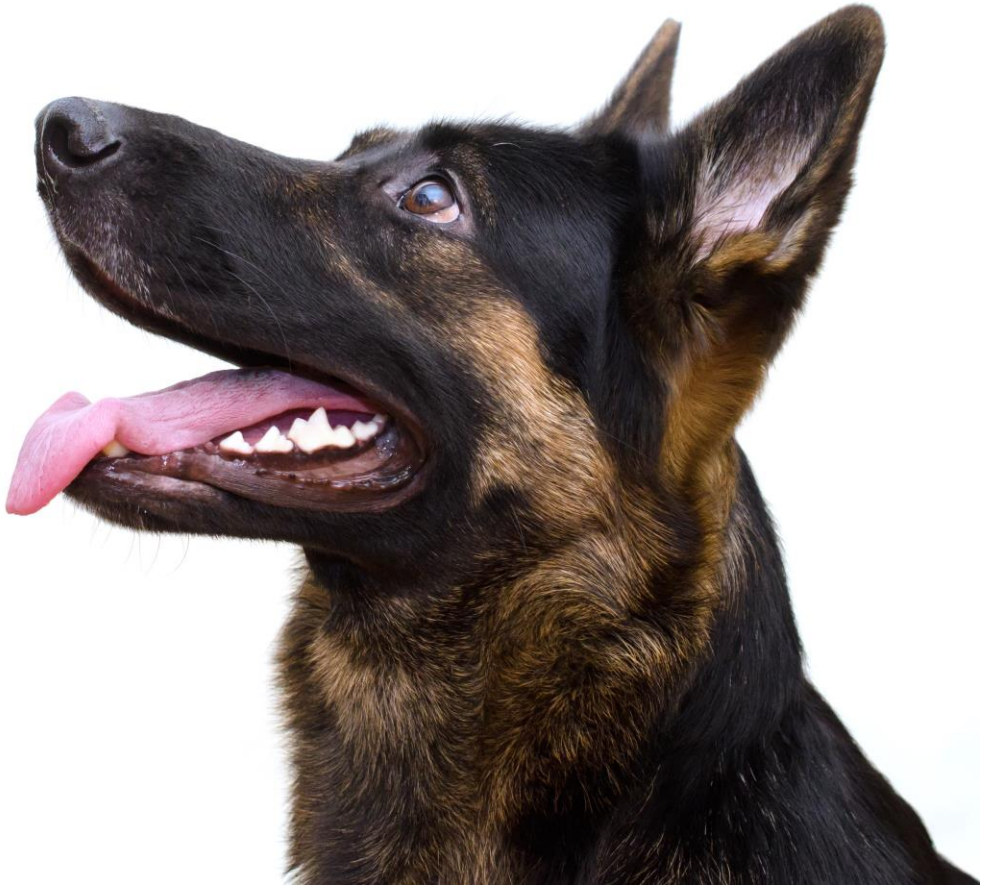
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Common mistake #17:

-Testing TT4 in dogs receiving thyroid supplementation at the wrong time

How To Monitor Response to Thyroxine Supplementation

- Start monitoring 4 weeks after starting supplementation
- Timing of blood sampling (peak)
  - Measure TT4 4-6hrs post pill
  - Except for Thyforon which is 3 hrs
- Measuring FT4 has no benefit for monitoring
- TSH can be measured but not necessary



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Common mistake #18:

-Confusing therapeutic ranges and RIs when monitoring treatment for hypothyroidism

Thyroid Monitoring- Goals

+ Peak TT4 should be in upper half of ref range or slightly above it

†Total T4 [a]	57.8	nmol/L	13.0 - 51.0



+ If peak TT4 is less than 35nmol/l, increase dose

+ Increased TSH may also support need for higher dose
  + But not generally performed for monitoring



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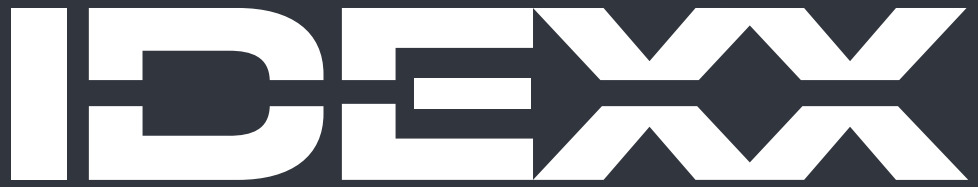
The 2 biggest mistakes you can make:

- 1. NOT providing history with your submissions for endocrine testing

- 2. Testing an animal for endocrine disease when there are no supportive signs



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