

CUSHING'S SYNDROME

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WITS BRANCH OCT 2024

CUSHING'S SYNDROME

GOAL OF TALK

- HOW WILL WE SUSPECT IT?
- WHAT CONFUSES WILL WE IGNORE?
- HOW WILL WE PROVE IT?
- WHAT WILL WE DO?
- WHEN WILL WE DO IT?
- WHAT ARE THE RISKS ?
- HOW WILL WE MONITOR ?

CUSHING'S DISEASE

CLINICAL PROBLEM BROUGHT ABOUT BY CHRONIC OVER EXPOSURE TO GLUCOCORTICOIDS, USUALLY 8 AND OLDER.

- NATURALLY OCCURRING
 - PITUITARY-DEPENDENT (PDH): 85% - 90%
 - ADRENAL DEPENDENT (ADH): 10 – 15%
- IATROGENIC CAUSES
 - USUALLY CHRONICALLY ADMINISTERED [DO THEY KNOW?]

RELATIVELY CHARACTERISTIC CLINICAL PICTURE

- INSIDIOUS ONSET MEANS PRESENTATION OCCURS AT VARIABLE STAGES
- CHANGES CAN BE SUBTLE, ESPECIALLY EARLY IN THE DISEASE

DEATH USUALLY CAUSED BY SECONDARY PROBLEMS RATHER THAN FROM CUSHING'S DIRECTLY

CUSHING'S DISEASE - CLIN SIGNS

COMMON ABNORMALITIES $\geq$ 8 YEARS

- POLYDIPSIA (PD)
- POLYURIA (PU)
- POLYPHAGIA
- PANTING
- ABDOMINAL DISTENSION
- HEPATOMEGALY
- ALOPECIA
- MUSCLE WEAKNESS
- HYPERTENSION

LESS COMMON MANIFESTATIONS

- LETHARGY
- MUSCLE LOSS
- CUTANEOUS HYPERPIGMENTATION
- COMEDOMES
- THIN SKIN
- POOR HAIR REGROWTH
- TESTICULAR ATROPHY

RARELY

- CALCINOSIS CUTIS

HOW NB ARE CLINICAL SIGNS?

- **VERY VERY VERY IMPORTANT!**
 - & DO NOT IGNORE SIGNS THAT DON'T FIT
- INAPPETENCE
- PRURITIS
- DON'T HAVE MULTIPLE CHANGES
- NEVER NEVER NEVER NEVER - ALKP ONLY

CUSHING'S SYNDROME - DIAGNOSIS

TO MANAGE WE'LL NEED TO DIAGNOSE IT.

- CONSULT — HISTORY, CLINICAL, URINE AND U/S SCAN
- BLOODS — IN HOUSE CHEM 15 AND FBC AND SMEAR
- ENDOCRINE TEST RESULTS WHICH CONFIRM THE DIAGNOSIS ?

VOTE

- ☐ ACTH STIMULATION TEST ?
- ☐ LOW DOSE DEXAMETHASONE SUPPRESSION TEST ?

CUSHING'S SYNDROME DIAGNOSIS - BLOODS

COMPLETE BLOOD COUNT

- STRESS LEUKOGRAM (I.E. NEUTROPHILIA WITHOUT A LEFT SHIFT, LYMPHOPAENIA, EOSINOPAENIA, MONOCYTOSIS)
- THROMBOCYTOSIS - COMMON
- RAISED HT

BIOCHEMISTRY PANEL:

- ELEVATION OF ALP OCCURS IN 85-95% OF DOGS WITH HAC,
- INDUCTION OF A UNIQUE CANINE CORTICOSTEROID-INDUCED
- ALKP>>>>>ALT

CUSHING'S SYNDROME - DIAGNOSIS – CHEM

SERUM CHEMISTRY:

- ALKP – ISOENZYME - CAN BE MARKED (>1000 U/L)
- DEGREE OF ELEVATION DOES NOT CORRELATE WITH SEVERITY OF HAC.
- INCREASED ALT [ALKP>>>>ALT]
- HYPERCHOLESTEROLEMIA,
- HYPERTRIGLYCERIDEMIA,
- HYPERGLYCAEMIA – 5% HAVE CONCURRENT DM
- HYPOPHOSPHATEMIA, AND DECREASED BUN.

CUSHING'S SYNDROME - DIAGNOSIS

URINALYSIS:

URINE SPECIFIC GRAVITY (<1.020)

PROTEINURIA OCCURS IN >50% - MILD TO MODERATE =UPC <5

URINE CULTURE:

UTI 50% AT THE TIME OF DIAGNOSIS

RADIOGRAPHY:

HEPATOMEGALY 80-90%

PENDULOUS ABDOMEN AND DYSTROPHIC MINERALIZATION OF ABDOMINAL STRUCTURES

CALCIUM-CONTAINING UROLITHIASIS

CUSHINGS

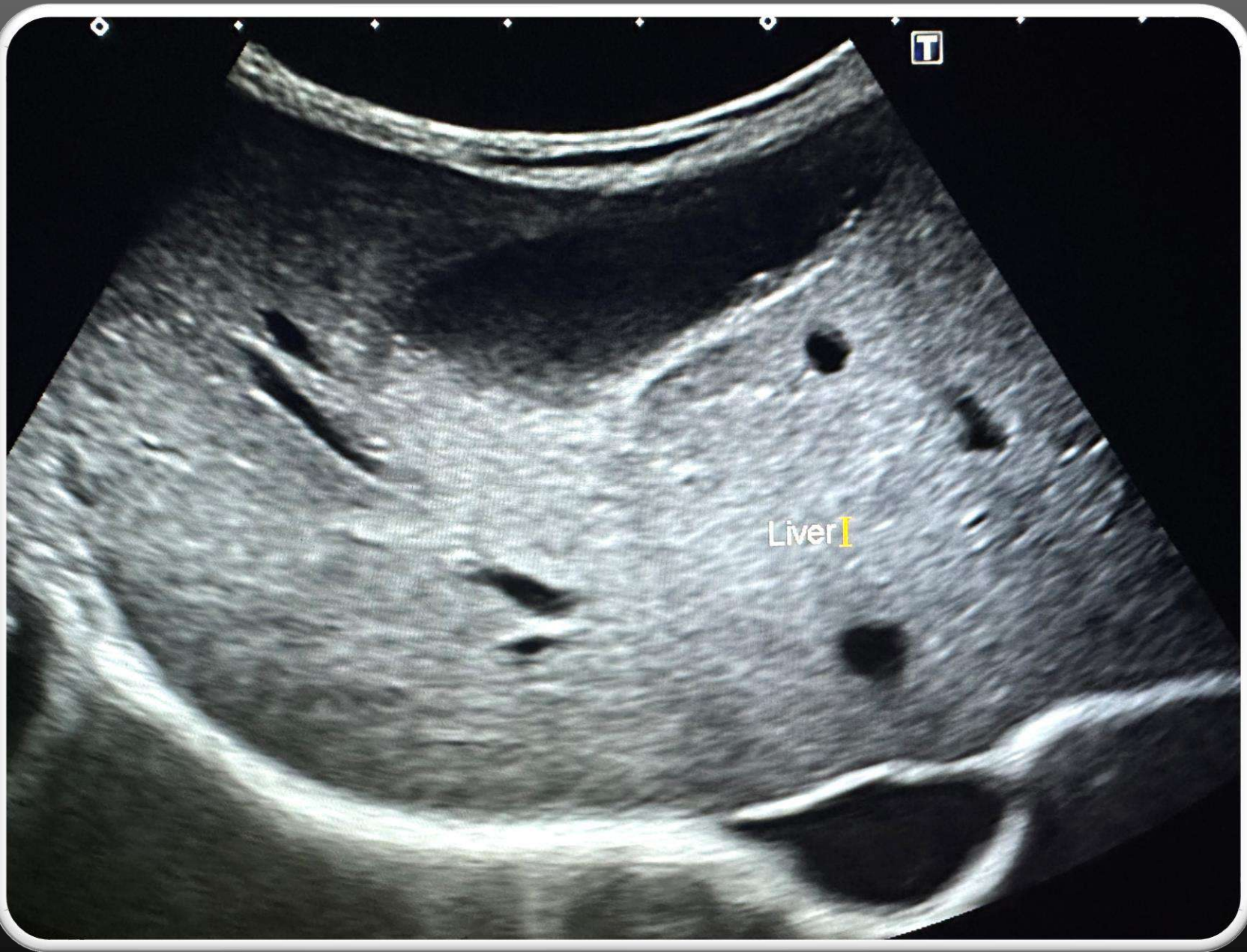
LET'S LOOK AT AN EASY CASE TO
DECIDE IF WANT CORTISOL TESTING.



TYPICAL.
CUSHING'S
CASE -
ADVANCED

CUSHINGOID BOSTON – EVEN THOUGH WE DON'T KNOW HOW DIAGNOSED

- IS THIS DOG HAVING A GOOD QUALITY OF LIFE
- RESEARCH SHOWS...
- NEED BETTER CONTROL
- LET,S GET A MDB ON THIS CASE



BOSTON
TERRIER
CUSHING'S

BOSTON TERRIER CUSHING'S

Test	Results	Reference Inter
<u>RBC</u>	9.69 x10 ¹² /L	5.65 - 8.87
<u>HCT</u>	* 67.8 %	37.3 - 61.7
<u>HGB</u>	23.4 g/dL	13.1 - 20.5
<u>MCV</u>	70.0 fL	61.6 - 73.5
<u>MCH</u>	24.1 pg	21.2 - 25.9
<u>MCHC</u>	34.5 g/dL	32.0 - 37.9
<u>RDW</u>	21.7 %	13.6 - 21.7
%RETIC	1.3 %	
<u>RETIC</u>	126.0 K/ μ L	10.0 - 110.0
<u>RETIC-HGB</u>	28.6 pg	22.3 - 29.6
<u>WBC</u>	9.57 x10 ⁹ /L	5.05 - 16.76

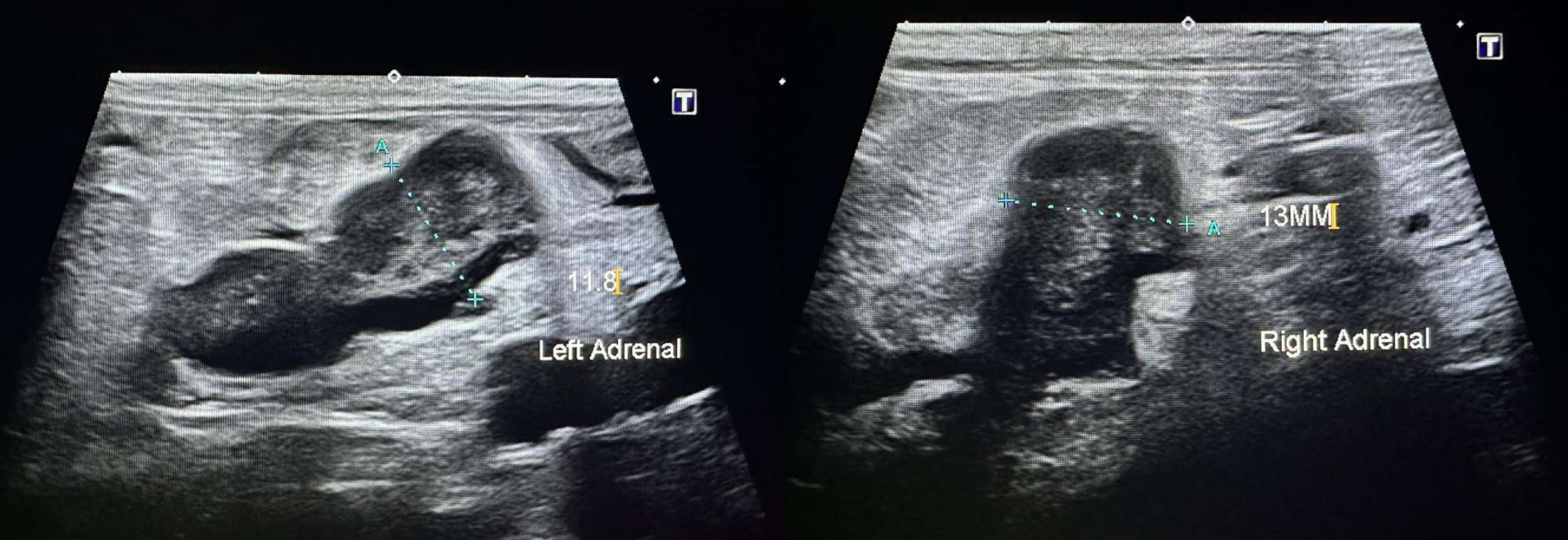
%BASO	1.0 %	
<u>NEU</u>	8.02 x10 ⁹ /L	2.95 - 11.64
<u>LYM</u>	0.70 x10 ⁹ /L	1.05 - 5.10
<u>MONO</u>	0.72 x10 ⁹ /L	0.16 - 1.12
<u>EOS</u>	0.03 x10 ⁹ /L	0.06 - 1.23
<u>BASO</u>	0.10 x10 ⁹ /L	0.00 - 0.10
<u>PLT</u>	524 K/ μ L	148 - 484
<u>MPV</u>	9.9 fL	8.7 - 13.2
<u>PDW</u>	8.3 fL	9.1 - 19.4
<u>PCT</u>	0.52 %	0.14 - 0.46

<u>TP</u>	58 g/L	62 - 82
<u>ALB</u>	26 g/L	22 - 39
<u>GLOB</u>	32 g/L	25 - 45
<u>ALB/GLOB</u>	0.8	
<u>ALT</u>	156 U/L	10 - 125
<u>ALKP</u>	1646 U/L	23 - 212
<u>GGT</u>	19 U/L	0 - 11
<u>TBIL</u>	4 µmol/L	0 - 15
<u>CHOL</u>	11.02 mmol/L	2.84 - 8.26
<u>Na</u>	152 mmol/L	144 - 160
<u>K</u>	4.0 mmol/L	3.5 - 5.8
<u>Na/K</u>	38	
<u>Cl</u>	114 mmol/L	109 - 122
<u>Osm Calc</u>	300 mmol/kg	

<u>GLU</u>	6.23 mmol/L	3.89 - 7.95
<u>CREA</u>	43 µmol/L	44 - 159
<u>UREA</u>	3.8 mmol/L	2.5 - 9.6
<u>BUN/CREA</u>	21	
<u>PHOS</u>	1.61 mmol/L	0.81 - 2.20
<u>CA</u>	2.33 mmol/L	1.98 - 3.00
<u>TP</u>	58 g/L	52 - 82
<u>ALB</u>	26 g/L	22 - 39
<u>GLOB</u>	32 g/L	25 - 45
<u>ALB/GLOB</u>	0.8	

BOSTON TERRIER CUSHING'S

- DO WE AGREE CUSHING'S
- DO WE AGREE CUSHING'S NOT CONTROLLED
- DO YOU NEED ANY TESTS TO KNOW MORE
- CHANGE IN RX TO BE DISCUSSED LATER



BOSTON TERRIER CUSHING'S



FINDING LEFT ADRENAL

FINDING RIGHT ADRENAL



CUSHING'S SYNDROME – DIAGNOSIS U/S

MORE OF A DIFFERENTIATING TOOL THAN RADIOGRAPHY BECAUSE BOTH ADRENAL GLANDS CAN BE ROUTINELY VISUALIZED

IN DOGS WITH PDH

- BILATERAL ADRENAL ENLARGEMENT MAY BE FOUND.
- SENSITIVITY AND SPECIFICITY OF BILATERAL ENLARGEMENT FOR DIAGNOSING PDH IS UNKNOWN
- IN ADDITION, BODY SIZE IS AN IMPORTANT FACTOR
- DOGS WITH CHRONIC DISEASE THAT DO NOT HAVE HAC CAN ALSO HAVE BILATERAL ADRENAL ENLARGEMENT

Reference range (upper limit, median and lower limit) in mm for the maximal adrenal gland thickness in 86 healthy dogs

	≥2.5-5 kg		5-10 kg		10-20 kg		20-40 kg	
	Left	Right	Left	Right	Left	Right	Left	Right
upper	4.8	5.5	5.6	6.0	6.2	7.7	7.4	9.4
median	4.2	4.1	4.3	5.2	5.0	5.6	6.1	7.1
lower	3.4	3.2	3.4	3.8	3.9	4.2	5.2	5.4

n: 86 clinically healthy dogs; ≥2.5-5 kg: 21 dogs, >5-10 kg: 22 dogs, >10-20 kg: 22 dogs, >20-40 kg: 21 dogs
Reference range based on the 10 to 90th percentile

ULTRASOUND WITH ADRENAL TUMOURS

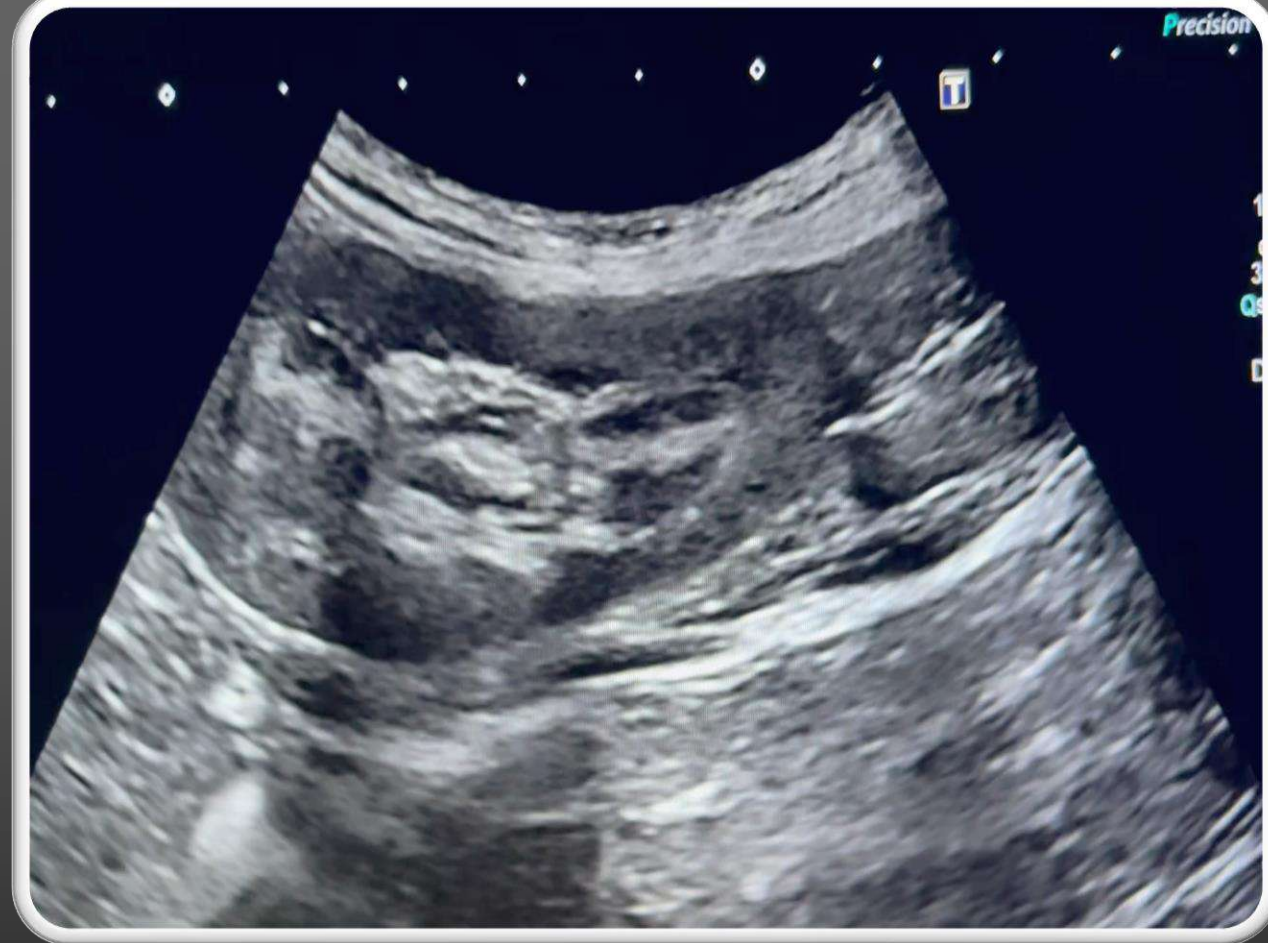
- DEFINES LOCATION, SIZE, AND ORGAN INVOLVEMENT OF ADRENAL MASSES
- VISUALIZATION OF BOTH ADRENAL GLANDS IS ESSENTIAL
- MODERATE ASYMMETRY, CONTRALATERAL ADRENOCORTICAL ATROPHY
 - (I.E. ADRENAL WIDTH $<4-5$ MM),
- DESTRUCTION OF NORMAL TISSUE ARCHITECTURE ARE CONSISTENT WITH AT.
- THE AFFECTED ADRENAL GLAND MAY ONLY APPEAR ENLARGED



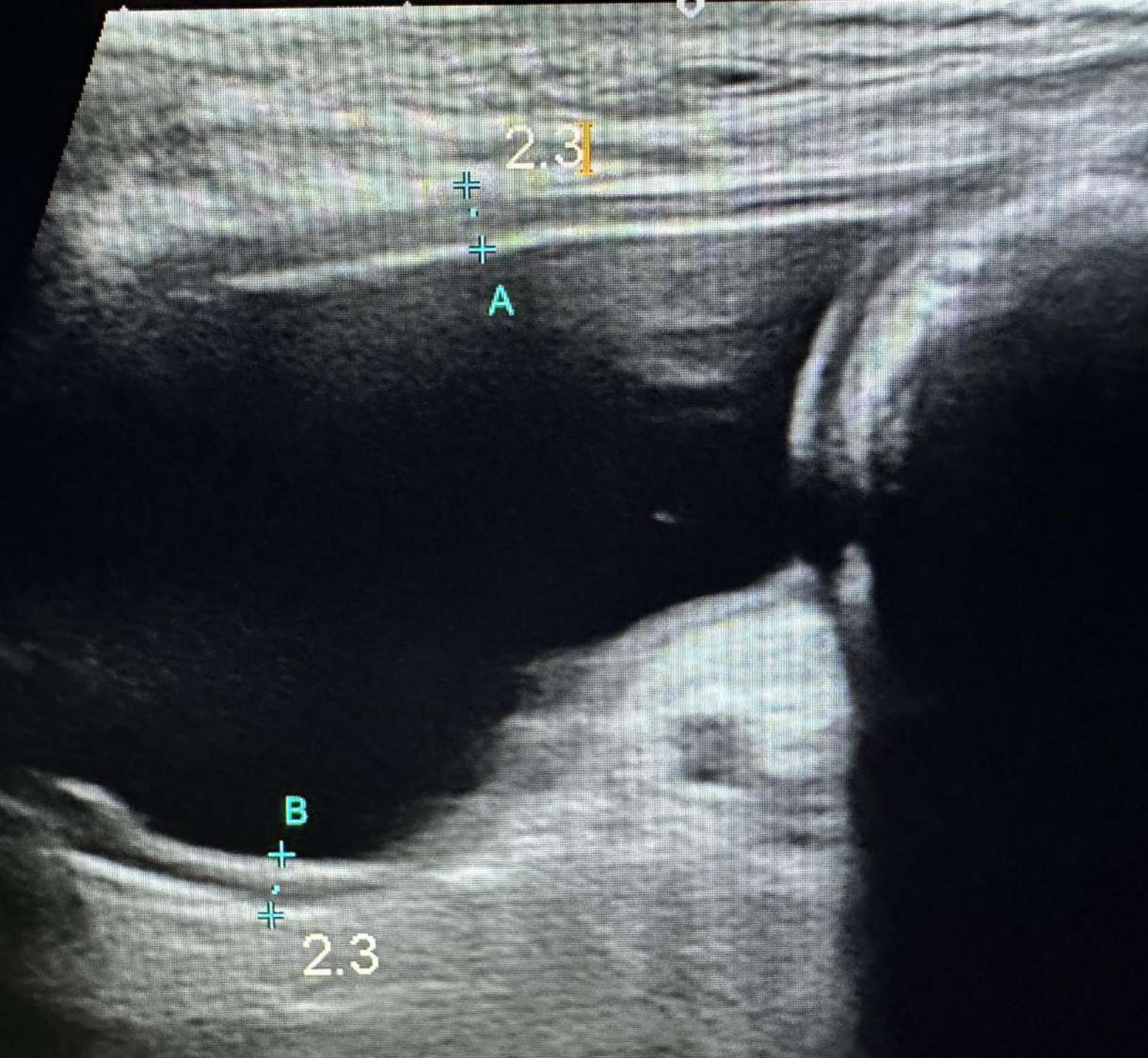
CUSHING'S – SCOUT UTI CC



CUSHING'S
– SCOUT UTI
CC



CUSHING'S – SCOUT UTI CC



- REMEMBER TO CHECK LIVER AND BLADDER AND GB AS WELL AS ADRENALS AND PANCREAS

CUSHING'S – SCOUT UTI CC

REMEMBER TO DO A MDB ON EVERY CASE

- UTI – ALWAYS CULTURE URINE
- APPETITE NOT BRILLIANT - NOT CUSHING'S OVERCONTROLLED SO CO MORBIDITY
 - COULD DO ACTH TO BE SURE
 - SO CAREFUL INCREASE T. DOSE
- CC – NOTHING WORKS EXCEPT REMOVE GLUCOCORTICOIDS
 - BEST WAY TO DO THAT???
 - IF USE TRILOSTANE – 2X/DAY AND HIGHER DOSE
 - LYSODREN

CUSHINGS

ADRENAL TUMOURS INCLUDING INCIDENTALOMA'S

Primary adrenal tumours that secrete hormones
(cortisol, sex hormones, catecholamines, or aldosterone)

Incidental mass's = incidentaloma's

ULTRASOUND ADRENAL TUMOURS

ADRENAL ADENOMA VS CARCINOMA

- UNLIKELY BASED ON APPEARANCE OF THE MASS.
- ADRENAL GLAND WIDTH >2 CM CORRELATES HIGHLY WITH MALIGNANCY
- INVASION OF THE CAUDAL VENA CAVA IS SUGGESTIVE OF A CARCINOMA.
- ATROPHY OF THE CONTRALATERAL GLAND MAY NOT ALWAYS BE DETECTABLE BY ULTRASONOGRAPHY
- NO SIGNIFICANT DIFFERENCE EXISTS BETWEEN DIMENSIONS OF NORMAL ADRENALS AND ADRENALS CONTRALATERAL TO AT !!!!!!!!!!!
- THE NORMAL, 2-LAYER APPEARANCE DEPICTING MEDULLA AND CORTEX MAY STILL BE SEEN IN ATROPHIED GLANDS [NOT TUMOROUS GLANDS]

INCIDENTALOMA'S

NONFUNCTIONAL ADRENAL TUMOURS

MYELOLIPOMAS,

LIPOMAS,

METASTATIC LESIONS,

HEMATOMAS, ABSCESES,

GRANULOMAS, OR CYSTS.

APPROXIMATELY 4% OF NORMAL DOGS MAY HAVE INCIDENTALOMAS, AND IN A STUDY OF 151 DOGS WITH INCIDENTALOMAS, 83% WERE >9 YEARS OF AGE (COOK 2014). IN THIS STUDY, A LESION WAS DEFINED AS EITHER AN ADRENAL GLAND >10 MM WIDE **OR** A DISTINCT NODULE OR MASS THAT WAS PRESENT IN THE GLAND. IN ORDER TO BE CLASSIFIED AS "INCIDENTAL," THERE COULD BE NO CLINICAL SIGNS OR PHYSICAL EXAM FINDINGS ASSOCIATED WITH AN ADRENAL MASS.

CUSHING'S DISEASE DIAGNOSIS - ULTRASOUND

CO-INCIDENTALOMA'S

- ULTRASOUND FOR DIFFERENT REASON
- OFTEN HAVE RAISED ALKP IN SMALL BREED DOGS AND ADRENAL MASS WITH OTHER ADRENAL NORMAL
- ONE SERIES 2/3, ANOTHER SERIES 4/5

QUANDARY

- TESTING
- RE U/S TIMES

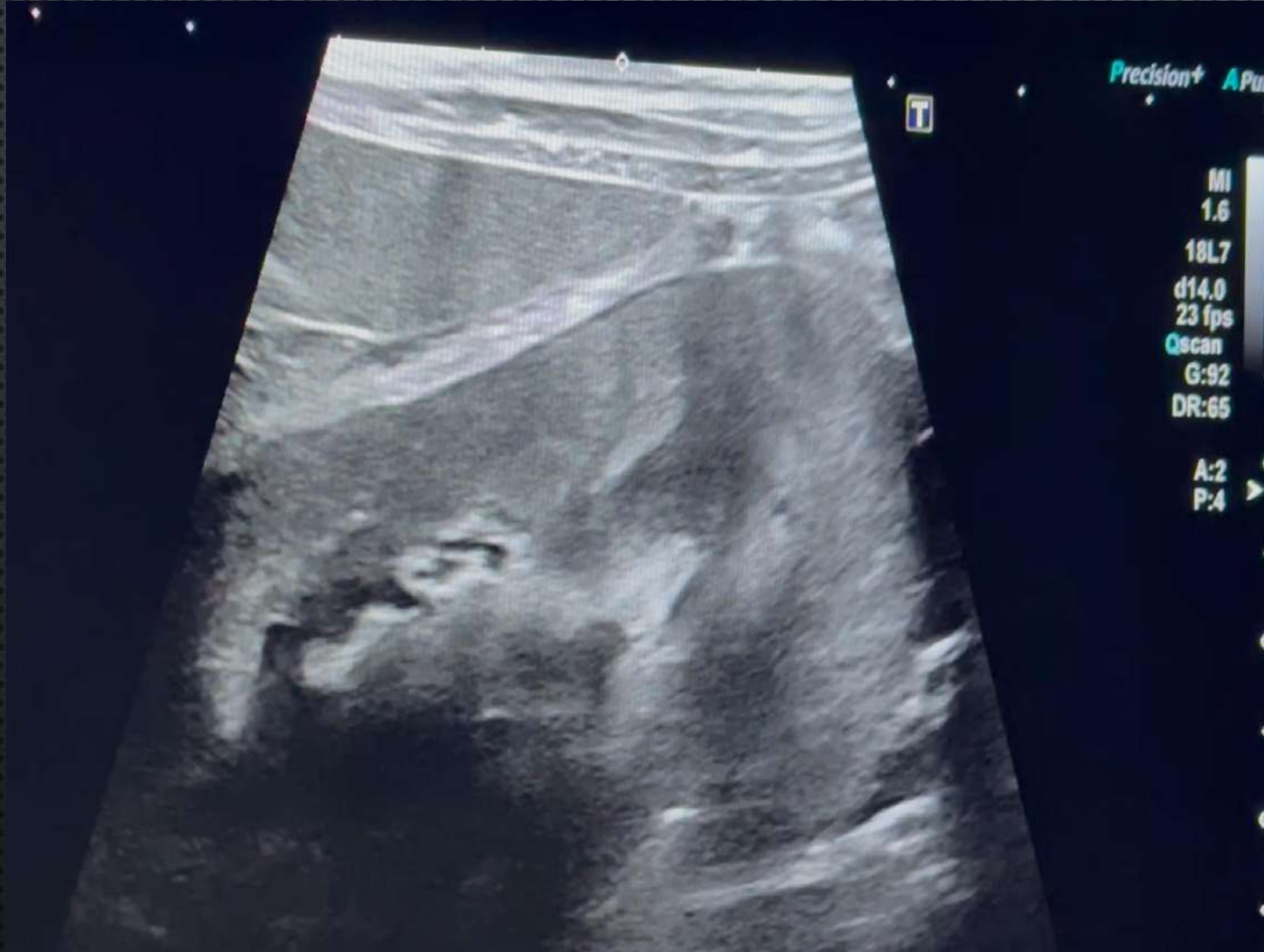
INCIDENTALOMA'S

- MOST LESIONS WERE UNILATERAL [BILATERAL IN 11% OF THE DOGS]
- MEDIAN MAXIMUM DIMENSION OF THE LESIONS WAS 12 MM (RANGE: 3–60 MM)
- 20% WERE >20 MM.
- VASCULAR INVASION WAS ONLY NOTED IN 9/163
- ADENOMAS WERE 17 MM OR SMALLER,
- PHEOS AND CARCINOMAS WERE >20 MM (UP TO 46 MM).

NOTE

- ALL TUMOURS UNDER 20 MM WERE BENIGN, AND VASCULAR INVASION WAS CONSISTENT WITH PHEOCHROMOCYTOMA.

INCIDENTALOMA – LEFT RECHECK AFTER 1 MONTH - WORSE VS GONE?



LEFT

CUSHINGS – ADRENALS.

- WHILE ON THIS TOPIC
- LET'S QUICKLY CHAT ABOUT ROUTINE ADRENAL SURGERY

OUTCOME IN DOGS UNDERGOING ADRENALECTOMY FOR SMALL ADRENAL GLAND TUMOURS WITHOUT VASCULAR INVASION.

VET COMP ONCOL. DECEMBER 2020;18(4):599-606.

JACQUELINE V J CAVALCANTI ¹, OWEN T SKINNER ², PHILIPP D MAYHEW ³, JAMES C COLEE ⁴, SARAH E BOSTON ⁵

ARTICLE ABSTRACT

VETERINARY STUDIES HAVE REPORTED THE OUTCOME OF ADRENALECTOMIES IN DOGS; HOWEVER, THESE STUDIES TYPICALLY INCLUDE A WIDE VARIETY OF ADRENAL TUMOUR SIZES, INCLUDING CASES WITH OR WITHOUT VASCULAR INVASION. THE PURPOSE OF THIS STUDY WAS TO REPORT OUTCOME IN A COHORT OF DOGS WITH HISTOLOGICALLY CONFIRMED **SMALL ADRENAL TUMOURS WITHOUT VASCULAR INVASION** TREATED WITH ADRENALECTOMY. THIS RETROSPECTIVE STUDY WAS CONDUCTED USING DATA FROM THE UNIVERSITY OF FLORIDA AND UNIVERSITY OF CALIFORNIA-DAVIS DATABASES BETWEEN 2010 AND 2017. DOGS WERE INCLUDED IF THEY UNDERWENT EXCISION OF AN ADRENAL GLAND TUMOUR WITH A **MAXIMAL DIAMETER $\leq$ 3 CM**, WITHOUT EVIDENCE OF VASCULAR INVASION TO ANY LOCATION AS ASSESSED VIA COMPUTED TOMOGRAPHY. FIFTY-ONE DOGS MET THE INCLUSION CRITERIA. THE SHORT-TERM SURVIVAL RATE OF DOGS UNDERGOING ADRENALECTOMY WAS 92.2%, AND ONE-YEAR DISEASE-SPECIFIC SURVIVAL WAS 83.3%. TWENTY-EIGHT OF 51 (54.9%) DOGS WERE DIAGNOSED WITH A MALIGNANCY. MINOR COMPLICATIONS WERE OBSERVED COMMONLY INTRA-OPERATIVELY AND POST-OPERATIVELY. MAJOR COMPLICATIONS WERE OBSERVED IN SIX DOGS, AND INCLUDED SUDDEN DEATH, RESPIRATORY ARREST, ACUTE KIDNEY INJURY, HAEMORRHAGE, HYPOTENSION AND ASPIRATION PNEUMONIA. SHORT-TERM MORTALITY OCCURRED IN FOUR DOGS. SUDDEN DEATH AND HAEMORRHAGE WERE THE MOST COMMON MAJOR COMPLICATIONS LEADING TO DEATH. WHILE ADRENALECTOMY IS SOMETIMES CONTROVERSIAL BECAUSE OF THE HIGH PERIOPERATIVE MORTALITY RATES PREVIOUSLY REPORTED, THE RESULTS OF THIS STUDY SUPPORT THAT ADRENALECTOMY FOR SMALL TUMOURS WITH NO VASCULAR INVASION CAN BE PERFORMED **WITH LOW RISK**.

CUSHINGS

CONFIRMING THE DIAGNOSIS

CUSHINGS SYNDROME – ENDOCRINE TESTING

Suspicion of HAC is established from.....

- History
- Physical examination
- Results of routine laboratory tests
- Ultrasonography.

Confirmation of HAC requires.....

- specific endocrine tests
- Screening tests
(e.g. low-dose dexamethasone suppression test, ACTH stimulation test)

CUSHING'S ENDOCRINE TESTING

- NB – WHAT I SAY NEXT DEPENDS ON PATIENT SELECTION
- WE ONLY WANT TO TEST DOGS THAT FULFILL MANY OF THE SIGNS
 - HISTORY
 - CLINICAL
 - BIOMARKERS
 - ULTRASOUND

WHO SHOULD NOT BE TESTED FOR CUSHINGS

WHO SHOULD NOT BE TESTED FOR CUSHINGS?

- IF THE ONLY ABNORMALITY IS AN INCREASED SERUM ALKALINE PHOSPHATASE (ALKP)
- THE DOG IS OTHERWISE APPARENTLY HEALTHY.

IT IS DIFFICULT ENOUGH TO INTERPRET ENDOCRINE TESTS IN DOGS WITH CLINICAL SIGNS OF THE DISEASE

- IF THEY HAVE NO CLINICAL SIGNS, ALL OF THE ENDOCRINE TESTS CAN BECOME VERY DIFFICULT TO INTERPRET BECAUSE OF FALSE POSITIVE AND FALSE NEGATIVE RESULTS.
- DO NOT TEST A DOG FOR HYPERADRENOCORTICISM IF THE DOG IS SICK
(E.G., VOMITING, ANOREXIA, WEIGHT LOSS, ETC).
- MANY NON-SPECIFIC ILLNESSES AND OTHER SYSTEMIC DISEASES WILL PRODUCE FALSE POSITIVE RESULTS WITH THE ENDOCRINE TESTS.

REMEMBER, THE DIAGNOSIS OF HYPERADRENOCORTICISM IS NOT AN EMERGENCY DIAGNOSIS.

WHO SHOULD NOT BE TESTED FOR CUSHINGS

*WHO SHOULD **NOT** BE TESTED FOR CUSHINGS?*

- REMEMBER, THE DIAGNOSIS OF HYPERADRENOCORTICISM IS NOT AN EMERGENCY DIAGNOSIS.
- IT IS THEREFORE ALWAYS GOOD TO ASK ONESELF: IF THE TEST RESULTS WOULD INDICATE HYPERADRENOCORTICISM, WOULD I THEN FEEL CONFIDENT TO START TREATING WITH LYSODREN OR TRILOSTANE GIVEN THE CLINICAL PICTURE OF THE PATIENT? IF THE ANSWER IS "NO", IT IS PROBABLY BEST NOT TO TEST FOR IT IN THE FIRST PLACE

SO, WHAT TEST CONFIRM CUSHING'S IF I DO SUSPECT IT

AS A GENERAL RULE WE LIKE TO USE WHERE POSSIBLE:

SUPPRESSION TESTS FOR EVALUATING DISORDERS RESULTING FROM “OVERACTIVE ENDOCRINE PROBLEMS”

AND

STIMULATION TESTS FOR CLARIFYING “UNDERACTIVE ENDOCRINOPATHIES”

RUN CORTISOL LEVELS AT REFERENCE LABS

DIAGNOSING CUSHING'S - ACTH

Pros

- Only takes 1 hour
- Fewer false positive results than a LDDST
- used in situations *where a 'sick' dog* requires testing.

Note that testing a dog that is anorexic, vomiting, losing weight, etc. is contraindicated; however, testing a dog with diabetes or stable heart disease can be performed.

- An ACTH stimulation test is the screening test of choice in this situation (but can still produce false positive results in “stressed” patients).

Will find exposure to exogenous steroids (iatrogenic hyperadrenocorticism), although a good history usually identifies these cases.

DIAGNOSING CUSHING'S - ACTH

Cons

- Uses Synacthen (which be expensive, section 21)
- More **false negative** results than a LDDST.
- Approximately 20-30% of dogs with hyperadrenocorticism will have ACTH stimulation test results within the reference range
- An additional 20-30% of dogs with hyperadrenocorticism will have "borderline" test results
 - 50%

The test is notorious for producing **false negative results** in dogs with cortisol-secreting adrenal tumors (AT), but dogs with PDH (pituitary-dependent hyperadrenocorticism) also frequently have normal stimulation tests.

- Not differentiate PDH or AT

DIAGNOSING CUSHING'S ACTH V LDDST

IF THE LDDS IS GENERALLY A BETTER SCREENING TEST, SO WHEN SHOULD THE ACTH STIMULATION TEST BE USED?

- IN A SUSPECT PATIENT THAT HAS A SYSTEMIC ILLNESS LIKE DIABETES MELLITUS.
- MONITORING THE RESPONSE TO THERAPY (TRILOSTANE OR LYSODREN)
- DOCUMENT IATROGENIC HYPERADRENOCORTICISM
- DIAGNOSE ADDISON'S DISEASE.

CONTRARY TO POPULAR BELIEF, IT IS NOT NECESSARY TO RUN A BASELINE ACTH STIMULATION TEST PRIOR TO TREATMENT FOR HYPERADRENOCORTICISM

IT IS NOT IMPORTANT WHAT THE CORTISOL CONCENTRATIONS ARE PRIOR TO THERAPY--WHAT MATTERS ARE THE POST-THERAPEUTIC CLINICAL RESPONSE [CORTISOL CONCENTRATIONS]

ACTH SUMMARY

ACTH STIMULATION TEST

- POORLY DIAGNOSTIC IN A PROPORTION OF CASES:
 - POST ACTH CORTISOL LESS THAN UPPER LIMIT OF THE NORMAL RANGE
 - POST ACTH CORTISOL BETWEEN 500 TO 750 NMOL/L
- EXTREMELY ACCURATE WHEN POST ACTH CORTISOL > 1000 NMOL/L
- SO, IT WORKS IN A % OF CASES AND ITS CONVENIENT BUT.....
- IT'S SENSITIVITY IS GENERALLY REPORTED AS AROUND 80% IF SELECT CASES VERY CAREFULLY.

DIAGNOSING CUSHING'S - LDDST

Pros

- Fewer false negative test results than the ACTH stimulation test
 - approximately 90% of dogs with hyperadrenocorticism will have an 8-hour post-Dexamethasone cortisol concentration >38
- Identifies the underlying cause of the disease in 50% of the cases.

The 3 criteria for diagnosing PDH on the LDDST include:

If the 8 hour cortisol value is $>39\text{nmol/l}$ but $<50\%$ of the resting cortisol value
& the 4-hour cortisol value is $<27,58\text{ nmol/l}$
&/or the 4-hour cortisol concentration is $<50\%$ of the resting cortisol value

Cons

Takes 8 hours to run the test

More false positives if the dog is systemically ill or on exogenous steroids

DIAGNOSING CUSHING'S SUMMARY

ACTH STIMULATION TEST

CONVENIENT

LESS EXPENSIVE

****CONCERN REGARDING FALSE NEGATIVES [CAN APPROACH 40-50%]

LOW DOSE DEXAMETHASONE SUPPRESSION TEST

LESS CONVENIENT

MORE EXPENSIVE

CONCERN REGARDING FALSE POSITIVES

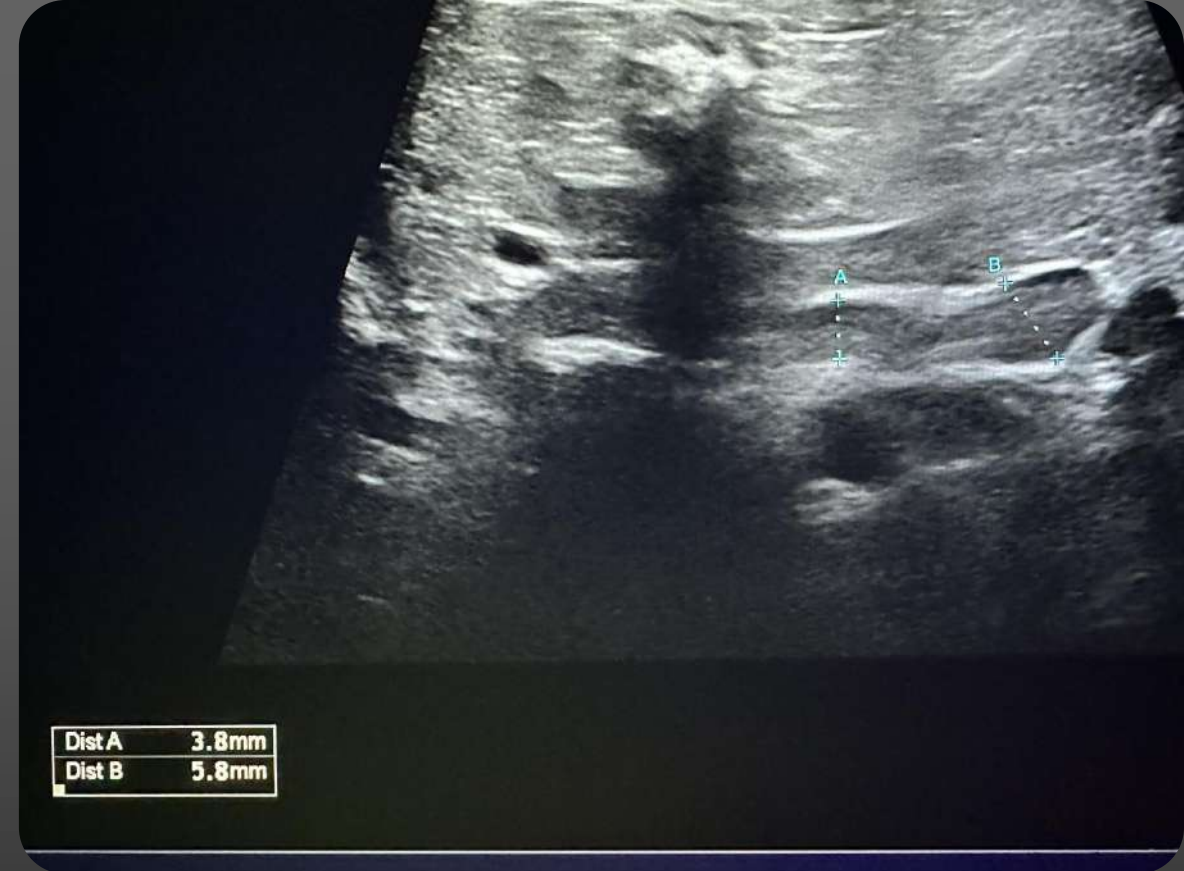
BUT WE CAN CONTROL THIS RELATIVELY EASILY BY CHOOSING OUR PATIENTS AND



LULU MARITZ – ALKP 1600, PUPD



LULU



LULU MARITZ – ADRENALS



LULU MARITZ NOT CUSHINGS EARLY GB MUCOCOELE CHANGE

HX:

- ILL, V AND D, ANOREXIA
- SPLENIC LYMPHOMA!

BUT TESTS:

ACTH – 211 TO 930

LDDST – DID NOT SUPPRESS AND ESCAPED

LULU – WHAT'S YOUR POINT DAVE

**CARE IN INTERPRETING DYNAMIC TESTING OF
HYPOTHALAMIC PITUITARY ADRENAL AXIS IN DOGS WITH
POTENTIAL NON-ADRENAL ILLNESS**

SO, WHO SHOULD BE TESTED THEN?

WHO SHOULD NOT BE TESTED FOR CUSHINGS

REMINDER:

- IF THE TEST RESULTS WOULD INDICATE CUSHING'S
- WOULD I THEN FEEL CONFIDENT TO START TREATING WITH LYSODREN OR TRILOSTANE GIVEN THE CLINICAL PICTURE OF THE PATIENT?

IF THE ANSWER IS "**NO**", IT IS PROBABLY BEST **NOT TO TEST** FOR IT IN THE FIRST PLACE

CUSHING'S ENDOCRINE TESTING

- NB – WHAT I SAID TILL NOW – DEPENDS ON PATIENT SELECTION
- WE ONLY WANT TO TEST DOGS THAT FULFILL MANY OF THE SIGNS
 - HISTORY
 - CLINICAL
 - BIOMARKERS
 - ULTRASOUND

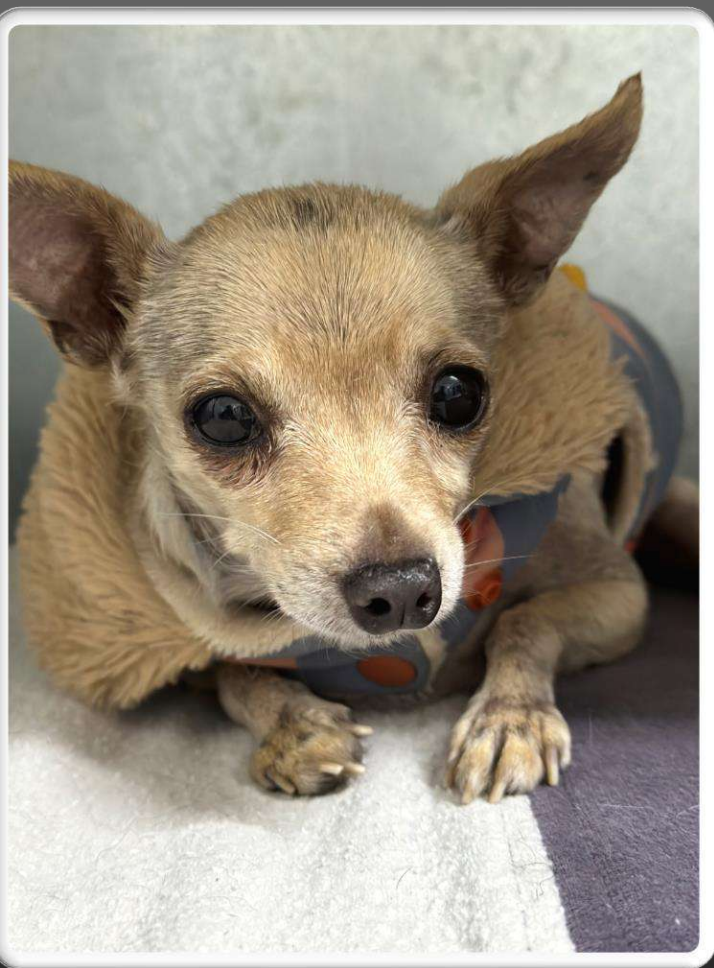
IN THIS CASE SCENARIO LDDST IS YOUR TEST

IF YOU DON'T DO ALL I HAVE ADVISED, THEN ACTH IS YOUR TEST BUT YOU PROBABLY WANT IT OVER 1000

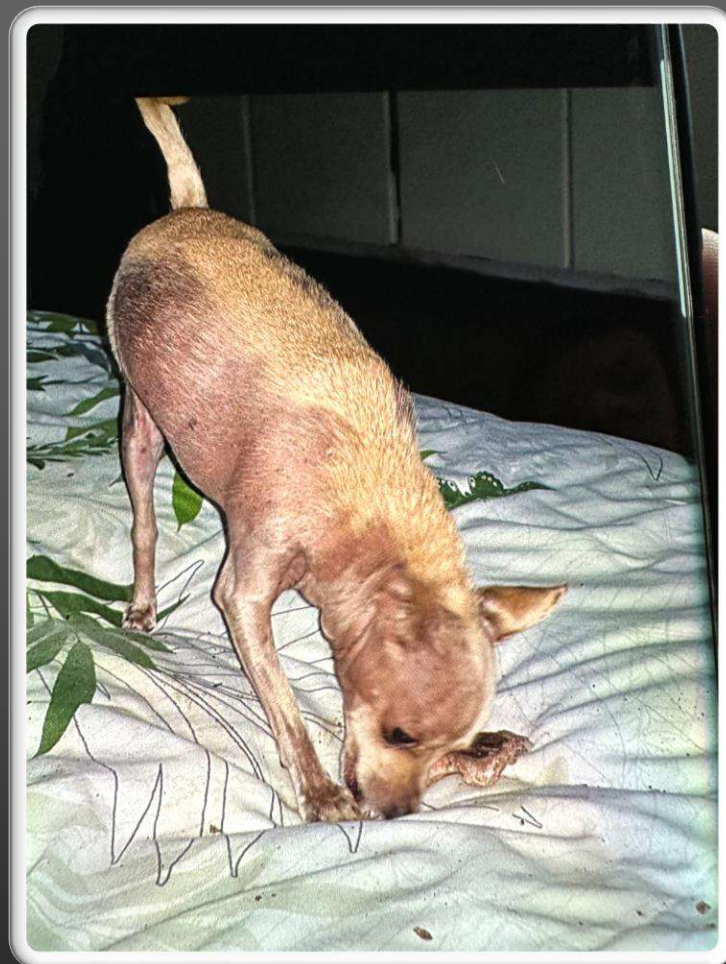




M
1.
18L
d18.
28 f
Qscan
G:8
DR:0
A
P



9 years old



7 months old

WHO NOT TO TEST - TAKE A HX

- 9 YEARS OLD
- ALKP 1650
- URINE SG 1.039
- ALOPECIA LIFE LONG
- NO PUPD
- NO POLYPHAGIA
- WEAKNESS
- L AND `R ADRENAL MID
NORMAL SIZE

WHO NOT TO TEST

**NO OTHER CLIN SIGNS AT
ALL**

- ALKP 975
- ADRENAL MASS
- ACTH TO 820



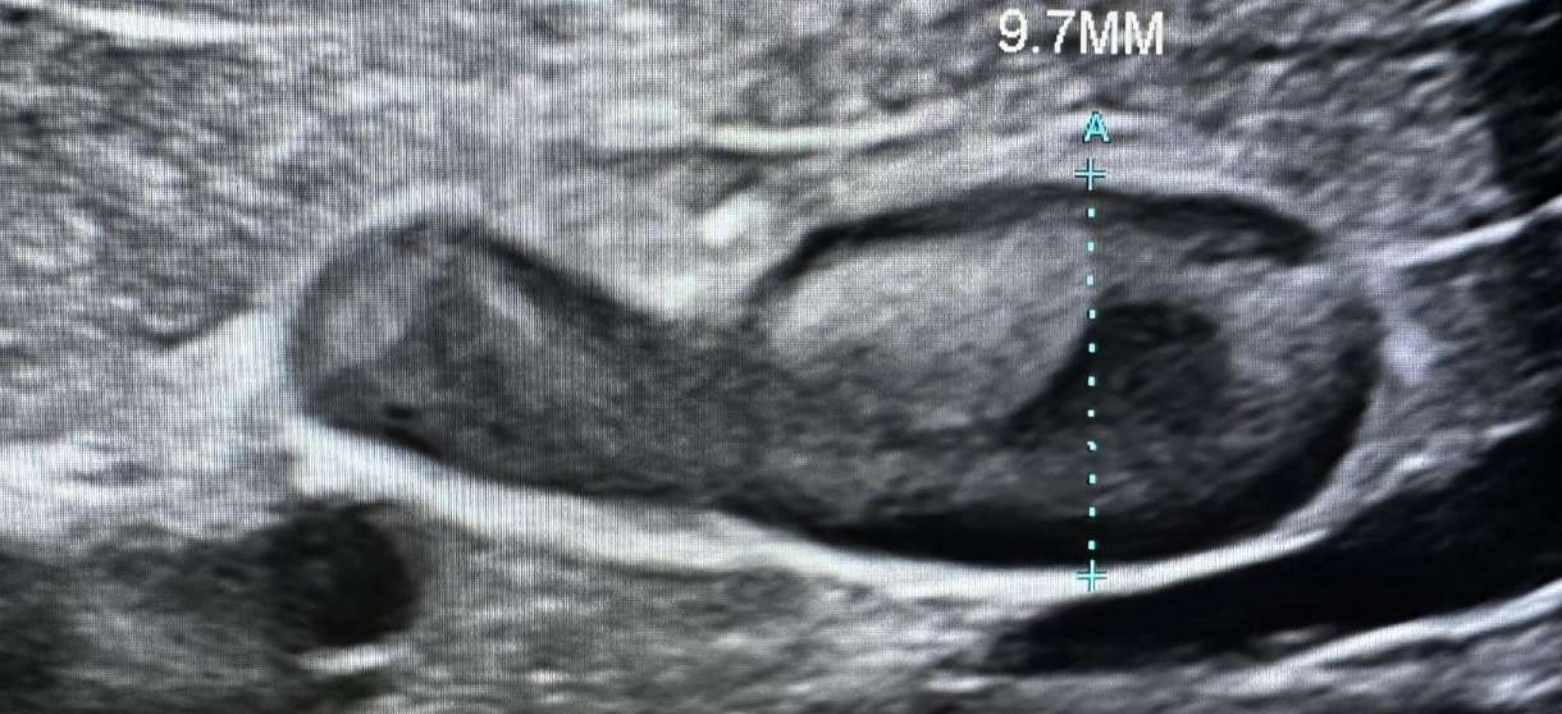
WHAT IF YOU
JUST CAN'T
DECIDE





HARD CASE
JUST CAN'T DECIDE –
CUSHING'S ?

ALKP - 212
PUPD - MILD
POLYPHAGIA - MILD
ADRENAL MASS
OTHER ADRENAL NOT
SMALL
NOT SARDS
REF VETS ACTH 750



STANDARD ARTICLE  Open Access 

Development and internal validation of a prediction tool to aid the diagnosis of Cushing's syndrome in dogs attending primary-care practice

Imogen Schofield , David C. Brodbelt, Stijn J. M. Niessen, David B. Church, Rebecca F. Geddes, Noel Kennedy, Dan G. O'Neill

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Cushing's Predictor

Step 1: Dog signalment

Neuter status:

Female-neutered



Current age (years):



< 7



≥ 7

Breed:

Other breed or crossbreed



< Back

Proceed >

Cushing's Predictor

Step 2: Presenting clinical signs

Polydipsia	☒ yes	☐ no
Vomiting	☐ yes	☒ no
Potbelly/hepatomegaly	☒ yes	☐ no
Alopecia	☒ yes	☐ no
Pruritus	☐ yes	☒ no

Cushing's Predictor

Step 3: Laboratory factors

Urine specific gravity:

Not dilute (> 1.020)



Serum ALKP:

Not Elevated



< Back

Proceed



Step 4: Summary

Dog demography

- neuter status: Female-neutered (-1 pts)
- current age: ≥ 7 (1 pts)
- breed: Other breed or crossbreed (0 pts)

Presenting clinical signs

- Polydipsia: yes (2 pts)
- Vomiting: no (0 pts)
- Potbelly/hepatomegaly: yes (3 pts)
- Alopecia: yes (2 pts)
- Pruritus: no (0 pts)

Laboratory factors

- Urine specific gravity: Not dilute (> 1.020) (-2 pts)
- Serum ALKP: Not Elevated (-3 pts)

Cushing's Predictor

Total points: 2

Predicted likelihood of Cushing's syndrome: 53%

This means that, of 100 dogs with these characteristics, 53 will eventually turn out to have a diagnosis of Cushing's syndrome.

More information about the scientific background of the tool can be found here: <https://doi.org/10.1111/1365-3113.12555>

What is the probability that my patient has Cushing's syndrome, based on the extra information from the endocrine test?

Do you have results from an endocrine test for Cushing's syndrome?

< Back

Start Over

Save to MyCalculations

Copy to clipboard

Cushing's Predictor

Endocrine test results: click the test(s) from which you have results.

ACTH stimulation test

Low Dose Dexamethasone Suppression test

Urinary Corticoid Creatinine Ratio

< Back

Start Over

ACTH stimulation test

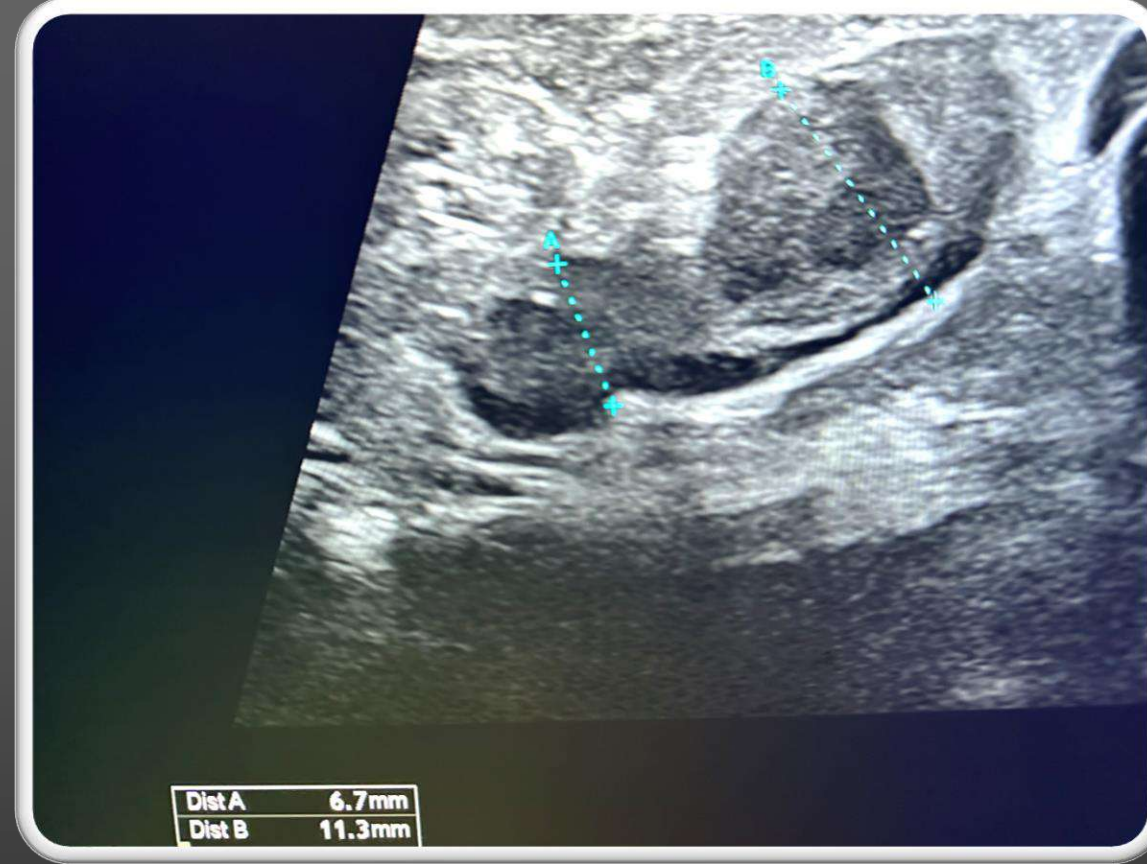
Is the ACTH stimulation test positive or negative?

☒ positive ☐ negative ☐ inconclusive

For a prevalence of 53%, the positive predictive value (PPV) of this test is 90%

This means that there is a 90% probability that your patient has Cushing's syndrome.

OK



CO-INCIDENTALOMA?
RE-U/S AFTER 1 MONTH THEN EVERY FEW
MONTHS AND MONITOR

CUSHING'S SYNDROME - THERAPY

- WHEN DO YOU START THERAPY?
 - PUPD?
 - COAT CHANGE?
 - QUALITY OF LIFE?
 - UTI?
 - WEAKNESS ?
 - CALCINOSIS CUTIS?
- WHAT THERAPY DO YOU START?

CUSHING'S SYNDROME – THERAPY - GOALS

EFFECTIVE TREATMENT SHOULD

- MODIFY CLINICAL SIGNS
 - 50% OF NORMAL
 - VS
 - EFFECTIVELY BACK TO NORMAL
- MODIFY CLINICAL PATHOLOGY - BIOMARKER
 - 50% OF NORMAL
 - VS
 - EFFECTIVELY BACK TO NORMAL
- MODIFY SERUM CORTISOL

CUSHING'S DISEASE THERAPY

TREATMENT OPTIONS

PITUITARY DEPENDENT HYPERADRENOCORTICISM:

- TRILOSTANE
- MITOTANE
- SURGICALLY - HYPOPHYSECTOMY/ADENALECTOMY

ADRENAL DEPENDENT HYPERADRENOCORTICISM:

- SURGICALLY
- MEDICALLY
 - TRILOSTANE
 - LYSODREN

CUSHING'S DISEASE THERAPY

LYSODREN

- LOADING
- MAINTENANCE PHASE
- MONITORING – ACTH STIM TESTS



CUSHING'S DISEASE THERAPY - TRILOSTANE

- REDUCES GLUCOCORTICOID ACTIVITY THROUGH A NUMBER OF DIFFERENT MECHANISMS
- START AT 2 MG/KG/24H WITH FOOD (AND ADJUST OVER TIME)

BUT

OFTEN/USUALLY ENDS UP BD [WITH FOOD]

NOTE - WE ARE SO SCARED OF OVERDOSING THAT WE END UP UNDERDOSING

- AT COST TO PATIENT AND OWNER
- WHAT'S THE WORST THAT HAPPENS WHEN OVERDOSE?

TRILOSTANE – HOUSE-KEEPING RULES

- USE **SAME** BRAND ONGOING
- TRY NOT SPLIT CAPSULES
- DOSE WITH FOOD
- PREGNANCY

CUSHING'S DISEASE THERAPY - TRILOSTANE

SET EXPECTATIONS BEFORE YOU START.

- IN A PROPORTION OF CASES (5-10%) CLINICAL RESPONSE IS POOR
- RISK OF TRANSIENT VS PERMANENT HYPOADRENOCORTICISM
- REGULAR REVIEW DOSE RATE RECOMMENDATIONS AND DOSE PRECISION
- CONSIDER MORE THAN TWICE DAILY DOSING
- CONSIDER SURGERY

CUSHING'S DISEASE-THERAPY TRILOSTANE

MY DRUG LABEL

DOSE 1 CAPSULE 1X/DAY IN THE AM WITH FOOD

RECHECK 2 WEEKLY TILL DOG WELL CONTROLLED.

1. IF BECOMES A NORMAL DOG – BRILLIANT
2. IF STILL HUNGRY/THIRSTY/POT BELLIED/PANTING – TOO LITTLE
3. IF SUDDENLY AN OLD DOG, NO ZEST, NO APPETITE, JUST LIES, MAYBE VOMIT AND DIARRHOEA.

PANIC, STOP MEDS AND SEE DAVE ASAP.

CUSHING'S DISEASE – TRILOSTANE RECHECKS

START AT

2 MG/KG ONCE DAILY IN AM WITH FOOD

OR

1–1.5 MG/KG/12H WITH FOOD

MONITORING AT 2, 4, 6 WEEK CHECK UP'S

TRILOSTANE – 2, 4, 6 WEEK CHECK UP'S

VOTE:

ACTH TEST 3-4 HR POST-DOSE [ALWAYS SAME]

- POST-ACTH CORTISOL IN THE REFERENCE RANGE FOR BASAL CORTISOL

VS

- PRE AND 3 H POST BASAL CORTISOL
 - CORTISOL UNDER 125 ISH

VS

- BIOMARKERS – LEUKOGRAM, ALKP & CHOLESTEROL AND URINE SG

Vs

- HISTORY OF CLIN SIGNS AND BIOMARKERS

NB – WHEN DOING AN ACTH TO MONITOR TRILOSTANE

- IF THE ACTH STIMULATION TEST WAS PERFORMED STARTING 2-4 HOURS
- THE AM TRILOSTANE WAS GIVEN WITH FOOD
- CORTROSYN OR SYNACTHEN WERE USED
- THE CORTISOL CONCENTRATIONS WERE ASSAYED BY A REPUTABLE LABORATORY

CUSHING'S – TRILOSTANE THERAPY ADJUSTMENTS

HAND OUT

- JSVC. 2 WEEKLY INQUISITIONS,
ACTH TO SEE IF OVERDOSE MOSTLY
SOMETIMES ACTH TO CHECK IF UNDERDOSING
- EUROPE
- NORTH AMERICA

CUSHING'S DISEASE - SURGERY

SURGICAL MANAGERMENTS FOR PDH

OUR TWO OPTIONS ARE:

1. TO REMOVE THE SOURCE OF THE PROBLEM:

- THE WHOLE PITUITARY, ADENO-HYPOPHYSIS & POSTERIOR PITUITARY

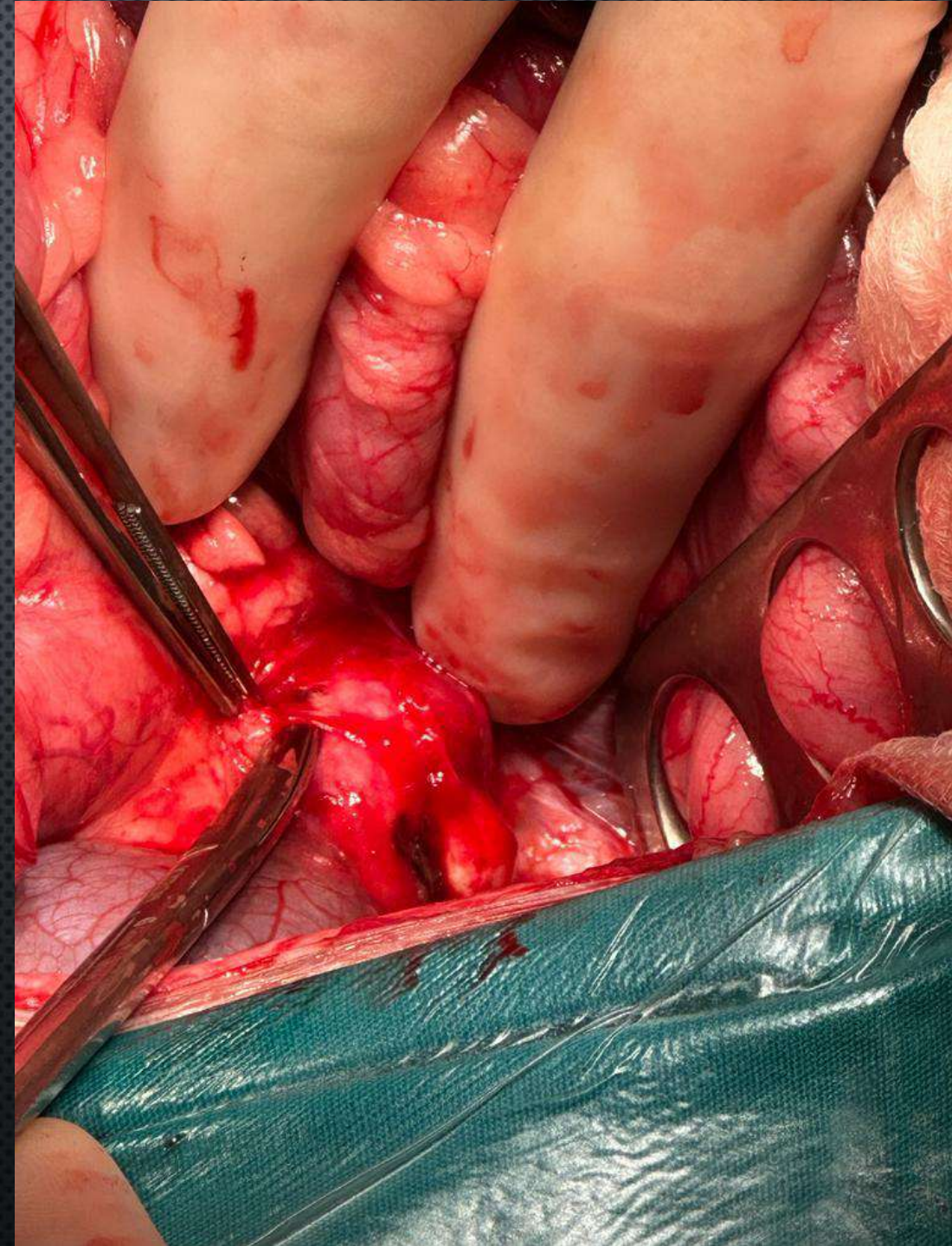
2. REMOVE THE RESPONSE END-ORGAN:

- BOTH WHOLE ADRENALS, CORTEX & MEDULLA

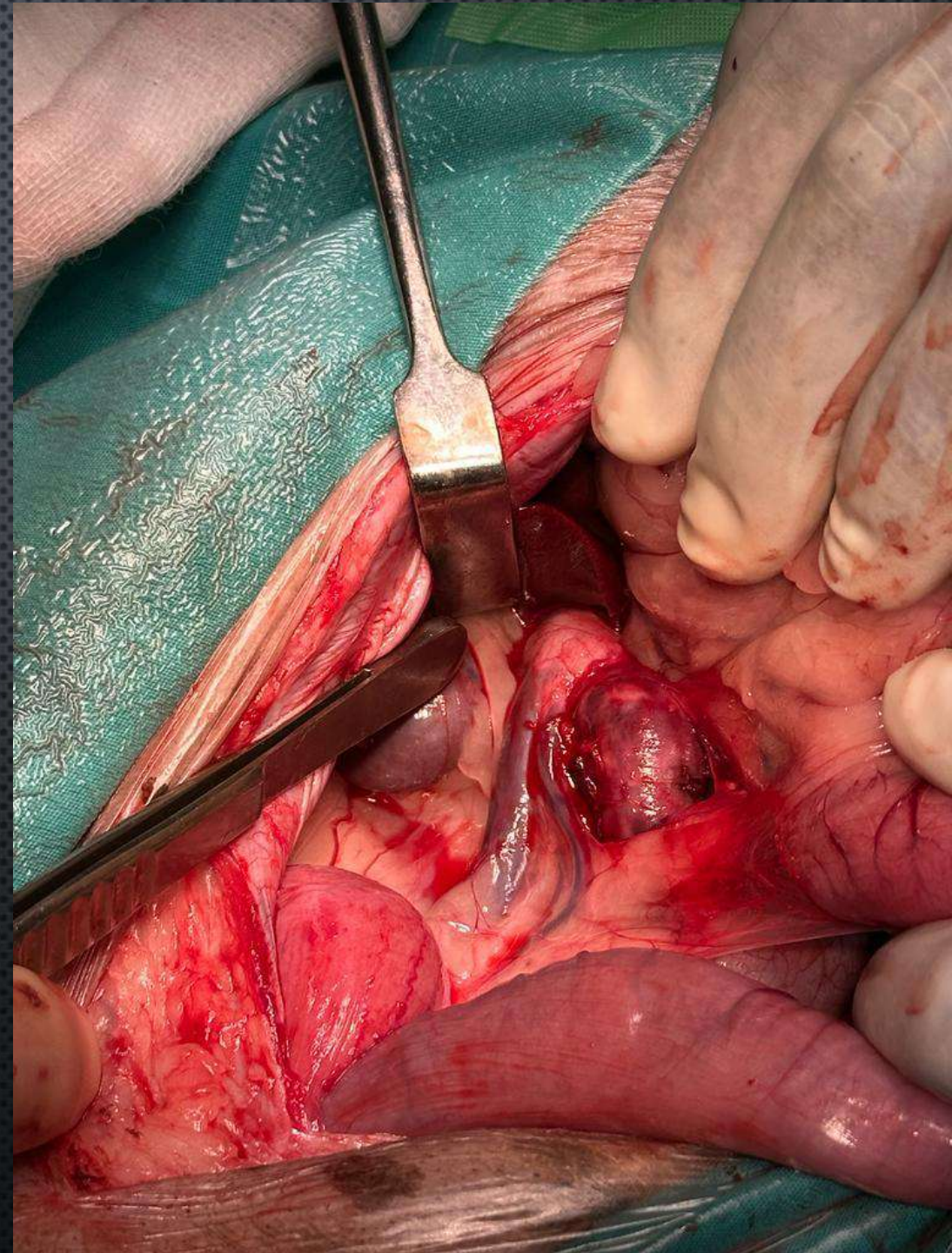


CUSHING'S DISEASE
- REMOVING
ADRENALS

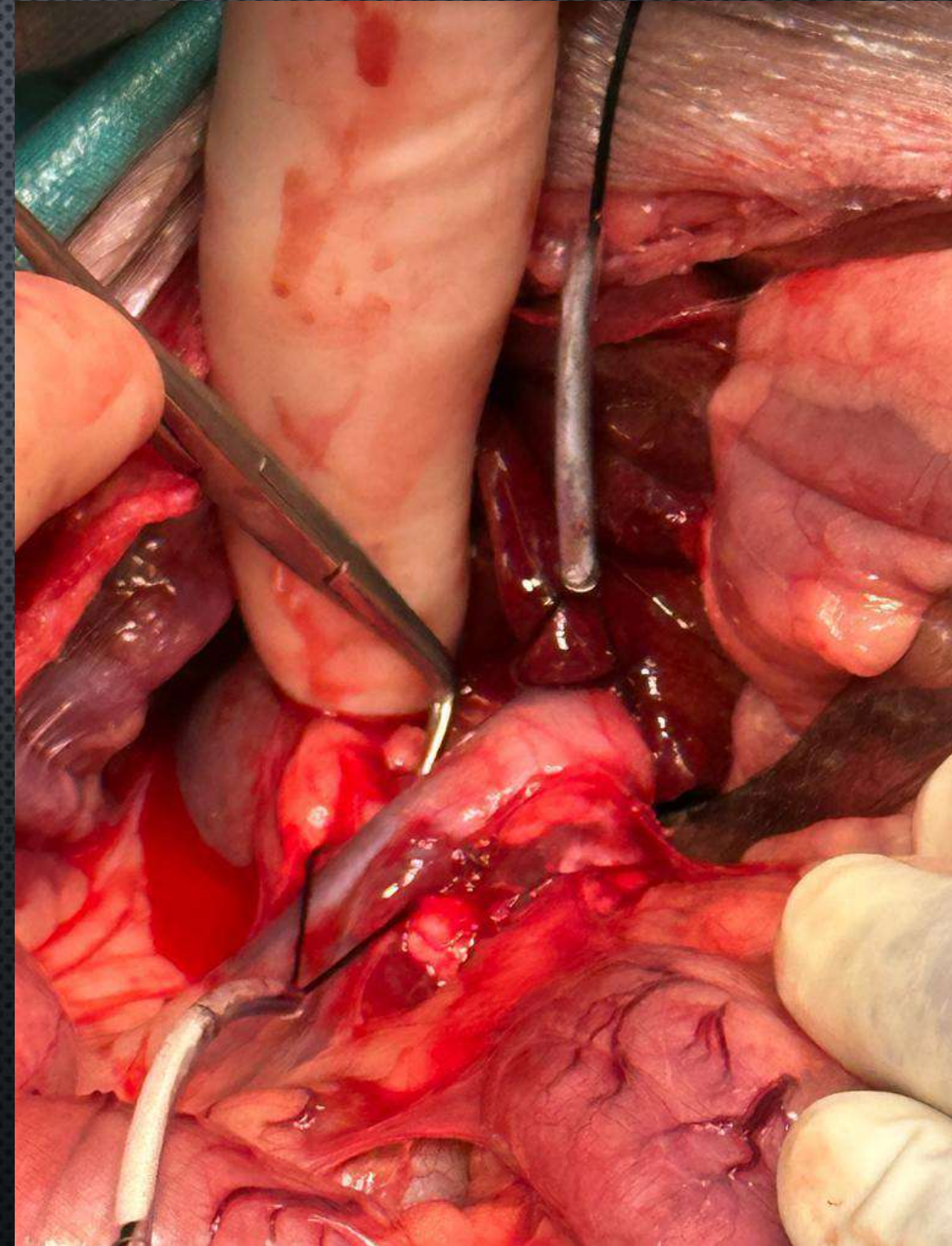
DACHSHUND:
R ADRENAL TUMOUR INTO
CVC



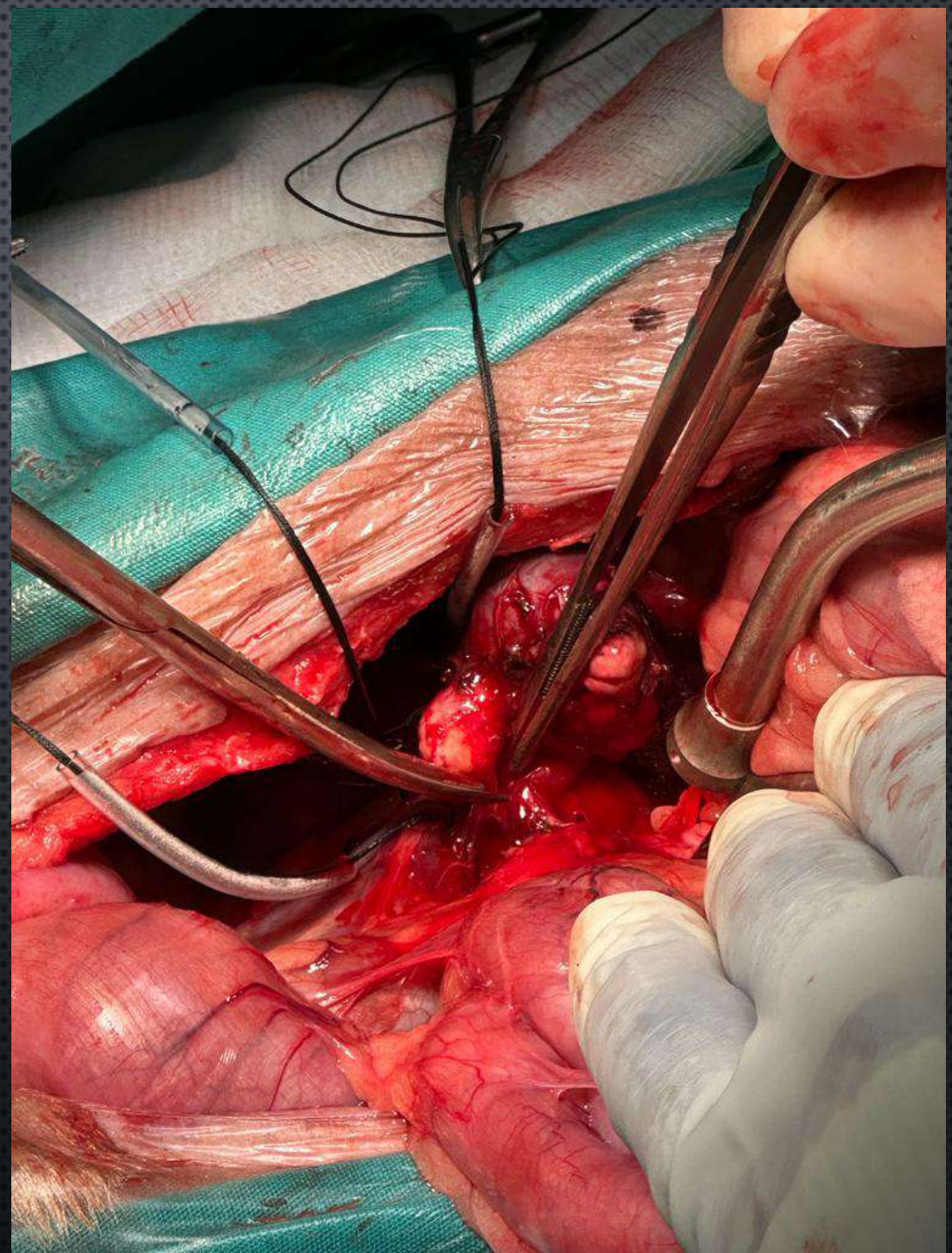
R ADRENAL TUMOUR IN CVC



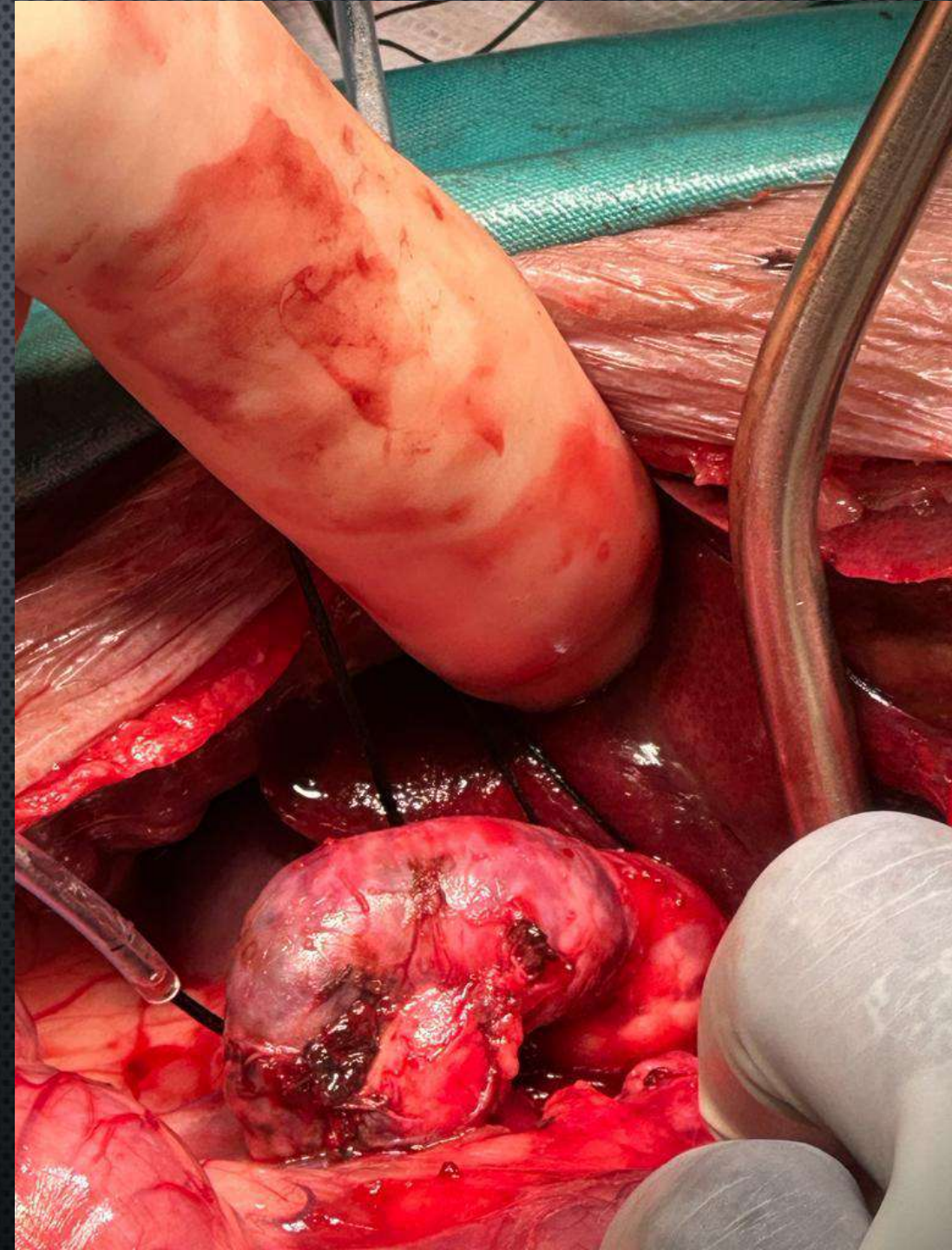
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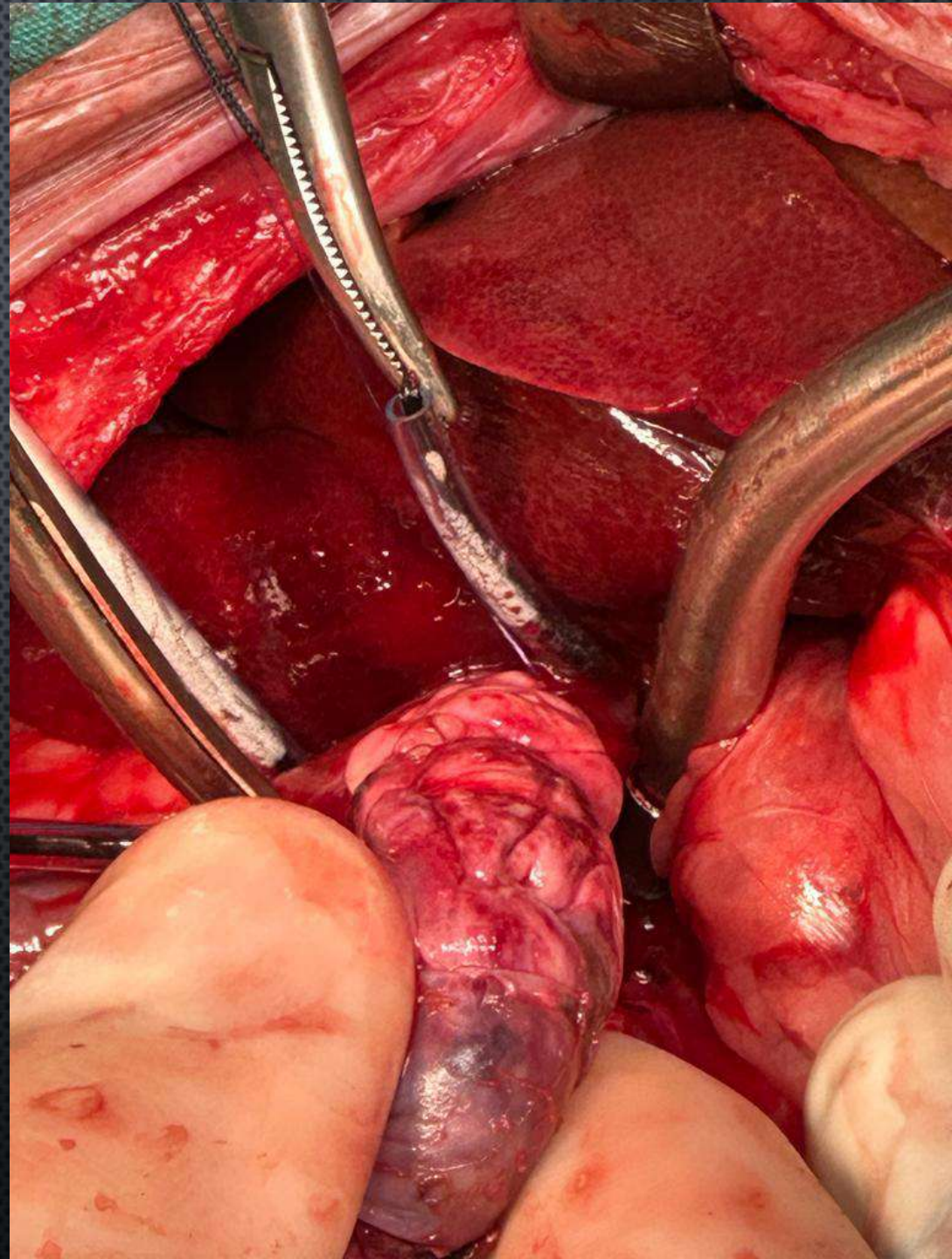
R ADRENAL IN CVC



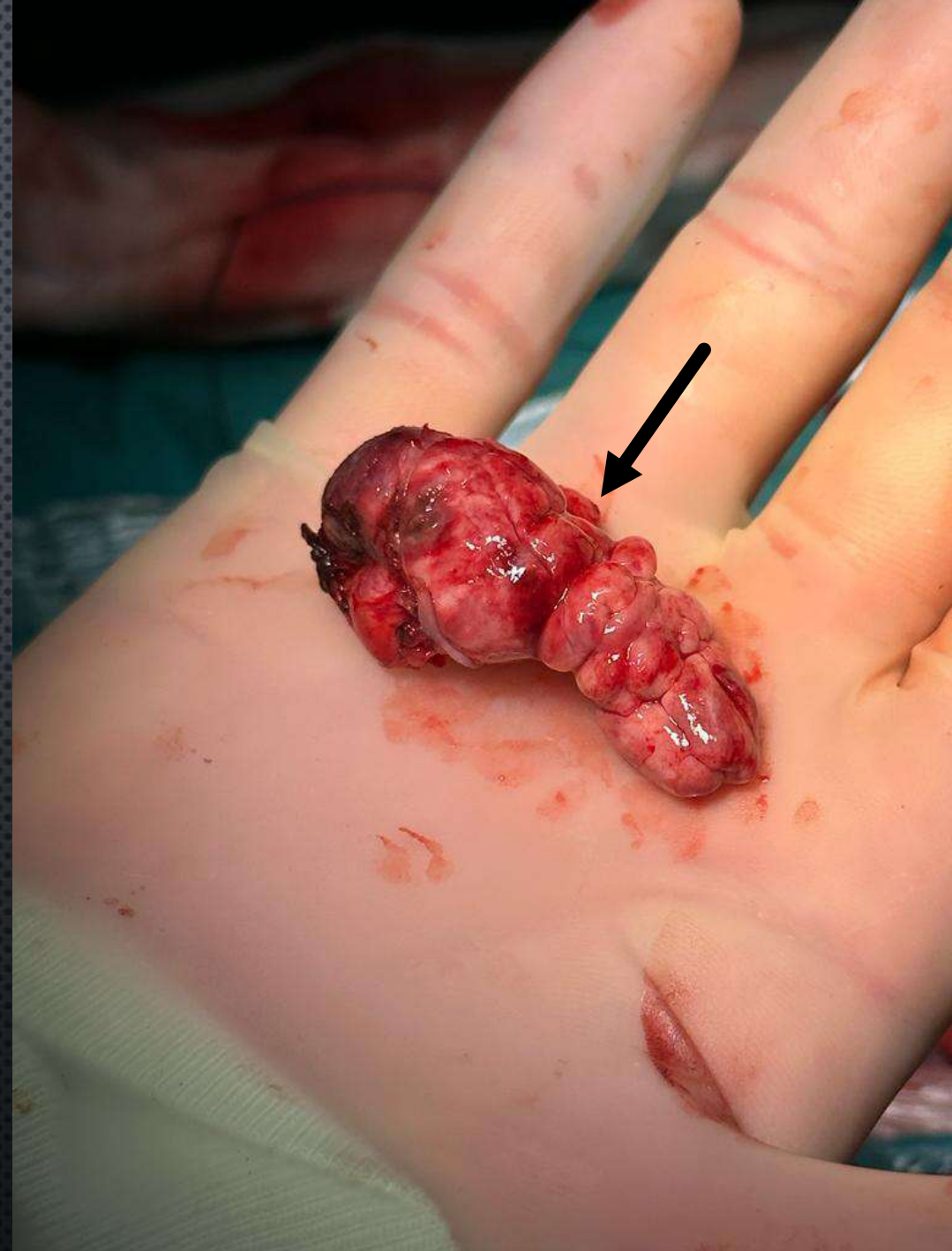
SIALOADENOS WITH
R ADRENAL TUMOUR IN CVC



SIALOADENOS WITH
R ADRENAL TUMOUR IN CVC



R ADRENAL
– 2/3RDS WAS IN CV



CUSHING'S –BILATERAL ADRENALECTOMY

HYDROCORTISONE INFUSION

- HYDROCORTISONE SODIUM SUCCINATE
- 1 MG/ML SOLUTION
 - 0.5 MG/KG/HR FOR 24 HOURS
 - 0.25 MG/KG/HR FOR 24 TO 48 HOURS
- INTRODUCE ORAL MEDICATION:
 - CORTISONE ACETATE 0.5MG/KG/12H - 24H
 - DEOXYCORTISONE PIVALATE 1 - 1.5 MG/KG/28 DAYS [PERCORTEN]
 - MOST CAN GO AS LOW AS 0.8 TO 1 MG/KG/4 WEEKS

CUSHING'S DISEASE – SUMMARY SLIDE

OPTIMISING MANAGEMENT

NEED TO BEAR IN MIND WHAT WE ARE TRYING TO ACHIEVE

- RELIABLE REDUCTION OF CLINICAL SIGNS
- NEED TO ACHIEVE A BALANCE BETWEEN ENSURING THERE IS:
 - REAL AND CLEAR “NORMALISATION” OF THE DOG
 - ONLY MILD FEAR ABOUT “OVERDOING IT” AND CREATING HYPOADRENOCORTICISM
- CONSIDER USING “BIOMARKERS” AS WELL AS HISTORY AND CLINICAL +/-

SERUM CORTISOL LEVELS

ALMOST NORMALIZE SERUM ALP AND NORMALISE CHOLESTEROL

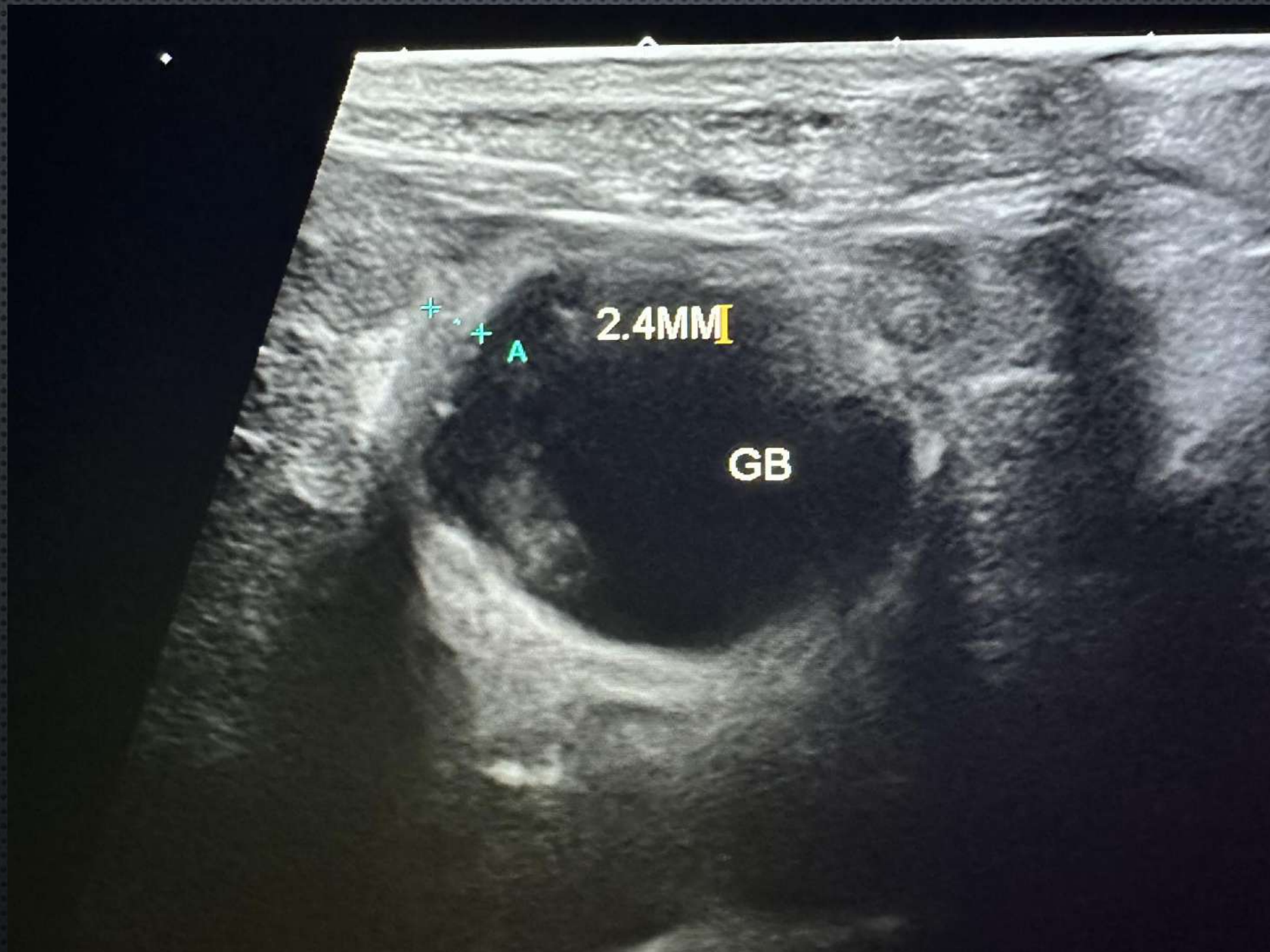
PRESENCE OF A STRESS LEUKOGRAM

NORMAL SERUM Na AND K CONCENTRATIONS

URINE SG > 1.020



GB WALL
OBVIOUS







BACK TO
BENTLEY ON.
RECHECK NO.
2 AFTER 8
WEEKS AT JSVC

BENTLEY VISIT I – TRILOSTAN 30 TO 40 MG BD

Test Date: 04 May 2023 10:50 AM

<u>TP</u>	58 g/L	52 - 82
<u>ALB</u>	26 g/L	22 - 39
GLOB	32 g/L	25 - 45
<u>ALB/GLOB</u>	0.8	
<u>ALT</u>	156 U/L	10 - 125
<u>ALKP</u>	1646 U/L	23 - 212
<u>GGT</u>	19 U/L	0 - 11
<u>TBIL</u>	4 µmol/L	0 - 15
<u>CHOL</u>	11.02 mmol/L	2.84 - 8.26
Na	152 mmol/L	144 - 160

BENTLEY VISIT II – TRILOSTAN 40 TO 50 MG BD

BENTLEY: 45798 Terry and Nolene Brown

Catalyst One

Test Date: 26 June 2023 12:03 PM

Test	Results	Reference Interval
<u>CA</u>	2.40 mmol/L	1.98 - 3.00
<u>ALKP</u>	894 U/L	23 - 212

BENTLEY VISIT III – TRILOSTAN 50 MG BD

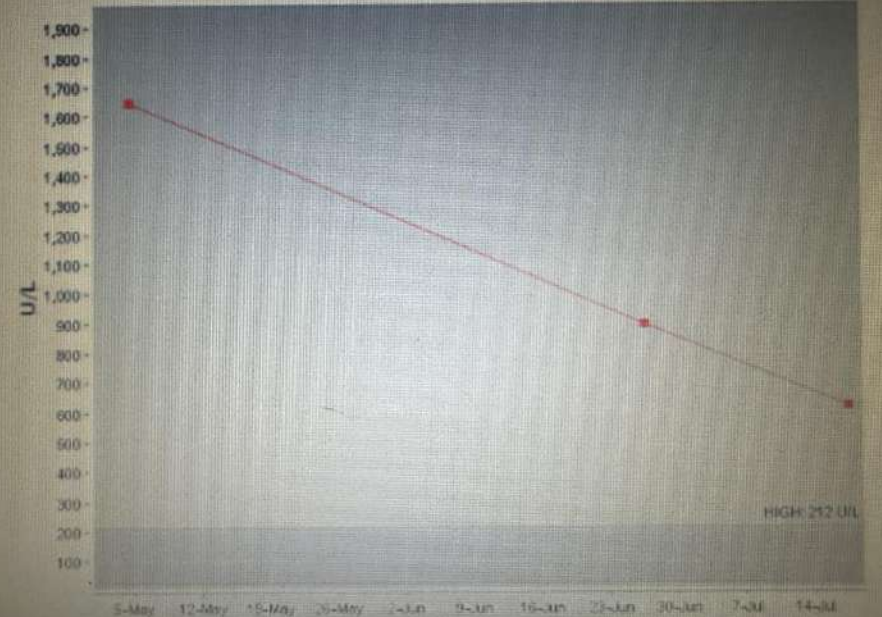
Catalyst One

Test Date: 17 July 2023 11:19 AM

Test	Results	Reference Interval	LOW	HIGH
GLU	6.20 mmol/L	3.89 - 7.95		
CREA	46 µmol/L	44 - 159		
UREA	3.8 mmol/L	2.5 - 9.6		
BUN/CREA	21			
TP	58 g/L	52 - 82		
ALB	27 g/L	22 - 39		
GLOB	31 g/L	25 - 45		
ALB/GLOB	0.9			
ALT	106 U/L	10 - 125		
ALKP	615 U/L	23 - 212		

Patient name: Bentley
Species: Canine
Breed: Boston Terrier

Age: 12 Years



Coat - looks better and shinier - wow
Alopecia - bald abdomen and legs and neck - definitely tiny bit of growth
Lower legs - look less licked - but not normal [dave thinks its CC causing itching]
CC - between shoulder blades - wow better
Heart murmur - loudest Left PMI
Mouth and teeth look Ok
Still - Obvious URT tract stenosis with insp noise BUT way less effort for first time that Dave has seen
Temp 37.8 RR 16 hr 155 ish

Advised:

URT - needs sorting as will cause pulmonary fibrosis thru hypoxaemia and then PH
- so when cushings a bit better controlled scope and surgery [lets plan for - Mid Sept]

Skin and coat

- needs cushings controlled - maybe its all CC

Heart

- MMVD - continue Vetmedin and monitor SRR which at 23 is great
- owners know to panic if repeatedly over 30

Cushings - dose is probably enough

- stay on 50 mg bd and recheck in 2 months if not suddenly an old dog with no zest and really flat
- then panic

BENTLEY ADVICE.

Cushings - dose is probably enough

- stay on 50 mg bd and recheck in 2 months if not suddenly an old dog
- then panic

NOTE - if we are unsure regards progression

- we will do a 3-4 h post Am doing ACTh stim at Parkmore
- that will tell us if we are overdosing if his appetite drops more
- that will tell us if we are underdosing if Alkp chol and hair growth not normalise

CHECKING GB FOR MUCOCOELE





URT STRESS OF BREATHING
VS INCIDENTALOMA VS
PHAEOCHROMOCYTOMA
VS ADH VS PDH

HANNAH

- 11-YEAR-OLD YORKIE
- FULL GAMBIT OF SIGNS BUT ESP. POLYPHAGIA AND MUSCLE WEAKNESS
- LARGE ADRENALS 10- AND 12-MM DIAMETER
- ALKP 1800, CHOL 10, URINE SG 1.007, HT 60, PLATELETS 760
- LDDST DOES NOT SUPPRESS AND ESCAPES

DO YOU AGREE ITS CUSHING'S – WOULD YOU TREAT?

HANNAH – 5.6 KG

- TRILOSATNE STARTED 10 MG OID
- AFTER 4 WEEKS NO HELP AT ALL SO 15 MG OID
- AFTER 4 WEEKS NO HELP AT ALL SO 10 MG BD
- AFTER 4 WEEKS A BIT BETTER
- AFTER 6 WEEKS STILL OVERTLY CUSHING OID SO 20 MG BD
- AFTER 6 WEEKS STILL POLYPHAGIC BUT SIGNS A LOT BETTER – 25 MG BD
- ETC
- CONTROLLED CLINICALLY AND BIOMARKERS 35 MG BD

HANNAH 5 KG

- 35 MG DOSED 2X/DAY WITH FOOD [RECHECK 4 MONTHLY]
- 28 MONTHS LATER – SUDDENLY AN OLD DOG WITH NO ZEST AND NOT EAT
 - PANIC – STOP MEDS CALL DAVE
 - CLIN, BLOODS, URINE ALL FINE
- NEEDED MEDROL $\frac{1}{4}$ 4 MG TAB DAILY FOR 3 WEEKS
 - THEN EOD 2-3 WEEKS THEN ATE FINE
- CUSHINGOID AGAIN 9 WEEKS LATER
- RESTARTED 5 MG ONCE DAILY
- WELL CONTROLLED CLINICALLY AND BIOMARKERS TILL PASSED ON FROM MMVD



STOFFEL



STOFFEL – LOOKS LIKE BUTTER WOULD NOT MELT IN HIS ..

JULY '23

DOING WELL, CLINICALLY HEALTHY,
HOWEVER, PU/PD FOR LAST FEW WEEKS

DRY FLAKING SKIN- OWNER REPORTS PUSTULES, WITH FLAKING
SKIN,

URINE SG 1.005, PH7, PROT 1+

NORMAL FBC AND CHEM 15 WITH LYTES

STOFFEL

FEB '24 - ATTACKED BY EAGLE - LEG FRACTURE

MARCH '24

- OBVIOUS PLUMP ADRENALS BUT NORMAL LAYERING
 - RHS - 8.4
LHS - 8.1 CAUDAL AND 7.6 CRANIAL POLE
- URINE SG 1.010
- TOTAL T4 - 6.31 WITH cTSH - 0.096
- LDDST – 104 TO 79 TO 101
-

STOFFEL – 7 MAY

TRILOSTANE 15MG/CAP

1 CAPSULE 1X/DAY IN AM WITH FOOD

- IF ALL CUSHING'S SIGNS CLEAR
- THAT'S' OUR GOAL [WITHIN 6 WEEKS]
- IF STILL HAS SIGNS - UNDERDOSING SO UP DOSE AFTER 4-6 WEEKS

IF SUDDENLY AN "OLD DOG" WITH POOR LUST FOR LIFE AND NOT EAT WELL OR VOMITS OR DIARRHOEA STOP MEDS ASAP AND CALL DAVE - PANIC

STOFFEL – LAST WEEK MAY

3 WEEKS INTO TRILOSTANE RX

- LAST 2 DAYS NO TRILOSTANE AS NOT EATING.
- LAST NIGHT ATE SOME DROE WORS, REFUSED THIS MORNING.
- VOMITED TWICE YESTERDAY AM AND PM. MOSTLY BILE AND SOME FOOD

OCT 29TH - OVER 5 MONTHS SINCE STOPPED TRILOSTANE

- PRED - 1/4-TAB DOSED EOD - OWNERS CAN'T DO LESS THAN THAT YET

[BUT WAS 1/2 TAB DAILY 6 WEEKS AGO]

- PERCORTEN - VERY LOW DOSE AT 0.8 MG/KG/DOSE

WE ARE TRYING TO GO FURTHER AND FURTHER APART

WAS 5 WEEKS AGO

- LIBRELLA

HELP IS BRILLIANT AND HE EVEN DOES STAIRS

ROCKET C



ROCKET C

- CC CONTROLLED – STARTED BD MEDS AT 1.5 TO 2MG/KG BD
- POT BELLY CONTROLLED
- PUPD CONTROLLED
- POLYPHAGIA CONTROLLED
- BIOMARKERS 70% PLUS IMPROVED

ROCKET C



ROCKET C



ROCKET
C



ROCKET C

- THEN APPETITE STARTED TO DROP OFF
 - SO - STOPPED TRILOSTANE
- PUPD WAY WORSE BUT APPETITE STILL POOR
 - SO ACTH – TO 1200
- SO MRI



ROCKET C

- SHIVERING A LOT
- VISION CHANGE / LOSS
- POOR APPETITE
- CHANGED BEHAVIOUR



SKYE B

- PH FROM LONG TERM URT STENOSIS
- BONEY MASS ON SKULL
- MMVD
- CUSHING'S — SEEN BASICALLY BALD WITH POT BELLY AND PUPD, LARGE ADRENALS BUT NOT POLYPHAGIA

SKYE B

- 13 KG DOG STARTED ON 10 MG OID FOR 6 WEEKS
 - OWNERS READ WRONG GOOGLE REVIEWS
- THEN 20 MG OID FOR 6 WEEKS
- THEN 20 MG BID FOR 2-4-6 WEEKS AND 1 MONTH CHECK
- THEN SIGNS OF OVERDOSE 6 WEEKS LATER SO STOPPED
 - PANIC

SKYE B

- WHEN STOPPED – HT 32 WITH HIGH LYMPH'S, NORMAL LYTE'S – APRIL
 - BUT BEST COAT HE HAD HAD FOR 18 MONTHS
- CUSHING'S SIGNS BACK – END MAY – RESTARTED 10 MG OID
- WITHIN 3 WEEKS SIGNS OF OVERDOSE AND NEEDED LOW DOSE PRED FOR 6 WEEKS TO GET HIM TO EAT
- NOW NOV AND NO SIGNS BACK YET