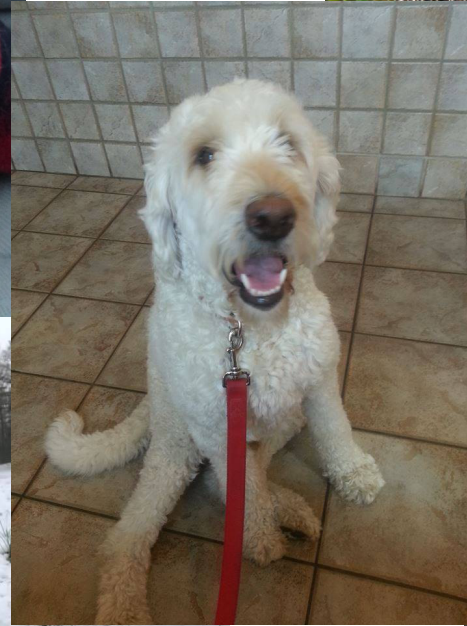


Addison's Disease

The Great Pretender



Presented by Dani Merriss, RVT, VTS (ECC, SAIM)



Typical Symptoms of Addison's Disease

- Vomiting
- Diarrhea
- Anorexia
- Lethargy
- Weight Loss
- "ADR"
- Increased Thirst
- Increased Urination
- Muscle Weakness
- Shaking or shivering

These symptoms can wax and wane for weeks to months to years in some undiagnosed dogs



What is Addison's?

Hypoadrenocorticism – A deficiency in the production of steroids by the adrenal glands

- **Primary:** Due to destruction of adrenal cortex
 - Typical: A deficiency of both mineralocorticoids and glucocorticoids
 - Atypical: A deficiency of only glucocorticoids
- **Secondary:** A deficiency of ACTH secretion by the pituitary gland
 - Causes glucocorticoid deficiency only



Adrenal Gland Physiology

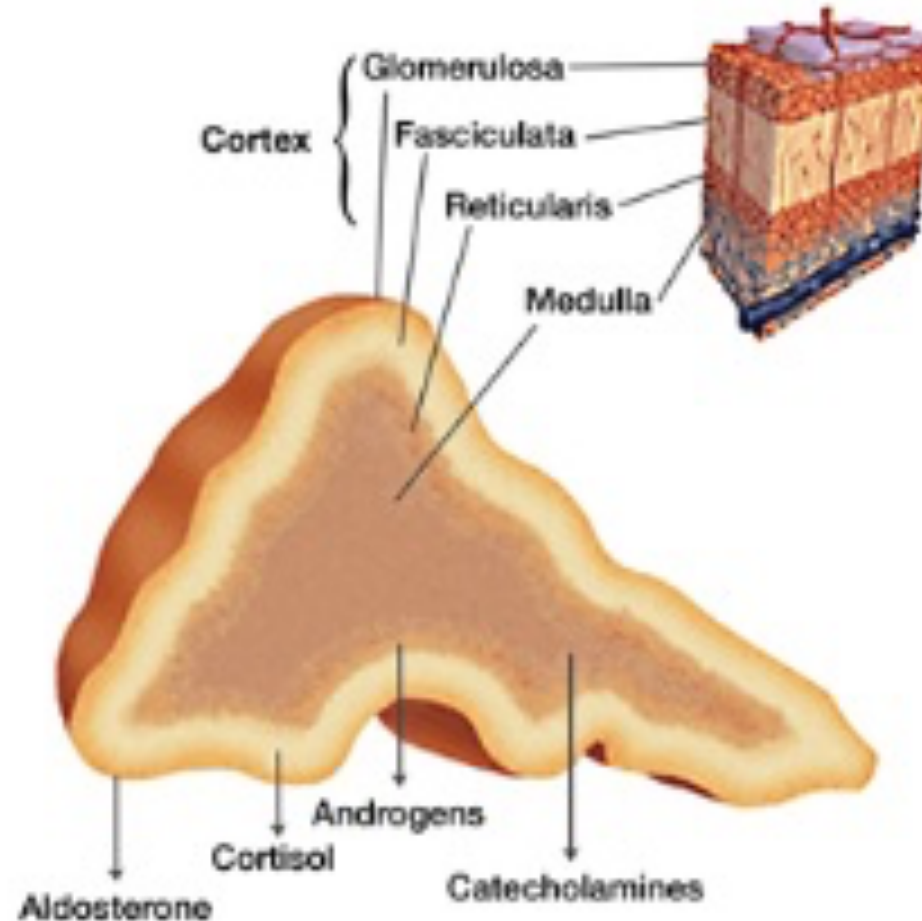
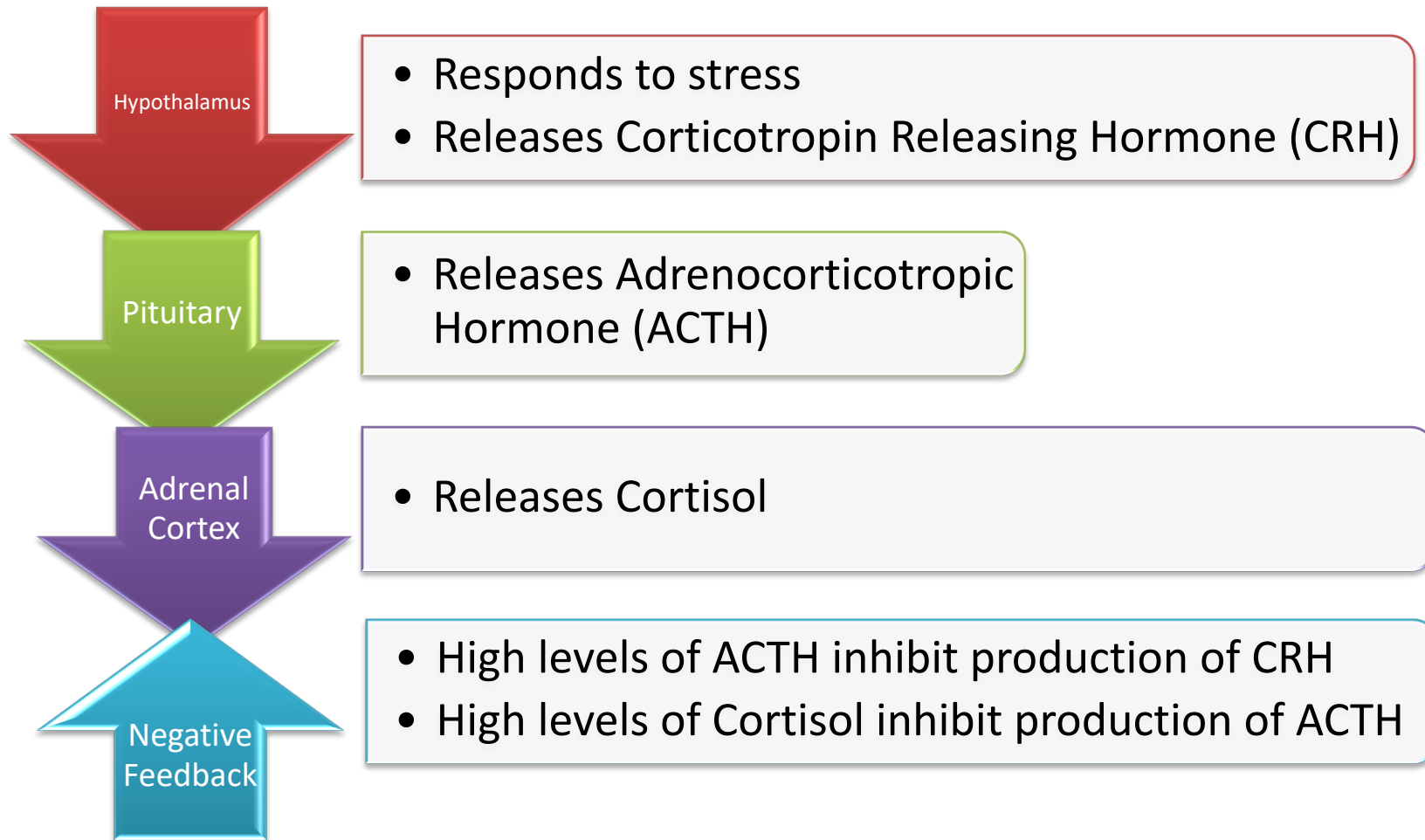


Photo credit: Today's Veterinary Practice
Sept/Oct 2014, Canine Hypoadrenocorticism.
Lottati & Bruyette



Hypothalamus – Pituitary – Adrenal (HPA) Axis



Endogenous Glucocorticoids (Cortisol)

- Promotes gluconeogenesis
 - Maintain normal blood glucose
- Anti-inflammatory properties
- Maintain integrity of GI tract
- Improve peripheral vascular resistance
 - Enhance vascular response to catecholamines



Symptoms of Cortisol Deficiency

Hypoglycemia

Nausea

Anorexia

Vomiting

Diarrhea

Weight Loss

Low Blood
Pressure

GI
Hemorrhage



Renin-Angiotensin-Aldosterone-System (RAAS)

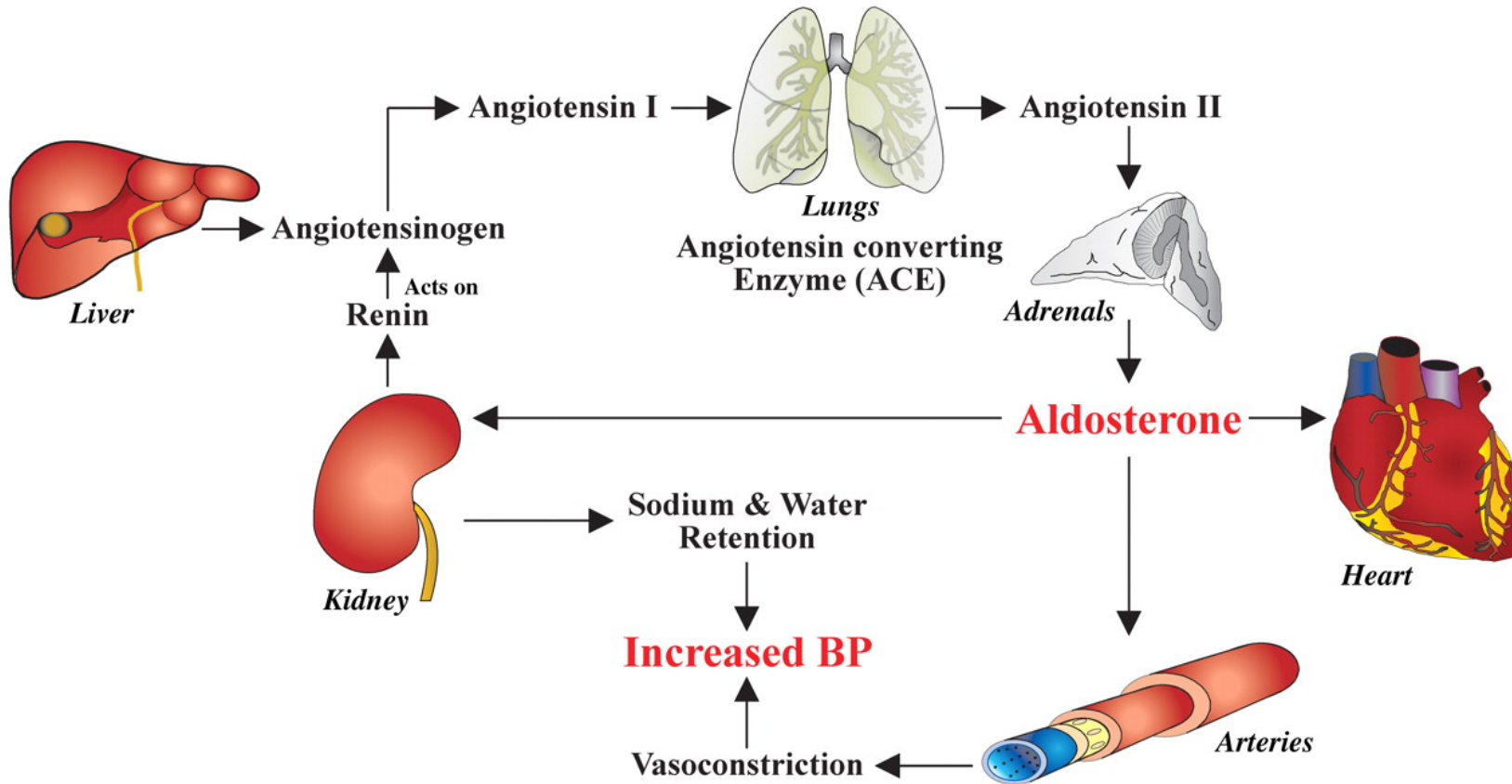


Photo Credit: Renal Fellow Network,
08/27/09 Blog post, Nathanhellman



Endogenous Mineralocorticoids (Aldosterone)

- Facilitate exchange of sodium and potassium
 - Sodium retention and potassium excretion
- Maintain normal blood pressure
 - Sodium retained promotes fluid retention, which increases blood volume



Symptoms of Aldosterone Deficiency

Increased Thirst

Increased Urination

Low Blood Pressure

Symptoms of Hyperkalemia

- Bradycardia
- Muscle Weakness
- Collapse



Signalment

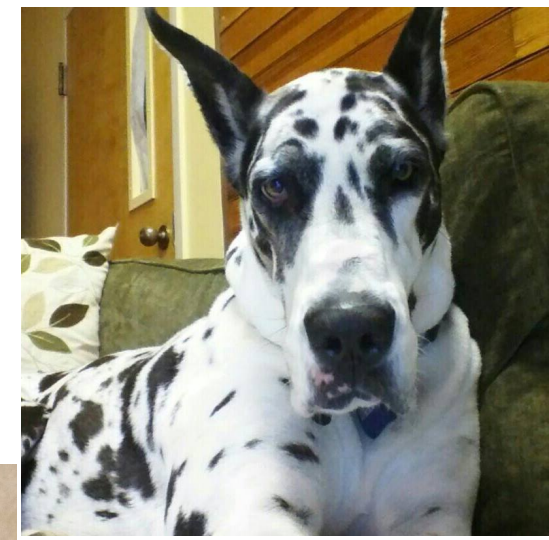
- Average age of diagnosis is 4-6 years
 - Can be as young as 4 weeks or as old as 14 years
 - Secondary AD is typically older dog (possible pituitary tumor)
- Females make up 70% of diagnosed cases
 - Portuguese Water Dogs, Bearded Collies and Standard Poodles are equal male/female



Breeds With Higher Incidence of AD

- Bearded Collie *
- Basset Hound
- Great Dane
- Port. Water Dog *
- German SH Pointer
- Westie
- Saint Bernard

*Genetic Link Found



Breeds Continued

- Standard Poodle *
- Rottweiler
- Wheaten
- Nova Scotia Duck
- Tolling Ret +/-*
- Airedale
- Springer Spaniel
- Lab

*Genetic link found



Diagnosing Addison's Disease

Chemistry

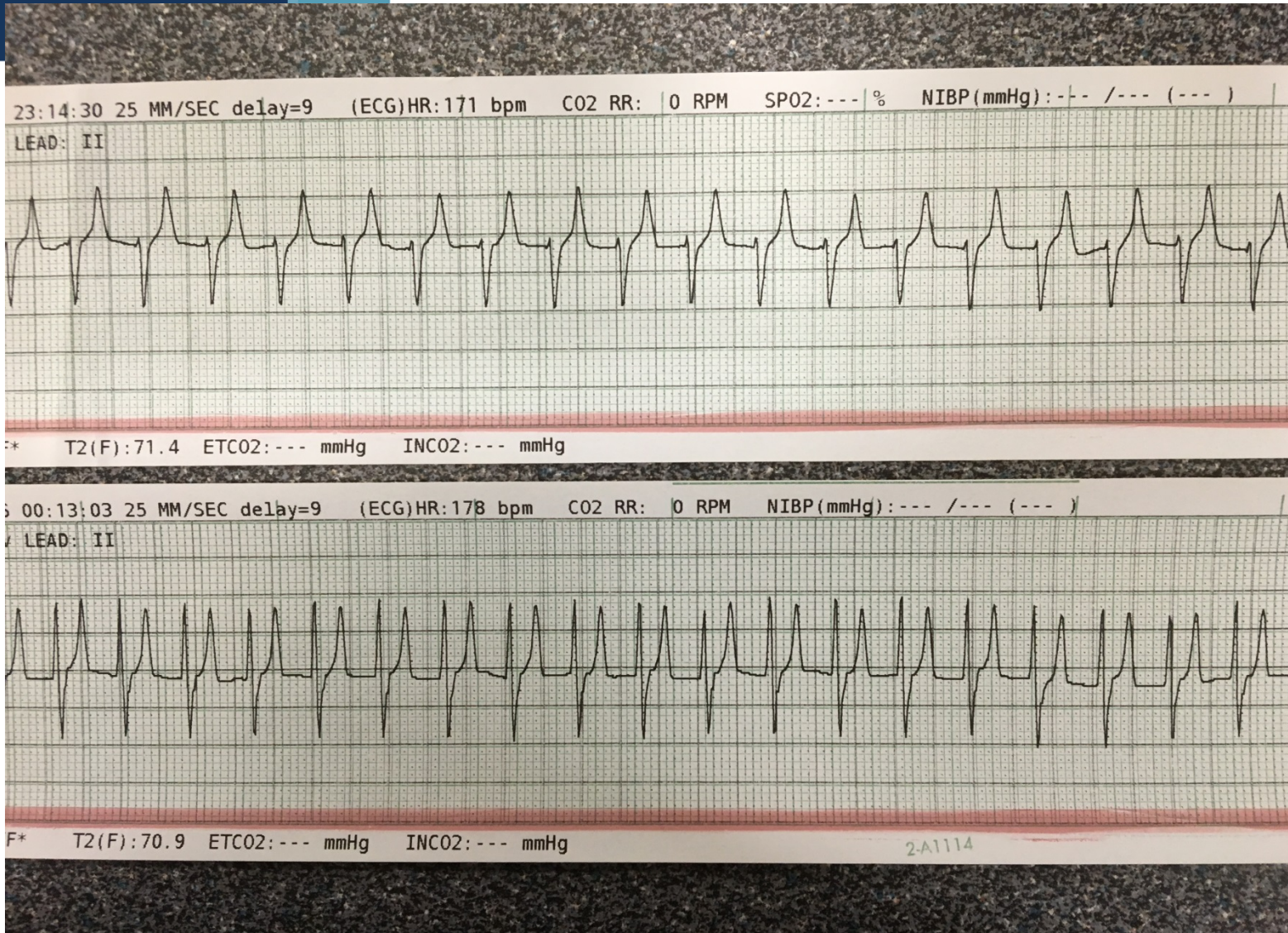
- **Sodium/Potassium ratio <27** (Primary typical only!)
- Pre-renal azotemia (secondary to dehydration)
- Other possible changes (seen in ~30% of cases)
 - Hypoglycemia
 - Elevated liver enzymes
 - Low albumin
 - Low cholesterol
 - High calcium

Urinalysis

- Dilute urine, usually <1.030, often much less



EKG Changes With Hyperkalemia



Potassium 10.3

Atrial
standstill

No P wave

Tall tented T
wave

Bizarre wide
complexes

Potassium 8.0



Confirming Addison's Disease

Cortisol baseline test

- Can be done in house with Idexx Snap reader
- Results >2.0 make Addison's less likely
- Can NOT be used for ACTH Stim
 - Will get falsely high results on “post” stim sample

ACTH Stim

- Gold standard for diagnosing AD
- “Pre” sample is drawn, then Cosyntropin (synthetic ACTH) is injected IV
- “Post” sample is drawn 60-120 minutes later (depending on protocol used)
- AD dogs will have poor response to ACTH (low “post” numbers)



Important Things To Remember!

Patient can NOT be on most steroids

- Prednisone and hydrocortisone interfere with cortisol assay = false results
- Dexamethasone does not interfere and can be given safely

Most patients need immediate treatment

- Do not wait for results of ACTH stim before starting treatment!
- Can start life saving treatments without starting long term medications

Rule out AD “look-alikes”!

- Renal disease will cause azotemia, isosthenuria, and hyperkalemia
- Severe whipworm infestations will cause very similar bloodwork to AD



Treating the Addisonian Crisis

- **IV fluids! NaCl 0.9%**
 - Bolus and calculate % dehydration to replace deficit
 - NaCl chosen to replace sodium deficit
- **Treat hyperkalemia**
 - Dextrose +/- insulin IV moves potassium intracellularly
 - Monitor EKGs: Bradycardia and arrhythmias common
 - Consider calcium gluconate if life threatening rhythm (cardioprotective effects)
- **Treat hypoglycemia**
 - Dextrose bolus +/- CRI
 - May worsen if insulin is given



- **GI medications**

- Address nausea (maropitant, ondansetron)
- Consider GI protectant for possible GI bleed (sucralfate, omeprazole)

- **Glucocorticoid replacement**

- Dexamethasone SP only until ACTH stim test is performed!

- **Blood?**

- Some have severe anemia (GI bleed)



Long Term Management

Glucocorticoid replacement

- Primary typical AD
- Primary atypical AD
- Secondary AD

Mineralocorticoid replacement

- Primary typical AD ONLY!



Glucocorticoid Options

Prednisone

- Most common drug used
- Higher dose at crisis (0.1-0.22mg/kg)
- Maintenance dose = much lower
 - 0.1-0.2mg/kg initial, then lower dose (Peterson, 2003 Addison's Roundtable discussion)
 - On average, 1mg SID per 100 lbs (Greco, 2003 Addison's Roundtable discussion)

Prednisolone

- Can be used for patients with elevating liver enzymes

Cortisone, Hydrocortisone

- Shorter half life, need twice daily dosing



Finding the Ideal Dose

Too Little Glucocorticoid:

- Decreased appetite
- Nausea
- Vomiting
- Loose stool
- Diarrhea
- Shaking/shivering
- Weakness

Too Much Glucocorticoid:

- Excessive panting
- Increased thirst
- Increased urination
- Increased appetite
- Agitation
- Aggression
- Coat color/quality changes



Prednisone Reduction Schedule

- Week 1: Alternate 3.75mg on days 1,3,5,7 and 5mg on days 2,4,6
- Week 2: Hold at 3.75mg for 7 days
- Week 3: Alternate 2.5mg on days 1,3,5,7 and 3.75mg on days 2,4,6
- Week 4: Hold at 2.5mg for 7 days
- Week 5: Alternate 2mg on days 1,3,5,7 and 2.5mg on days 2,4,6
- Week 6: Hold at 2mg for 7 days
- Week 7: Alternate 1.5mg on days 1,3,5,7 and 2mg on days 2,4,6
- Week 8: Hold at 1.5mg for 7 days
- Week 9: Alternate 1.25mg on days 1,3,5,7 and 1.5mg on days 2,4,6
- Week 10: Hold at 1.25mg for 7 days
- Week 11: Alternate 1mg on days 1,3,5,7 and 1.25mg on days 2,4,6
- Week 12: Hold at 1mg for 7 days



Stress

- Addison's dogs do not have the physical capability to respond to a stressful situation like a normal dog would
- Give additional glucocorticoid for stressful situations – physical or emotional
 - Surgery
 - Trauma/severe injury
 - Grooming, vet visits, showing, hunting, etc



Mineralocorticoid Options

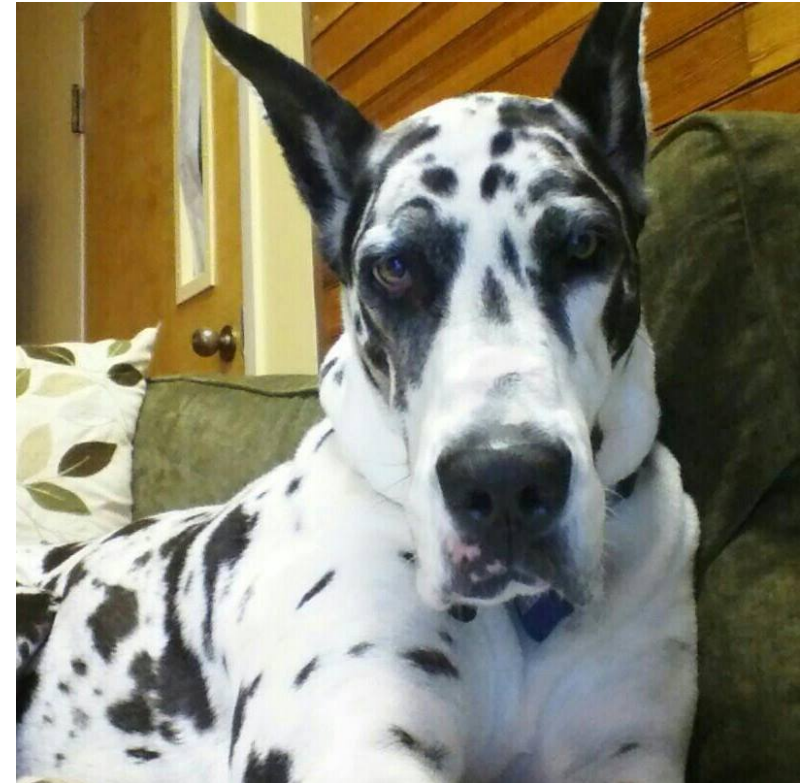
Desoxycorticosterone Pivalate (DOCP)

- Percorten V
- Zycortal

OR

Fludrocortisone Acetate

- Florinef
- Astonin H
- Generic
- Compounded



DOCP

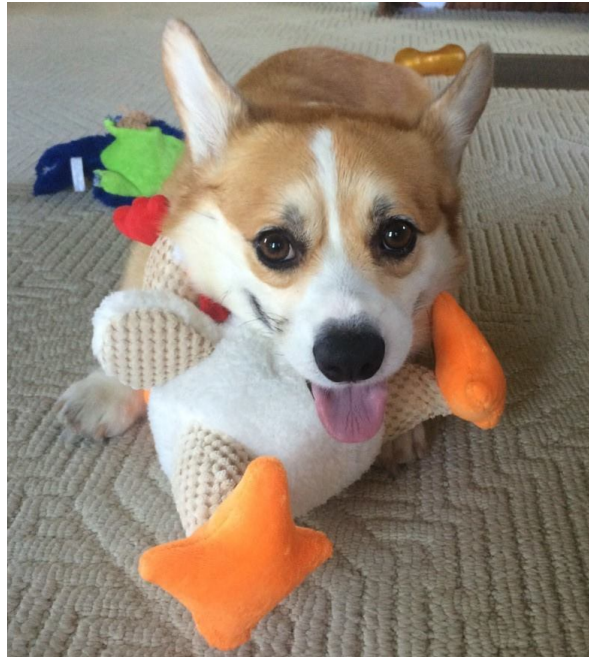
- DOCP is an injectable form of mineralocorticoid replacement
- It is ideally dosed SQ or IM every 28 days
- Available in two brands
 - Percorten V: Available in US and Canada
 - Zycortal: Available in US, Canada, Australia and many European countries



DOCP

CONS:

- Expensive, especially when at higher dose than needed
- Is an injection, requiring a vet visit unless giving at home



PROS:

- Only needs to be given every 28 days
- Stable electrolyte levels once at ideal dose
- Completely separate mineralocorticoid and glucocorticoid dosing
- Less electrolyte testing (compared to fludrocortisone)
- Veterinary drug FDA approved for dogs



Monitoring DOCP

- Initial dose is typically 2.2 mg/kg
- Electrolytes should be checked at day 14 and day 28 of initial cycle or with any large reductions
- Next injection should be given when potassium is at/above halfway point
- Reduce by 10% for every week past 28 days



- Low dose protocol: 1.0mg/kg
 - Get to lowest ideal dose quicker, less incidence of hypokalemia, less expensive for client
- Once at lowest ideal dose, check electrolytes every 3-6 months
- Some vets prefer to leave at high dose and stretch out dosing interval
 - Requires more frequent electrolyte testing and clients must monitor closely for signs of hyperkalemia
 - Possibility of highs and lows with lytes



Fludrocortisone

- Fludrocortisone is an oral form of mineralocorticoid replacement
- Initial dose 0.1mg/10lb divided into twice daily dose
- Dose is increased as dogs develop resistance to it
- Has glucocorticoid properties: 0.25mg pred equivalent/0.1mg tablet
- Is a human medication



Fludrocortisone

CONS:

- Requires more frequent electrolyte testing
- Dogs become resistant, requiring higher and higher dosing
- Too much glucocorticoid causes side effects (especially medium/large breed dogs)
- Hard to find in some areas
- Human medication

PROS:

- Is orally administered
- Is potentially less expensive (small breed dogs)



Monitoring Fludrocortisone

- Initial dose 0.1mg/10lbs, divided
- Check electrolytes 7-14 days after dose changes to assess progress
- Ideal potassium is midrange or just below
- Some dogs have problem with persistent hyponatremia
 - Consider adding salt to diet



- Often dogs need a very low dose of prednisone or none at all due to glucocorticoid properties of fludrocortisone
- As dose increases, (or initially with large breed dogs) side effects of too much glucocorticoid will be seen
 - Panting
 - PU/PD
 - Urinary accidents



Primary Atypical Addison's

- Glucocorticoid deficiency only
- Thought to be from incomplete destruction of adrenal cortex
- A large percentage will convert to primary typical AD within a year!
- Test electrolytes monthly for first three months, then every 2-3 months in first year



- Instruct owners on symptoms of hyperkalemia
- Dogs will fail the ACTH stim test but have normal electrolytes
- Renal values and urinalysis should be normal
- May also still have hypoglycemia, low blood pressure, elevated liver enzymes
- More likely to be misdiagnosed!



Secondary AD

- Caused by a lack of ACTH secretion
 - Pituitary problem
 - Neoplasia or vascular event
- Normal adrenal glands!
 - Normal electrolytes (normal mineralocorticoid production)
 - Will never convert to Primary Typical AD
- Glucocorticoid deficiency only
 - Treat with prednisone



Diagnosing Secondary AD

- Endogenous ACTH levels
 - Should be high with primary AD
 - Large amounts of ACTH released to try and stimulate cortisol release with no negative feedback (no cortisol)
 - Will be low with secondary AD
- Corticotropin Releasing Hormone (CRH) Stim
 - Can be done if ACTH level is inconclusive
- MRI
 - May show mass, thrombosis, stroke or trauma
 - Typically performed for other symptoms/reasons



Case Study: Primary Typical AD

“Lovey”

- Six-year-old, female spayed greyhound
- History of chronic ulcerative periodontal stomatitis (CUPS)



- Entering complaint: **Weight loss and lethargy**
- History:
 - Two-year history of intermittent loose stool and poor appetite
 - Had been thought to be secondary to parasites and CUPS/severe dental disease
 - Had been dewormed multiple times and had three dentals with massive extractions
 - Had normal bloodwork at last dental, six months prior
 - Was adopted two years ago off of a racetrack
 - One week history of lethargy
 - No current medications





- Notice poor body condition? This was actually an improvement!
- Picture taken 14 days after diagnosis and wt gain of 4kg



Physical Exam:

- Wt loss: Patient had lost 15lbs since last physical exam three months prior (23% of her body wt)
 - Current wt: 23.2kg
- Dehydration: Patient was estimated to be 7-10% dehydrated
- Weakness and lethargy: Patient had dull mentation and was reluctant to walk or stand
 - Neurologic exam showed no CP or cranial nerve defects



C
B
C

Req ID: 183664-3 - Thursday 5/29/2014 18:27:00

Test	Results	Reference Range
RBC	8.41 M/uL	5.39 - 8.70
MCV	63 fL	59 - 76
MCH	24.1 pg	21.9 - 26.1
MCHC	38.4 g/dL	32.6 - 39.2
WBC	8.6 K/uL	H 4.5 - 7.5
LYMPHS	44.2 %	
MONOS	6.7 %	
BASO	0.0 %	
PLATELETS	166 K/uL	H 80 - 150
HGB	20.3 g/dL	13.4 - 20.7
HCT	52.9 %	50.0 - 65.0
EOS	0.0 %	
NEUT SEG	49.1 %	
RETIC CNT	0.2 %	
ABS BASO	0 /uL	0 - 100
ABS EOS	0 /uL	L 70 - 1490
ABS LYMPHS	3801 /uL	1060 - 4950
ABS MONOS	576 /uL	130 - 1150
ABS NEUTS	4223 /uL	2940 - 12670
ABS RET	17 K/uL	10 - 110

Lab Comments: Asc: 1200018894
RE: 3034 REMARKS
REMARKS
SLIDE REVIEWED MICROSCOPICALLY.
NO PARASITES SEEN
REACTIVE LYMPHOCYTES PRESENT
HEMOLYSIS PRESENT, RBC,HCT,MCV,MCH,AND MCHC AFFECTED BY
OF HEMOLYSIS.
PLEASE NOTE NORMAL REFERENCE RANGE FOR GREYHOUNDS (NO
GREYHOUNDS):

*Elevated WBC
--Possibly due to
severe dental disease?

*Borderline mild anemia



C H E M I S T R Y

Req ID: 183664-3 - Thursday

5/29/2014 18:27:00

Test	Results		Reference Range
GLU	108 mg/dL		63 - 114
BUN/UREA	52 mg/dL	H	9 - 31
CREA	3.3 mg/dL	H	0.5 - 1.5
PHOS	5.7 mg/dL		2.5 - 6.1
Ca	9.0 mg/dL		8.8 - 11.2
Sodium	129 mmol/L	L	142 - 152
Potassium	5.6 mmol/L	H	4.0 - 5.4
Chloride	104 mmol/L	L	108 - 119
BICARB	19 mmol/L		13 - 27
TP	5.3 g/dL	L	5.5 - 7.5
ALB	2.2 g/dL	L	2.7 - 3.9
GLOB	3.1 g/dL		2.4 - 4.0
A/G Ratio	0.7		0.7 - 1.5
ALT	53 U/L		18 - 121
AST	59 U/L	H	16 - 55
ALKP	54 U/L		5 - 160
APLEV	23		
CIALP	26 U/L		0 - 35
GGT	1 U/L		0 - 13
LDH	131 IU/L		50 - 380
TBIL	0.2 mg/dL		0.0 - 0.3
CHOL	64 mg/dL	L	131 - 345
TRIG	45 mg/dL		20 - 150
AMYL	1148 U/L		337 - 1469
LIPA	337 U/L		138 - 755
CK	840 U/L	H	10 - 200

*Elevated BUN

*Elevated Creatinine

*Low TP

*Low ALB

*Low Chol

*High AST

*High Potassium

*Low Sodium

*Low Chloride

*Na/K ratio: 23



U R I N A L Y S I S

Test	Results	Refer
COLOR	YELLOW	
CLARITY	CLEAR	
SP GRAVITY	1.026	
PH	6.5	
PROTEIN	NEGATIVE	
GLUCOSE	NEGATIVE	
KETONES	NEGATIVE	
BLOOD	NEGATIVE	
BILIRUBIN	NEGATIVE	
UROB	NORMAL	
WBC	NONE SEEN HPF	
RBC	0-2 HPF	
BACTERIA	NONE SEEN HPF	
EPI CELL	RARE (0-1) HPF	
MUCUS	NONE SEEN	
CASTS	NONE SEEN HPF	
CRYSTALS	NONE SEEN HPF	

Lab Comments: Asc: 1200018925
 RE: 900 COLLECTION METHOD CYSTOCENTESIS

*Inappropriate urine specific gravity in comparison to patient level of dehydration

*Otherwise normal



Initial Treatments:

- Calculate fluid deficit: $BW(\text{kg}) \times \% \text{ dehydration} = \text{fluid deficit in L}$
 - $23.2\text{kg} \times 0.1 = 2.32\text{L}$
- Maintenance fluid rate: 60ml/kg/day
 - $60 \times 23.2 = 1392 / 24 = 58\text{ml/hr}$
- Address any ongoing losses
 - Polyuria
 - No vomiting or diarrhea currently



- IV fluids: NaCL
 - 1000ml bolus over first hour
 - Remaining fluid deficit 1320ml to be administered over 24 hours (55ml/hr)
 - Decision was made to run her at 1 1/2x maintenance (to address polyuria) + fluid deficit
 - $58\text{ml/hr} \times 1.5 + 55\text{ml/hr} = 142\text{ml/hr}$



Additional Treatments:

- Maropitant 1mg/kg IV q 24
- Pantoprazole 1mg/kg IV q 24
- Sucralfate 1gm PO q 8
- Dexamethasone SP 0.25mg/kg IV once
- Clindamycin 300mg PO q12
- Tramadol 100mg PO q8-12



Additional Diagnostics:

- Fecal
 - Negative for parasites
- EKG
 - Normal QRS with no bradycardia
 - Arrhythmias typically seen with $K > 7.0$
- ACTH Stim
 - “Pre” Cortisol: 0.6 ug/dl (2-6)
 - “Post” Cortisol: 0.8 ug/dl (6-18)



Day 2

- Weight: 25kg (+1.8kg)
 - Remember fluid deficit of 2.3L x wt of 1.0kg/L = 2.3kg expected weight gain
- More alert
- Still polyuria present
 - Ongoing losses
- Bloodwork improved
 - Na/K ratio = 29
 - Azotemia resolved

Test	Results	Reference Range
GLU	= 114 mg/dL	74 - 143
BUN/UREA	= 24 mg/dL	7 - 27
CREA	= 1.2 mg/dL	0.5 - 1.8
Sodium	= 140 mmol/L	L 144 - 160
Potassium	= 4.9 mmol/L	3.5 - 5.8
Chloride	= 108 mmol/L	L 109 - 122
TP	= 3.9 g/dL	L 5.2 - 8.2
ALB	= 1.6 g/dL	L 2.3 - 4
ALB/GLOB	= 0.7	
ALT	= 58 U/L	10 - 100
ALKP	= 88 U/L	23 - 212
BUN/CREA	= 20	
Na/K	= 29	



Day 2: Continued Treatments

- Continued IV fluids at 2x maintenance (120ml/kg/day)
- Start oral prednisone 15mg PO
- Administer DOCP 2.2mg/kg IM



Long Term Management of Case:

- Day 28 lytes:

Test	Results	Reference Range
Sodium	= 149 mmol/L	144 - 160
Potassium	= 3.7 mmol/L	3.5 - 5.8
Chloride	= 110 mmol/L	109 - 122
Na/K	= 40	

- Day 72 lytes:

Test	Results	Reference Range	Low
Sodium	= 150 mmol/L	144 - 160	
Potassium	= 4.8 mmol/L	3.5 - 5.8	
Chloride	= 109 mmol/L	109 - 122	
Na/K	= 31		



- Prednisone: Was kept high for one week, then slowly reduced
 - Lovey's optimum dose is 1.25mg q24
 - This is higher than typical, however her CUPS went out of remission when lowered
- DOCP: Second injection was administered on day 72 using low dose protocol (1mg/kg = 26mg or 1.1ml)
 - Her electrolytes were tested at day 28 of each cycle, and her dose reduced accordingly
 - Her current DOCP dose is 0.45 ml (11.3 mg, 0.38mg/kg) SQ q28 days
- Current wt is 30-31kg (her normal, healthy weight)



Case Study: AD By Choice

- Bobbi, a 14yr FS English Springer Spaniel
- History of urinary incontinence and occasional UTIs



- Presented to ER 05/09 for acute onset nystagmus, ataxia and strabismus
- Patient was hospitalized on IV fluids and maropitant IV
- MRI revealed stroke in left medulla
- Owner was interested in full work up to determine cause of hypercoagulability



Diagnostics

- Echocardiogram: Normal
- Thyroid panel: Normal
- Abdominal U/S: Mild bilateral adrenal enlargement, otherwise normal
- Urinalysis + Culture: UTI
- ACTH Stim: Normal
- Sex hormone profile: Atypical Cushing's Disease



Case Continued:

- Patient was discharged on maropitant, amoxicillin, mirtazapine, and clopidogrel and told to follow up with rehabilitation therapy
- Bobbi returned to the ER on 05/25 with a return of neurologic symptoms including rotary nystagmus and a head tilt
- A second MRI showed a second stroke in the right cerebellum



- Bobbi was transferred to the internal medicine department the next day
- The decision was made to pursue adrenal ablation
 - The owner owned an AD dog and was familiar with the disease
 - There was significant concern that she was still having strokes while being medicated

Adrenal ablation permanently destroys the adrenal cortex, making the dog an Addisonian. It is achieved by administering mitotane 50mg/kg PO q24hrs for 30 days



Follow Up:

- Unfortunately, Bobbi suffered a third stroke before the adrenal ablation was complete
- The owner elected to have her put to sleep at that time





Any Questions?



Danielle.Merriss@medvetforpets.com

www.facebook.com/groups/CanineAddisonsResoucesandEducation

