Canine Hypoadrenocorticism

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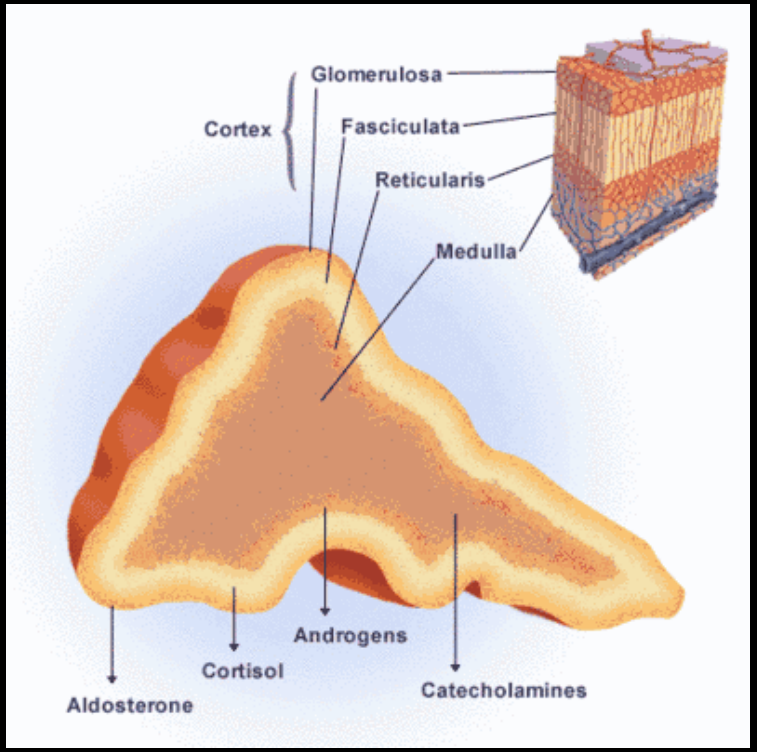
CANINE HYPOADRENOCORTICISM

Adrenal Physiology

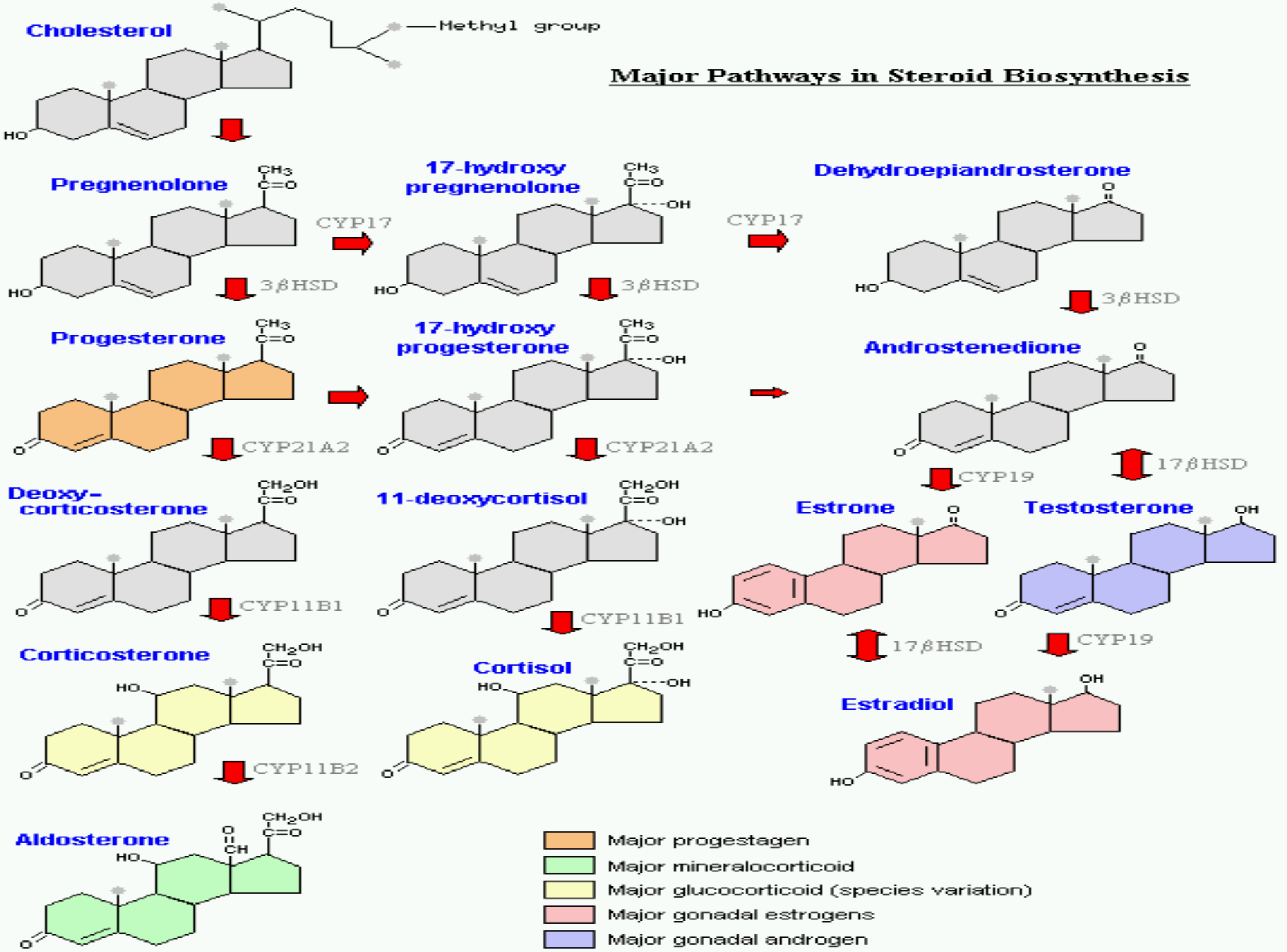
The adrenal gland is a two-part structure located on the cranial pole of each kidney and is essential for life.

Produces hormones

- Epinephrine
- Estrogen
- Testosterone
- Cortisol
- Aldosterone



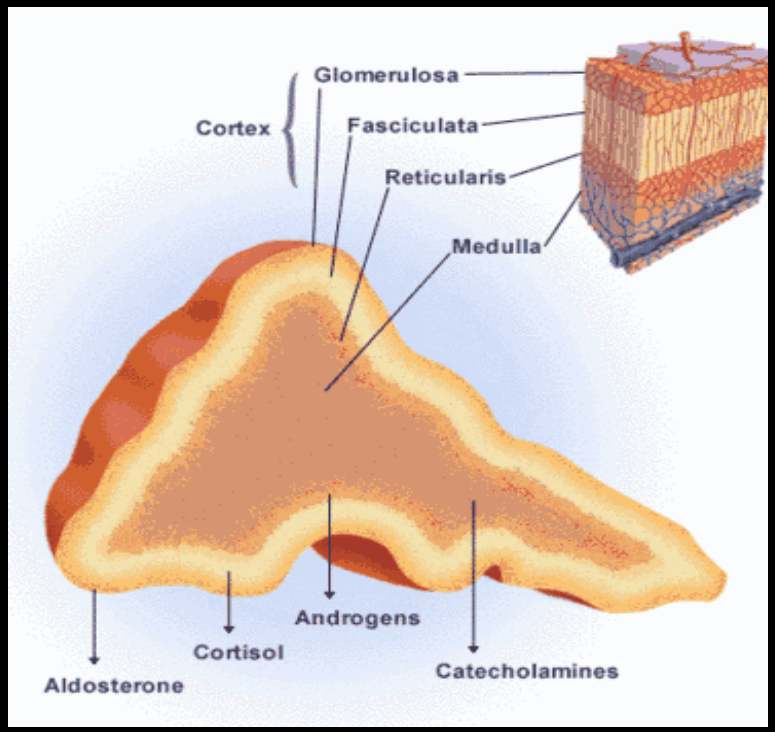
Major Pathways in Steroid Biosynthesis



CANINE HYPOADRENOCORTICISM

The outer zona glomerulosa of the cortex is primarily involved with the synthesis and secretion of the mineralocorticoid, aldosterone.

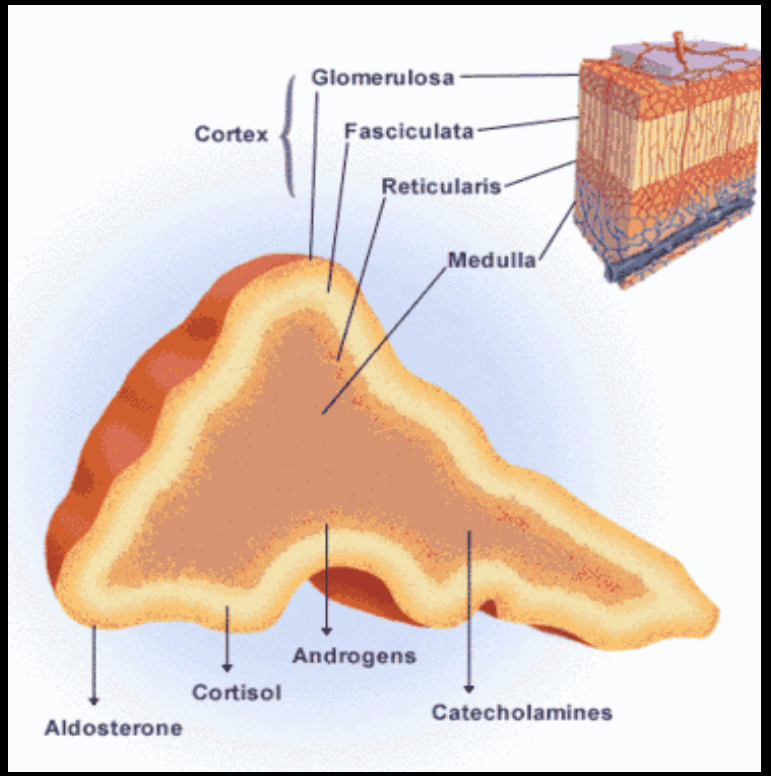
The middle zona fasciculata synthesizes and secretes glucocorticoids, of which cortisol is the most important in mammals.



CANINE HYPOADRENOCORTICISM

The inner zona reticularis of the adrenal cortex secretes primarily adrenal sex steroids (androgens and estrogens).

Depending on the cause, hypoadrenocorticism is associated with dysfunction of some or all of the three outer zones.

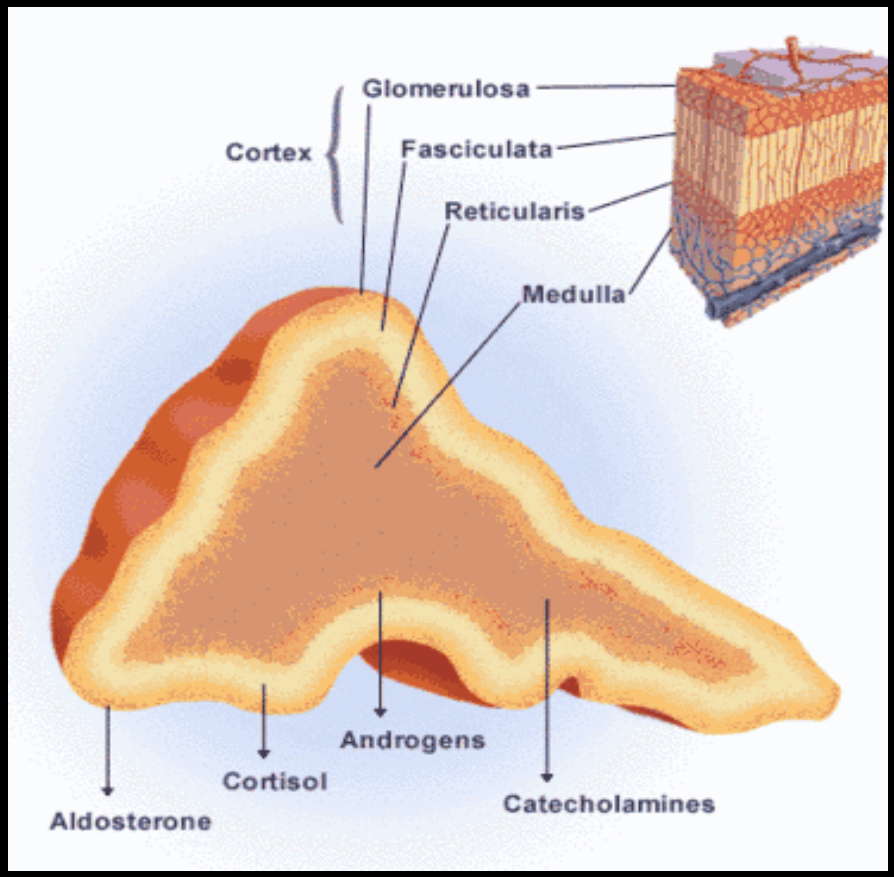


CANINE HYPOADRENOCORTICISM

Zona fasiculata and zona reticularis secrete glucocorticoids.

Dysfunction is associated with:

- Addison's disease.
- Long term administration of glucocorticoids
- Lysodren, trilostane
- Isolated glucocorticoid insufficiency

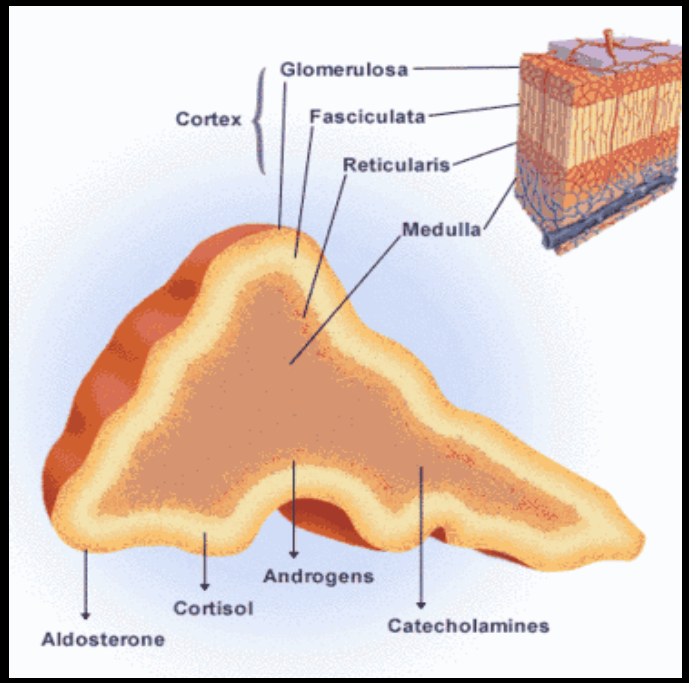


CANINE HYPOADRENOCORTICISM

Zona glomerulosa secretes mineralocorticoids (aldosterone).

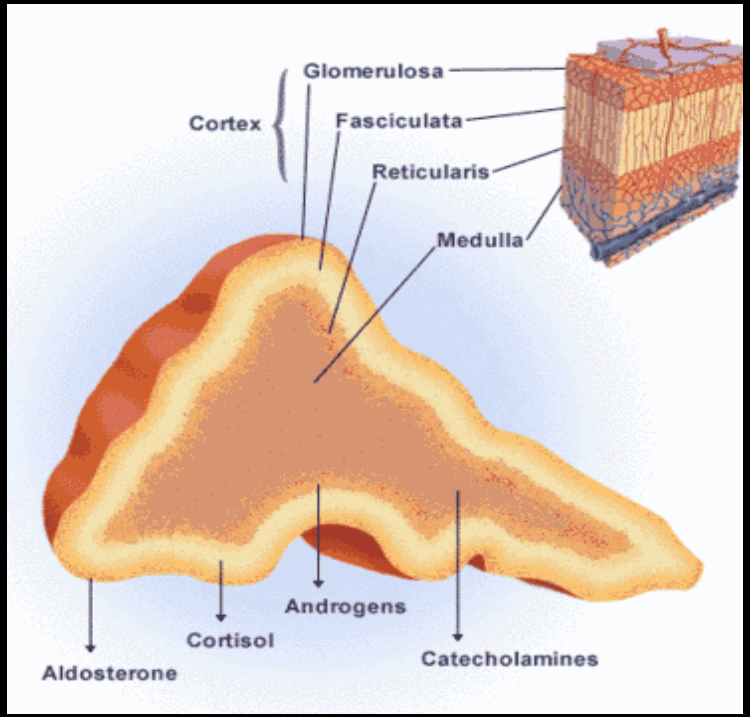
Dysfunction is associated with:

- Addison's disease (Idiopathic hypoadrenocorticism)
- Lysodren, trilostane
- Isolated aldosterone deficiency



CANINE HYPOADRENOCORTICISM

The adrenal medulla secretes catecholamines but is not affected in hypoadrenocorticism.



CANINE HYPOADRENOCORTICISM

Glucocorticoids

Glucocorticoid deficiency often manifests as anorexia, vomiting, melena, lethargy, and weight loss; it also predisposes to hypoglycemia and results in impaired excretion of free water.

Regulate metabolism of:

- Glucose
- Protein
- Fat

CANINE HYPOADRENOCORTICISM

Glucocorticoids

Released in times of stress; Inhibit inflammation

Regulated by:

- Hypothalamus
  - Secretes corticotropin releasing hormone (CRH) which stimulates pituitary release of ACTH.
- Pituitary gland
  - Secretes adrenocorticotrophic hormone (ACTH) which stimulates release of glucocorticoids from the adrenal gland. ACTH also "feeds back" to reduce the secretion of CRH.

CANINE HYPOADRENOCORTICISM

Aldosterone

Actions

- Increased retention of Na+
- Increased water reabsorption
- Enhanced excretion of K+ and H+

Sites of Action:

Renal tubule (primary site) reabsorption of Na+ at the proximal convoluted tubule. Promotes Na, Cl, and water resorption. Under normal circumstances, this mechanism maintains normal blood volume and blood pressure.

CANINE HYPOADRENOCORTICISM

Regulation of Aldosterone

Angiotensin II

- Stimulates adrenal gland to release aldosterone
- Produced in response to low blood pressure

Elevated Plasma Potassium

- Increases synthesis of aldosterone by the zona glomerulosa
- Comparable potency to angiotensin II

CANINE HYPOADRENOCORTICISM

Plasma Na+ concentration

- Sensitizes glomerulosa cells to other aldosterone secretagogues (ACTH, Angiotensin II). Large fluctuations in plasma Na+ may directly influence aldosterone secretion

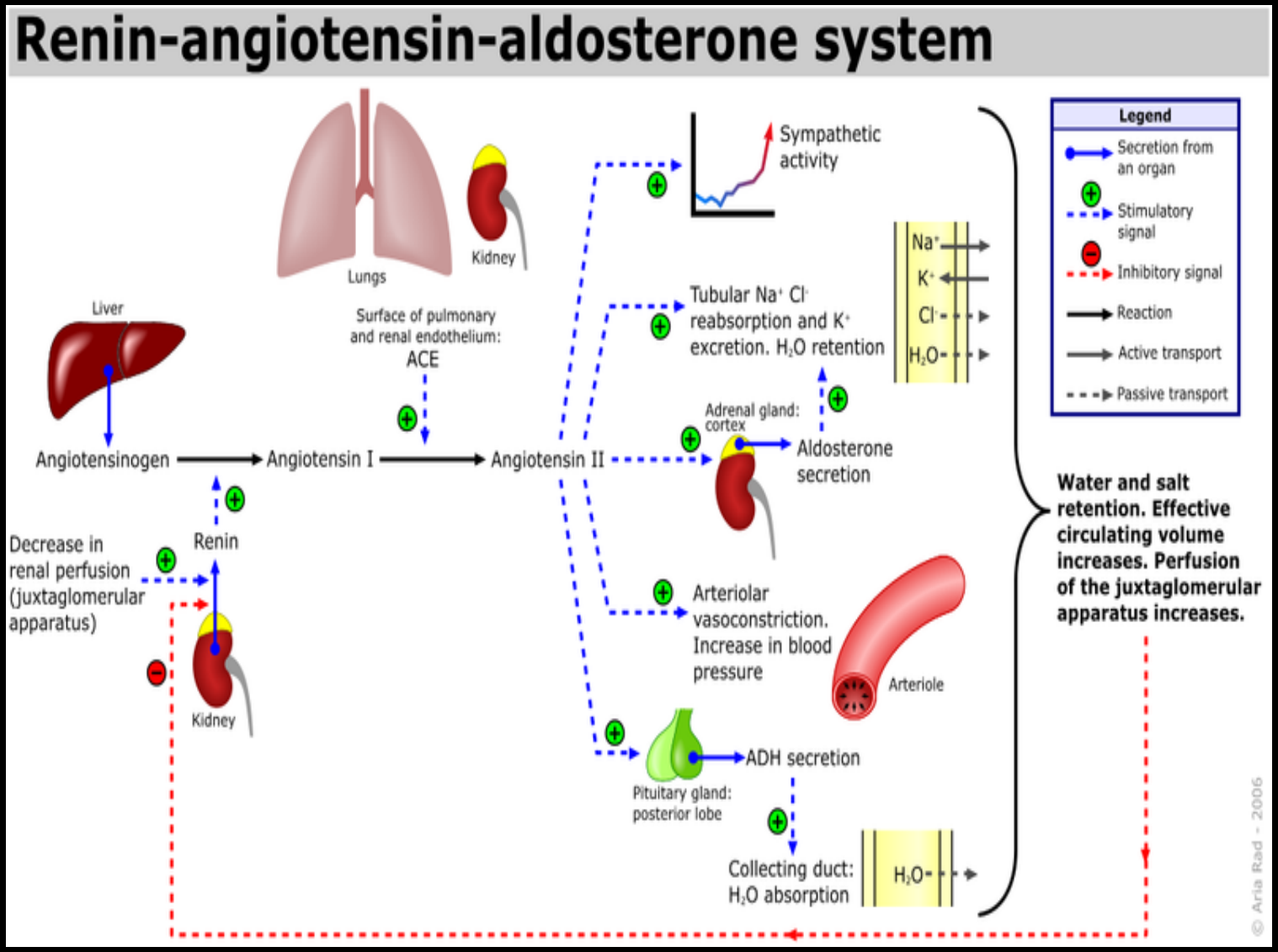
Atrial Natriuretic Peptide (ANP)

- Released by myocardium in response to elevated blood pressure
- Inhibitory effect on the stimulated release of aldosterone (zona glomerulosa); Protective effect with excessive aldosterone concentrations

ACTH

- Minimal effect on aldosterone secretion (more potent for glucocorticoids)

Renin-angiotensin-aldosterone system



CANINE HYPOADRENOCORTICISM

Etiology of Hypoadrenocorticism

Idiopathic

- Multiple inflammatory infiltrates (lymphocytes, plasma cells, etc)
- Suggests immune component

Medications

- Trilostane, Lysodren

Infiltrative disease

- Tuberculosis in man; fungal disease, LSA.

CANINE HYPOADRENOCORTICISM

Etiology of Hypoadrenocorticism

Autoantibodies against Cytochrome P450 Side-Chain Cleavage Enzyme in Dogs (Canis lupus familiaris) Affected with Hypoadrenocorticism (Addison's Disease).

Dogs with hypoadrenocorticism were more likely to be P450scc autoantibody positive than hospital controls (24% vs. 1.2%, respectively; $p = 0.0016$).

Sex was significantly associated with the presence of P450scc autoantibodies in the case population, with 30% of females testing positive compared with 17% of males ($p = 0.037$).

Significant associations with breed ($p = 0.015$) and DLA-type (DQA1*006:01 allele; $p = 0.017$) were also found

Boag AM, Christie MR, McLaughlin KA, et al: PLOS One 2015 Nov 30;10(11)

CANINE HYPOADRENOCORTICISM

Results in:

- Atrophy/destruction of adrenal cortices (>85%)
- Loss of glucocorticoids
- Loss of mineralocorticoids

CANINE HYPOADRENOCORTICISM

Secondary hypoadrenocorticism

Iatrogenic (reversible)

Dog is given large doses of glucocorticoids which suppress CRH and ACTH release (produces secondary adrenal cortical atrophy)

Isolated glucocorticoid insufficiency

Results

Decreased ACTH production

Decreased release of CRH

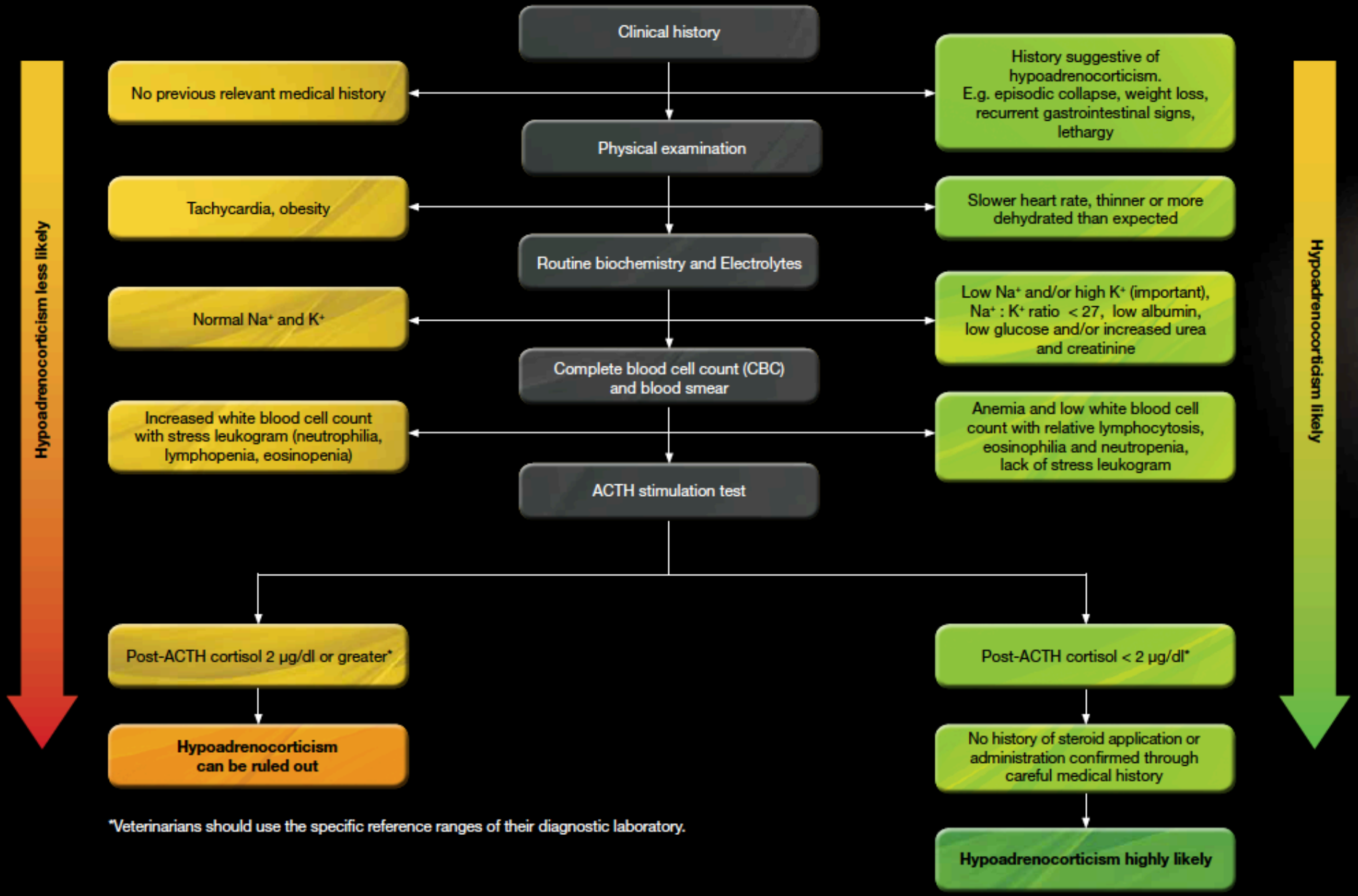
Reduction in glucocorticoids only

Mineralocorticoids are NOT affected in these situations.

CANINE HYPOADRENOCORTICISM

A diagnosis of hypoadrenocorticism is based on a combination of:

- Clinical signs
- Evaluation of laboratory parameters
- Specific function tests.



*Veterinarians should use the specific reference ranges of their diagnostic laboratory.

CANINE HYPOADRENOCORTICISM

Clinical Signs

Vomiting
Anorexia
Weakness

Depression
Weight loss
Diarrhea

Signs wax and wane

CANINE HYPOADRENOCORTICISM

FINDING	% OF CASES
Anemia	6 - 25
Azotemia	25 - 85
Eosinophilia	2 - 25
Lymphocytosis	16 - 22
Hypercalcemia	12 - 25

CANINE HYPOADRENOCORTICISM

FINDING	% OF CASES
Hyperkalemia	67 - 96
Hyponatremia	54 - 80
Na/K ratio <27	91 - 97
USG < 1.030	57 – 75

CANINE HYPOADRENOCORTICISM

Normal electrolytes with:

- Isolated ACTH deficiency
- Destruction of fasiculata and reticularis alone
- Early stage disease

CANINE HYPOADRENOCORTICISM

Isolated Glucocorticoid Insufficiency
Or
Atypical Hypoadrenocorticism

PARAMETER	HYPOADRENOCORTICISM	
	TYPICAL	ATYPICAL
Age	Young to middle age	Middle to older age
LABORATORY ANALYSIS		
Anemia	Present	Present*
Azotemia	Present*	Present
Eosinophilia/ lymphocytosis	Present	Present
Hypercalcemia	Present*	Absent
Hyperkalemia/ hyponatremia Na:K ratio < 27	Present*	Absent
Hypoalbuminemia	Present	Present*
Hypocholesterolemia	Absent	Present*
Hypoglycemia	Present	Present
Urine specific gravity < 1.030	Present	Present
THERAPY		
Glucocorticoid replacement	Required	Required
Mineralocorticoid replacement	Required	Not required

CANINE HYPOADRENOCORTICISM

Sex Predilection

Studies show that this disease is primarily a disease of the spayed female dog (75%)

Castrated males are 2-3 X more likely to develop hypoadrenocorticism

CANINE HYPOADRENOCORTICISM

Age

Average age of diagnosis = 4.3 - 5.4 Years

Lower risk < 4yrs

High risk 4-10yrs

Lower risk > 10yrs

CANINE HYPOADRENOCORTICISM

Breed Odds Ratio	A	B
Airedale Terrier	2.61	
Basset Hound	3.38	3.90
Bearded Collie	4.19	
German Shorthaired Pointer	2.52	3.90
Great Dane	7.63	11.98
Poodle (std & mini)	3.55	
Poodle (std)	8.90	

CANINE HYPOADRENOCORTICISM

Breed Odds Ratio	A	B
Portuguese Water Dog		46.66
Rottweiler	1.25	2.60
Springer Spaniel	2.54	5.85
West Highland White Terrier	5.93	11.42
Wheaton Terrier		6.68

CANINE HYPOADRENOCORTICISM

Diagnosis of Hypoadrenocorticism

Resting cortisol levels (> 2.0 ug/dl)

Can be used to r/o diagnosis

Subnormal response to ACTH stimulation

Endogenous ACTH

- Sample handling
- Primary vs secondary disease

CANINE HYPOADRENOCORTICISM

ACTH Stimulation test:

1) Take a baseline cortisol sample

2) Give ACTH:

   Cortrosyn 5 ug/kg IV or IM, sample 1 hour post injection.

   Animals with primary hypoadrenocorticism have a pre and post cortisol of < 5 ug/dl

   Most have a pre and post < 1 ug/dl

CANINE HYPOADRENOCORTICISM

Treatment for Addison's disease is in two phases:

Emergency therapy for "Addisonian Crisis"

Maintenance therapy (Lifelong)

CANINE HYPOADRENOCORTICISM

Addisonian Crisis

- Weakness/depression
- Acute collapse
- Bradycardia/arrhythmias
- Hypovolemic shock

CANINE HYPOADRENOCORTICISM

Emergency Treatment

1. Take blood sample for serum chemistry and ACTH stim test.
2. Isotonic saline IV at 60-80 ml/kg/h for 1-2 hr, then maintenance (5% dextrose for hypoglycemic patients).
3. ACTH stimulation test
4. Steroid therapy (one of the following):

    a. dexamethasone sodium phosphate 2 mg/kg IV (repeat in 2-6 hr if necessary)

    b. prednisolone sodium succinate 2-10 mg/lb IV (do not use if ACTH stimulation test is in progress)

    c. dexamethasone 0.5-2.0 mg/kg IV

CANINE HYPOADRENOCORTICISM

Emergency Treatment

5. If severe acidosis present, administer bicarbonate after 2 hours of fluid therapy.

6. Correct hypothermia.

7. Administer mineralocorticoids

Fludrocortisone acetate 0.02 mg/kg/day P0 or
Desoxycorticosterone pivalate 1-2 mg/kg IM

CANINE HYPOADRENOCORTICISM

Maintenance Therapy

1. IV isotonic saline to correct hypovolemia and normalize laboratory parameters.
2. Fludrocortisone acetate 0.02 mg/kg/day P0 or DOCP 1-2 mg/kg IM q 25 days
3. With DOCP use prednisone or prednisolone,

   0.2-0.4 mg/kg/d P0 or cortisone acetate 1 mg/kg/d P0
4. During periods of stress, increase glucocorticoid dose 2 to 5 times.
5. Monitor laboratory values weekly until stabilized.

DOCP desoxycorticosterone pivalate

CANINE HYPOADRENOCORTICISM

NaCl fluids will fix most of the problems:

Hyponatremia, hypovolemia, and hyperkalemia.

Azotemia generally resolves within 24 hours with proper treatment. This is not seen with renal failure.

Dexamethasone in any form will NOT affect cortisol levels. (i.e. will not affect diagnostic tests such as ACTH stimulation or baseline cortisol level)

CANINE HYPOADRENOCORTICISM

Treatment (Chronic)

Fludrocortisone acetate (Florinef)

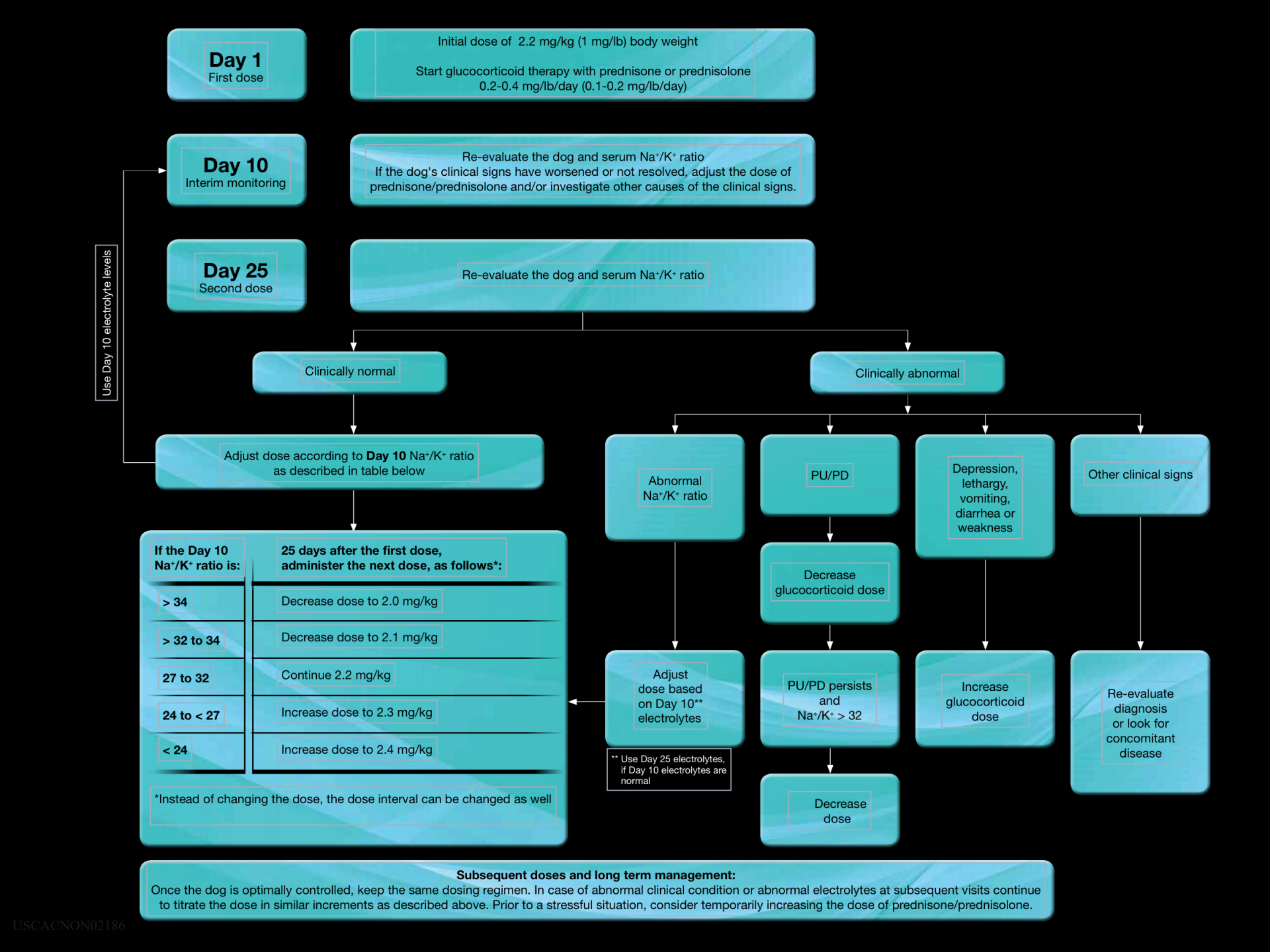
- Daily
- Oral
- Some glucocorticoid activity
- Large doses often needed

CANINE HYPOADRENOCORTICISM

Treatment (Chronic)

Desoxycorticosterone pivalate

- Pure mineralocorticoid Injection
  ~ every 25 days
- Must give with prednisone or prednisolone
  (0.2-0.4 mg/kg/day PO)



CANINE HYPOADRENOCORTICISM

Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial

Interpretation Patients with adrenal insufficiency on conventional glucocorticoid replacement therapy multiple times a day exhibit a pro-inflammatory state and weakened immune defense. Restoration of a more physiological circadian glucocorticoid rhythm by switching to a once-daily, modified-release regimen reduces bodyweight, normalizes the immune cell profile, reduces recurrent infections, and improves the quality of life of patients with adrenal insufficiency.

CANINE HYPOADRENOCORTICISM

Prognosis

All patients with primary hypoadrenocorticism require life-long medical therapy. Once patients are well regulated, evaluate them at least 2 times each year, with a physical examination and routine bloodwork. Although canine hypoadrenocorticism is serious and, sometimes, life-threatening, early identification and proper treatment can result in an excellent long-term prognosis in most patients.

Recommended Reading

Kintzer P, Peterson M. Treatment and long-term follow-up of 205 dogs with hypoadrenocorticism. J Vet Intern Med 1997; 11(2):43-49.