## Addison's Disease (Adrenal Gland Insufficiency)

Addison's disease, also known as adrenal gland insufficiency or hypoadrenocorticism, is an uncommon condition in which the patient's adrenal glands no longer supply the body with two classes of hormones, called glucocorticoids and mineralocorticoids. These hormones help regulate cellular metabolism and electrolyte balance in the body. According to the most recent edition of the Merck Veterinary Manual (Merck, 2015), this disease is characterized by gastroenteritis (vomiting and diarrhea), loss of body condition, lethargy and weakness, and inability to respond to stress. Although this condition has been recognized in dogs for more than 60 years, it remains difficult to diagnose, primarily because the animal's symptoms mimic those associated with several other diseases. However, when the disease is identified, treatment is very effective, allowing affected dogs to lead normal healthy lives. In order to understand how Addison's disease develops, it is important to first understand something about the anatomy and physiology of the adrenal glands themselves.

### Anatomy and Physiology of the Adrenal Glands

The adrenal glands are a pair, are complex, multifunctional organs that are located on top of the kidneys ('ad renal' – near the kidney). The outer layer of the gland (the cortex) produces three types of hormones: glucocorticoids, mineralocorticoids and small amounts of sex hormones.

In healthy animals, production of glucocorticoids is regulated by signals received from the brain. The hypothalamus is the region in the brain that produces a hormone called corticotrophin-releasing hormone (CRH), which stimulates another part of the brain, the pituitary gland, to release a hormone called adrenocorticotrophic hormone (ACTH). ACTH is released into the bloodstream and travels to the adrenal glands where it causes them to release glucocorticoids in the form of cortisol. When there is a healthy amount of cortisol circulating in the blood, this is sensed by the hypothalamus, which then reduces its production of CRH, and this causes the pituitary gland to stop releasing ACTH. The end result is a reduction in the production of cortisol by the adrenal glands. Because the healthy level of cortisol in the blood is exerting a negative influence on the production of CRH and ACTH by the brain, this is known as negative feedback. When the concentration of cortisol in the blood decreases, the hypothalamus and pituitary gland respond by releasing more CRH and ACTH, respectively, which stimulates the adrenal glands to produce more cortisol until circulating concentrations are restored.

Unlike the glucocorticoids, production of the mineralocorticoids is regulated by a system that starts with special cells in the kidneys, called the juxtaglomerular cells. These cells, which are located near the functional unit of the kidney called the glomerulus, sense the concentration of sodium in the blood, which is very important in the regulation of blood pressure. When the sodium concentration in the blood is low, the juxtaglomerular cells produce a chemical called renin, an enzyme that converts a substance in the blood called angiotensinogen to angiotensin I. Angiotensin I is then converted by another enzyme, which is located primarily in the blood vessels in the lungs, to angiotensin II. Angiotensin II has two effects: 1) stimulating the adrenal glands to produce aldosterone, the main mineralocorticoid, and 2) constricting small blood vessels to increase blood pressure (see **Figure 5.1**).

| Common Clinical Findings |
| --- |
| Lethargic and Listless |
| Vomiting or Regurgitation |
| Weight Loss or Weakness |
| Abnormal Cortisol Response to ACTH Stimulaton |

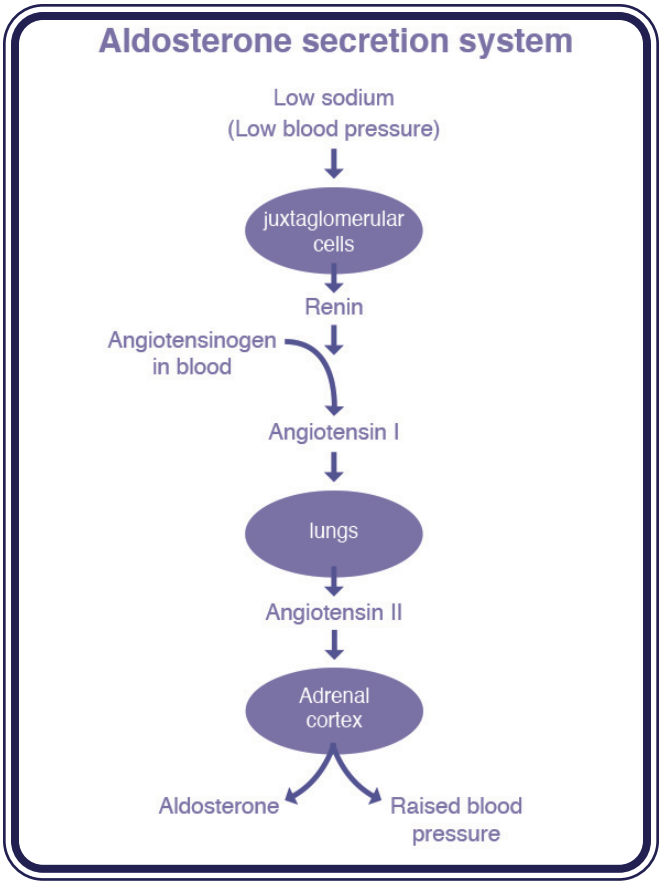


**Figure 5.1 - A graphic representation of the production of aldosterone by the adrenal cortex. In response to low blood sodium concentration, the juxtaglomerular cells in the kidney release renin, which converts angiotensinogen to angiotensin I, which then is converted to angiotensin II. This latter compound stimulates the adrenal glands to secrete aldosterone, which returns blood sodium concentration to normal and increases blood pressure.**

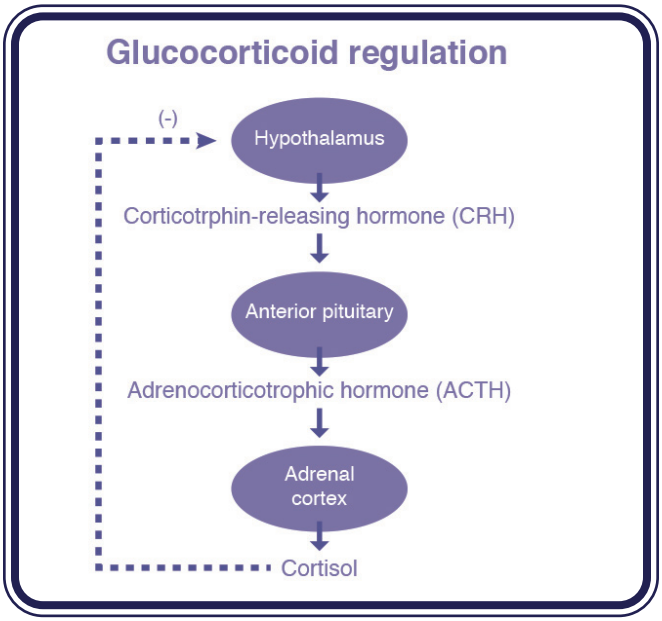


**Figure 5.2 - A graphic representation of the negative feedback regulation of cortisol production by the adrenal cortex.**

Aldosterone then causes the kidneys to absorb additional sodium and water from the fluid that it has filtered, which helps return blood sodium concentrations towards normal and increase blood pressure. At the same time, aldosterone causes the kidney to excrete potassium into the urine, which helps balance the electrolytes in the body.

## How does this disease develop?

Addison's disease is characterized by the lack of production of glucocorticoids and mineralocorticoids (see **Figure 5.2**. The disease can occur either as a result of an abnormality in the brain that then fails to stimulate the adrenal glands to perform their functions or in the adrenal glands themselves. When the problem originates in the brain, there is insufficient production of either CRH by the hypothalamus or ACTH by the pituitary gland. Lacking sufficient production of CRH or ACTH, the adrenal glands fail to function normally, production of cortisol and aldosterone is reduced, and the glands shrink in size (atrophy) (see **Figure 5.3**). This form of Addison's disease occurs infrequently.

Most cases of Addison's disease occur because the adrenal glands have been damaged and are no longer able to make cortisol and aldosterone, even when stimulated by ACTH and angiotensin II, respectively. In rare instances, special chronic inflammatory diseases (i.e., granulomatous diseases), hemorrhagic infarctions (blood clots forming and lodging in the adrenals and other tissues), cancer of the adrenals, and trauma can induce enough damage to the adrenal glands to cause Addison's disease. In the majority of cases of Addison's disease in dogs and people, an autoimmune process is responsible for destroying the adrenal glands. That means that the patient's own antibodies have destroyed the cells in the adrenal glands, much like other antibodies destroy foreign invaders like bacteria or viruses. The underlying processes that stimulate this autoimmune attack on the adrenals are not known, but are the subject of active research. For some reason, females are twice as likely to develop Addison's disease as males.

## Which clinical signs occur in dogs with Addison's disease?

Clinical signs of Addison's disease often are vague and nonspecific, with many affected dogs being lethargic, listless, anorexic, and reluctant to exercise or even do normal activities. Very often, these signs appear to wax and wane, making it even more difficult for owners to decide when to seek veterinary care. More than half of affected dogs have episode of vomiting or regurgitation of food,

> “Addison’s disease is characterized by the lack of production of glucocorticoids and mineralocorticoids.”

weakness, and weight loss. Diarrhea occurs in approximately one-third of dogs with the disease. The severity of the clinical signs may progress rapidly in some dogs and very slowly in others. Acute exacerbation of the condition may occur when the dog’s lifestyle is changed, for instance this may occur when the dog is moved, boarded or is examined by a veterinarian. Although dogs with Addison’s disease may vary in age, the typical dog is 4-5 years old and female. These characteristics should not be surprising as many immune-mediated diseases occur more commonly in females than males.

All clinical signs of Addison’s disease are due to the deficiencies of glucocorticoids (cortisol) and mineralocorticoids (aldosterone). For example, cortisol deficiency affects the body’s metabolism, which results in a loss of appetite, vomiting, abdominal pain, weight loss and lethargy. Because aldosterone is critical for balancing electrolytes (reabsorbing sodium and excreting potassium) and maintaining blood pressure, a deficiency in aldosterone reduces serum sodium concentration, and lowers blood pressure as the result of reduced circulating blood volume. Dogs with low blood sodium concentration may lose weight, feel weak, have small hearts and produce dilute looking urine even though they may be dehydrated. High blood potassium concentrations can cause life-threatening problems with heart rhythm (called ‘arrhythmias’). In fact, some affected dogs may develop such high blood concentrations of potassium that severe alterations occur in heart function and blood pressure, resulting in the development of shock. This clinical scenario is often referred to as an “Addisonian crisis”. Unfortunately, Westies appear to be at a high risk for developing Addison’s disease, as are Great Danes, Poodles, Portuguese Water Dogs, Soft-coated Wheaten Terriers, Nova Scotia Duck Tolling Retrievers and others. The results of recent studies suggest that there is a genetic predisposition for the disease in some breeds.

## How is Addison’s disease diagnosed?

Due to the wide variety of clinical signs that can occur and the fact that many of these are nonspecific (i.e., can occur in dogs with other diseases), Addison’s disease is difficult to diagnose. As a result, many more dogs are suspected of having Addison’s disease than end up being diagnosed with the condition. In one report, 15% of dogs tested for Addison’s disease ended up having it (Lennon et al, 2007).

A reliable screening test for Addison’s disease involves the measurement of cortisol in the blood. Most dogs with the disease have low resting levels of cortisol, whereas dogs with

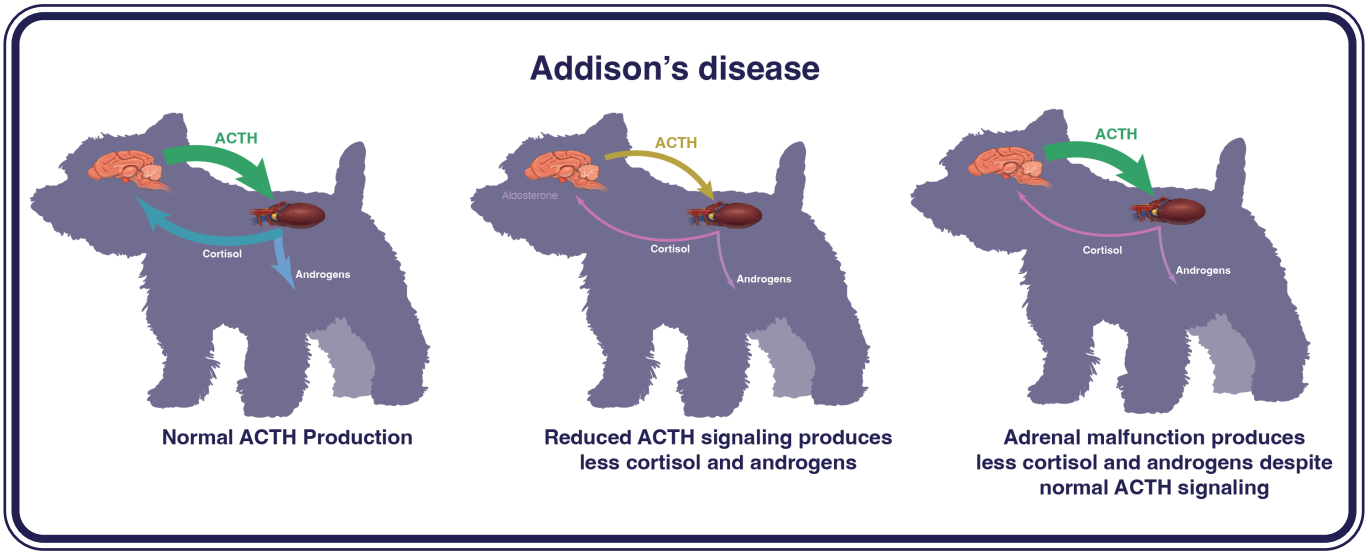


**Figure 5.3 - This illustration depicts the normal interaction between the pituitary and adrenal glands. This results in stimulation of the adrenal glands by ACTH and production of cortisol and androgens, and the normal negative feedback effect of blood cortisol levels on the pituitary gland. In contrast, decreased production of ACTH or malfunction of the adrenal glands results in reduced synthesis of cortisol and androgens.**

a high resting cortisol level are extremely unlikely to have the disease. When a low resting cortisol concentration is measured, the follow-up approach is to determine whether or not the adrenal glands will respond when stimulated. This is achieved by administering ACTH and measuring changes in cortisol concentration an hour later. If the dog's adrenal glands are normal, they should respond to the ACTH by increasing their production of cortisol. As a result, the blood concentration of cortisol will be significantly increased when measured an hour later. In contrast, the adrenal glands of a dog with Addison's disease will not respond to the ACTH, and the blood cortisol value measured after ACTH administration will be unchanged. It is important to know that any corticosteroids being given as a treatment as a result of the animal's clinical signs will interfere with this diagnostic approach. Consequently, it is important for these treatments to be stopped at least 24 hours before an ACTH stimulation test is performed.

While it is common to measure cortisol concentrations before and after an ACTH stimulation test, much less is known about circulating concentrations of aldosterone in dogs with Addison's disease. In a recent study, however, aldosterone concentrations were measured in healthy dogs, in dogs with clinical signs similar to those associated with Addison's disease, and in dogs with the disease. Concentrations of aldosterone were significantly lower in dogs with confirmed Addison's disease when compared with dogs in the other two groups. Furthermore, aldosterone concentrations were not increased after administration of ACTH in the dogs with Addison's disease. These findings confirm that damage to the adrenal cortex affects production of both glucocorticoids and mineralocorticoids similarly.

The ACTH stimulation test does not distinguish between hypoadrenocorticism due to abnormalities of the adrenals and the pituitary gland. In order to make this distinction, blood concentrations of ACTH must be measured. When the abnormality primarily affects the adrenal glands, ACTH concentrations will be high as the lack of cortisol production will not provide the normal negative feedback effect on the pituitary gland. As a result, it will continue to produce ACTH.

In contrast, if the abnormality primarily affects the pituitary gland, blood concentrations of ACTH will be low, due to the fact that it is not being produced by the pituitary gland. Dogs with the pituitary gland abnormalities may eventually respond to enough ACTH given by the veterinarian, whereas those with abnormal adrenal glands will not (i.e., their adrenal glands will continue to fail to produce cortisol).

In addition to the aforementioned blood tests, veterinarians may also use radiography (x-rays), ultrasonography, and electrocardiography (ECG; measurements of the heart's electrical output) to help make a definitive diagnosis of Addison's disease. Radiographic findings detected in many dogs with Addison's disease include reduced size of the heart, liver or specific blood vessels in the lung or abdomen. Ultrasound findings in affected dogs often include adrenal glands that appear smaller than normal, although this is not a consistent finding. The most commonly identified ECG abnormalities include those associated with excessively high blood concentrations of potassium.

## Treatment

The key to treating dogs with Addison's disease is to address immediate life-threatening aspects of the disease first and then to consider what needs to be done long-term. Clearly, dogs with poorly functioning adrenal glands will need to be treated for the rest of their lives; owners should be made aware of this immediately and be willing to accept the responsibilities associated with the need for life-long therapy. Fortunately, the prognosis for a healthy, happy life is extremely good.

For dogs in a hypoadrenocortical crisis, the veterinarian's initial focus is to restore blood volume with IV fluids, correct electrolyte abnormalities by slowly, but consistently increasing the sodium concentration in the blood with sodium-containing fluids IV, restoring blood glucose and glucocorticoid levels to normal. The dog's responses to these initial treatments are monitored closely to ensure that tissue perfusion and blood pressure increase appropriately. Fluid therapy also is important to rehydrate the animal, reestablish normal kidney function and correct all serious electrolyte imbalances (e.g., reduce high blood potassium concentrations) that could adversely affect metabolism and heart function. Blood glucose concentrations are restored by administering IV fluids containing dextrose and closely monitoring changes in blood glucose levels.

Finally, a fast acting glucocorticoid is given to replace the glucocorticoids not being produced by the animal's adrenal glands. Typically this is done with an injectable glucocorticoid, such as dexamethasone, until the dog has recovered sufficiently to be treated with oral glucocorticoids. During the acute crisis, treatment with a mineralocorticoid is not critical, and many veterinarians prefer to incorporate this as part of the long-term care plan.

## Current Research About Addison's Disease

**Lathan P. Laboratory Diagnosis of Thyroid and Adrenal Disease. Vet Clin North Am Small Anim Pract 2023 Jan;53(1):207-224.**

Diagnosis of thyroid and adrenal disease can be confusing. Whereas the definitive diagnosis of hyperthyroidism and hypoadrenocorticism are relatively straightforward, hypothyroidism and naturally occurring Cushing's syndrome are more complicated. In a patient with compatible clinical signs, a single increased T4 is enough to confirm hyperthyroidism, but a low T4 alone is never enough to confirm hypothyroidism. A flatline result (post-stimulation cortisol <2 ug/dL) on an ACTH stimulation test confirms hypoadrenocorticism, but not all dogs with naturally occurring Cushing's syndrome have increased ACTH stimulation test results. This article explains which diagnostics should be pursued for these endocrinopathies, and how to interpret them.

**Del Baldo F, Ferriani MG, Bertazzolo W et al. Urinary cortisol-creatinine ratio in dogs with hypoadrenocorticism. J Vet Intern Med 2022 Mar;36(2):482-487.**

Basal serum cortisol ≥2 µg/dL (>55 nmol/L) has high sensitivity but low specificity for hypoadrenocorticism. This study was performed to determine whether the urinary corticoid:creatinine ratio can be used to differentiate dogs with hypoadrenocorticism from healthy dogs and those with diseases mimicking hypoadrenocorticism. Based on the results of this study, the urinary corticoid:creatinine ratio seems to be a valuable and reliable screening test for hypoadrenocorticism in dogs. The greatest advantage of this test is the need for only a single urine sample.

**Lathan P, Thompson AL. Management of hypoadrenocorticism (Addison's disease) in dogs. Vet Med (Auckl) 2018 Feb 9:9:1-10.**

Hypoadrenocorticism (Addison's disease) is an endocrine condition seen in small animal practice. Dogs with this disease can present in a variety of ways from acute hypovolemic collapse to vague, chronic, waxing, and waning clinical signs. In the most common form of this disease, animals have both mineralocorticoid and glucocorticoid deficiency, resulting in hyponatremia and hyperkalemia, and signs of cortisol deficiency. The etiology may be immune-mediated destruction of the adrenal cortex, drug-induced adrenocortical necrosis, enzyme inhibition, or infiltrative processes such as neoplastic or fungal disease. Much less commonly, dogs have signs of cortisol deficiency, but no electrolyte changes. This is referred to as atypical hypoadrenocorticism. Treatment of dogs with an acute presentation prioritizes correcting the hypovolemia, hyperkalemia, acidosis, and hypoglycemia. Fluid therapy addresses most of these issues, but other therapies may be required in the most severe cases. For chronic management, all patients with Addison's disease will require replacement of glucocorticoids (usually prednisone), and most patients require replacement of mineralocorticoids.

## Acknowledgements

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## Relevant References

Baumstark ME, Sieber-Ruckstuhl NS, Müller C, Wenger M, Boretti FS, Reusch CE. Evaluation of aldosterone concentrations in dogs with hypoadrenocorticism. J Vet Intern Med. 2014 Jan Feb;28(1):154-9.

Boag AM, Catchpole B. A review of the genetics of hypoadrenocorticism. Top Companion Anim Med. 2014 Dec;29(4):96-101.

Boag AM, Christie MR, McLaughlin KA, Syme HM, Graham P, Catchpole B. Autoantibodies against cytochrome P450 side-chain cleavage enzyme in dogs affected with hypoadrenocorticism (Addison's Disease). PLoS One 2015; 10(11): e0143458

Bovens C, Tennant K, Reeve J, Murphy KF. Basal serum cortisol concentration as a screening test for hypoadrenocorticism in dogs. J Vet Intern Med. 2014 Sep-Oct;28(5):1541-5.

Chase K, Sargan D, Miller K, Ostrander EA, Lark KG, "Understanding the genetics of autoimmune disease: two loci that regulate late onset Addison's disease in Portuguese Water Dogs" International Journal of Immunogenetics 33(3):17984, 2006

Famula TR, Belanger JM, Oberbauer AM, "Heritability and complex segregation analysis of hypoadrenocorticism in the standard poodle" Journal of Small Animal Practice 44:8, 2003

Greco DS, "Hypoadrenocorticism in small animals" Clinical Techniques in Small Animal Practice 22(1):32-5, 2007
Jarrett RH, Norman EJ, Squires RA, "Licorice and canine Addison's disease" New Zealand Veterinary Journal 53(3):214, 2005

Javadi S, Galac S, Boer P, Robben JH, Teske E, Kooistra HS, "Aldosteronetorenin and cortisoltoadrenocorticotropic hormone ratios in healthy dogs and dogs with primary hypoadrenocorticism" Journal of Veterinary Internal Medicine 20(3):55661, 2006.

Klein SC, Peterson ME. Canine hypoadrenocorticism: part II. Can Vet J. 2010 Feb;51(2):179-84.

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

Lathan P, Moore GE, Zambon S, Scott-Moncrieff JC. Use of a low-dose ACTH stimulation test for diagnosis of hypoadrenocorticism in dogs. J Vet Intern Med. 2008 Jul-Aug;22(4):1070-3.

Lennon EM, Boyle TE, Hutchins RG, et al. Use of basal serum or plasma cortisol concentrations to rule out a diagnosis of hypoadrenocorticism in dogs: 123 cases (2000-2005). J Am Vet Med Assoc 231:413-416, 2007

MacMillan KL, "Neurologic complications following treatment of canine hypoadrenocorticism" The Canadian Veterinary Journal 44(6):4902, 2003.

Meeking S, "Treatment of acute adrenal insufficiency" Clinical Techniques in Small Animal Practice 22(1):369, 2007.

Oberbauer AM, Benemann KS, Belanger JM, Wagner DR, Ward JH, Famula TR, "Inheritance of hypoadrenocorticism in bearded collies" American Journal of Veterinary Research 63(5):6437, 2002.

Ramsey I, Roberts E, Spence S. Management of Addison's disease in dogs. Vet Rec. 2016 May 7;178(19):478.

Riesen SC, Lombard CW. ECG of the Month. Atrial fibrillation secondary to hypoadrenocorticism. Journal of the American Veterinary Medical Association 229(12):18902, 2006

Short AD, Catchpole B, Boag AM, Kennedy LJ, Massey J, Rothwell S, Henthorn PS, Littman MP, Husebye E, Ollier B. Putative candidate genes for canine hypoadrenocorticism (Addison's disease) in multiple dog breeds. Vet Rec. 2014 Nov 1;175(17):430.

Short AD, Boag A, Catchpole B, Kennedy LJ, Massey J, Rothwell S, Husebye E, Ollier B. A candidate gene analysis of canine hypoadrenocorticism in 3 dog breeds. J Hered. 2013 Nov-Dec;104(6):807-20.

Thompson AL, ScottMoncrieff JC, Anderson JD, "Comparison of classic hypoadrenocorticism with glucocorticoiddeficient hypoadrenocorticism in dogs: 46 cases (1985-2005)" Journal of the American Veterinary Medical Association 230(8):11904, 2007

Van Lanen K, Sande A. Canine hypoadrenocorticism: pathogenesis, diagnosis, and treatment. Top Companion Anim Med. 2014 Dec;29(4):88-95.