

CHAPTER 1

Hypoadrenocorticism in Dogs

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Pathogenesis

- Primary hypoadrenocorticism results from the destruction of >90% of the adrenal cortex.
- Most cases are presumed to be due to an immune-mediated process.
- Combined glucocorticoid and mineralocorticoid deficiency occur most frequently, but isolated glucocorticoid deficiency (“atypical hypoadrenocorticism”) is probably underdiagnosed.

Classical Signs

- Young to middle-age dogs are predisposed, as are poodles, West Highland White Terriers, and Great Danes.
- Addison’s disease is known as the “Great Pretender” because nonspecific signs such as lethargy, decreased appetite, and weight loss predominate.
- Gastrointestinal signs such as vomiting and diarrhea are also common.
- Patients may present in hypovolemic shock or following collapse.

Diagnosis

- ACTH stimulation test demonstrates minimal cortisol response.

Treatment

- Glucocorticoid and mineralocorticoid supplementation, ± intravenous fluids and supportive therapy.

I. Pathogenesis

A. Pathophysiology:

1. Most patients with naturally occurring hypoadrenocorticism (“Addison’s disease”) suffer from combined glucocorticoid and mineralocorticoid deficiency:

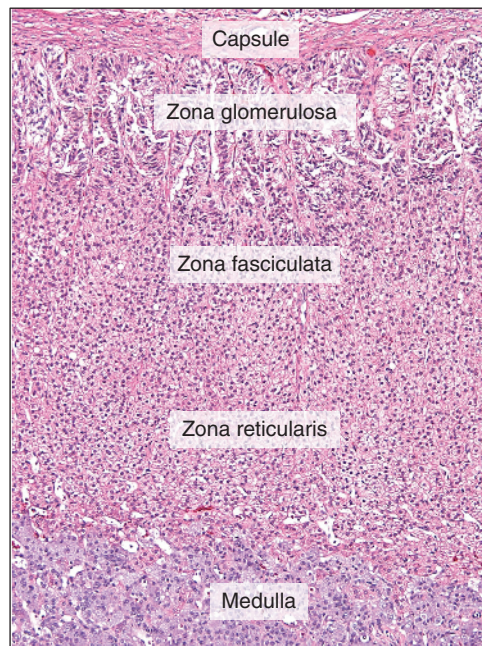


Figure 1.1 The adrenal cortex is made up of three layers—the zona glomerulosa, zona fasciculata, and zona reticularis. The zone glomerulosa is responsible for mineralocorticoid synthesis, whereas the inner two layers are responsible for glucocorticoid and sex hormone synthesis. (Image provided by Dr. Jim Cooley.)

- a. Aldosterone is a mineralocorticoid secreted in the outermost layer of the adrenal cortex, the zona glomerulosa (Figure 1.1). The major action of aldosterone is the conservation of sodium and water, and excretion of potassium and hydrogen ions (acid), from the distal renal tubule. In normal dogs, secretion of aldosterone is stimulated by hypovolemia and hyperkalemia and is primarily regulated by the renin-angiotensin-aldosterone system (RAAS). In patients with hypoadrenocorticism and subsequent aldosterone deficiency, hyponatremia, hyperkalemia, and hypovolemia are common.
 - b. Cortisol is a glucocorticoid produced in the inner-most layers of the adrenal cortex, the zonae fasciculata and reticularis. Cortisol has activity in almost every cell in the body. Functions include stimulation of gluconeogenesis and erythropoiesis, maintenance of gastrointestinal mucosal integrity, and suppression of the inflammatory response. Additionally, cortisol has important roles in the maintenance of blood pressure and contractility of the heart. Cortisol requirements increase during times of stress. Cortisol release from the adrenal cortex is controlled by adrenocorticotropic hormone (ACTH) (Figure 1.2). Cortisol deficiency in dogs with hypoadrenocorticism may result in gastrointestinal signs, lethargy, hypoglycemia, hypotension, and anemia.
2. Some patients with hypoadrenocorticism suffer from isolated glucocorticoid deficiency. In these cases, aldosterone secretion is preserved, and electrolyte abnormalities are **not** present. Patients with **isolated glucocorticoid deficiency** are often said to have “**atypical hypoadrenocorticism**” or “**atypical Addison’s disease**.”
- B. Etiology:**
1. **Primary hypoadrenocorticism results from the destruction of greater than 90% of the adrenal cortex.** Most cases of naturally occurring hypoadrenocorticism in dogs are idiopathic, most likely due to immune-mediated destruction of the adrenal cortex. Rarely, infiltration of the adrenal cortex by fungal disease, amyloidosis, or neoplasia has been reported. Trauma, hemorrhage, and infarction may also lead to hypoadrenocorticism.
 2. **Drug-induced adrenocorticolysis can also result in hypoadrenocorticism in dogs being treated for hyperadrenocorticism:**

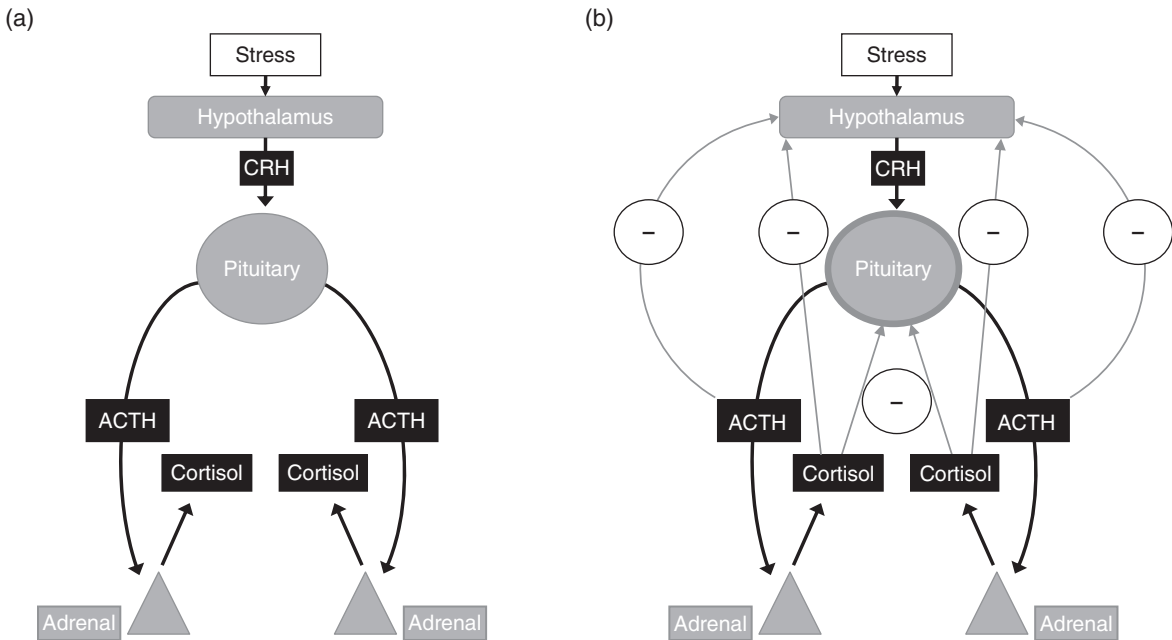


Figure 1.2 (a) The hypothalamic pituitary axis without negative feedback. Corticotropin-releasing hormone (CRH) is released by neurons in the hypothalamus and transported to the anterior pituitary by portal circulation. CRH then stimulates the release of ACTH from the pituitary gland into systemic circulation. ACTH then stimulates the synthesis and secretion of cortisol. (b) Negative feedback is the mechanism by which the endocrine system regulates secretion of its hormones. In the HPA-axis, ACTH feeds back to the hypothalamus to inhibit continued release of CRH, which then leads to decreased release of ACTH. Cortisol feeds back to both the hypothalamus to decrease CRH secretion, and to the pituitary gland to decrease ACTH release. By this mechanism, the HPA-axis is able to maintain the physiologically necessary concentration of cortisol in the bloodstream—not too much, nor too little.

a. Adrenocortical necrosis caused by mitotane is usually selective to the zonae fasciculata and reticularis, resulting in decreased cortisol production. However, inadequate monitoring or use in a particularly sensitive patient may lead to destruction of the cells of the zona glomerulosa, resulting in aldosterone deficiency as well.

b. The other commonly used medication to treat hyperadrenocorticism is trilostane. As an inhibitor of at least one enzyme involved in steroid synthesis (3β -hydroxysteroid dehydrogenase), trilostane overdose may lead to cortisol deficiency and, less frequently, aldosterone deficiency. Additionally, idiosyncratic adrenocortical necrosis has been reported to occur in some dogs taking trilostane, resulting in hypoadrenocorticism.

3. Hypoadrenocorticism secondary to decreased ACTH production is characterized by isolated glucocorticoid deficiency since ACTH has little regulatory control of aldosterone production:

a. The most common form of secondary hypoadrenocorticism is iatrogenic, resulting from exogenous glucocorticoid administration (Figure 1.3). Exogenous glucocorticoids inhibit the release of adrenocorticotrophic hormone (ACTH) from the pituitary gland. Adrenal gland atrophy then occurs, resulting in decreased secretion of cortisol. Following acute withdrawal of the exogenous glucocorticoid, a stressful event will cause increased release of ACTH, but the atrophied adrenal glands will be unable to respond by secreting an appropriate amount of cortisol, which may result in signs of cortisol deficiency. Chronic administration of glucocorticoids is more likely to result in hypoadrenocorticism than short-term use, and longer-acting repository steroids (such as methylprednisolone acetate) are more potent suppressors of ACTH than shorter-acting glucocorticoids (such as oral prednisolone). Topical, otic, and ophthalmic preparations containing glucocorticoids may also lead to iatrogenic hypoadrenocorticism, particularly in smaller patients.

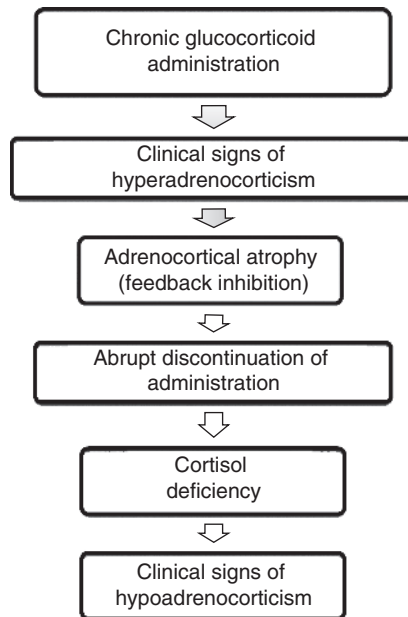


Figure 1.3 Diagrammatic representation of the relationship between iatrogenic hyperadrenocorticism and iatrogenic hypoadrenocorticism. Chronic glucocorticoid administration leads to clinical signs of glucocorticoid excess (“iatrogenic hyperadrenocorticism”). At the same time, the exogenous glucocorticoid provides feedback inhibition to the pituitary gland, decreasing the production of ACTH. Without ACTH, the dog’s own adrenal glands atrophy. While the dog is still taking the exogenous glucocorticoids, the dog will appear to have hyperadrenocorticism. Upon abrupt withdrawal of the steroid, the dog’s own atrophied adrenal gland will be unable secrete cortisol, potentially resulting in clinical signs of hypoadrenocorticism. Clinical signs may be seen more often following a stressful event in these patients.

b. Naturally occurring causes of secondary hypoadrenocorticism include pituitary masses, trauma, or other lesions that inhibit ACTH release.

4. At this time, the etiology of atypical hypoadrenocorticism (isolated glucocorticoid deficiency) is unknown. ACTH deficiency has been ruled out in many cases. It may be the result of partial immune-mediated destruction of the adrenal cortex, sparing the zona glomerulosa. Although some have hypothesized that atypical hypoadrenocorticism is simply an early manifestation of “typical” hypoadrenocorticism, many patients never lose their ability to secrete aldosterone.

C. Risk factors for hypoadrenocorticism:

1. Dogs with other immune-mediated endocrinopathies, such as diabetes mellitus and hypothyroidism, may be at increased risk for hypoadrenocorticism.
2. Dogs with the disease are more likely to have clinical signs during or following a stressful event.

II. Signalment

A. Any breed of dog may be afflicted with hypoadrenocorticism, including mixed-breeds. However, an increased prevalence of hypoadrenocorticism has been documented in all sizes of poodles, West Highland white terriers, Great Danes, bearded collies, Portuguese water dogs, Leonbergers, Nova Scotia duck-tolling retrievers, and possibly Saint Bernards.

B. A genetic basis has been proved in standard poodles, Bearded collies, and Nova Scotia duck-tolling retrievers.

C. Young to middle-aged dogs (2–5 years old) are predisposed. However, dogs of any age can be diagnosed with hypoadrenocorticism. Nova Scotia duck-tolling retrievers may be diagnosed at a younger age, as early as 2 months.

- D. Females appear to be predisposed in some studies, while other studies reveal a more equal distribution between the sexes.
- E. Dogs diagnosed with isolated glucocorticoid deficiency have a similar signalment to those with combined mineralocorticoid/glucocorticoid deficiency. As a population, however, dogs with atypical Addison's tend to be 2–3 years older at diagnosis compared to those with typical Addison's.

III. Clinical Signs

A. **The clinical manifestation of hypoadrenocorticism is highly variable in presenting complaint, chronicity, and severity.** Some dogs present for chronic clinical signs, whereas others present more acutely in “Addisonian crisis.” Rigid rules differentiating acute from chronic hypoadrenocorticism do not exist; the pathophysiology is the same, and these presentations represent a continuum of disease progression. If not diagnosed and treated early in the course of the disease, many dogs with chronic signs will decompensate and present in crisis. However, they will be discussed separately, since initial treatment differs. Likewise, dogs with isolated cortisol deficiency (atypical hypoadrenocorticism) will also be discussed separately in order to highlight the contrasting features.

1. Chronic hypoadrenocorticism:

- a. Addison's disease often causes vague, nonspecific clinical signs that can be confused with other diseases, thus earning it the moniker “The Great Pretender” (Table 1.1). Most patients experience **lethargy, decreased appetite, and weight loss** with varying severity. The owner may report that the patient just is not acting normally. A **waxing and waning pattern**, with improvement of clinical signs specifically noted following fluid or steroid administration, is common (Schaer and Chen 1983; Herrtage 2000).
- b. **Vomiting and diarrhea** are frequently reported, with or without concurrent **melena**. Rectal examination may also reveal melena previously unnoticed by owners. Dogs occasionally present with abdominal pain. These gastrointestinal signs are thought to occur due to loss of the “trophic” effects of cortisol on the gastrointestinal mucosa. Exacerbation of or onset of gastrointestinal signs following a stressful event is often noted in dogs later diagnosed with hypoadrenocorticism. Thus, it is critical that hypoadrenocorticism is considered in patients diagnosed with “stress colitis,” particularly if the diarrhea is accompanied by melena, vomiting, and/or generalized lethargy and weakness.
- c. Patients may also exhibit **polyuria and polydipsia**. This is likely due to a combination of the decreased renal medullary concentration gradient resulting from hyponatremia, and decreased sodium (and, consequently, water) resorption in the collecting ducts of the kidney.
- d. Some dogs with hypoadrenocorticism present with **generalized or hindlimb weakness**, which may be the primary presenting complaint (Figure 1.4). Reflexes are generally normal in these dogs. The reason for this weakness is unclear. Generalized debility is a plausible explanation, but some of these dogs have hindlimb weakness only. Another hypothesis is that electrolyte abnormalities lead to aberrant neuromuscular function. Whatever the cause, hypoadrenocorticism should be considered in patients that are “down in the hindlimbs.”
- e. Some dogs with hypoadrenocorticism have concurrent **megaesophagus**. Rarely, regurgitation is the major presenting complaint in dogs with hypoadrenocorticism. The severity of the megaesophagus is variable; **regurgitation** may be noted, but radiographic evidence without clinical signs is also possible. The esophageal dilation seems to be less severe than that seen in other cases of megaesophagus. Proposed explanations for this megaesophagus include disturbed neuromuscular function caused by electrolyte abnormalities and muscle weakness secondary to cortisol deficiency. Hypoadrenocorticism is one of the few underlying causes of megaesophagus in which appropriate treatment results in the resolution of esophageal abnormalities, so it should be ruled out in all cases of megaesophagus.
- f. **Muscle cramping** has been described in two Standard Poodles with hypoadrenocorticism. Again, aberrant electrolyte concentrations are hypothesized to cause an underlying neuron conduction abnormality.

2. Acute hypoadrenocorticism:

- a. Approximately 30% of dogs with hypoadrenocorticism present in **hypovolemic shock**. Any of the clinical signs described for patients with chronic hypoadrenocorticism may be found in dogs with an

Table 1.1 Clinical signs and physical exam findings in dogs with hypoadrenocorticism.

Clinical signs and physical exam findings	Incidence (%)
Lethargy/depression	90
Decreased appetite/anorexia	80
Vomiting	80
Weakness	70
Weight loss	45
Diarrhea	40
Waxing/waning illness	40
Dehydration	40
Hypothermia	35
Shaking/shivering	30
Weak pulses	30
Polyuria/polydipsia	25
Melena	15
Painful abdomen	15

Data modified from Willard et al. (1982); Peterson et al. (1996); and Melian and Peterson (1996).



Figure 1.4 Hypoadrenocorticism is known as “The Great Pretender” because of the variety of presenting complaints and clinical signs seen in patients. This 8-year-old bearded collie presented for hindlimb weakness and collapse. Serum chemistry revealed hyperkalemia and hyponatremia, and ACTH stimulation confirmed hypoadrenocorticism.

acute presentation. History may reveal chronic gastrointestinal signs with acute presentation of vomiting and/or diarrhea. Collapse secondary to hypovolemia and/or generalized weakness is not uncommon.

b. Classic signs of hypovolemic shock are usually present, including **weak pulse, pale mucous membranes, and prolonged capillary refill time; hypothermia** occurs occasionally. Heart rate, however, is variable. Whereas most dogs in hypovolemic shock are tachycardic (>160 bpm), **patients in hypoadrenocortical crisis often have a normal to decreased heart rate.** This is due to the effects of

hyperkalemia in lowering the heart rate. Thus, the presence of a decreased or normal heart rate (“relative bradycardia”) in a patient in hypovolemic shock should raise suspicion of hyperkalemia and hypoadrenocorticism. Rapid treatment and correction of cardiac changes associated with hyperkalemia is critical for the survival of the patient.

c. **Melena** is frequently present in patients in Addisonian crisis, and may be severe enough to necessitate blood transfusion. Hematochezia is seen less frequently. Melena may be noted on initial exam, or may not be evident until after beginning therapy. Progressively decreasing hematocrit during treatment (more than by hemodilution alone) should increase suspicion of melena, and the possibility of melena should not be excluded due to its initial absence in feces or upon rectal examination. Ileus may decrease gastrointestinal (GI) transit enough to delay its appearance for 1–2 days. It is not uncommon for melena to appear 2–3 days into treatment. For this reason, hospitalization is recommended until the hematocrit stabilizes or increases.

d. Generalized muscle weakness results in **shaking** and/or **shivering** in some patients.

e. Rarely, severe hypoglycemia leads to **seizures** in dogs with Addison’s disease.

3. Atypical hypoadrenocorticism:

a. Dogs with isolated cortisol deficiency generally present with the same **nonspecific clinical signs** (lethargy, weight loss, and anorexia) as other dogs with hypoadrenocorticism.

b. **Gastrointestinal signs** (vomiting and diarrhea) are also common, and **megaesophagus** and **seizures** (secondary to hypoglycemia) have been reported with atypical hypoadrenocorticism as well.

c. **Atypical Addisonians infrequently present in acute crisis.** This is probably because **hyperkalemia** and **hyponatremia do not occur** in these dogs. **Hypotension is possible**, however, as a result of **decreased** vascular tone in the absence of cortisol. Acute collapse secondary to hypoglycemia and hemorrhagic shock secondary to GI hemorrhage has also been reported in this group of Addisonian patients.

d. Patients with atypical Addison’s disease have a slightly longer duration of clinical signs prior to diagnosis. This may be due to the fact that diagnosis is delayed because there are no electrolyte disturbances to stimulate the clinician’s suspicion of hypoadrenocorticism.

IV. Diagnosis

A. Chronic hypoadrenocorticism:

1. Most of the diagnostics performed in dogs with hypoadrenocorticism are done early in the workup, often prior to significant suspicion of hypoadrenocorticism. **A complete blood count, serum biochemistry analysis, and urinalysis should be performed in each patient with clinical signs consistent with hypoadrenocorticism (Table 1.2).** It is critical that electrolyte analysis is included in the biochemistry panel, as sodium and potassium abnormalities are often the first specific indicators of hypoadrenocorticism. Additionally, electrolyte disturbances are common in patients with gastrointestinal signs of any etiology, and need to be addressed during treatment:

a. Serum biochemistry and urinalysis:

1) Most dogs with “typical” hypoadrenocorticism are **hyperkalemic** (90%) and **hyponatremic** (85%) at diagnosis. Potassium concentration usually remains below 8 mEq/L, but may be as high as 11 mEq/L. Sodium concentrations are usually in the range of 120–140 mEq/L, but may be as low as 100 mEq/L. Some present with one abnormality without the other (e.g., hyperkalemia without hyponatremia). **Hypochloremia** often parallels hyponatremia and is seen in approximately half of the patients. Electrolyte disturbances are not always present early in the course of disease; they may appear when the patient’s disease progresses, or not at all, as with atypical hypoadrenocorticism. Emphasis is sometimes placed on calculation of the **Na⁺/K⁺ ratio**. The lower the sodium and the higher the potassium concentration, the lower the ratio. The lower the ratio, the higher the likelihood that the patient has Addison’s disease (Adler et al. 2007). However, a high ratio does not rule out hypoadrenocorticism, nor does a low ratio definitively diagnose it; thus, the utility of the ratio is debatable. Any dog with hyponatremia or hyperkalemia should be considered a suspect for hypoadrenocorticism, regardless of the ratio.

Table 1.2 Clinicopathologic abnormalities common with hypoadrenocorticism.**Clinicopathologic abnormalities associated with hypoadrenocorticism**

Hyperkalemia
 Hyponatremia
 Hypochloremia
 Azotemia
 Isosthenuria
 Hypoalbuminemia
 Hypercalcemia
 Hypocholesterolemia
 Lymphocytosis
 Lack of stress-related neutrophilia
 Eosinophilia

2) Azotemia is a frequent finding, and is usually prerenal in nature. Both **creatinine** (increased in 65% of cases) and **blood urea nitrogen (BUN)** (increased in 90%) concentrations increase as a result of decreased renal perfusion due to hypovolemia; BUN may be further increased by GI blood loss. Phosphorus is also usually increased in azotemic patients (70% of all Addisonians):

a) Despite the **prerenal** nature of the azotemia, most dogs with hypoadrenocorticism also have a urine-specific gravity <1.030 (frequently <1.020). This is more dilute than would be expected in most patients with prerenal azotemia alone. For this reason, many of these patients are incorrectly thought to be in renal failure. It is imperative that clinicians **consider hypoadrenocorticism as a differential diagnosis in any azotemic dog**, particularly if the dog has a history of gastrointestinal signs.

3) Impaired excretion of acid (H⁺ions) in the distal tubule results in mild **metabolic acidosis** in half the canine Addisonians.

4) Approximately 15% of Addisonian dogs have **hypoalbuminemia**. Although the mechanism remains to be elucidated, it is likely due to loss through gastrointestinal hemorrhage, impaired gastrointestinal absorption, or decreased hepatic synthesis.

5) Although hypocortisolemia should result in decreased hepatic gluconeogenesis, **hypoglycemia occurs infrequently** (15%) in dogs with hypoadrenocorticism, and is usually subclinical. However, dogs with hypoadrenocorticism have been reported to present for hypoglycemic seizures. **Hypoadrenocorticism should always be a differential diagnosis for an adult dog with severe hypoglycemia.**

6) Total and ionized hypercalcemia occurs frequently, in approximately 30% of hypoadrenocortical dogs (Adamantos et al. 2008). Mild increases in calcium are most common, but severe hypercalcemia is possible. The reason for this hypercalcemia is unclear, but is likely related to decreased renal clearance. Hypoadrenocorticism accounts for anywhere from 5% to 25% of dogs with hypercalcemia; thus, **it should be considered a differential diagnosis in the workup of hypercalcemic dogs.**

7) Decreased hepatic production and gastrointestinal malabsorption are suspected to cause **hypocholesterolemia** in approximately 10% of Addisonian dogs.

8) Hepatic hypoperfusion and cholestasis may play a role in the mild to moderate increases in **alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST)** seen in 20–30% of hypoadrenocortical dogs.

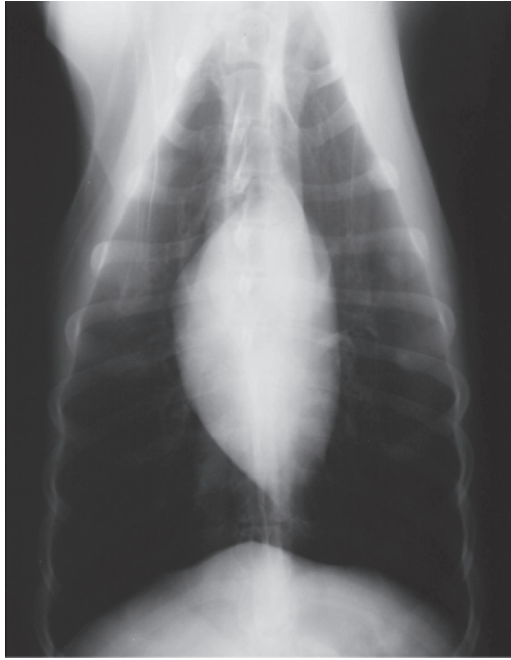


Figure 1.5 Microcardia is a nonspecific indicator of hypovolemia, and is frequently seen in dogs with hypoadrenocorticism.

b. Complete blood count:

1) Cortisol released during illness in dogs with normal adrenocortical function often results in the “stress leukogram” of neutrophilia, lymphopenia, monocytosis, and eosinopenia. These changes, particularly lymphopenia, are often absent in dogs with hypoadrenocorticism. Lymphocytosis and eosinophilia, part of the “reverse stress leukogram,” are only present occasionally (10% of cases), while the final component, neutropenia, is rarely present. Despite the infrequent occurrence of the reverse stress leukogram, the **absence of a stress leukogram in a sick patient should heighten suspicion of hypoadrenocorticism.**

2) Approximately 30% of dogs are **anemic** at diagnosis of hypoadrenocorticism, with the proportion increasing to approximately 70% following rehydration. The anemia is typically **normochromic, normocytic, nonregenerative,** and mild. Dogs with more severe anemia almost always have evidence of gastrointestinal blood loss, even if not evident at presentation.

2. Radiographs and ultrasound are often performed in patients that present for gastrointestinal signs, including most patients with hypoadrenocorticism. Although results are generally nonspecific, there are some findings commonly present in Addisonian dogs:

a. Thoracic radiographs usually reveal nonspecific signs of hypovolemia, including **microcardia and decreased size of the caudal vena cava and pulmonary vessels (Figure 1.5).** Megaesophagus may also be seen, as discussed above.

b. Abdominal radiographs and ultrasound may reveal microhepatica, consistent with hypovolemia. Adrenal gland length and thickness, on average, are lower in Addisonians than in normal dogs (Figure 1.6). However, there is significant overlap between values in normal and Addisonian dogs. One study reported that the length and thickness of the left adrenal in a small group of hypoadrenocortical dogs was 10.0–19.7 mm (median, 13.1 mm) and 2.2–3.0 mm (median, 2.4 mm), respectively. The same measurements (length, thickness) of the left adrenal in a group of normal dogs were 13.2–26.3 mm (median, 17.4 mm) and 3.0–5.2 mm (median, 4.1 mm). Despite the trend in smaller adrenal gland measurements in hypoadrenocortical patients, the difference in values is not significant enough to definitively differentiate between normal and Addisonian patients.

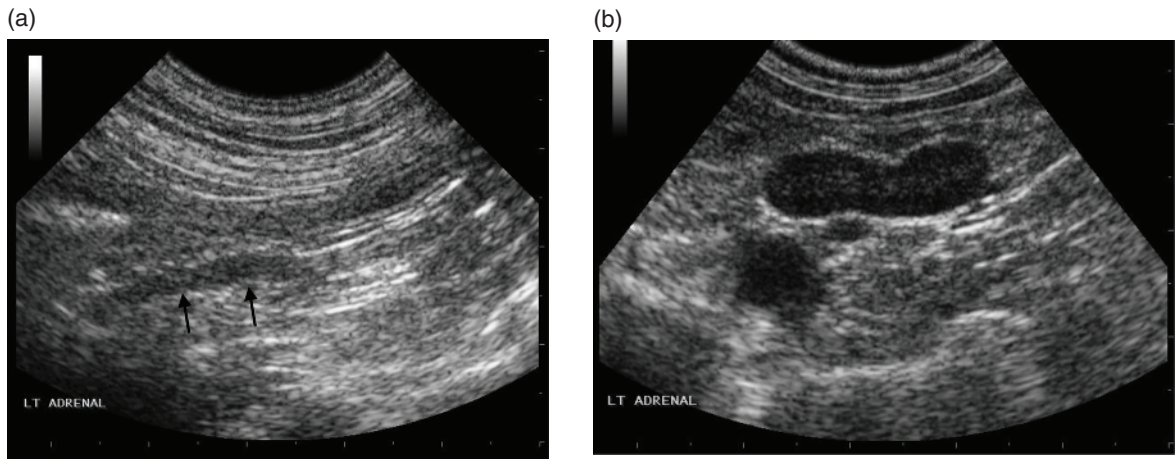


Figure 1.6 (a) Abdominal ultrasound often identifies very small adrenal glands in dogs with hypoadrenocorticism. Note how thin this left adrenal gland is (3.3 mm), compared to the one from a normal dog in (b). (b) Note the peanut shape and width (6.7 mm) of this normal left adrenal gland, compared to the gland from an Addisonian dog in (a). (Images provided by Drs. Erin Brinkman and Erica Baravik.)

3. Specific endocrine tests:

a. The ACTH stimulation test is required for definitive diagnosis of hypoadrenocorticism. A supra-physiologic dose of ACTH is given to maximally stimulate the adrenal glands (Figure 1.7). In dogs with normally functioning adrenal glands, ACTH stimulation will result in a significant increase in cortisol concentration. In hypoadrenocortical dogs, minimal to no increase in cortisol concentration will occur:

1) Protocol:

- a)** A baseline blood sample is obtained.
- b)** Synthetic ACTH (cosyntropin or tetracosactrin), 5 µg/kg (0.005 mg/kg) (up to a maximum of 250 µg/dog) is given, intravenously (Lathan et al. 2008).
- c)** A 1 h post-ACTH blood sample is drawn.
- d)** Pre- and post-ACTH samples are submitted for cortisol analysis.
- e)** Due to inconsistent results, compounded ACTH gel is not recommended for the diagnosis of hypoadrenocorticism.
- f)** In canine Addisonian suspects, intravenous administration of cosyntropin is recommended over intramuscular administration due to potentially altered intramuscular absorption in dehydrated and/or hypovolemic patients.

2) Interpretation of the ACTH stimulation test is based on the value of the post-sample:

- a)** A post-sample of $<2.0 \mu\text{g/dL}$ (55 nmol/L) is consistent with a clinical diagnosis of hypoadrenocorticism. Lack of response to ACTH stimulation demonstrates that the adrenal cortex is incapable of secreting cortisol, even when stimulated with a much higher amount of ACTH than the body produces:
 - i.** The ACTH stimulation test does not differentiate between primary adrenocortical failure and secondary hypoadrenocorticism due to decreased ACTH secretion. Without the trophic effects of ACTH, the adrenal cortex atrophies, disabling a response to exogenous ACTH. Thus, dogs with primary and secondary hypoadrenocorticism both fail the ACTH stimulation test.
 - ii.** Patients with iatrogenic hypoadrenocorticism, resulting from acute withdrawal following prolonged administration of exogenous glucocorticoids, will also have a post-stimulation cortisol concentration $<2.0 \mu\text{g/dL}$ (55 nmol/L). However, these patients should be easy to differentiate based on historical evidence of glucocorticoid administration.



Figure 1.7 An ACTH stimulation test is required for definitive diagnosis of hypoadrenocorticism. In order to avoid problems with absorption, synthetic ACTH (cosyntropin) is given intravenously in Addison's disease suspects.

- b)** A post-sample $>2\ \mu\text{g/dL}$ ($55\ \text{nmol/L}$) rules out the clinical diagnosis of hypoadrenocorticism in most patients.
- c)** Administration of glucocorticoids prior to the ACTH stimulation test can alter the test in two different ways:
 - i.** Several synthetic glucocorticoids, including prednisone and methylprednisolone, cross-react with the cortisol assay. Thus, both the pre- and post-stimulation cortisol concentrations will be falsely elevated following administration of other glucocorticoids. To avoid this, the only glucocorticoids that should be given near the time of the test are dexamethasone and triamcinolone. Short-acting glucocorticoids, such as prednisone or methylprednisolone succinate, should be withheld for 12–24 h before the test. Longer-acting repository steroids, such as methylprednisolone acetate, may cross-react with the assay for up to 4 weeks following administration. If glucocorticoid supplementation is necessary prior to completion of the ACTH stimulation test, dexamethasone or triamcinolone should be given.
 - ii.** Short-term administration of glucocorticoids within a month of the test may lead to decreased response to ACTH, depending on patient sensitivity, dosage, and duration of treatment. Exogenous glucocorticoid administration (oral or topical) inhibits the release of endogenous ACTH, which causes atrophy of the adrenal cortex. Following removal of the source of exogenous glucocorticoid, the adrenocortical function slowly recovers. However, if an ACTH stimulation test is performed prior to full recovery, the post-stimulation cortisol may be below normal. A post-ACTH cortisol concentration between $2\ \mu\text{g/dL}$ ($55\ \text{nmol/L}$) and $5\ \mu\text{g/dL}$ ($138\ \text{nmol/L}$) is often the result of recent steroid administration as compared to spontaneous hypoadrenocorticism:

- i) Chronic administration of glucocorticoids may lead to suppression of the hypothalamic pituitary axis (HPA) and subsequent decreased response to ACTH for more than a month following discontinuation of the medication.
 - 3) For the diagnosis of hypoadrenocorticism, the use of synthetic ACTH (cosyntropin or tetracosactrin) is recommended. Compounded gel formulations are available, but testing results are not as consistent with the gels as they are with synthetic ACTH:
 - a) If compounded ACTH gel must be used, it is recommended to obtain two post-stimulation cortisol samples at 1 and 2 h, due to inconsistent results from the use of the gel.
 - 4) After a 250 µg vial of cosyntropin or tetracosactrin is opened, it can be frozen in plastic syringes and stored for up to 6 months. ACTH binds to glass, so glass syringes should not be used. Freezing in 50 µg aliquots allows dosing for 10 kg dogs with each syringe and minimizes waste. Once thawed, cosyntropin should not be refrozen; a frost-free freezer should NOT be used because of the freeze/thaw cycles.
 - b. A baseline cortisol concentration is a relatively inexpensive way to rule out hypoadrenocorticism.** In almost all patients with hypoadrenocorticism, a baseline cortisol sample will be <2 µg/dL (55 nmol/L) (often <1 µg/mL (28 nmol/L)), so a baseline cortisol sample >2 µg/dL (55 nmol/L) rules out hypoadrenocorticism in a given patient. However, since normal dogs can have baseline cortisol samples <2 µg/dL (55 nmol/L), an ACTH stimulation test MUST be performed to confirm hypoadrenocorticism. **A baseline cortisol concentration can only be used to rule out hypoadrenocorticism—NOT to confirm it:**
 - 1) In rare cases, a patient with clinical hypoadrenocorticism may have pre- and post-stimulation cortisol values between 2 µg/dL (55 nmol/L) and 3 µg/dL (83 nmol/L). Therefore, strong clinical suspicion of hypoadrenocorticism would mandate an ACTH stimulation test in a dog with baseline values between 2 µg/dL (55 nmol/L) and 3 µg/dL (83 nmol/L).
- B. Acute hypoadrenocorticism:**
1. Patients presenting in hypoadrenocortical crisis have similar diagnostic findings as patients with chronic clinical signs (see above). However, abnormalities are often more severe and can be immediately life-threatening (Figure 1.8):
 - a. **Hyperkalemia and hyponatremia are often marked in patients in crisis.** Hyponatremia results in weakness, but severe hyperkalemia may be immediately life-threatening. Individual patients vary in susceptibility to the debilitating effects of hyperkalemia, but potassium concentrations less than 7.0 mEq/L generally cause few specific clinical signs. Values between 7.0 and 9 mEq/L result in weakness and moderate to severe cardiac dysfunction, and may be fatal. Values >9.0 mEq/L usually lead to severe cardiac dysfunction and are often fatal:
 - 1) Cardiac function in these patients should be monitored by electrocardiogram (ECG). Although ECG changes do not correlate exactly with specific potassium concentrations, they tend to appear in the following order, with increasing severity of hyperkalemia:
 - a) Increased T-wave amplitude.
 - b) Shortened Q–T interval.
 - c) Decreased P-wave amplitude.
 - d) Prolonged P–R interval.
 - e) Absent P-wave (sinoatrial standstill).
 - f) Severe bradycardia.
 - g) Asystole.
 - h) Bizarre QRS complexes, including paroxysmal ventricular tachycardia and ventricular fibrillation, may also be seen.
 - b. **Most patients in Addisonian crisis will have significant prerenal azotemia** on presentation, which resolves upon correction of hypovolemia. Severe or prolonged hypovolemia, however, can result in ischemic renal damage secondary to hypoperfusion. If tubular epithelial damage results from the ischemia, renal azotemia may occur; however, with appropriate supportive care most patients fully recover renal function. Severe gastrointestinal blood loss is more common in patients in crisis, and may also lead to more severe azotemia (increased BUN).

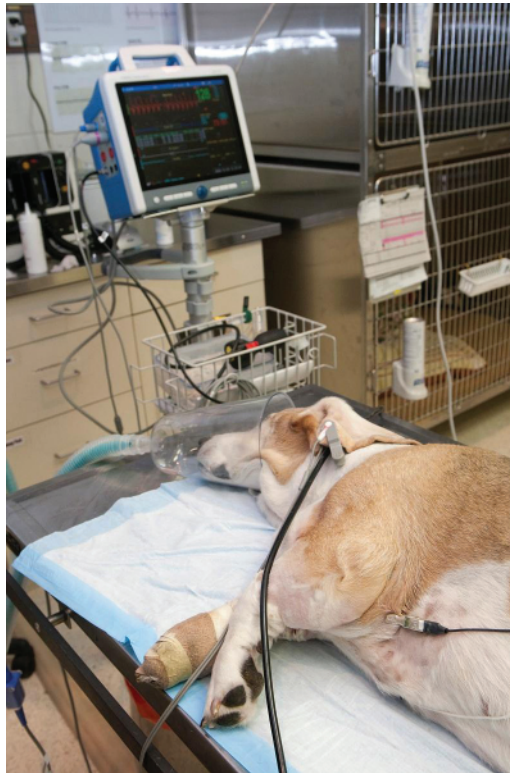


Figure 1.8 Stressful events often precipitate hypoadrenocortical crises. This 8-year-old Basset hound underwent anesthesia for mass removal from a toe, and collapsed the next day. She presented nonresponsive, in severe hypovolemic shock. Electrocardiogram revealed spiked T-waves and flattened P-waves, the first evidence of hyperkalemia. Preanesthetic serum chemistry (2 days before presentation) revealed a potassium concentration at the high end of normal and normal sodium concentration. Following collapse, her potassium concentration was 8.3 mEq/L, and sodium concentration was still within reference range (143 mEq/L).

- c. Hemogram findings are similar between the chronic and acute presentation. Anemia may be more severe with the acute form due to gastrointestinal blood loss, and is often much more apparent following rehydration. Since patients in hypovolemic shock are severely stressed, **the absence of a stress leukogram in this situation should alert the clinician to consider hypoadrenocorticism.**
- C. Atypical hypoadrenocorticism:**
1. Dogs with isolated glucocorticoid deficiency may have any of the same laboratory abnormalities as dogs with combined mineralocorticoid and glucocorticoid deficiency, with the exception of hyperkalemia, hyponatremia, and hypochloremia. However, there are some differences in the frequency and severity of these abnormalities:
 - a. Since patients with atypical hypoadrenocorticism are much less likely to present in hypovolemic shock, fewer patients are azotemic. The degree of azotemia is usually less severe than that found in typical Addisonians.
 - b. Anemia is more common in dogs with isolated cortisol deficiency. This is most likely because atypical Addisonians are less hemoconcentrated at presentation (when values are taken for use in comparative studies) than typical Addisonians. Atypical patients have lower serum albumin concentrations than typical patients, as well, supporting the hemoconcentration hypothesis.
 - c. **Serum cholesterol concentrations are lower in dogs with atypical hypoadrenocorticism.** The explanation for this is not clear; it may reflect the more protracted course of disease prior to diagnosis.

2. Specific endocrine tests:

- a. The ACTH stimulation test is required for definitive diagnosis of atypical hypoadrenocorticism; interpretation is the same as for typical hypoadrenocorticism.
- b. Although atypical Addison's is an uncommon disease, treatment is simple and inexpensive. Because patients without mineralocorticoid deficiency do not have electrolyte abnormalities, atypical hypoadrenocorticism should be considered in most patients with unexplained gastrointestinal signs, lethargy, weight loss, and polyuria/polydipsia (PU/PD). **Measurement of the baseline cortisol concentration can be very helpful for ruling out hypoadrenocorticism in these patients.**
- c. Patients with secondary hypoadrenocorticism and with atypical hypoadrenocorticism have similar clinical signs, due to their shared isolated cortisol deficiency. **Endogenous ACTH levels should be measured to differentiate between primary and secondary hypoadrenocorticism.** High levels indicate that the patient has primary hypoadrenocorticism (due to lack of negative feedback on the pituitary from cortisol), whereas low values are consistent with secondary hypoadrenocorticism. Since secondary hypoadrenocorticism is caused by a pituitary lesion, this information is helpful in directing further diagnostics, such as advanced imaging of the brain, in these cases. Additionally, patients with secondary hypoadrenocorticism should never acquire electrolyte abnormalities, whereas patients with atypical Addison's may.
- d. Pre- and post-ACTH stimulation aldosterone concentrations may be measured to help confirm isolated cortisol deficiency. Dogs with atypical Addison's should exhibit an increase in aldosterone concentration following stimulation, while minimal to no increase in aldosterone concentration is suggestive of a combined mineralocorticoid and glucocorticoid deficiency:
 - 1) Unfortunately, interpretation of post-stimulation aldosterone concentrations is not straightforward, as cut-off values between dogs that will develop electrolyte abnormalities and dogs that will not, have not been established. At this time, it appears that dogs with normal electrolyte concentrations, but minimal increase in aldosterone concentration following ACTH stimulation, may be at risk of developing electrolyte abnormalities in the near future.

V. **Differential Diagnoses**

A. Chronic and acute hypoadrenocorticism

The differential diagnoses for Addison's disease include conditions leading to **hyperkalemia** and **hyponatremia**, **gastrointestinal signs**, and **azotemia** (Table 1.3). Focusing on the causes of hyperkalemia and hyponatremia is usually most beneficial, as there are fewer rule-outs than for gastrointestinal disease and azotemia:

- 1. **Patients with Addison's disease are commonly misdiagnosed with acute renal failure (ARF) due to the overlap of clinical signs and diagnostic findings.** Gastrointestinal signs often accompany ARF due to the stimulation of the chemoreceptor trigger zone by uremic toxins. ARF may also result in hyponatremia and hyperkalemia in oliguric and anuric dogs. Azotemia is present in most patients with hypoadrenocorticism and all patients with ARF. Usually, prerenal causes of azotemia are differentiated from renal causes by evaluation of the urine-specific gravity. Dogs with renal azotemia lose the capacity to concentrate urine, so the urine is typically isosthenuric (1.008–1.012). In most dogs with prerenal azotemia, urine concentrating ability is maintained, and the urine specific gravity (USG) is >1.030, an appropriate response to dehydration.

In many dogs with Addison's disease, however, the USG is <1.020, despite the absence of underlying renal disease. Thus, clinicians may inadvertently believe that a dog with Addison's disease actually has ARF. Considering that the prognosis for a patient with hypoadrenocorticism is usually good, whereas prognosis for ARF is variable, misdiagnosis may not only delay appropriate treatment, but may sway the owners toward euthanasia.

There are several ways to differentiate the two diseases. The first is to perform an ACTH stimulation test; unfortunately, results are not generally available immediately or during emergency hours. Practically speaking, **dogs with hypoadrenocorticism respond to fluid therapy much more quickly than dogs with renal failure.** Azotemia typically decreases within the first 12–24h, and the dog's clinical

Table 1.3 Differential diagnoses.**Differential diagnoses for hyperkalemia and hyponatremia**

Hypoadrenocorticism

Acute renal failure

Urinary tract obstruction/uroabdomen

Trichuriasis

Severe gastrointestinal disease

Peritoneal effusion

Chylothorax

Diabetic ketoacidosis

Congestive heart failure

Hepatic failure/cirrhosis

Primary polydipsia

Inappropriate anti-diuretic hormone (ADH) secretion

Mannitol administration

Hypothyroid myxedema

Massive tissue trauma

- Crush injury
- Aortic thromboembolism
- Rhabdomyolysis

Diuretic administration

- Furosemide
- Spironolactone

ACE-inhibitor administration

Metabolic acidosis

Pregnancy

Artifacts

- Erythrocyte lysis in Japanese breeds
- Marked thrombocytosis
- Marked leukocytosis

The conditions highlighted in gray represent the most common differential diagnoses in dogs with hyponatremia and hyperkalemia that are later diagnosed with hypoadrenocorticism.

condition often improves within the first 2 h. Additionally, hyperkalemia and hyponatremia rarely occur in dogs with ARF unless anuria or oliguria is present following rehydration. Thus, if the patient is producing an adequate amount of urine following rehydration, the hyperkalemia and hyponatremia are much less likely to be caused by ARF. Occasionally, oliguria or anuria is misdiagnosed in an Addisonian patient. The most common reason for this is failure to allow for adequate rehydration prior to determining whether urine output is adequate.

2. Urinary tract obstruction and uroabdomen often result in hyperkalemia, hyponatremia, and potentially abdominal pain, and should be ruled out in Addisonian suspects.

3. Dogs suffering from **whipworm infestation** may also have hyperkalemia, hyponatremia, vomiting, and diarrhea, in addition to melena (“pseudohypoadrenocorticism”). For this reason, all patients with suspected hypoadrenocorticism should have a fecal examination performed. It is also possible for a dog to have both hypoadrenocorticism and whipworm infection, causing more severe disease than either alone:

a. **Severe gastrointestinal disease** from other causes (Ancylostomiasis, Coccidiosis, idiopathic hemorrhagic gastroenteritis) may also lead to pseudohypoadrenocorticism.

4. Other reported causes of concurrent hyperkalemia and hyponatremia include **peritoneal effusion, chylothorax, congestive heart failure, pregnancy, and severe acidosis.**

B. Atypical hypoadrenocorticism:

1. Most patients with atypical hypoadrenocorticism present for gastrointestinal signs, and may have hypocholesterolemia and hypoalbuminemia. Thus, other causes of GI disease with malabsorption, such as **inflammatory bowel disease** and **lymphangiectasia**, are often considered concurrently. Additionally, since signs are often exacerbated following a stressful event, dogs with hypoadrenocorticism may be thought to have “**stress colitis**” or **hemorrhagic gastroenteritis**. It is imperative that atypical Addison’s disease be considered in these cases so that it is not missed.

2. Some dogs with **polyuria and polydipsia** are also eventually diagnosed with atypical hypoadrenocorticism, and PU/PD may be their only presenting complaint. The potential differential diagnoses are too extensive to list here, but hypoadrenocorticism should remain on the list of differential diagnoses for patients with polyuria and polydipsia.

VI. Treatment

A. Chronic hypoadrenocorticism:

1. Treatment of combined cortisol and aldosterone deficiency requires lifelong glucocorticoid and mineralocorticoid supplementation. Chronic therapy is started in patients that do not present in crisis, and following stabilization of those patients that do:

a. Mineralocorticoids are given to control hyperkalemia, hyponatremia, and hypochloremia. Either a twice daily pill, fludrocortisone, or a monthly injection, desoxycorticosterone **pivalate** (DOCP), can be used for mineralocorticoid supplementation:

1) DOCP is a long-acting injectable mineralocorticoid with no glucocorticoid activity. It is initially administered at a dose of 2.2 mg/kg, subcutaneously or intramuscularly, every 25 days:

a) Adjustment of dose and dosing interval are based on electrolyte concentrations measured at specific times following administration:

i. Electrolytes are first rechecked 2 weeks after the injection. Dosage of the FOLLOWING injection will be adjusted based on these values:

i) If sodium and potassium concentrations are within the reference range, the dose remains the same.

ii) If hyponatremia or hyperkalemia is present, dose should be increased by about 10%.

iii) If hypernatremia or hypokalemia is present, dose should be decreased by about 10%.

iv) In small patients (5 kg or less), doses may be adjusted by up to 25% at a time.

v) If it is determined that the dose should be increased, measurement of electrolytes at day 25 is recommended to ensure that electrolyte values are not dangerously altered. However, adjustment of dose interval (see below) is postponed until after the following injection.

ii. Dosing interval is determined by measurement of electrolytes on day 25:

i) If sodium and potassium concentrations are within reference range, the dosing interval should remain the same, and the injection is to be given every 25 days.

ii) If hyponatremia or hyperkalemia is present, the dosing interval should be decreased by 1–2 days, and the next injection should be given in 23–24 days.

- iii) If hypernatremia or hypokalemia are present, the dosing interval should be increased by 1–2 days, and the next injection should be given in 26–27 days.
 - iv) Following each dosing interval change, the interval should be adjusted based on electrolyte concentrations measured prior to the next DOCP administration, as described above.
 - iii. Electrolytes should be rechecked at the above intervals each time the dose or dosing interval is changed, and then every 3–6 months thereafter.
 - iv. DOCP is an expensive medication, and owners will frequently ask for ways to decrease the cost. If electrolyte concentrations are normal on the day of the injection, the interval may be increased by 2 days, up until the interval is 30 days (or approximately once per month). This helps decrease expense and also helps owners remember the date of the next injection:
 - i) Although some dogs may only require injections every 6 weeks, monthly injections are recommended in order to help establish a consistent routine for the owner. Longer dose intervals are acceptable, but may result in decreased owner compliance.
 - v. Another way to decrease expense is to decrease the total dose. Some dogs do well on 1 mg/kg/month. However, the starting dose should be 2.2 mg/kg, and the dose decreased slowly (10% at a time) as long as electrolyte concentrations remain in the reference range immediately prior to the next injection. Use of this protocol saves money; however, using a lower dose leaves less room for error on the dosing interval. **It is imperative that owners wishing to use a lower dose adhere tightly to the dosing schedule.**
 - vi. The potential cost savings associated with prolonging the dose interval and/or decreasing the dose must be weighed against the expenses associated with the required monitoring following each adjustment. These adjustments are much more cost-effective for larger patients.
 - vii. Some owners will attempt to decrease cost by extending the dosing interval themselves. **Owners must be sternly warned that doing this increases the chances of their dog going into Addisonian crisis, which will most definitely be more costly, and potentially result in the death of their pet.**
 - b) Subcutaneous administration results in good control in most patients. However, there are occasional patients whose electrolyte values do not correct as expected. This may be due to an absorption problem. Most of these patients respond well to intramuscular injection.
 - c) There are few side effects of DOCP, although polyuria and polydipsia have been reported. It is less common with DOCP than with fludrocortisone, and may actually be due to the prednisone that the dog is on concurrently. However, if PU/PD are suspected to be due to the DOCP, decreasing the dose may decrease or eliminate this side effect.
 - d) All patients receiving DOCP will need additional daily glucocorticoid supplementation.
- 2) Fludrocortisone is a shorter-acting oral mineralocorticoid with some glucocorticoid activity. The initial dose is 0.02 mg/kg/day, divided:
- a) The dose is adjusted based on weekly electrolyte concentrations, until the dose stabilizes:
 - i. If the patient's electrolyte values are within reference range, the dose is maintained.
 - ii. If hyperkalemia or hyponatremia is present, the dose is increased by 0.05–0.1 mg/day.
 - iii. If hypokalemia or hypernatremia is present, the dose is decreased by 0.05–0.1 mg/day.
 - iv. If mild hyponatremia is present without concurrent hyperkalemia, salting the food at a dose of 0.1 mg/kg/day may help. Salting is not usually necessary long term, however.
 - b) Once the dose has stabilized, electrolytes should be rechecked every 3–6 months. The dose frequently needs to be increased within the first 1.5 years of therapy.
 - c) Polyuria, polydipsia, and less frequently polyphagia, panting, and hair loss are reported in some dogs on fludrocortisone. These signs can usually be attributed to the glucocorticoid properties of fludrocortisone, and should resolve if the patient is switched to DOCP (with concurrent prednisone).

b. Glucocorticoid supplementation usually controls the nonspecific and gastrointestinal signs of hypoadrenocorticism. Prednisone is the most frequently used glucocorticoid. The physiologic dosage of prednisone is 0.1–0.25 mg/kg/day:

1) The prednisone dose is titrated “to effect,” according to clinical signs. The dose is increased if lethargy, anorexia, vomiting, diarrhea, or melena occurs. The client is instructed to pay close attention to the dog’s attitude, and the dose should be increased if the dog is not “acting herself.” The dose is decreased if side effects of glucocorticoid excess are present, such as PU/PD, polyphagia, or panting.

2) The prednisone dose needs to be increased by 2–10 times when the dog is in a stressful situation. This may include any trips to the veterinarian (such as to check electrolytes), new visitors in the home, a new addition to the household, vacation, etc. The increased dose is started the day or morning prior to the beginning of the stressful event, and continued for a day or two afterward. With time and guidance, the client should be able to determine the optimal dose for the patient in times of stress:

i. Remember that **any unrelated illness places additional physiologic stress on the patient and will require additional glucocorticoid administration.**

ii. It must also be noted that an **increase in clinical signs, such as vomiting or diarrhea, suggests that the prednisone dose needs to be increased.** Physiologic doses of prednisone should not cause gastric ulceration or other gastrointestinal side effects, so gastrointestinal signs usually mandate an increase in prednisone dose.

3) Whereas fludrocortisone has some glucocorticoid activity, DOCP does not. Thus, **all patients on DOCP need daily glucocorticoid supplementation**, whereas about half of the patients on fludrocortisone do not:

i. Dogs taking fludrocortisone should be started on 0.1 mg/kg/day of prednisone, divided BID or once daily. At the 1 week electrolyte recheck examination, the dose may be decreased by 50% if signs of cortisol deficiency (such as gastrointestinal signs or lethargy) are not present. It may be discontinued if these signs are still absent 1 week later. The dose should be increased at any point when signs of cortisol deficiency return, and the dose should be increased during stressful situations, as described above.

B. Acute hypoadrenocorticism:

1. An Addisonian crisis is an immediately life-threatening condition that requires rapid intervention. **The initial goals of treatment are in order of importance to correct hypovolemia, hyperkalemia, and associated arrhythmias, hypoglycemia, acidosis, and hypercalcemia, if present:**

a. **Aggressive intravenous fluid resuscitation is the first priority**, as it corrects hypovolemia, hyponatremia, hypochloremia, and most cases of hyperkalemia and metabolic acidosis. One-third to one-half of the shock volume (90 mL/kg) of an isotonic replacement crystalloid should be given initially. Response should be assessed based on heart rate, pulse quality/blood pressure, capillary refill time, and mental status. Additional fluids should then be given if necessary:

1) Because of the high sodium and chloride content, and lack of potassium, 0.9% NaCl has traditionally been recommended as the fluid of choice for treating patients in adrenocortical crisis. However, Normosol-R and lactated Ringer’s solution (LRS) are preferred by some clinicians. The low potassium content in these fluids still allows for correction of hyperkalemia, and they correct acidosis more quickly than 0.9% saline.

2) Hetastarch (hydroxyethyl starch) may also be used for treatment of hypovolemic shock, particularly in hypoalbuminemic patients. A dose of 5–10 mL/kg is given as a bolus with the initial bolus of crystalloids for more rapid fluid resuscitation.

3) **Care should be taken not to increase the sodium concentration more than 0.5 mEq/h (12 mEq/day) in patients with hyponatremia.** An abrupt change in extracellular sodium concentration (and subsequent osmolality) may lead to myelinolysis and neurologic signs. Hypertonic saline should NEVER be used to treat a patient in Addisonian crisis.

b. If hypoglycemia is suspected or proven, an IV dose of 1 mL/kg of 25% dextrose in saline (a 1:1 mixture of 50% dextrose and 0.9% saline) should be administered. This should be followed by a

1.25–5% solution of dextrose in the patient's crystalloid fluids. Five percent dextrose (D5W) should not be given, as the fluid becomes hypotonic after the dextrose is metabolized, resulting in inadequate intravascular fluid expansion.

c. Fluid therapy alone is usually adequate to treat the hyperkalemia. However, in cases of severe hyperkalemia (>9.0 mEq/L) and/or life-threatening arrhythmias (severe bradycardia, absent P-wave, idioventricular rhythm), specific therapy is indicated:

1) Calcium gluconate is administered for its cardioprotective effects, which are rapid and will often maintain the patient's life while allowing time for fluids and other therapies to take effect. It does not, however, decrease the potassium concentrations. 0.5–1.5 mL/kg of calcium gluconate is given slowly over 15 min, while monitoring the ECG for new arrhythmias (such as shortened Q-T interval) and further decreased heart rate due to calcium administration. Administration should be stopped if new arrhythmias occur.

2) Intravenous regular insulin may also be given in concert with dextrose to drive potassium intracellularly. 0.2–0.5 U/kg of regular insulin is given, followed by 2 g of dextrose (diluted to 25% in an isotonic crystalloid) per unit of insulin administered. Blood glucose concentration should then be monitored and dextrose should be added to the replacement fluids to produce a 1.25–2.5% dextrose solution.

d. Glucocorticoid deficiency may contribute to the hypotension seen in dogs in crisis, and is also responsible for the hypoglycemia, gastrointestinal signs, and general debility. Supplementation should be implemented following initiation of therapy for hyperkalemia and hypovolemia. Dexamethasone sodium phosphate, at a dose of 0.25 mg/kg IV, is recommended. Since it has 7–8 times the glucocorticoid activity as prednisone, this is equivalent to 2 mg/kg of prednisone, or 10 times the physiologic dose:

1) Other glucocorticoids, such as hydrocortisone sodium succinate (0.5 mg/kg/h) and prednisolone sodium succinate (2 mg/kg), have also been recommended. Hydrocortisone is an ester of cortisol, with equivalent glucocorticoid and mineralocorticoid activity:

i. Most synthetic glucocorticoids, with the exception of dexamethasone and triamcinolone, interfere with the cortisol assay. Thus, only these glucocorticoids should be given prior to completing the ACTH stimulation test. This advantage and its availability make dexamethasone the author's glucocorticoid of choice for treating an Addisonian crisis.

ii. Although dexamethasone and triamcinolone do not interfere with the cortisol assay, they do inhibit ACTH release, resulting in adrenocortical suppression. Administration of even a single dose of 0.1 mg/kg of dexamethasone can result in decreased cortisol response to ACTH administration for 3 or more days. However, post-stimulation cortisol concentrations should not be less than 2 μ g/dL (55 nmol/L), as seen in clinical hypoadrenocorticism, following a single dose. Administration of multiple doses of dexamethasone, or chronic administration, will result in adrenocortical atrophy and decreased cortisol concentration following ACTH stimulation for a longer period of time, and could lead to iatrogenic hypoadrenocorticism.

e. Additional supportive therapy should be provided as necessary. For example, dogs with gastrointestinal signs (vomiting, diarrhea, and melena) are given **gastroprotectants**, including H_2 -blockers and sucralfate. Due to the potential for bacterial translocation from the GI tract, the author also administers prophylactic ampicillin, although this is controversial. Some dogs have such severe GI blood loss that packed red blood cell or whole blood transfusion is necessary.

f. Following initial stabilization, frequent reassessment is necessary. Fluid rates should be adjusted to correct dehydration and azotemia, while keeping up with maintenance requirements and ongoing losses. Electrolyte values should be rechecked following fluid resuscitation, and then frequently (q 6–12 h) until the potassium and sodium concentrations stabilize. Too rapid correction of hyponatremia should be avoided.

g. Following definitive diagnosis of hypoadrenocorticism, mineralocorticoid supplementation should be provided. Intravenous therapy is continued until the dog is able to eat and maintain hydration on her own:

1) Since correcting hyponatremia too rapidly can result in myelinolysis, mineralocorticoid supplementation should be postponed until the sodium concentration is closer to normal (approximately 132 mEq/L) in patients with severe hyponatremia.

h. Dexamethasone or another parenteral glucocorticoid is continued at a dose of 0.2 mg/kg/day until prednisone is tolerated. Prednisone is then administered at 1 mg/kg divided BID until the patient leaves the hospital, after which it is slowly tapered to physiologic dose:

1) **Most patients respond quickly to therapy and dramatically improve within hours.** However, more debilitated patients, particularly the ones with severe hyperkalemia, may take 2–3 days to see great improvement. Dogs are usually hospitalized for 3–5 days following an Addisonian crisis.

C. Atypical hypoadrenocorticism:

1. Dogs with isolated cortisol deficiency require only glucocorticoid supplementation. Prednisone is initially given at 0.1–0.25 mg/kg/day. Dose titration is the same as described above. **The goal is to give enough prednisone to control the dog's clinical signs of hypoadrenocorticism, but not so much as to cause side effects of glucocorticoid supplementation.** Additional prednisone (2–10 times the normal dose) must be given prior to stressful events.

2. **Some dogs with atypical hypoadrenocorticism will develop mineralocorticoid deficiency following initial diagnosis.** In two studies (Lifton et al. 1996; Thompson et al. 2007), only 3 out of 29 dogs with isolated cortisol deficiency developed mineralocorticoid deficiency, from 3 weeks to 7 months following initial diagnosis. However, another case series suggests that over half of these dogs will develop mineralocorticoid deficiency at a later time. At this time, it is impossible to determine which dogs will do so. Thus, vigilant monitoring by the owner is imperative. Reevaluation of electrolytes at 1 and 3 months following initial diagnosis, and then every 6 months thereafter, seems prudent in these cases:

a. **Patients with secondary hypoadrenocorticism are glucocorticoid deficient only,** requiring prednisone administration as described above. Unlike dogs with atypical hypoadrenocorticism, these patients should never develop electrolyte abnormalities.

VII. Prognosis

A. With prompt diagnosis and appropriate treatment, the prognosis for patients with naturally occurring hypoadrenocorticism is excellent, and patients usually enjoy a good quality and normal span of life. The need for consistent treatment and patient monitoring must be stressed to owners, as skipping medication or prolonging the treatment interval for DOCP (without direction from a veterinarian) may lead to hypoadrenocortical crisis.

B. With prompt diagnosis and appropriate treatment, the prognosis for patients with iatrogenic hypoadrenocorticism is also excellent. The hypoadrenocorticism may be transient or permanent, depending on the cause.

VIII. Prevention

A. At this time, it is not possible to prevent idiopathic primary hypoadrenocorticism in most dogs. However, selective breeding may help decrease the prevalence in some breeds in which the mode of inheritance has been determined, such as the Standard Poodle, Portuguese water dog, and Nova Scotia Duck-tolling retriever.

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