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INTERNAL MEDICINE

Diagnosis and Long-Term Management of Canine Hypoadrenocorticism

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Hypoadrenocorticism (HOAC; Addison's disease) is an uncommon endocrine disease of dogs with a prevalence ranging from 0.06% to 0.28%.¹⁻³ However, among dogs with chronic gastrointestinal signs, the prevalence has been reported to reach 4%.⁴ With vague clinical signs, nonspecific clinicopathologic changes, and a relatively low disease prevalence, canine HOAC is often referred to as "the great pretender."

The biggest challenge in the diagnosis of HOAC is recognizing when it should be a differential.

Once HOAC is suspected, obtaining a definitive diagnosis is relatively straightforward. Although HOAC can be life-threatening, early identification and treatment can result in an overall excellent long-term prognosis.

PATHOETIOLOGY

Primary HOAC accounts for 95% of canine HOAC cases and is characterized by the loss of functional adrenocortical tissue. In health, the adrenal cortex consists of 3 functionally and

Topic Overview

Canine hypoadrenocorticism (Addison's disease) is an endocrine condition caused by a deficiency of glucocorticoids (primarily cortisol), often with a concurrent deficiency in mineralocorticoids (primarily aldosterone). Most resources on hypoadrenocorticism focus on acute management of the addisonian crisis or general principles of diagnosis and treatment. However, long-term management requires careful reassessment of each patient while considering comorbidities and patient variability. This article reviews key concepts in the pathoetiology, diagnosis, and treatment of canine hypoadrenocorticism. A case example is used to illustrate how long-term therapy and monitoring should be adjusted on a case-by-case basis.

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Learning Objectives

- A definitive diagnosis of hypoadrenocorticism (HOAC) is established by demonstrating a diminished cortisol reserve using the adrenocorticotrophic hormone (ACTH) stimulation test.
- Dogs with HOAC have pre- and post-ACTH cortisol concentrations ≤ 2 $\mu\text{g/dL}$. Post-ACTH cortisol concentrations between 2 and 8 $\mu\text{g/dL}$ do not provide a definitive diagnosis of HOAC.
- Desoxycorticosterone pivalate (DOCP) dosages lower than the manufacturer's recommended dose are effective in most dogs with HOAC. Younger dogs require higher doses and large-breed dogs require lower doses.
- After reaching a dosing interval of 28 to 30 days, most clinicians recommend adjusting the dose of DOCP to control hyperkalemia and hyponatremia rather than continuing to extend the dosing interval.
- Glucocorticoid doses provided in most veterinary textbooks are often too high for long-term management of canine HOAC and can lead to hypercortisolism. Most patients can be managed on prednisone doses of 0.05 to 0.1 mg/kg/day.
- Hydrocortisone is the glucocorticoid of choice for humans with adrenal insufficiency and can be used in dogs that develop clinical signs of hypercortisolism from prednisone use. Hydrocortisone is 4 times less potent than prednisone.
- The doses of glucocorticoid and mineralocorticoid replacement therapy needed vary greatly between patients. It is important to monitor each patient for clinical signs of uncontrolled HOAC as well as for signs of hypercortisolism.

morphologically distinct zones: the zona glomerulosa, zona fasciculata, and zona reticularis. Only the zona glomerulosa contains the enzyme aldosterone synthase, meaning it is the sole producer of mineralocorticoids (e.g., aldosterone). The zonae fasciculata and reticularis both synthesize glucocorticoids (e.g., cortisol) and androgens. When 85% to 90% of this functional adrenocortical tissue is destroyed, primary HOAC results.

Although large studies describing the underlying histopathologic abnormalities in dogs with HOAC are lacking, lymphoplasmacytic inflammation of the adrenal glands caused by an immune-mediated adrenalitis is suspected in most cases.⁵ This immune-mediated etiology is further supported by the presence of autoantibodies in some dogs.⁶ Although thought to be less common than immune-mediated destruction of the adrenal cortex, primary HOAC can also result from infiltrative disease (e.g., neoplasia, granulomatous diseases) or iatrogenically from the administration of drugs used to treat hyperadrenocorticism (e.g., trilostane, mitotane).⁷

Most dogs with primary HOAC present with hyponatremia and hyperkalemia in conjunction with low cortisol, reflecting deficiencies of both mineralocorticoids and glucocorticoids. However, a small subset of dogs with HOAC present with normal

electrolyte levels.⁸⁻¹¹ Some of these dogs go on to develop electrolyte derangements supportive of mineralocorticoid deficiency, while others maintain normal levels.^{10,12} The latter are referred to as having eunatremic, eukalemic hypoadrenocorticism (EEH), a term that has recently replaced the term “atypical” HOAC. Why some dogs with HOAC develop electrolyte changes while others do not is not fully understood. In some dogs with EEH, the zona glomerulosa appears to be spared in the immune-mediated cortical destruction,⁵ while in others, renal compensation is thought to maintain normal electrolytes in the face of subnormal aldosterone concentrations.¹⁰

Secondary and tertiary HOAC result from disease of the pituitary gland and hypothalamus, respectively, and are collectively known as central HOAC. The most common cause of secondary HOAC is the sudden cessation of long-term steroid therapy that has resulted in suppression of adrenocorticotrophic hormone (ACTH) secretion by the pituitary gland. Spontaneous central HOAC is rare in dogs but can be caused by neoplasia or intracranial trauma.¹³ Given that aldosterone secretion is primarily regulated by circulating potassium and angiotensin II concentrations rather than ACTH, dogs with central HOAC do not have concurrent mineralocorticoid deficiency.¹⁴

SIGNALMENT

The median age of diagnosis for dogs with HOAC is 4 years, although it has been reported in dogs aged 2 months to 14 years.¹⁴ Female dogs have a higher risk of developing HOAC than male dogs, with 60% to 70% of HOAC patients being female.^{1,14} Compared with dogs with concurrent mineralocorticoid deficiency, dogs with glucocorticoid deficiency alone (i.e., EEH) are generally older (median age, 6 to 7 years).^{8,11}

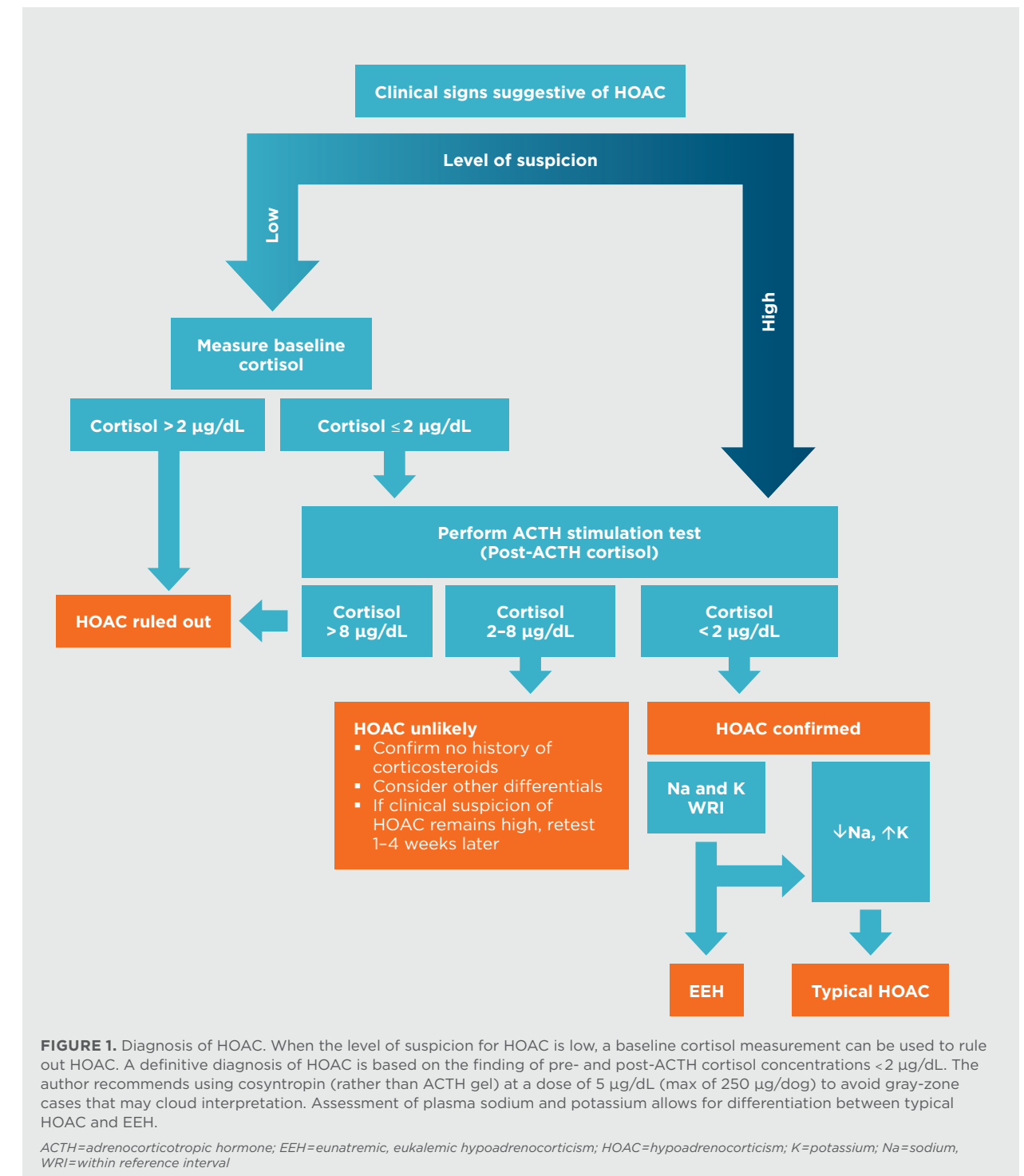
Although HOAC can occur in any breed of dog, a strong heritable component has been identified in standard poodles, Portuguese water dogs, Nova Scotia duck tolling retrievers, and bearded collies.¹⁵ Great Danes, Rottweilers, West Highland white terriers, and wheaten terriers have been shown to have an increased risk of HOAC, but inheritance has not been proven.¹⁶

PRESENTATION

The clinical presentation of HOAC is highly variable.

Some dogs present for acute collapse while others present with a chronic history of intermittent nonspecific signs, such as vomiting, diarrhea, hyporexia, or lethargy. Dogs with HOAC can present with mild, waxing and waning episodes of illness that worsen during times of stress or in a life-threatening

state known as an addisonian crisis. The clinical manifestations seen with HOAC are related to deficiencies in glucocorticoids and mineralocorticoids and have been summarized elsewhere.¹⁷



BOX 1 When to Consider Hypoadrenocorticism

Hypoadrenocorticism should be considered in dogs presenting with:

- Acute collapse and hypovolemia with the expected electrolyte changes (i.e., hyponatremia, hyperkalemia)
- Chronic gastrointestinal signs, even if they are intermittent
- Unexplained hyperkalemia with or without hyponatremia
- Sickness without expected stress leukogram
- Megaesophagus
- Polyuria and polydipsia
- Hypercalcemia
- Unexplained eosinophilia
- Unexplained hypoglycemia

DIAGNOSTIC OVERVIEW

HOAC can present in a variety of ways, sometimes with vague, intermittent clinical signs. Consequently, the biggest challenge in diagnosis is recognizing when HOAC should be a differential. **BOX 1** highlights scenarios in which evaluation for HOAC should be considered. The general approach to HOAC diagnosis is provided in **FIGURE 1**.

Screening for Hypoadrenocorticism

When the clinical suspicion of HOAC is not particularly high but it is important to consider HOAC as a possible diagnostic differential before proceeding to other diagnostic tests (e.g., dogs presenting with chronic gastrointestinal signs), a baseline cortisol test should be performed. A baseline cortisol concentration > 2 µg/dL rules out HOAC, with a reported sensitivity of 99.4% to 100%.¹⁸⁻²⁰ However, if the baseline cortisol is ≤ 2 µg/dL, an ACTH stimulation test must be performed to definitively rule HOAC in or out.

In a pooled sample of 190 dogs with HOAC across 3 studies,¹⁸⁻²⁰ all but 1 dog had a baseline cortisol ≤ 2 µg/dL. Consequently, if the suspicion of HOAC is high in a dog with a baseline cortisol of 2.1 to 3 µg/dL, ACTH stimulation could be performed, provided other diagnostic differentials have been considered and the dog has no recent history of glucocorticoid administration.

Definitive Diagnosis of Hypoadrenocorticism

Definitive diagnosis of HOAC necessitates demonstration of a diminished cortisol reserve using the ACTH stimulation test (**TABLE 1**). During an ACTH stimulation test, a supraphysiological dose of synthetic ACTH (e.g., cosyntropin) is administered, and the cortisol concentration is measured 1 hour later. A diagnosis of HOAC is defined by a post-ACTH cortisol concentration ≤ 2 µg/dL.¹⁶ In most dogs with HOAC, both pre- and post-ACTH cortisol concentrations are < 1 µg/dL. As diagnosis is based on the post-ACTH cortisol concentration alone, some clinicians might choose to forgo measurement of pre-ACTH cortisol to reduce expenses.

Interpreting Equivocal Test Results

A post-ACTH cortisol concentration > 2 µg/dL but below the accepted cutoff for adequate adrenal reserve (8 µg/dL) does not provide a definitive diagnosis of HOAC. Possible explanations for an inadequate response to an ACTH stimulation test include prior glucocorticoid administration; loss of potency of the administered ACTH product (most often due to poor or extended storage); errors in administration or sample collection; and previous treatment with mitotane, trilostane, or ketoconazole.¹⁶ As HOAC is believed to result from immune-mediated destruction of the adrenal glands, it is possible that dogs early in the disease course may have borderline results, but this is

poorly documented. In 1 study, 7 dogs with suspected EEH but equivocal post-ACTH cortisol concentrations were followed for a median of 2 years; ultimately none of them were diagnosed with HOAC.²⁵

If an equivocal ACTH stimulation result is obtained, it is recommended to (1) confirm the dog was not recently exposed to glucocorticoids, (2) ensure the test was appropriately conducted and the cosyntropin properly stored, and (3) consider other differentials. If the clinical suspicion of HOAC remains high, retesting in 1 to 4 weeks can be considered.

Testing Dogs on Glucocorticoids

When administration of glucocorticoids is clinically necessary prior to performing the ACTH stimulation test, dexamethasone should be used, as it does not cross-react with the cortisol assay.¹⁶ However, it should be noted that dexamethasone, like all glucocorticoids, suppresses the hypothalamic-pituitary-adrenal (HPA) axis. In healthy beagles, a single dose of 0.1 mg/kg IV dexamethasone decreased cortisol concentrations after ACTH stimulation for up to 3 days.²⁶ Although the response was suppressed, there was still adequate stimulation to exclude a diagnosis of HOAC. Thus, an ACTH stimulation test can be still performed after a single dose of dexamethasone. Longer durations of treatment with dexamethasone prior to testing are likely to result in a false-positive diagnosis of HOAC.

If a clinician wants to test for HOAC in a dog that is currently on or has recently received glucocorticoids, the glucocorticoids must be tapered off and followed by a 3-week minimum washout period. In a study of 12 dogs that received oral prednisone (0.55 mg/kg PO q12h) for 35 days, HPA axis recovery was complete by 2 weeks; however, this study only included healthy male research dogs.²⁷ A recent study evaluated the length of time it took the HPA axis to recover (defined as an ACTH-stimulated cortisol concentration > 6 µg/dL) in 20 dogs receiving intermediate-acting steroids for the treatment of various conditions.²⁸ Most dogs (17/20) exhibited HPA axis recovery by 16 to 18 days; however, recovery took over 8 weeks in 2 dogs.²⁸ The time to HPA axis recovery was not associated with patient body weight, median daily dose, cumulative dose, maximum dose, or duration of treatment.²⁸

Although the author recommends waiting a minimum of 3 weeks following glucocorticoid discontinuation to evaluate the HPA axis, it should be noted that false-

positive results on the ACTH stimulation test are still possible in a small number of patients. In such scenarios, if the ACTH-stimulated cortisol concentration falls between 3 and 8 µg/dL and the patient is clinically stable, it is recommended to retest at a later date, as a post-stimulation cortisol value within this range is more suggestive of recent glucocorticoid administration than true HOAC.¹⁵

Cost of Testing

The cost of synthetic cosyntropin has led to investigations into more cost-effective dosing and storage strategies. In 1 study, a 1-µg/kg dose of cosyntropin was equivalent to the standard dose of 5 µg/kg for screening dogs with clinical signs of HOAC.²³ However, it should be noted that only 2 dogs in this study had HOAC. Furthermore, 1 dog had an equivocal ACTH-stimulated cortisol concentration of 3.4 µg/dL when 1 µg/dL of cosyntropin was used, whereas the ACTH-stimulated cortisol concentration using the standard 5-µg/dL dose was 12.3 µg/dL, allowing HOAC to be ruled out. Consequently, the author prefers to use the standard cosyntropin dose (5 µg/kg) to avoid gray-zone cases that may cloud interpretation. To save on costs, reconstituted cosyntropin can be stored in plastic syringes (it will bind to glass) and frozen for up to 6 months without losing efficacy.²⁹ The author's institution freezes cosyntropin in 0.2-mL (50-µg) aliquots so that 1 aliquot is needed per 10 kg of body weight.

Role of Aldosterone Measurement

Mineralocorticoid deficiency is usually inferred from documenting the presence of hyponatremia, hyperkalemia, or both at initial diagnosis. However, it has been shown that sodium and potassium concentrations correlate poorly with aldosterone concentrations.¹⁰ This lack of correlation and the knowledge that dogs with EEH can go on to develop electrolyte derangements make measuring aldosterone an attractive option.

Aldosterone secretory capacity can be evaluated by measuring aldosterone concentrations before and 1 hour after administration of synthetic ACTH.³⁰ By definition, it is expected that dogs with typical HOAC will have low baseline and ACTH-stimulated aldosterone concentrations, whereas those with isolated glucocorticoid deficiency (EEH, central HOAC) will have normal aldosterone concentrations.⁸ However, this

TABLE 1 ACTH Stimulation Test Using Cosyntropin^a

STEP	NOTES
Important history questions	- Has the dog received glucocorticoids within 3 weeks of the test? - If yes, reschedule the test. - A single dose of dexamethasone (no cross-reactivity with the cortisol measured by the assay) is acceptable if the ACTH stimulation test is performed within 24 hours of administration. - Has the dog recently received mitotane, trilostane, or ketoconazole? - If yes, consider iatrogenic HOAC.
Patient preparation	No fasting is necessary, unless the specific cortisol assay utilized is influenced by lipemia.
Protocol	- Collect 1 mL of serum for baseline cortisol concentration: - Collect blood into a red-top tube and allow it to clot at room temperature. - Centrifuge, draw off serum, and transfer to a tube suitable for frozen storage and/or shipping. - Freeze the sample if it will not be shipped for at least 12 hours. - Administer 5 µg/kg^b (maximum of 250 µg/dog) synthetic ACTH (cosyntropin) IV.^c - One hour following administration, collect 1 mL of serum for post-ACTH cortisol concentration, following the same steps as for baseline collection.
Interpretation	- Pre- and post-ACTH cortisol concentration both < 2 µg/dL = HOAC - Post-ACTH cortisol concentration 2–8 µg/dL = HOAC unlikely

ACTH = adrenocorticotropic hormone; HOAC = hypoadrenocorticism.

^aThe author prefers to use cosyntropin (Cortrosyn; Amphastar Pharmaceuticals, amphastar.com) and avoids compounded ACTH gel due to inconsistent results.²¹ If gel is used, a different protocol is necessary.²²

^bA 1 µg/kg dose of cosyntropin has been shown to be equivalent to a 5 µg/kg dose for screening of dogs with suspected HOAC; however, only 2 dogs with HOAC were included in this study.²³

^cUnintentional perivascular injection of cosyntropin does not significantly alter test results.²⁴

is not always the case. Some HOAC patients can have electrolyte derangements despite normal aldosterone concentrations, while others maintain electrolyte balance despite low plasma aldosterone concentrations.¹⁰

Whether mineralocorticoid supplementation in dogs with EEH is of benefit remains to be determined. Thus, in dogs with EEH it is reasonable to provide glucocorticoid supplementation alone and monitor electrolytes and clinical signs. However, some clinicians may elect to evaluate ACTH-stimulated aldosterone concentrations in EEH cases and institute mineralocorticoid supplementation when concentrations are low. This practice is unlikely to be harmful but, as yet, has no known benefit.

Potential Role of Renin Activity

In states of aldosterone deficiency, the inability to retain sodium leads to hypovolemia and subsequent renin release. Thus, a low plasma aldosterone concentration in the face of a high plasma renin activity can allow differentiation of primary and secondary HOAC. In humans, renin is also used to evaluate mineralocorticoid dose and is more effective than monitoring electrolytes or blood pressure.³¹ In dogs, plasma renin activity has been shown to be higher in dogs with primary HOAC than in healthy dogs or dogs with diseases mimicking HOAC.³² In addition, the aldosterone-to-renin ratio has been shown to be a more sensitive measure of mineralocorticoid deficiency than aldosterone or renin alone, with no observed overlap between healthy dogs and dogs with HOAC.³³ Unfortunately, measurement of plasma renin activity is currently not commercially available.

THERAPEUTIC APPROACH

Treatment of HOAC largely depends on patient presentation. Some dogs present in an acute, life-threatening addisonian crisis with severe electrolyte derangements and hypovolemia and require acute stabilization and intensive therapy. Others exhibit chronic, less severe clinical signs. Although many dogs need fluid therapy and supportive care in the acute setting, the mainstay of treatment for all dogs with HOAC is lifelong supplementation of glucocorticoids with or without mineralocorticoid replacement. Acute management of the addisonian crisis has been thoroughly covered elsewhere.^{15,17} Long-term treatment options, including recommended doses and adjustments, are summarized in **TABLE 2**.

See the **CASE EXAMPLE** sidebar for the 6-year-long management of a female flandoodle with HOAC.

Glucocorticoid Supplementation

All patients with HOAC, whether primary, secondary, or EEH, require glucocorticoid supplementation.

It should be noted that glucocorticoid dose adjustments are based purely on clinical signs. An ACTH stimulation test is not helpful in patients with HOAC undergoing treatment and thus should not be performed. Gastrointestinal signs for which no other etiology can be identified should prompt a dose increase, while signs of hypercortisolism (polyuria, polydipsia, panting, polyphagia) indicate that the dose needs to be decreased. Unexplained lethargy can be a clinical sign of uncontrolled HOAC as well as hypercortisolism.

Initial Dose

In the acute setting, parenteral supplementation with dexamethasone sodium phosphate (0.14 mg/kg IV), which has 7 times the glucocorticoid activity of prednisone,³⁷ is often used.^{15,22} The patient is then discharged on an oral glucocorticoid such as prednisone. Although the physiologic dose of prednisone is 0.1 to 0.2 mg/kg/day, patients are typically started at a higher dose (0.5 mg/kg/day) to mimic the body’s normal stress response to being sick or visiting the veterinary clinic. This dose is then decreased to a physiologic dose (0.2 mg/kg/day) within 1 week following discharge. The glucocorticoid dose continues to be tapered over the following weeks to months based on clinical signs and side effects.

Maintenance Doses and Adjustments

Maintenance glucocorticoid dosages for HOAC are usually 0.1 to 0.2 mg/kg/day; however, some dogs, particularly large-breed dogs, do well on doses as low as 0.03 mg/kg/day. The author prefers to use hydrocortisone for maintenance HOAC treatment as it is 4 times less potent than prednisone and therefore facilitates small dose adjustments. In addition, hydrocortisone possesses more mineralocorticoid activity than prednisone. Hydrocortisone is the glucocorticoid replacement of choice in humans with adrenal insufficiency³⁸; however, few studies have evaluated its use in dogs with HOAC. In 1 survey-based study of 274 dogs with HOAC, 6% were

receiving hydrocortisone.³⁹ Most of these dogs were switched from prednisone to hydrocortisone due to intolerable adverse effects; improvement in adverse effects was reported following the medication switch.

In humans, the starting dose of hydrocortisone is 0.2 mg/kg/day.³⁸ As prednisone is 4 times more potent than hydrocortisone, this translates to a prednisone dose of 0.05 mg/kg/day. In dogs, the author recommends a hydrocortisone starting dose of 0.5 mg/kg q12h (equivalent to 0.25 mg/kg/day prednisone). As hydrocortisone is a short-acting glucocorticoid, the daily dose should be divided into twice-daily administration.

Stress Doses

As dogs with HOAC are unable to mount a normal physiologic response to stress, it is recommended to double their glucocorticoid dose during times of stress (e.g., veterinary visits, house guests, boarding, concurrent illness). Most often this is accomplished by increasing the dose the day prior to a known stressful event and continuing it a day or 2 following.

Mineralocorticoid Supplementation

Mineralocorticoid supplementation is indicated in all patients with primary HOAC to correct hyperkalemia, hyponatremia, and hypochloremia.⁴⁰ There are 2 options: (1) monthly injections of deoxycorticosterone pivalate (DOCP) or (2) oral,

TABLE 2 Long-Term Replacement Therapy for HOAC^a

REPLACEMENT FOR	MEDICATION	INITIAL DOSE	ADJUSTMENTS
Glucocorticoid deficiency (all dogs with HOAC)	Prednisone or prednisolone	0.25–0.5 mg/kg PO q24h ■ Initiate at 0.5 mg/kg PO q24h for 5 days ■ Then decrease to 0.2 mg/kg PO q24h	■ Decrease to dose at which clinical signs continue to be controlled and there is no evidence of hypercortisolism ■ Typical end dose: 0.05–0.1 mg/kg/day ■ Double dose during times of stress (e.g., groomer, boarding, vet visits)
	Hydrocortisone	0.5–1 mg/kg PO q12h ■ Initiate at 1 mg/kg PO q12h for 5 days ■ Then decrease to 0.5 mg/kg PO q12h	■ Decrease to dose at which clinical signs continue to be controlled and there is no evidence of hypercortisolism ■ Typical end dose: 0.1–0.4 mg/kg/day, but dose should continue to be divided into q12h dosing given short-acting nature of hydrocortisone ■ Double dose during times of stress (e.g., groomer, boarding, vet visits)
Mineralocorticoid deficiency (dogs with primary HOAC and hyperkalemia and/or hyponatremia or low plasma aldosterone)	DOCP	■ Small dogs or dogs aged < 3 years: 1.5 mg/kg SC or IM q25d^b ■ Large dogs (> 30 kg [66 lb]): 1.1 mg/kg SC or IM q25d^c	■ See FIGURE 2
	Fludrocortisone acetate	0.01–0.02 mg/kg PO q12h ^d	■ Concurrent prednisone administration can be discontinued in ~50% of cases ■ Dose may need to be increased to resolve hyperkalemia and/or hyponatremia ■ If clinical signs of hypercortisolism on fludrocortisone (after weaning off additional prednisone) occur, consider switching to DOCP

DOCP = desoxycorticosterone pivalate; HOAC = hypoadrenocorticism.
^aTwo options are provided for each glucocorticoid and mineralocorticoid supplementation; only 1 should be chosen (e.g., prednisone/prednisolone or hydrocortisone).
^bThe manufacturer-recommended dosage is 2.2 mg/kg q25d. A 2019 study determined that a starting dose of 1.5 mg/kg SC q28–30d DOCP was effective in most dogs. Younger dogs may require slightly higher doses.³⁴
^cThe manufacturer-recommended dosage is 2.2 mg/kg q25d. A 2021 study determined that a starting dose of 1.1 mg/kg SC q30d DOCP was effective in medium- and large-breed dogs over 2 years of age.³⁵
^dAlthough fludrocortisone acetate contains both a mineralocorticoid and glucocorticoid, concurrent treatment with prednisone is recommended in the initial stages of management as it shortens time to stabilization. Although some dogs may be successfully managed with once-daily dosing, many need twice-daily dosing; therefore, it is recommended to start with twice-daily dosing.³⁶

Case Example: Management of Hypoadrenocorticism in a Flandoodle

Presentation

Hannah, a 4-year-old female spayed flandoodle, presented to the University of Tennessee College of Veterinary Medicine for evaluation of chronic intermittent hyporexia and vomiting. Initial blood analysis revealed lymphocytosis, hypoalbuminemia, hypocholesterolemia, hyperphosphatemia, hypercalcemia, and mild azotemia (TABLE A). Sodium and potassium concentrations were normal and fell in the middle of the reference range. Given these findings, Hannah was suspected to have eunatremic, eukalemic hypoadrenocorticism (EEU).

Diagnosis

A baseline cortisol test was performed, with a result of less than 0.1 µg/dL. To confirm hypoadrenocorticism (HOAC), an adrenocorticotrophic hormone (ACTH) stimulation test was performed and revealed a subnormal response (post-ACTH cortisol concentration <0.1 µg/dL). Although Hannah's electrolytes were within the normal reference range, her aldosterone concentration was not assessed. EEH was diagnosed.

Initial Treatment

Hannah was started on glucocorticoid replacement

only: 0.5 mg/kg/day prednisone for the first week of treatment, followed by decrease to a maintenance dose of 0.2 mg/kg/day prednisolone with instructions to double the dose during times of anticipated stress or excitement. Hannah's clinical signs and blood abnormalities resolved on prednisone. Given the potential for EEH to progress to typical HOAC, her electrolytes were monitored.

Three months after her diagnosis, Hannah developed hyponatremia and hyperkalemia, consistent with typical HOAC. She was started on desoxycorticosterone pivalate (DOCP) at 1.1 mg/kg SC q25d and did well with this regimen. Given the expense of DOCP and desire for less frequent injections, Hannah's DOCP protocol was slowly adjusted while monitoring her electrolytes until she was on 0.4 mg/kg DOCP every 4 weeks.

Treatment for Addisonian Crisis

Hannah did well on this reduced dose of DOCP until she was sedated for routine abdominal imaging 3 years after her diagnosis of HOAC. Following this visit, Hannah developed acute vomiting and profuse hematochezia and presented to the emergency room in hypovolemic shock. She was found to have hyponatremia, hyperkalemia, hypoglycemia,

azotemia, hyperphosphatemia, and a mild mixed hepatopathy (TABLE B). Her DOCP dose was increased to 1.1 mg/kg SC every 4 weeks, and she received an anti-inflammatory dose of prednisone (0.5 mg/kg/day) for 1 week before returning to her maintenance dose of 0.2 mg/kg/day.

Dose Adjustment for Iatrogenic Hypercortisolism

Four years into treatment, Hannah's HOAC was well controlled. However, she had recurrent urinary tract infections (UTIs) and polyuria. She also was noted to have marked muscle wasting and truncal alopecia on her physical examination (FIGURE A1). These findings raised concern for iatrogenic hypercortisolism. Thus, her glucocorticoid dose was gradually decreased and she was switched to hydrocortisone to facilitate smaller dose changes.

Hannah's hydrocortisone dose was decreased until she was on 0.16 mg/kg/day hydrocortisone (equivalent to 0.04 mg/kg prednisone) per day. Following this adjustment, Hannah's haircoat began to grow back (FIGURE A2 AND A3) and went from having 6 to 7 UTIs per year to 0 to 1 UTIs per year. Hannah has been well controlled on this dosing regimen



FIGURE A. These images show how Hannah's alopecia, muscle condition, and weight improved over the course of 10 months with a decreased glucocorticoid dose. (1) At baseline, Hannah was receiving 0.2 mg/kg/day prednisone and weighed 30.4 kg (67 lb). She was then transitioned to a 0.04 mg/kg/day prednisone-equivalent dose of hydrocortisone (2.5 mg q12h hydrocortisone). (2) At month 6, hair regrowth was evident, and she weighed 34.5 kg (76 lb). (3) At month 10, her haircoat was normal and she weighed 35.2 kg (77.6 lb).

(0.14 mg/kg/day hydrocortisone and 1.1 mg/kg DOCP q28d) for the past 2 years.

Take-Away Messages

■ Dogs that present with normal electrolytes at the time of HOAC diagnosis (i.e., EEH) can go on to develop hyponatremia and hyperkalemia; thus, their electrolytes should be closely monitored.

■ Even while receiving treatment, patients are at risk for an addisonian crisis and should be closely monitored, especially during stressful events.

■ Although doses of DOCP less than the labeled dose can be successfully used, it is generally not advised to go below 0.7 mg/kg per month in any dog due to the risk of an addisonian crisis.

■ It is not uncommon for

dogs with HOAC to develop hypercortisolism secondary to treatment. Although the physiologic dose of prednisone is 0.1 to 0.2 mg/kg/day, some dogs, particularly larger breeds, often require lower doses. The dose should be based on each patient's clinical signs.

TABLE A Blood Analysis Results at Initial Presentation

ANALYTE	VALUE	REFERENCE RANGE
Albumin	2.8 g/dL	3.2–4.3 g/dL
Calcium	12.8 mg/dL	10–12 mg/dL
Cholesterol	90 mg/dL	130–354 mg/dL
Glucose	82 mg/dL	82–132 mg/dL
Creatinine	2.1 mg/dL	0.3–1.1 mg/dL
Phosphorous	5.8 mg/dL	2.5–6 mg/dL
Potassium	4.5 mmol/L	2.8–4.7 mmol/L
Sodium	145 mmol/L	141–147 mmol/L
Alanine aminotransferase	76 U/L	18–100 U/L
Alkaline phosphatase	30 U/L	13–240 U/L
Hematocrit	36.6%	40.5%–59.9%
White blood cells	13.5 × 10 ³ /µL	4.7–15.2 × 10 ³ /µL
Lymphocyte count	7.02 × 10 ³ /µL	1.1–3.96 × 10 ³ /µL

TABLE B Blood Analysis Results During Addisonian Crisis

ANALYTE	VALUE	REFERENCE RANGE
Albumin	3.6 g/dL	3.2–4.3 g/dL
Calcium	10.2 mg/dL	10–12 mg/dL
Cholesterol	386 mg/dL	130–354 mg/dL
Glucose	263 mg/dL	82–132 mg/dL
Creatinine	2.5 mg/dL	0.3–1.1 mg/dL
Phosphorous	8.9 mg/dL	2.5–6 mg/dL
Potassium	133 mmol/L	141–147 mmol/L
Sodium	5.1 mmol/L	2.8–4.7 mmol/L
Alanine aminotransferase	190 U/L	18–100 U/L
Alkaline phosphatase	347 U/L	13–240 U/L
Hematocrit	58.4%	40.5%–59.9%
White blood cells	8.3 × 10 ³ /µL	4.7–15.2 × 10 ³ /µL
Lymphocyte count	0.76 × 10 ³ /µL	1.1–3.96 × 10 ³ /µL

twice-daily administration of fludrocortisone. In 1 study of dogs with primary HOAC,³² DOCP was shown to suppress plasma renin activity more effectively than fludrocortisone, suggesting that DOCP might be a more effective replacement therapy.

DOCP

DOCP is a long-acting analog of deoxycorticosterone, the endogenous steroid hormone that is a precursor to aldosterone. Two formulations of DOCP are available: Percorten-V (Elanco, my.elanco.com) and Zycortal (Dechra, dechra-us.com), which has been proven to be noninferior to Percorten-V.⁴¹

Initial Dose

DOCP can be administered intramuscularly or subcutaneously⁴²; however, in the acute setting, intramuscular administration is favored for faster absorption. Although the labeled dose of DOCP is 2.2 mg/kg, a number of studies have proven that lower doses are effective in most dogs.^{34,35,43,44} Endocrinologists who study HOAC routinely initiate DOCP therapy at a dose of 1.5 mg/kg.¹⁵ Dogs aged 3 years or younger often require higher doses compared to older dogs.^{34,43} In contrast, larger-breed dogs often tolerate lower doses. One randomized clinical trial found that an initial DOCP dose of 1.1 mg/kg was safe and effective in 19 dogs with newly diagnosed HOAC.³⁵ The majority of dogs in this study were medium- and large-breed dogs, and only 2 dogs were younger than 2 years. Two dogs in this study weighed less than 10 kg (22 lb) and both developed nonsymptomatic hyperkalemia, whereas hyperkalemia was not noted in any other dog. The author’s approach is to start dogs that are younger than 3 years or weigh less than 30 kg (66 lb) on 1.5 mg/kg DOCP and to start large-breed dogs (weighing 30 kg or more) at an initial DOCP dose of 1.1 mg/kg.

Dosing Interval

DOCP is initially given every 25 days. Following initiation of treatment, electrolyte concentrations should be rechecked at 14 days and then at 25 days. As peak DOCP activity occurs at 10 to 14 days,²² the 14-day evaluation helps determine whether the dose is correct. The 25-day recheck confirms that the dosing interval is acceptable. If electrolytes remain normal at the 25-day recheck, it is recommended to wait until day 28 and then give the next dose of DOCP. This sets

the dosing interval to once monthly, which helps encourage owner compliance. The dosing interval can then be adjusted by 2 to 3 days each month, ensuring electrolyte concentrations are within the reference interval prior to each injection, until the desired dosing interval is met. Most clinicians adjust the dosing interval to a maximum of 28 to 31 days to facilitate owner convenience and improve compliance.¹⁵ For clients who give DOCP at home, the author aims for a dosing interval of 30 days, whereas for clients who prefer DOCP to be given in the clinic, the author sets the dosing interval at 28 days so that appointments fall on the same day of the week every 4 weeks.

One study evaluated the duration of action of DOCP in dogs with HOAC and found that at a dose of 2.2 mg/kg, individual dosing intervals ranged from 41 to 85 days, with a median of 56 days.⁴⁵ However, this study did not evaluate lower doses of DOCP or plasma renin activity, which is a better measure of mineralocorticoid dose than electrolytes in humans.³¹ The author prefers to adjust the dose as it allows for closer monitoring and the ability to administer DOCP before an addisonian crisis occurs.

Dose Adjustment

After the goal dosing interval is reached, the dose of DOCP can be decreased by 10% to 15% every month, measuring electrolyte concentrations immediately prior to each injection to ensure that they are still acceptable.¹⁵ If hypokalemia and/or hypernatremia is noted, the dose should be decreased incrementally until electrolyte concentrations are within the reference interval to maintain a dosing interval of 28 to 31 days. In 1 study, 7 dogs were able to be reduced to a median dose of 0.7 mg/kg every 28 to 30 days 2 years after diagnosis without developing electrolyte abnormalities.³⁴ The lowest dose reported in this study was 0.35 mg/kg every 28 to 30 days. The author’s approach to DOCP is provided in **FIGURE 2**.

Once patients are well regulated, recheck examinations can be decreased to every 4 to 6 months. Given the lack of commercially available plasma renin activity assays, monitoring of DOCP therapy in dogs is currently accomplished by regular assessment of serum electrolyte concentrations. One study investigated the utility of urine electrolytes as a surrogate of plasma electrolytes; however, no correlation was identified, indicating that monitoring of serum electrolytes continues to be the mainstay of treatment monitoring.⁴⁶

Fludrocortisone

Fludrocortisone acetate is a short-acting oral mineralocorticoid that is typically given twice daily. In contrast to DOCP, it possesses glucocorticoid activity.

Fludrocortisone is available as 0.1-mg tablets, and the typical initial dose is 0.01 to 0.02 mg/kg/day divided into 2 doses. For some dogs, once-daily dosing is sufficient; however, in 1 study, 12 out of 37 dogs with HOAC required twice-daily administration to resolve hyperkalemia and/or hyponatremia.³⁶ Although fludrocortisone exhibits glucocorticoid activity, some patients require additional supplementation of prednisone. Interestingly in the aforementioned study, twice-daily administration of fludrocortisone did not hasten the time to resolution of clinical signs and normalization of electrolytes compared with once-daily administration. However, concurrent administration of

prednisolone (median daily dose of 0.35 mg/kg) did, independent of frequency of fludrocortisone administration.³⁶ It is recommended that all dogs started on fludrocortisone be concurrently given glucocorticoids until their electrolytes and clinical signs have resolved. They can then be tapered to the lowest effective dose to control clinical signs. It is estimated that 50% of dogs given fludrocortisone need additional glucocorticoid supplementation in the long term.¹⁵

Although it seems like fludrocortisone would be better suited for treatment of HOAC as it possesses both glucocorticoid and mineralocorticoid activity, the combination of activity can make it difficult to find an optimal dosage. Sometimes a higher dose of fludrocortisone is needed to correct electrolytes, but the glucocorticoid activity associated with that dose causes signs of hypercortisolism (e.g., polyuria, polydipsia,

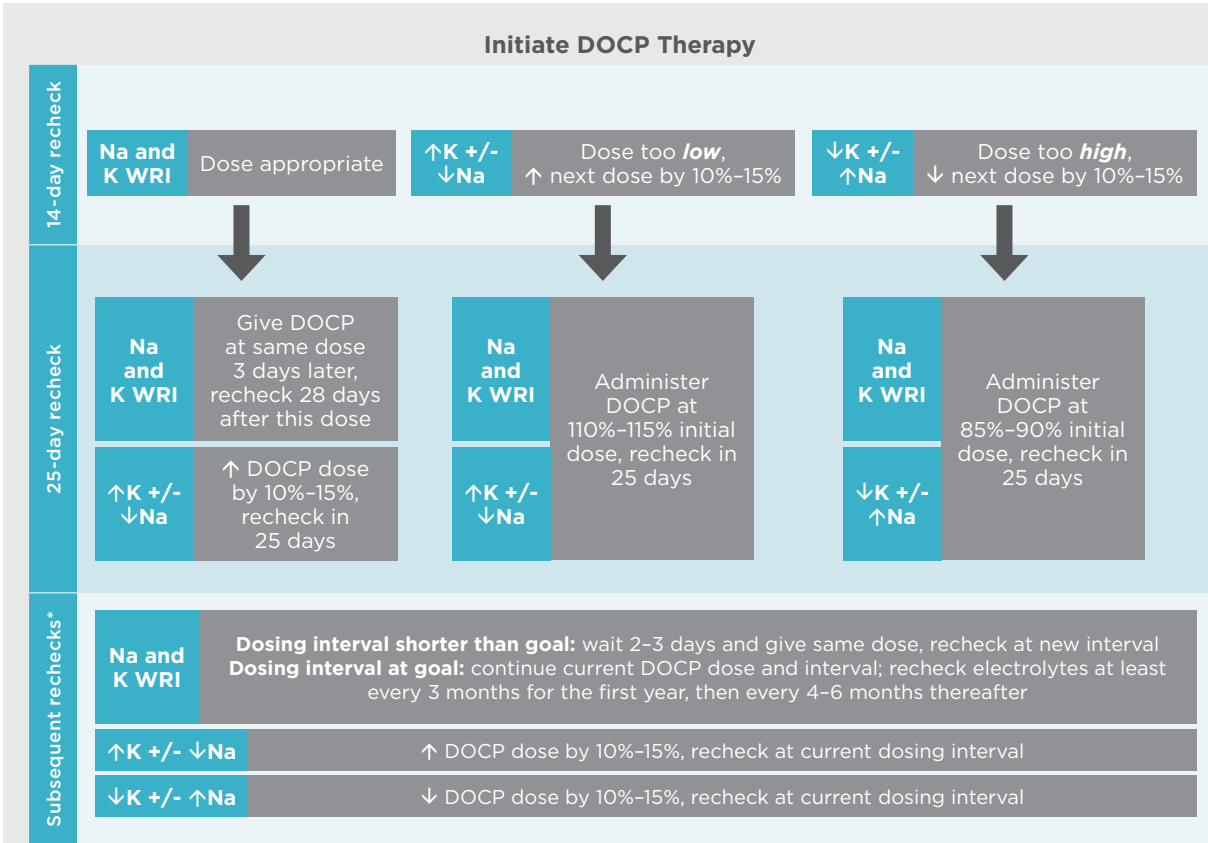


FIGURE 2. This diagram provides an approach to the adjustment of DOCP dose and dosing interval in dogs with HOAC. Initial DOCP dosing can be found in **TABLE 2**.

DOCP = desoxycorticosterone pivalate; K = potassium; Na = sodium; WRI = within reference interval.
*After the 14- and 25-day rechecks, subsequent rechecks are typically scheduled 25 to 30 days after the last DOCP injection; however, some dogs may require shorter dosing intervals to maintain electrolytes within the reference interval. The goal of these rechecks is to adjust the DOCP dose to maintain a dosing interval that is convenient for the owner. The author aims for a dosing interval of 28 to 30 days, as once-monthly DOCP administration is less likely to be forgotten.

alopecia). As signs of hypercortisolism can significantly affect quality of life for both dog and owner, these dogs are often switched from fludrocortisone to DOCP, which results in improved owner satisfaction.³⁹

Few studies have compared the effectiveness of fludrocortisone and DOCP. One study found no difference in clinical response to treatment or median survival times between patients treated with DOCP and patients treated with fludrocortisone. However, 27 of the 190 dogs on fludrocortisone in this study were switched to DOCP due to adverse effects, poor response to therapy, owner convenience, or financial considerations.⁴⁴ Thus, DOCP is the preferred mineralocorticoid for replacement therapy in dogs with HOAC except when owners strongly prefer oral therapy or the DOCP injections are not well tolerated.

PROGNOSIS

The long-term prognosis for dogs with primary HOAC is usually excellent with careful monitoring and medication dose adjustments. In 1 survey-based study, the biggest concerns for owners of dogs with HOAC were found to be the expense of veterinary care (67%) and the constant fear of their dog experiencing another acute adrenal crisis (49%).³⁹ The expense of mineralocorticoid supplementation can cause some owners to consider euthanasia; therefore, the clinician should work closely with the owner to safely decrease the dose. Although glucocorticoids are lifesaving at the start of therapy, many dogs experience adverse effects if maintained at initial dosing regimens and benefit from slowly decreasing the dose. The most important factor for success is owner education on the importance of closely following a consistent therapeutic plan (e.g., not skipping medications or prolonging DOCP dosing interval) and careful monitoring.

SUMMARY

HOAC in dogs is a lifelong endocrine condition characterized by inadequate production of adrenal hormones, primarily cortisol, and often aldosterone. Chronic management of this disease requires administration of glucocorticoids and mineralocorticoids to replace cortisol and aldosterone deficiencies, respectively. Dogs that present with EEH might go on to develop signs of mineralocorticoid deficiency (e.g., electrolyte derangements) weeks to months after the initial diagnosis, and thus they should be closely monitored within the first year. Dosing

requirements of glucocorticoids and mineralocorticoids are patient-specific, with younger dogs requiring higher doses of DOCP and larger-breed dogs requiring lower doses of both glucocorticoids and DOCP.

Evidence suggests that using lower doses of mineralocorticoids and extending dosing intervals beyond the labeled manufacturer recommendations can effectively manage HOAC in most dogs. Thus, clinicians should aim to reduce the dose and adjust frequency of DOCP administration to lower costs and improve client compliance. Unlike other endocrine diseases (e.g., hypothyroidism) in which blood hormone concentrations are used to evaluate control, the management of HOAC relies solely on monitoring clinical signs. It is essential to watch for signs of excessive glucocorticoid use (e.g., iatrogenic Cushing’s disease) to decrease the risk of intolerable adverse effects and complications, such as chronic recurrent urinary tract infections. With careful monitoring and appropriate dose adjustments, dogs with HOAC can live normal, healthy lives. **TVP**

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CE QUIZ QUESTIONS

1. Which of the following represents a physiologic dose of prednisone?
a. 0.1-0.2 mg/kg/day
b. 0.5-1 mg/kg/day
c. 1.5-2 mg/kg/day
d. >2 mg/kg/day

2. Which of the following is thought to be the most common cause of spontaneous hypoadrenocorticism in dogs?
a. Neoplasia of the pituitary gland
b. Granulomatous infiltrative disease of the adrenal glands
c. Intracranial trauma
d. Immune-mediated adrenalitis

3. Which of the following glucocorticoids does not interfere with the ACTH (adrenocorticotrophic hormone) stimulation test?
a. Dexamethasone
b. Hydrocortisone
c. Prednisone
d. Methylprednisolone

4. Which of the following patients is most likely to require a higher dose of desoxycorticosterone pivalate (DOCP)?
a. A large-breed dog with primary hypoadrenocorticism
b. A dog with eunatremic, eukalemic hypoadrenocorticism
c. A dog with hypoadrenocorticism in which fludrocortisone therapy failed
d. A 1-year-old dog with primary hypoadrenocorticism

5. A 14-day recheck after starting a dog with newly diagnosed hypoadrenocorticism on DOCP reveals that the dog has hypokalemia and hypernatremia. How should the DOCP dosing regimen be changed at the next injection?
a. 10% increase in dose
b. 10% decrease in dose
c. Extend the dosing interval by 3 days
d. Decrease the dosing interval by 3 days



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