Seeing the same dog with the same issue?

There could be a different conclusion.
How to recognize Addison’s disease

When presented with an affected dog, Addison’s disease may not be at the top of your rule-out list. Being more aware of this condition and considering it earlier in your diagnostic workup will shorten the length of time it takes to diagnose the disease and deliver appropriate treatment.

Addison’s disease is a potentially life-threatening condition. Clinical signs associated with the disease are nonspecific, can wax and wane, and dogs can respond to nonspecific therapy (e.g. intravenous fluid therapy). This condition can be easily mistaken for other diseases (e.g. kidney disease, gastroenteritis, neuromuscular disease and metabolic diseases).

The most common signs of Addison’s disease are:

<table>
<thead>
<tr>
<th>Clinical History</th>
<th>Common</th>
<th>Less common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>Inappetence</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>Diarrhea +/- Blood</td>
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<td></td>
<td></td>
<td>Melena (digested blood in stool)</td>
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<tr>
<td></td>
<td></td>
<td>Weight loss</td>
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<tr>
<td></td>
<td></td>
<td>Polyuria</td>
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<td></td>
<td></td>
<td>Polydipsia</td>
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<td></td>
<td></td>
<td>Bradycardia</td>
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<td></td>
<td></td>
<td>Hypothermia</td>
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<tr>
<td></td>
<td></td>
<td>Shivering/muscle stiffness</td>
</tr>
</tbody>
</table>

Almost all cases |
- Depression |
- Weakness |
- Bradycardia |
- Hypothermia |
- Shivering/muscle stiffness

Common |
- Inappetence |
- Lethargy |
- Diarrhea |
- Melena |
- Weight loss |
- Polyuria |
- Polydipsia |
- Bradycardia |
- Hypothermia |
- Shivering/muscle stiffness

Less common |
- Vomiting |
- Blood in stool |
- Polyuria |
- Polydipsia |
- Bradycardia |
- Hypothermia |
- Shivering/muscle stiffness

If left untreated, Addison’s disease can be acutely life-threatening.
Diagnosis

The gold standard for diagnosing Addison’s disease is the ACTH stimulation test, which assesses the ability of the adrenal gland to produce cortisol.

Although a low basal cortisol value can be useful to rule out Addison’s disease, it is not adequate for a diagnosis.

Affected dogs can present with a gradual onset of clinical signs or an acute life-threatening state (Addisonian crisis). Animals presenting in Addisonian crisis tend to have clinical signs suggestive of hypovolemic shock such as prolonged capillary refill times, weak peripheral pulses, weakness or collapse.

Affected animals may not be tachycardic despite being hypovolemic due to the bradycardic effects of hyperkalemia.

A thorough clinical history in these cases can increase a clinician’s suspicion of this disease and following a detailed physical examination, diagnostic investigations typically include hematology, serum biochemistry (including electrolytes), and potentially radiography, ultrasonography and electrocardiography.

Diagnostic indices of Addison’s Disease in descending order of frequency:

<table>
<thead>
<tr>
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<th>Serum biochemistry and Urinalysis</th>
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</thead>
<tbody>
<tr>
<td>Absence of stress leukogram in a stressed Pine animal</td>
<td>Hypernatremia</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>Azotemia</td>
</tr>
<tr>
<td>Nonregenerative anemia</td>
<td>Hypoalbumin</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>Uria specific gravity &lt;1.030</td>
</tr>
<tr>
<td></td>
<td>Hyperchloremia</td>
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<tr>
<td></td>
<td>Metabolic acidosis</td>
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<tr>
<td></td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
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</tbody>
</table>

Step-by-step diagnosis

1. Clinical history
   - History suggestive of hypoadrenocorticism e.g. episodic collapse, weight loss, recurrent gastrointestinal signs, lethargy.
   - Slower heart rate, thinner or more dehydrated than expected.

2. Physical examination
   - Low Na⁺ and low K⁺ (important), Na⁺ : K⁺ ratio < 27, low albumin, low glucose and/or increased blood urea nitrogen and creatinine.

3. Complete blood count (CBC) and blood smear
   - Increased white blood cell count with stress leukogram (neutrophilia, lymphopenia, eosinopenia).
   - Anemia and low white blood cell count with relative lymphocytosis, eosinophilia and neutropenia, lack of stress leukogram.

4. ACTH stimulation test
   - No previous relevant medical history
     - Post-ACTH cortisol 2 µg/dl or greater*
       - Hypoadrenocorticism can be ruled out
   - Hypoadrenocorticism highly likely
     - Post-ACTH cortisol < 2 µg/d*
     - No history of steroid application or administration confirmed through careful medical history.

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

Courtesy of Professor Ian Ramsey, University of Glasgow

Addison’s disease resembles many other illnesses so it can be challenging to recognize. It is often referred to as “the great pretender.” Fortunately, once Addison’s disease is suspected, confirming the diagnosis is as simple as running an ACTH stimulation test.
Treatment

Once Addison’s disease has been confirmed and the patient is hydrated (i.e., no continued evidence of vomiting, diarrhea, weakness, depression or dehydration); replacement therapy can begin. Long-term replacement therapy consists of glucocorticoid replacement at physiological doses (very low) and mineralocorticoid replacement.

The recommended therapy for glucocorticoid replacement is oral prednisone/prednisolone at 0.2-0.4 mg/kg/day (0.1-0.2 mg/lb/day).

For mineralocorticoid replacement, the treatment of choice is desoxycorticosterone pivalate (DOCP).

What is DOCP?

Desoxycorticosterone is a corticosteroid with primarily mineralocorticoid activity, similar to aldosterone.

In the kidney, desoxycorticosterone causes sodium and chloride ion retention, and hydrogen and potassium ion excretion, creating an osmotic gradient. The osmotic gradient promotes water absorption from the renal tubules resulting in increased extracellular fluid volume, leading to blood volume expansion, improved venous return to the heart, and increased cardiac output.

Seeing the same dog with the same issues? There could be a different conclusion.

ZYCORTAL Suspension

ZYCORTAL Suspension contains desoxycorticosterone pivalate which is a mineralocorticoid hormone indicated for use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison’s disease). ZYCORTAL Suspension was formulated and approved specifically for subcutaneous use.

The desoxycorticosterone pivalate (DOCP) in ZYCORTAL Suspension is a pure mineralocorticoid hormone that regulates electrolytes and water balance, which are impaired in cases of mineralocorticoid deficiency in Addison’s disease. DOCP has limited glucocorticoid activity, allowing the independent dose titration of mineralocorticoid without the risk of inducing marked side effects from glucocorticoid oversupplementation e.g. polyuria, polydipsia, polyphagia and muscle atrophy.

ZYCORTAL Suspension was formulated and approved specifically for subcutaneous use.

Initial Dose

ZYCORTAL Suspension is intended for long-term administration at intervals and doses dependent upon individual response.

Prognosis

Prognosis for dogs with Addison’s disease is excellent if treatment is maintained for life. Glucocorticoid supplementation may need to be increased in times of stress.

Regular monitoring will help ensure the dog’s clinical signs are properly managed for the life of the patient.
Efficacy

A double-blinded, multi-site, 180-day field study evaluated the effectiveness of ZYCORTAL Suspension compared to an existing FDA-approved desoxycorticosterone pivalate active control.

Non-inferiority was achieved compared to the existing FDA-approved control product containing DOCP.1

A dog was considered a treatment success if it remained clinically normal or had improved clinical signs compared to baseline and the Na+/K+ concentrations were within the reference range of the analyzer, or the Na+/K+ ratio was between 27-32.

The mean final dose for ZYCORTAL Suspension was 1.9 ± 0.27 mg/kg (range 1.2-2.5 mg/kg) and the mean final dose interval was 38.5 ± 12.5 days (range 20-99 days).

As with all drugs, side effects may occur. In field studies the most common side effects reported were polyuria, polydipsia, depression/lethargy, inappropriate urination, alopecia, decreased appetite/anorexia, panting, vomiting, diarrhea, shaking/trembling, polyphagia, urinary tract infection, urinary tract incontinence and restlessness. ZYCORTAL Suspension should be used with caution in dogs with congestive heart disease, edema, severe renal disease or primary hepatic failure. Dogs presenting in Addisonian crisis must be rehydrated with appropriate intravenous therapy before starting treatment with ZYCORTAL Suspension. Refer to the prescribing information for complete details or visit www.dechra-us.com/zycortal.

Monitoring and dose adjustment

Day 1
First dose

Day 10
Interim monitoring

Day 25
Second dose

Clincially normal

Clincially abnormal

Adjust ZYCORTAL Suspension dose according to Day 10 Na+/K+ ratio as described in table below

- Abnormal Na+/K+ ratio
- PU/PD
- Depression, lethargy, vomiting, diarrhea or weakness
- Other clinical signs

If the Day 10 Na+/K+ ratio is:
- > 34
- 32 to 34
- 27 to 30
- 24 to 27
- ≤ 24

Decrease glucocorticoid dose

Increase glucocorticoid dose

Decrease ZYCORTAL Suspension dose

Increase ZYCORTAL Suspension dose

Re-evaluate diagnosis or look for concurrent disease

Adjust ZYCORTAL Suspension based on Day 10 electrolytes

PU/PD persists and Na+/K+ > 32

Deviated dose to 2.0 mg/kg

Deviated dose to 2.1 mg/kg

Continue 2.2 mg/kg

Increase dose to 2.3 mg/kg

Increase dose to 2.4 mg/kg

"Instead of changing the dose, the dose interval can be changed as well. For more information, refer to the full prescribing information or contact Dechra Veterinary Technical Support at (866) 933-2472 or support@dechra.com.

"Use Day 25 electrolytes, if Day 10 electrolytes are normal

Subsequent doses and long-term management:

Once the dog is optimally controlled, keep the same dosing regimen. In case of abnormal clinical condition or abnormal electrolytes at subsequent visits, continue to titrate the dose in similar increments as described above.

Prior to a stressful situation, consider temporarily increasing the dose of prednisone/prednisolone.

The mean final dose for ZYCORTAL Suspension was 1.9 ± 0.27 mg/kg (range 1.2-2.5 mg/kg) and the mean final dose interval was 38.5 ± 12.5 days (range 20-99 days) with the majority of dogs having a dosing interval between 20 and 46 days.1

Non-inferiority was achieved compared to an FDA-approved control DOCP product.1

ZYCORTAL Suspension is efficacious, well tolerated and allows tailored dosing for each dog with Addison’s disease.

The percentage of dogs with treatment success is shown in the graph.

- ZYCORTAL Suspension (n=101)
- Control product (n=34)

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Switching dogs from fludrocortisone

Data from the ZYCORTAL Suspension clinical study has shown there is no significant difference in the efficacy of ZYCORTAL Suspension when given to newly diagnosed patients that started treatment with fludrocortisone Suspension compared to existing patients which started treatment with fludrocortisone and then switched to ZYCORTAL Suspension (p > 0.05). 2

In the clinical study, 31 dogs were enrolled who were receiving fludrocortisone prior to the administration of ZYCORTAL Suspension. Twelve of these dogs received fludrocortisone for >30 days; nineteen were treated for <7 days. When transitioning to ZYCORTAL Suspension, the majority of dogs (17/31) received the last dose of fludrocortisone on the same day of ZYCORTAL Suspension administration (Day 0). A “wash-out” or transition period was not required between the last administration of fludrocortisone and the first administration of ZYCORTAL Suspension. 2

TREATMENT OF ADDISONIAN CRISIS (ACUTE HYPOADRENOCORTICISM)

Acute and severe signs of Addison’s disease represent a life-threatening emergency. Aggressive intravenous fluid therapy, using isotonic crystalloids (0.9% NaCl, Lactated Ringer’s or Hartmann’s Solution) is critical to reversing the hypovolemic, hypotensive shock these dogs commonly experience. Fluid therapy will also temporarily address the life-threatening electrolyte imbalances. In stable, non-shock patients, diagnostic samples (CBC, biochemistry, urinalysis and baseline cortisol) can be collected before starting therapy. In shocked, critical patients, priority should be given to stabilizing the patient. Diagnostic samples can be collected once the patient is stable.

In addition to fluid therapy, intravenous administration of dexamethasone may help improve hemodynamically unstable patients. Published dosages for dexamethasone vary widely and range from 0.1 to 2.0 mg/kg. Ideally, an ACTH stimulation test should be performed prior to the administration of dexamethasone. Prednisone, prednisolone, methylprednisolone and cortisone acetate cross-react with the cortisol assay and may artificially elevate serum cortisol results. These steroids should not be used prior to performing an ACTH stimulation test.

After subcutaneous administration of 11 mg/kg body weight (five times the labeled starting/initial dose of 2.2 mg/kg) of ZYCORTAL Suspension, the plasma (fludrocortisone) and cortisol concentrations were 1.7 ± 0.6 µg/dL and 25 ± 15 µg/dL, respectively; success rates for the active control were 85.1% and 86.9% on Days 90 and 180, respectively. The number of dogs included in the study was 184; 152 dogs had a dosing interval between 20 and 45 days. An interim monitoring visit was scheduled at 24 to < 27 days.

**ZNORTAL**: ZNORTAL Suspension is a white opaque suspension. Each milliliter contains 2.2 mg of desoxycorticosterone pivalate, labeled as follows: 11.5 mg methylprednisolone, 1 mg prednisolone, 8.5 mg sodium chloride, 1 mg benzyl alcohol and water for injection (100%).

**INDICATION**: For use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoaldosteronism (Addison’s disease).

**CLINICAL PHARMACOLOGY**: Desoxycorticosterone is a corticosteroid with primarily mineralocorticoid activity, acting on the kidneys. In the kidney, desoxycorticosterone causes sodium and chloride ion retention, and hydrogen and potassium ion excretion, causing an osmotically potent diuretic effect. The corticosteroid promotes sodium and potassium absorption from the renal tubules, resulting in sodium and water loss. While this effect is useful in treating hypertension, leading to diuresis, expansion of extracellular volume and increased cardiac output.

ZYCORTAL Suspension is contraindicated in dogs that have previously had a hypersensitivity reaction to ZYCORTAL Suspension or active ingredients within ZYCORTAL Suspension. The active ingredients may cause pain, pruritus, urticarial rash, erythema and sterile inflammation. Decrease in weight may indicate fluid retention in accordance to sodium retention. Log retention is also observed at higher doses. Use with caution in animals with cardiac dysfunction.

**HUMAN WARNINGS**: For human use, keep all ingredients and drugs of the dog reach of children. Consult a physician in case of accidental human exposure.

**PREGNANCY**: For use in pregnant or nursing females, Swiss-lie, gestational, and lactating females should be treated with corticosteroids. Treatment with corticosteroids may result in increased fetal weight gain and decreased bone mineralization.

**ADVERSE REACTIONS**: Usually few, but infrequent, side effects were observed in the field study. Adverse reactions are summarized in Table 2.

**Table 2**: Percentage of Dogs with Adverse Reactions in the Field Study

<table>
<thead>
<tr>
<th>Reaction</th>
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<th>Active Control (n = 139 dogs)</th>
</tr>
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**DOSAGES AND ADMINISTRATION**: The effectiveness of ZYCORTAL Suspension may be reduced if potassium-sparing diuretics, such as spironolactone, are administered concomitantly.

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References
2. Data on file

Further reading

www.dechra-us.com

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