Are you seeing the same pattern of illness again and again?
It's time to think Addison’s disease
What is Addison’s disease (hypoadrenocorticism)?

Addison’s disease results from loss of production of corticosteroids, principally mineralocorticoids (mainly aldosterone) and glucocorticoids (mainly cortisol).

Immune mediated destruction of the adrenal glands is the most common cause of Addison’s disease. This form of disease is classified as primary hypoadrenocorticism and usually results in deficiencies of both glucocorticoids and mineralocorticoids, however cases of isolated glucocorticoid deficiency have been reported (atypical hypoadrenocorticism).

Secondary hypoadrenocorticism (caused by pituitary dysfunction), results in the deficiency of adrenocorticotropic hormone (ACTH). This is a very rare cause of canine hypoadrenocorticism and tends to result in glucocorticoid deficiency only.

If left untreated, Addison’s disease can present as an acute, life threatening emergency.
How to recognise Addison’s disease

Because Addison’s disease isn’t so easy to identify, being more aware of this condition is half the battle.

Addison’s disease is a potentially life-threatening condition. However as clinical signs associated with the disease are non-specific, can wax and wane, and dogs can respond to non-specific therapy (e.g. intravenous fluids) this condition can be easily mistaken for other diseases (e.g. kidney disease, gastroenteritis including parvovirus infection, neuromuscular and metabolic diseases).

The most common signs of Addison’s disease are:

<table>
<thead>
<tr>
<th>Clinical History</th>
<th>Almost all cases</th>
<th>Common</th>
<th>Less common</th>
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<tbody>
<tr>
<td>Inappetence</td>
<td>Weakness</td>
<td>Diarrhoea</td>
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<tr>
<td>Lethargy</td>
<td>Vomiting</td>
<td>Weight loss</td>
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<td></td>
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<td>Shivering/muscle stiffness</td>
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<td></td>
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<td>Polyuria</td>
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<td>Polydipsia</td>
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<tr>
<th>Physical examination</th>
<th>Almost all cases</th>
<th>Common</th>
<th>Less common</th>
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<tbody>
<tr>
<td>Depression</td>
<td>Dehydration</td>
<td>Bradycardia</td>
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<tr>
<td>Weakness</td>
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<td>Hypothermia</td>
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Depression due to Addison’s disease*
Microcardia secondary to hypovolaemia*
Bilious vomit**
Melena**
Masticatory muscle loss*
Young puppy with Addison’s disease*

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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 basal cortisol value <55 nmol/L is consistent with Addison’s disease, low basal cortisol by itself is not adequate for an accurate diagnosis (poorly specific) - an ACTH stimulation test is needed to confirm the presence of the disease.

**Diagnosis**

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

Affected animals may not be tachycardic despite being hypovolaemic due to the bradycardic effects of the hyperkalaemia.

A thorough clinical history can increase a clinician’s suspicion of Addison’s disease. Following a detailed physical examination, diagnostic investigations in suspected cases typically include haematology, serum biochemistry (including electrolytes), as well as potential additional investigations such as radiographs, ultrasonography and electrocardiography.

### Haematological and biochemical changes in descending order of frequency

<table>
<thead>
<tr>
<th>Haematology</th>
<th>Serum biochemistry</th>
<th>Urinalysis</th>
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</thead>
<tbody>
<tr>
<td>Absence of stress leukogram in a stressed/sick animal</td>
<td>Hyperkalaemia</td>
<td>Urine specific gravity &lt;1.030</td>
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<tr>
<td>Non-regenerative anaemia</td>
<td>Azotaemia</td>
<td></td>
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<tr>
<td>Eosinophilia</td>
<td>Hyponatraemia</td>
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<td>Lymphocytosis</td>
<td>Hyperphosphataemia</td>
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<td>Hypochloreaemia</td>
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<td></td>
<td>Metabolic acidosis</td>
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<td>Hypercalcaemia</td>
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<td></td>
<td>Hypoglycaemia</td>
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<table>
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<th>Urinalysis</th>
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<tbody>
<tr>
<td>Urine specific gravity &lt;1.030</td>
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</table>

**Tracings**

- **Not Addison’s disease**
- **Addison’s disease or Steroid administration**
Step by step diagnosis

**Clinical history**
- History suggestive of hypoadrenocorticism
  - E.g. episodic collapse, weight loss, recurrent gastro-intestinal signs, lethargy

**Physical examination**
- Slower heart rate, thinner or more dehydrated than expected

**Routine biochemistry (remember electrolytes)**
- Low Na⁺ and/or high K⁺ (important), Na⁺ : K⁺ ratio < 27, low albumin, glucose and/or increased urea and creatinine

**Haematology (blood smear)**
- Anaemia and low white blood cell count with relative lymphocytosis, eosinophilia and neutropenia, lack of stress leukogram

**ACTH stimulation test**
- Post-ACTH cortisol > 55 nmol/L
  - Hypoadrenocorticism can be ruled out
- Post-ACTH cortisol < 55 nmol/L
  - No history of steroid application confirmed
  - Hypoadrenocorticism highly likely

**Hypoadrenocorticism less likely**

**Hypoadrenocorticism more likely**

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

Courtesy of Professor Ian Ramsey, University of Glasgow

**Treatment**

Detection of Addison’s disease in the more subtle stages of the disease and initiation of appropriate medical therapy i.e. Zycortal and prednisolone, will reduce the risk of an Addisonian crisis developing, therefore potentially saving the dog’s life.

Along with greater awareness and correct diagnosis, Zycortal can reduce the risk of life-threatening Addisonian Crisis.
**Zycortal**

Zycortal is a prolonged-release suspension used as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism. It is the only veterinary-licensed product in Europe for the treatment of canine Addison’s disease.

A prolonged release suspension for injection provides the confidence that Addison’s disease will be controlled for the duration of approximately a month.

Zycortal contains desoxycortone pivalate (DOCP), which is a pure mineralocorticoid hormone that regulates electrolytes and water balance, which are impaired in cases of mineralocorticoid deficiency in Addison’s disease. Unlike some other mineralocorticoids, 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.

Individual dose titration for mineralocorticoid and glucocorticoid supplementation allows optimal control and reduces the risk of unwanted side effects.
In Europe, dogs with Addison’s disease were previously treated with a human registered product (fludrocortisone acetate), which predominantly has mineralocorticoid activity and to a lesser degree glucocorticoid activity. However, mineralocorticoid and glucocorticoid needs vary from dog to dog and depending on the progression of the disease, some dogs cannot be sufficiently controlled with fludrocortisone acetate. Zycortal contains desoxycorticone pivalate (DOCP) which has been shown to control serum electrolytes (sodium and potassium) more effectively than fludrocortisone acetate and is therefore considered the preferred drug for mineralocorticoid supplementation compared to fludrocortisone acetate.

**Zycortal contains DOCP, which controls serum electrolytes more effectively than fludrocortisone.**

Dogs with deficiencies of both mineralocorticoids and glucocorticoids will also need glucocorticoid supplementation, usually in the form of prednisolone. Zycortal is intended for long-term administration at intervals and doses dependent on the individual dog’s response. The initial dose is 2.2 mg/kg body weight administered by subcutaneous injection.

**Long-term administration allows for the long-term control of primary Addison’s disease.**

**Prognosis**

Prognosis for dogs with Addison’s disease is excellent provided that treatment is maintained for life. Dogs with Addison’s disease can go on to live a long and happy life. Glucocorticoid supplementation may need to be increased in times of stress.
## Monitoring and dose adjustment

### Day 1
First dose

Initial dose Zycortal 2.2 mg/kg.
Start glucocorticoid treatment (recommended initial dose of prednisolone = 0.2 - 0.4 mg/kg SID)

### Day 10
Interim monitoring

Check clinical signs and electrolytes. If clinically abnormal, adjust glucocorticoid dose and/or look for other causes.

### Day 25
Second dose

Check clinical signs and electrolytes

#### Clinically normal AND normal Na+/K+ ratio
Adjust dose according to Day 10 Na+/K+ ratio as described in table below

#### Clinically abnormal OR abnormal Na+/K+ ratio

**Abnormal Na+/K+ ratio**

Decrease glucocorticoid dose (contact Dechra Veterinary Technical Services (VTS) team for further advice)

**PU/PD**

Decrease glucocorticoid dose (if PU/PD persists and Na+/K+ ratio > 32 at next revisit)

**Depression, lethargy, vomiting, diarrhoea or weakness**

Increase glucocorticoid dose (NB: these clinical signs could also be due to mineralocorticoid deficiency – review electrolytes)

**Other clinical signs**

Decrease Zycortal dose

Re-evaluate diagnosis or look for concomitant disease

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### If the Day 10 Na+/K+ ratio is:

- **≥ 34**: Decrease dose to 2.0 mg/kg body weight
- **32 to < 34**: Decrease dose to 2.1 mg/kg body weight
- **27 to < 32**: Continue 2.2 mg/kg body weight dose
- **≥ 24 to < 27**: Increase dose to 2.3 mg/kg body weight
- **< 24**: Increase dose to 2.4 mg/kg body weight

*Instead of changing the dose, the dose interval can be changed. For more information contact Dechra Veterinary Technical Services (VTS) team at technical@dechra.com

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### 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. In time of stress the glucocorticoid dose may need to be increased.
Efficacy

Zycortal has been proven to be highly efficacious in controlling Addison’s disease with clinical success rates > 80%. It has been tested in an international multi-centre clinical field trial and was equally efficacious when compared to a US registered control product containing DOCP.

Treatment with Zycortal has been shown to be well-tolerated at the recommended dose².

Treatment success of Zycortal on day 90 and day 180 compared to control product (DOCP, registered in US only)².

*For additional dosing tables please contact Dechra technical services at technical@dechra.com

Dosing Table: Starting dose 2.2 mg/kg BW*

<table>
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<tr>
<th>KG BW</th>
<th>Volume Zycortal (mL)</th>
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</tbody>
</table>

*For additional dosing tables please contact Dechra technical services at technical@dechra.com
Switching dogs from existing treatment

Data from the Zycortal clinical study has shown that there were no significant differences in efficacy for newly diagnosed cases which started treatment with Zycortal compared to existing cases which started treatment with fludrocortisone and then switched to Zycortal \( (p > 0.05) \)\(^3\).

Dogs that switched from long-term fludrocortisone treatment to Zycortal did not show any adverse effects. Zycortal can therefore be given to newly diagnosed cases as well as cases that have previously received fludrocortisone.

Treatment of Addisonian crisis
(Acute Hypoadrenocorticism)

Acute and severe signs of Addison’s disease represent a life-threatening emergency and dogs need to be treated as soon as possible. Therapy aims to correct any hypotension, hypovolaemia, electrolyte imbalances, acidosis and hypoglycaemia which may be evident. Fluid therapy is the most important part of treatment at this stage, however it can mask the signs of Addison’s disease. If possible blood for haematology and serum biochemistry including electrolytes and the basal cortisol for an ACTH stimulation test should be taken before fluid therapy.

An ACTH stimulation test should be performed before mineralocorticoid/glucocorticoid supplementation, as the hypothalamic-pituitary-adrenal axis will be suppressed by the glucocorticoid and the result of the ACTH stimulation test will be hard to interpret. Initiation of medical treatment in these acute cases however, should not be delayed whilst waiting for the results of an ACTH stimulation test, if clinical suspicion of the disease is high.

Once the dog is clinically stable, it can be transitioned onto maintenance
Seeing the same dog with the same issues? There could be a different conclusion.
References
2. CVMP Assessment report for Zycortal (EMEA/V/C/003782/0000) 2015 pg 19

Further reading

ZYCORTAL: Zycortal contains deoxycortone pivalate

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