IDEXX

Diagnosing and Monitoring Suspected Cases of Canine Hypercortisolism and Hypoadrenocorticism.

Clinical Reference Guide

Hypercortisolism (Cushing's syndrome)

What is it?

Hypercortisolism (previously hyperadrenocorticism) is an increase in glucocorticoid activity due to elevated cortisol concentrations.

Cushing's syndrome refers to the spectrum of clinical syndromes resulting from prolonged exposure to elevated glucocorticoid concentrations, whether originating from within the body (endogenous) or external sources (exogenous).[1,2]

Pathophysiology

ACTH-dependent hypercortisolism

Pituitary-dependent hypercortisolism (PDH)[2]

+ Most common form of hypercortisolism—80%–85% of dogs with hypercortisolism have this form.[2]
+ An autonomous adrenocorticotropic hormone (ACTH)-secreting pituitary tumor leads to increased release of ACTH, which then leads to bilateral adrenal hypertrophy and excess cortisol release.
+ Most are adenomas, but invasive adenomas and carcinomas have been reported.[2]

ACTH-independent hypercortisolism

Autonomous cortisol-secreting adrenal tumor[2]

+ 15%–20% of Cushing's patients have this form.[2]
+ Adrenal tumor synthesizes and secretes excess cortisol.
    + Cortisol negatively feeds back on hypothalamus and pituitary, leading to decreased corticotropin-releasing hormone (CRH) and ACTH release.
    + Decreased production of CRH/ACTH cause atrophy of the contralateral adrenal gland.
+ Adenoma or carcinoma—carcinoma 63%–75% of the time.[2]
+ Usually solitary and unilateral—bilateral has been reported.[2]

Subdiagnostic Cushing's syndrome

A clinical syndrome in which a patient presents with clinical signs suggestive of Cushing's syndrome, yet dynamic testing results are normal.[1]

Iatrogenic Cushing's syndrome

Results from prolonged administration of exogenous glucocorticoids—systemic or topical—leading to clinical signs of hypercortisolism.[1]

Note: There are other uncommon forms of ACTH-dependent and ACTH-independent hypercortisolism, which are beyond the scope of this document.

Clinical signs

Common

+ Polyuria/polydipsia
+ Polyphagia
+ Panting
+ Abdominal distention
+ Endocrine alopecia
+ Hepatomegaly
+ Muscle weakness
+ Hypertension

Less common

+ Lethargy
+ Hyperpigmentation
+ Comedones
+ Thin skin
+ Poor hair regrowth
+ Urine leakage

Uncommon

+ Ligament rupture
+ Facial nerve palsy
+ Pseudomyotonia
+ Testicular atrophy
+ Persistent anestrus

Clinicopathologic findings

Hematology

+ Stress leukogram (most consistent finding lymphopenia)
+ Thrombocytosis
+ Erythrocytosis

Chemistry

+ Increased ALP (marked)
+ Increased ALT (mild)
+ Increased cholesterol
+ Decreased BUN
+ Mildly increased glucose
+ Mild hypernatremia and hypokalemia

Urinalysis

+ Low urine specific gravity (typically < 1.020)
+ Proteinuria
+ Bacteriuria

Predisposed breeds

+ Miniature poodle
+ Dachshund
+ Terrier breeds
+ Boxer
+ Standard schnauzer

Indications to test

Test patients:

+ With multiple clinical signs of disease.
+ With multiple laboratory abnormalities consistent with Cushing's syndrome.
+ Without any other underlying disease (or with a controlled underlying disease).
+ Who have not received any corticosteroids (topical, oral, or injectable) as they affect testing.

Important: Testing patients who do not meet these criteria can lead to false-positive results.

How to confirm hypercortisolism

A dynamic test is required to diagnose hypercortisolism. There are two different dynamic testing options:

Low-dose dexamethasone suppression test (LDDST):

+ The test of choice in most cases because it can confirm the diagnosis and sometimes differentiate pituitary from adrenal disease.[1–3]

ACTH stimulation test (ACTHST):

+ May be less affected by the stress of an underlying condition, such as diabetes mellitus.[3]
+ 1-hour test protocol (ideal for high-paced practices).
+ Can be used to help monitor patients on therapy for Cushing's syndrome.
+ The only test that diagnoses iatrogenic Cushing's syndrome.

Note: LDDST and ACTHST can both be impacted by the administration of exogenous steroids or stress related to nonadrenal illness.

To run an LDDST:

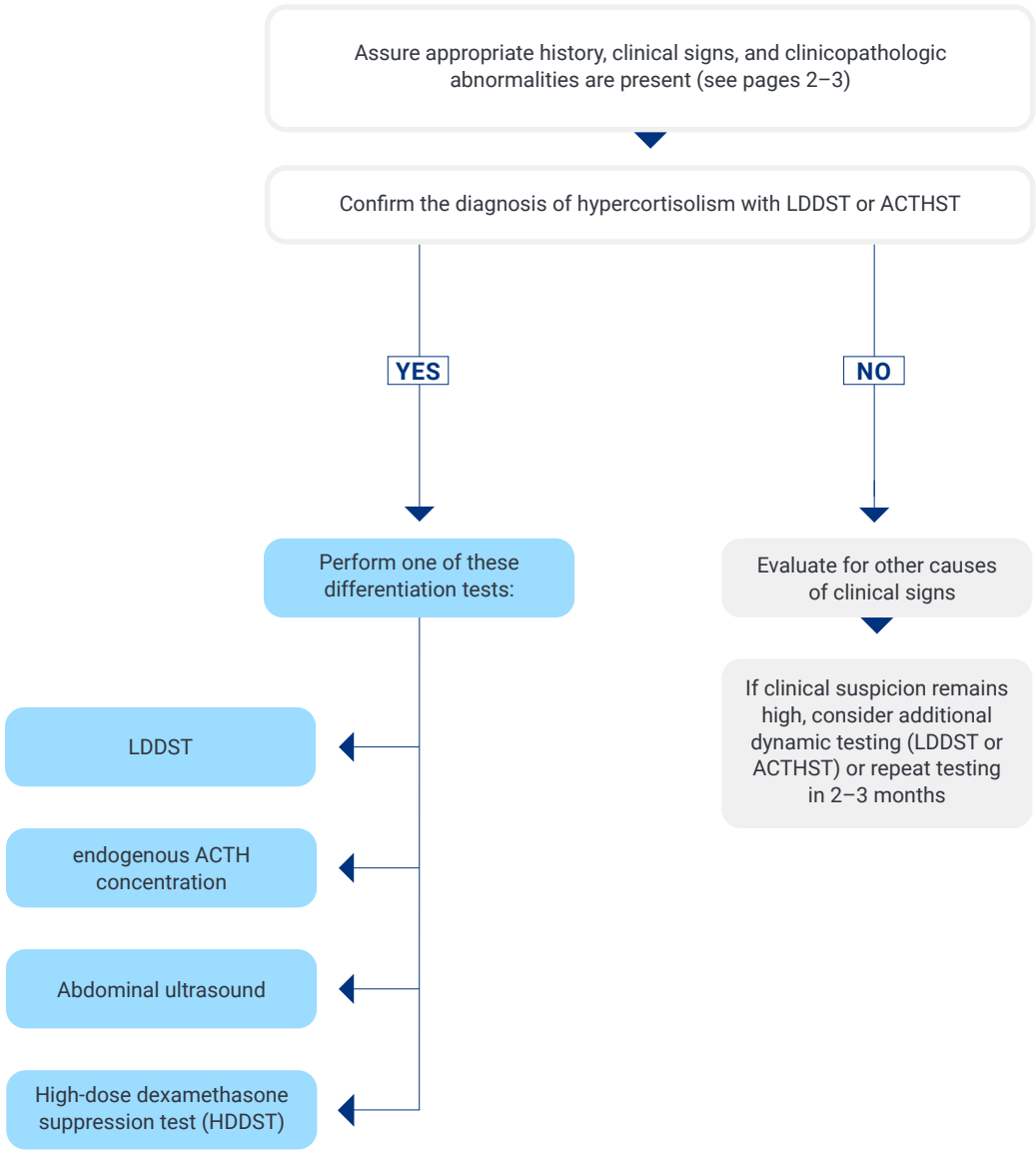
1. Collect a baseline cortisol sample.
2. Administer 0.01 mg/kg IV dexamethasone sodium phosphate or dexamethasone in polyethylene glycol.
3. 4 hours after injection, collect a second blood sample.*
4. 8 hours after injection, collect a third blood sample.

To run an ACTHST:

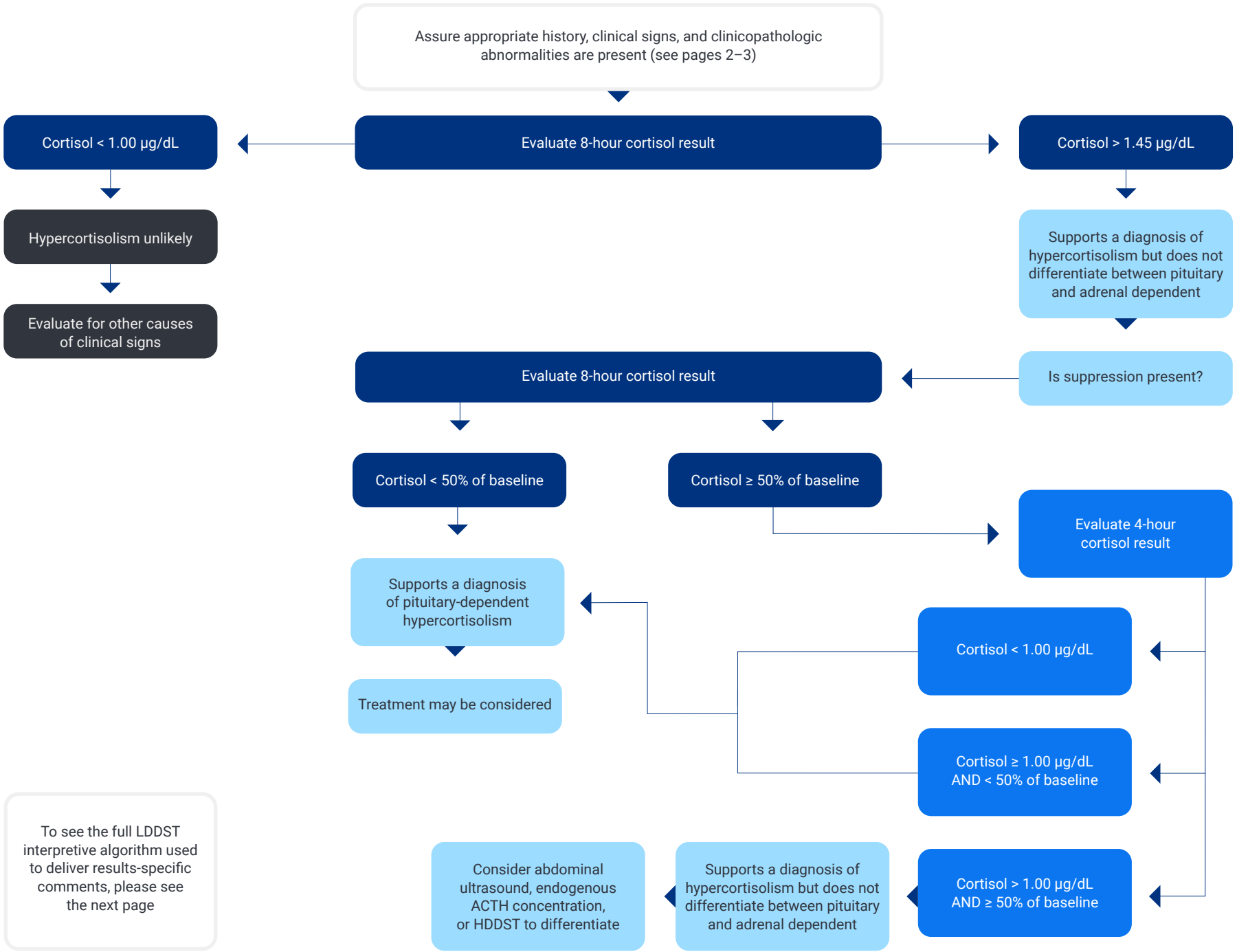
1. Collect a pre-ACTH sample.
2. Administer synthetic ACTH IV (5 µg/kg or up to 250 µg per dog) OR ACTH gel (2.2 IU/kg IM).
3. 1 hour after injection, collect a post-ACTH sample.
4. If using ACTH-depot (ACTH gel): 2 hours after injection, collect a second post-ACTH sample.

*The 4-hour sample is used to help differentiate pituitary from adrenal disease. Also, having a 4-hour blood sample ensures that patients with an inverse pattern (4-hour cortisol is higher than 8-hour cortisol) are not missed.

Diagnosing Cushing's syndrome.

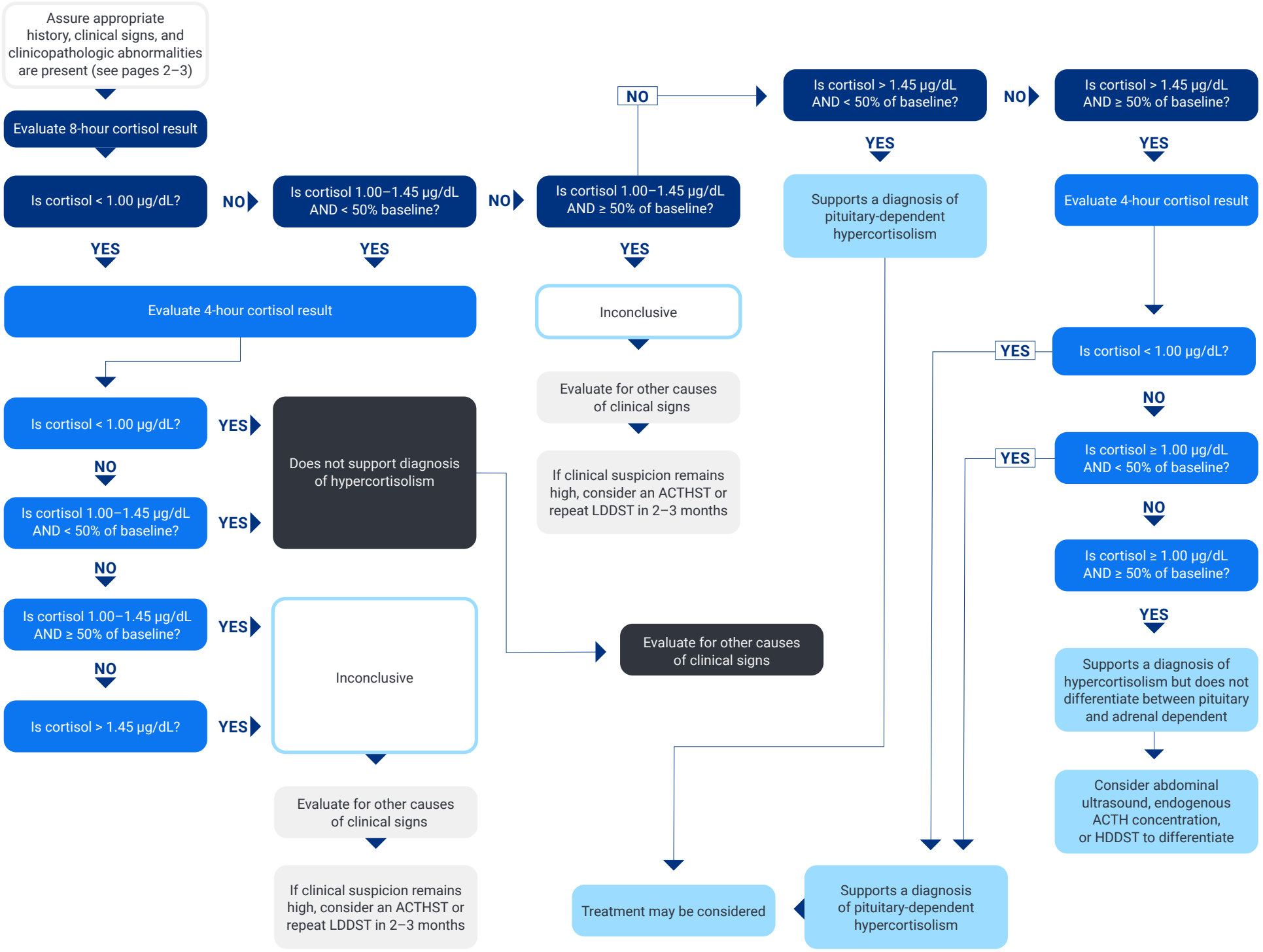


General algorithm: Diagnosing Cushing's syndrome with an LDDST.

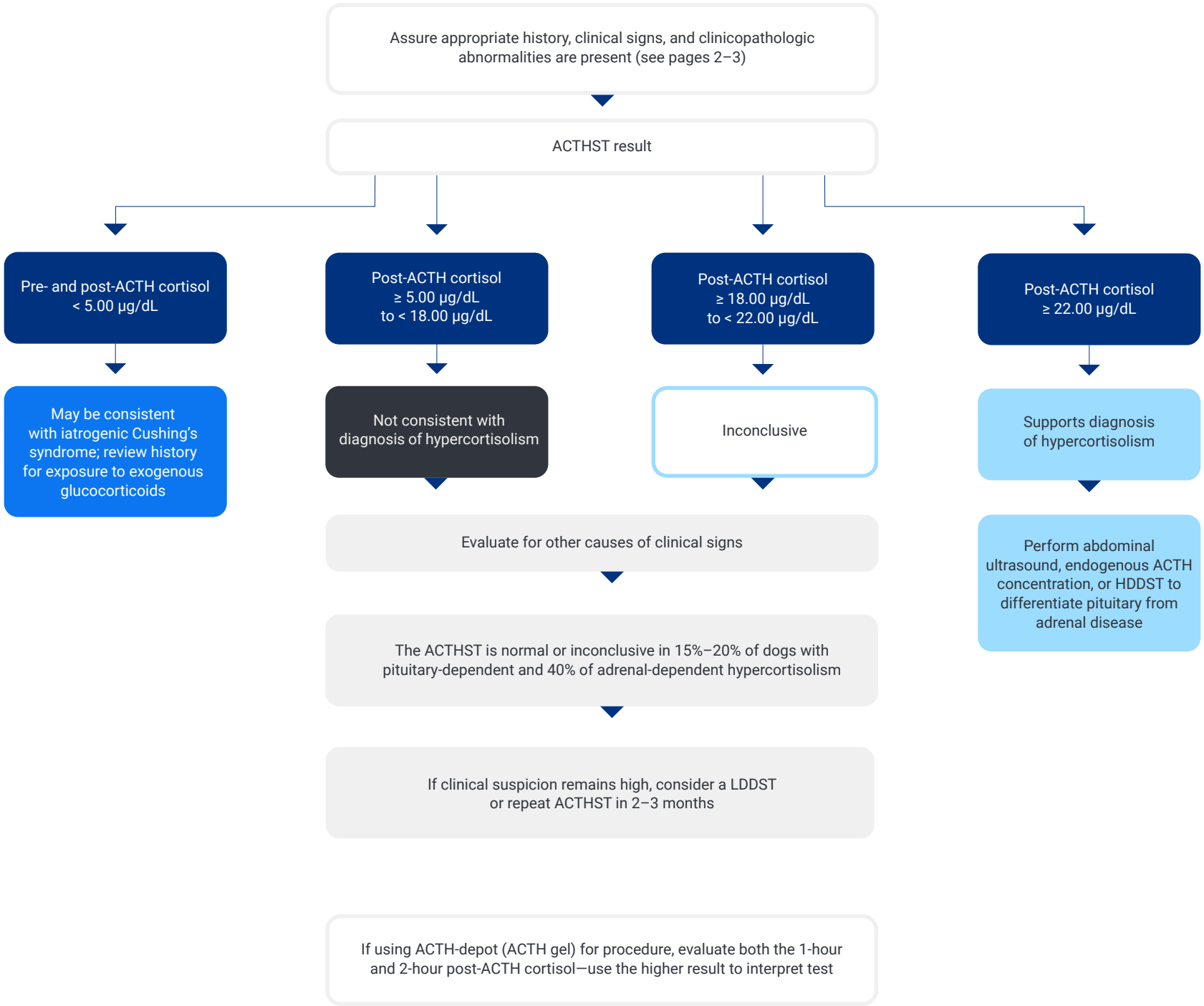


To see the full LDDST interpretive algorithm used to deliver results-specific comments, please see the next page

Full algorithm: Diagnosing Cushing's syndrome with an LDDST.



Diagnosing Cushing's syndrome with an ACTHST.



Differentiating pituitary vs. adrenal-dependent hypercortisolism with an HDDST.

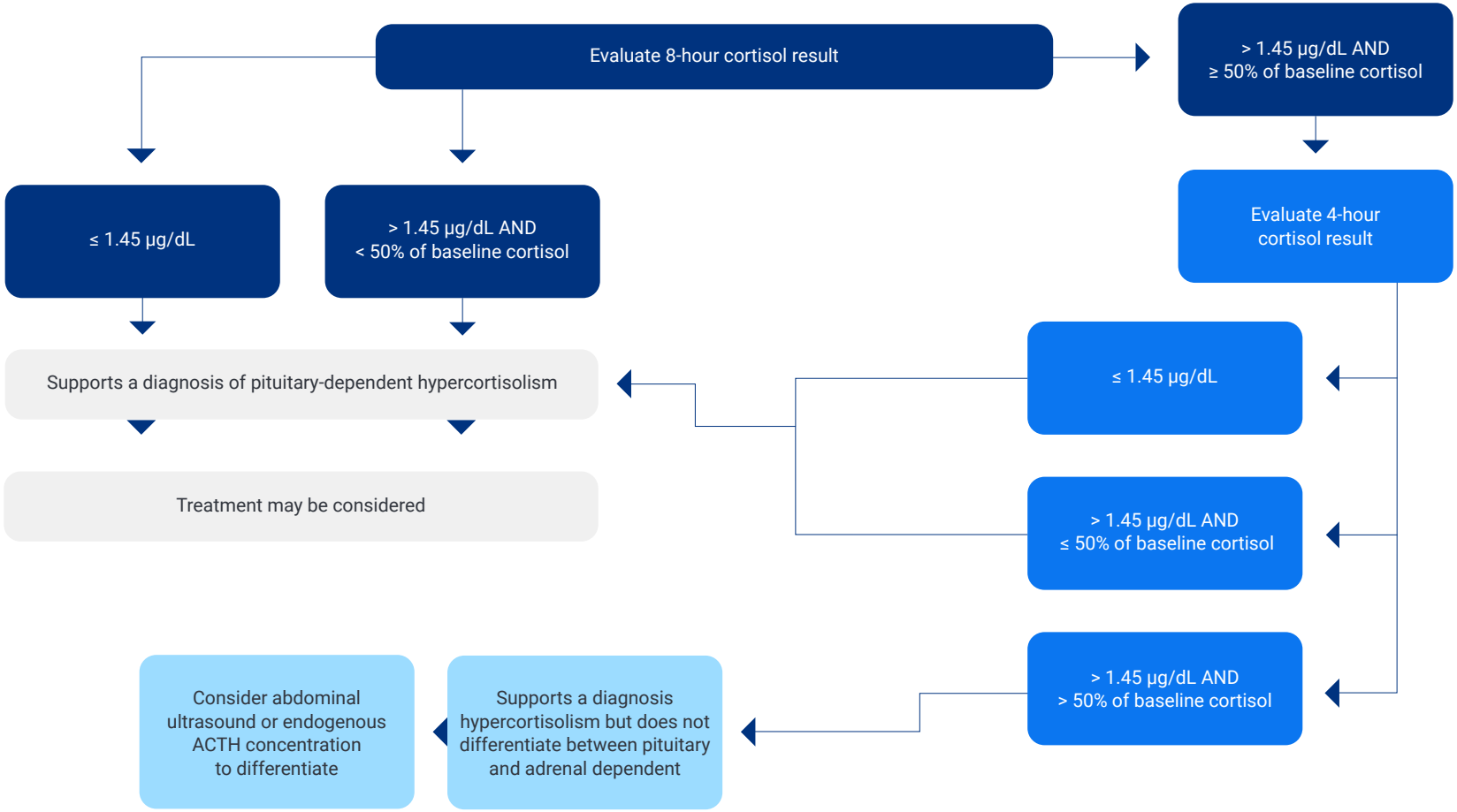
The ACTH stimulation test (ACTHST) cannot differentiate pituitary-dependent hypercortisolism (PDH) from adrenal-dependent hypercortisolism (ADH), and in some cases, the low-dose dexamethasone suppression test (LDDST) may also be nondiscriminatory. When differentiation is unclear, additional testing is necessary to guide treatment and provide prognostic information. Abdominal ultrasound is typically the most practical next step, although endogenous ACTH concentration or a high-dose dexamethasone suppression test (HDDST) can also be informative. Studies indicate that approximately 12% of dogs with PDH fail to suppress on an LDDST, yet do demonstrate suppression on an HDDST.[4]

Importantly, the HDDST should not be used to diagnose hypercortisolism—it is only appropriate after the disease has been confirmed using an LDDST or ACTHST.

To run an HDDST:

1. Collect a baseline cortisol sample.
2. Administer 0.1 mg/kg IV dexamethasone sodium phosphate or dexamethasone in polyethylene glycol.
3. 4 hours after injection, collect a second blood sample.
4. 8 hours after injection, collect a third blood sample.

Please note that administration of exogenous steroids or stress related to nonadrenal illness may affect the results and interpretation of the HDDST.



Monitoring dogs on trilostane therapy.

Trilostane therapy should be adjusted to the needs of the individual patient based on monitoring clinical signs, results of cortisol testing, and a biochemistry panel (including electrolytes).

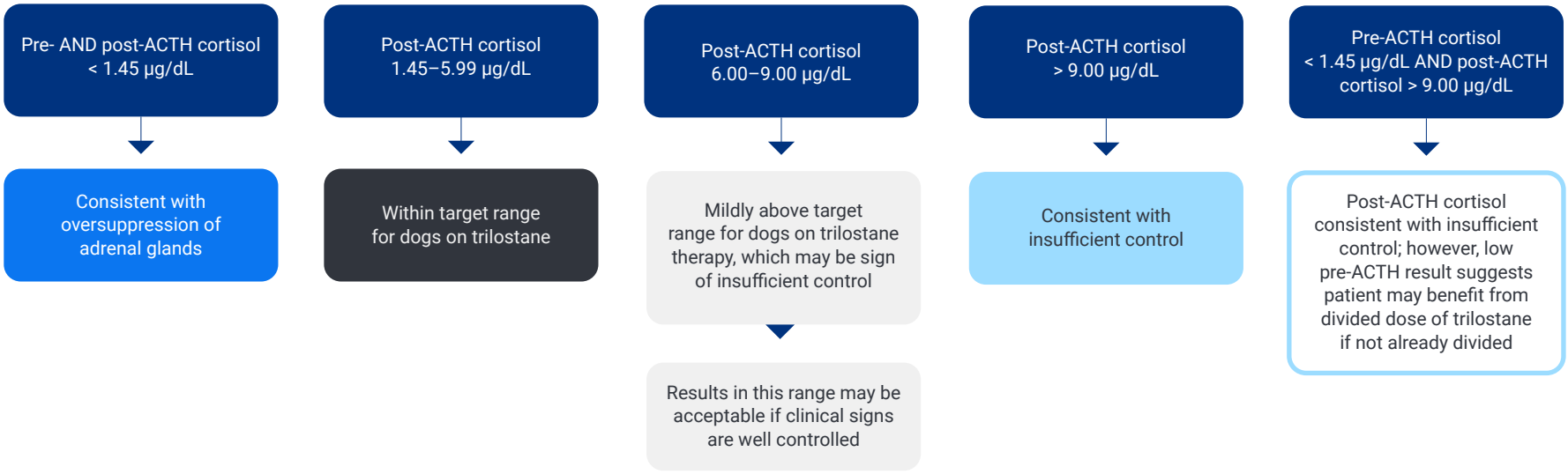
After beginning trilostane therapy, patients should be monitored at 10–14 days, 30 days, 90 days, and then every 3 months. Additionally, patients should be monitored 10–14 days after any dose adjustment.[5]

There are several methods to monitor cortisol in a patient on trilostane therapy.

+ ACTHST—test performed 2–3 hours post-pill.
    + When monitoring a patient over time, it is important to begin the ACTHST at the same time after trilostane administration each time the ACTHST is performed.
+ Pre-pill resting cortisol—test performed immediately prior to administration of morning trilostane pill.

Interpretation of results and treatment decisions should be made in light of clinical signs. Exact drug manufacturer recommendations may vary by region.

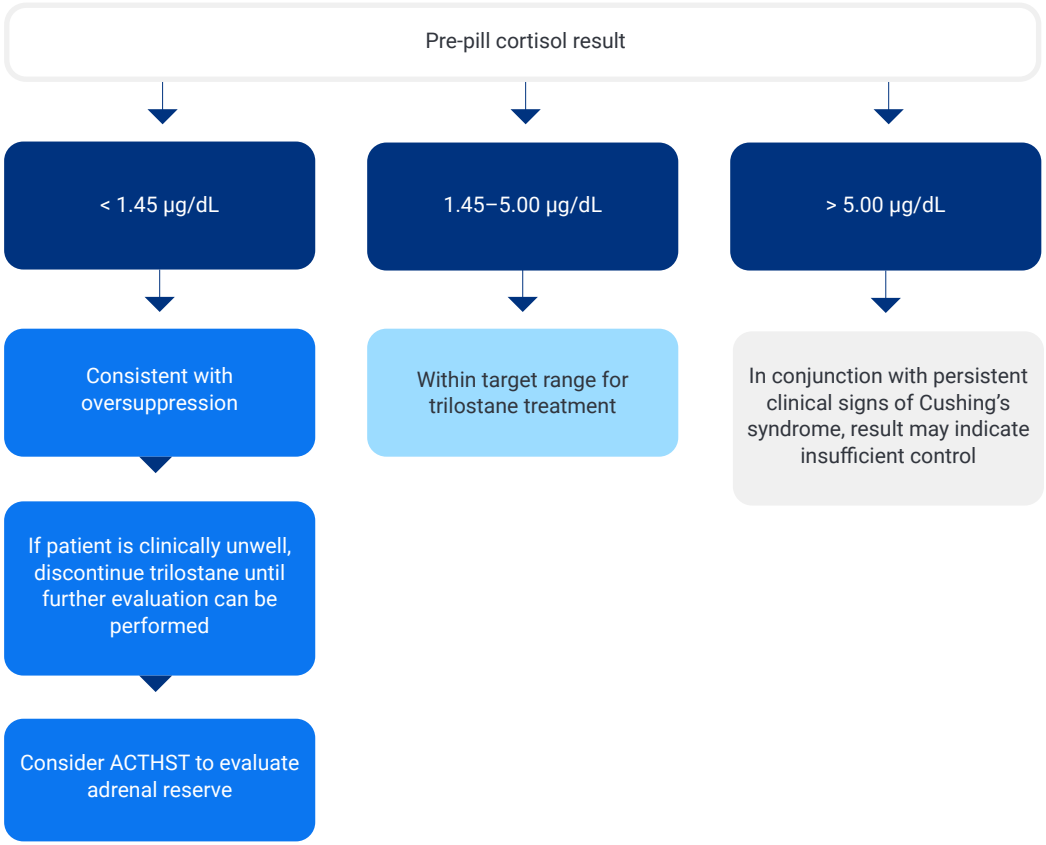
Monitoring with an ACTHST.



If using ACTH-depot (ACTH gel) for procedure, evaluate both the 1-hour and 2-hour post-ACTH cortisol—use the higher result to interpret test

Monitoring with a pre-pill resting cortisol.

Correlation with clinical signs and results of hematology and biochemistry is essential for correct interpretation of pre-pill resting cortisol results.



Hypoadrenocorticism (Addison's disease)

Pathophysiology

Primary hypoadrenocorticism (HA)

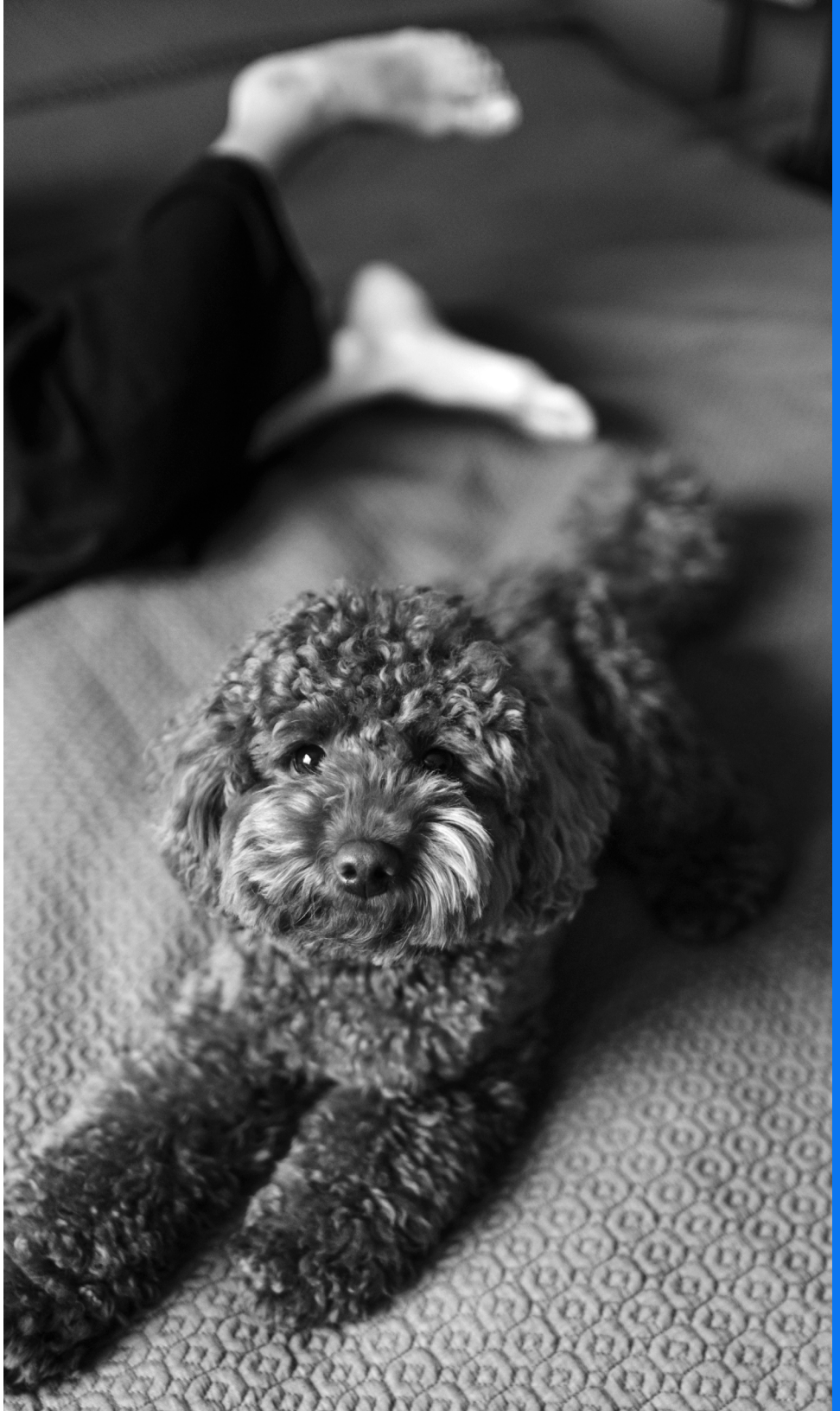
This is most common form of the disease and results from failure of the adrenal cortex to produce adequate glucocorticoids and mineralocorticoids. This typically occurs due to adrenal cortical atrophy secondary to immune-mediated destruction. Less commonly, primary HA may result from infiltrative or destructive processes affecting both adrenal glands, such as neoplasia, fungal infection, hemorrhage, or infarction. Iatrogenic primary HA can also occur following the administration of adrenal-targeting drugs like mitotane or trilostane.[1,6]

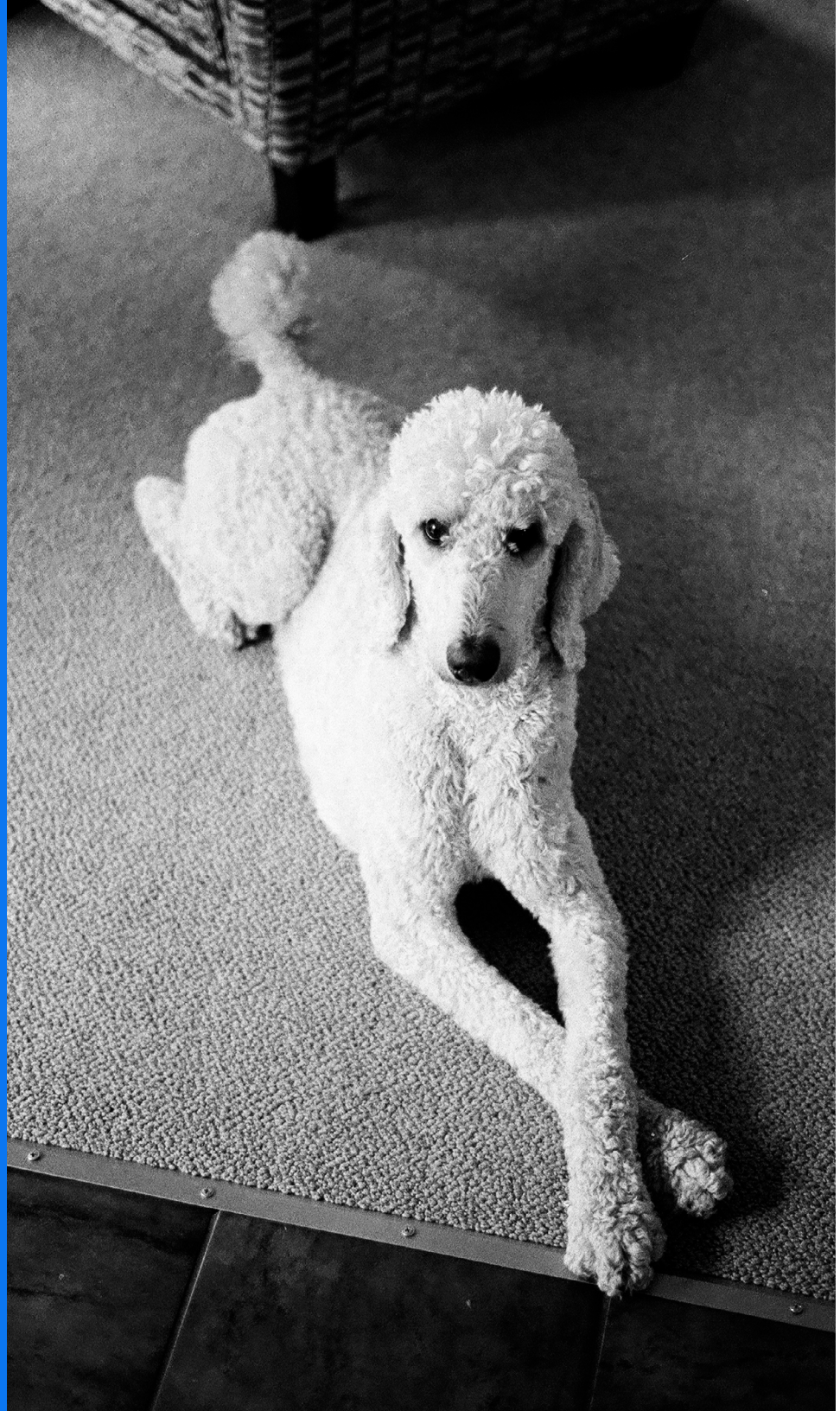
Eunatremic, eukalemic hypoadrenocorticism

Formerly referred to as atypical Addison's disease, this form is characterized by reduced glucocorticoid secretion with normal electrolyte levels. While some patients eventually develop electrolyte abnormalities consistent with typical Addison's disease, others maintain normal electrolyte levels throughout their lives.[1]

Secondary hypoadrenocorticism

This is an uncommon form of hypoadrenocorticism resulting from insufficient ACTH secretion, leading to glucocorticoid deficiency, while mineralocorticoid production typically remains unaffected. Rarely, mineralocorticoid deficiency may also occur due to impaired renin activity. Secondary hypoadrenocorticism may be naturally occurring, due to pituitary or hypothalamic dysfunction, or it may be iatrogenic due to surgery on the glands of the HPAA or abrupt withdrawal of glucocorticoid medication.[1,6]





Clinical signs

+ Can be vague
+ Mild to severe
+ May wax and wane
+ Anorexia, weight loss
+ Vomiting, diarrhea
+ Lethargy, weakness, shaking, collapse
+ Polyuria/polydipsia

Note: Sometimes stressful situations can push a borderline compensated dog with HA into an adrenal crisis.

Predisposed breeds

+ Leonberger
+ Pomeranian
+ Great Dane
+ Standard poodle
+ Bearded collie
+ Portuguese water dog
+ Cocker spaniel
+ Springer spaniel

Clinicopathologic findings

Hematology

+ Lack of a stress leukogram (most consistent finding normal to increased lymphocytes in a sick animal)
+ Mild anemia

Chemistry

+ Hyponatremia
+ Hyperkalemia
+ Hypoglycemia
+ Hypoalbuminemia
+ Hypocholesterolemia
+ Hypercalcemia
+ Elevated ALT/ALP
+ Azotemia

Urinalysis

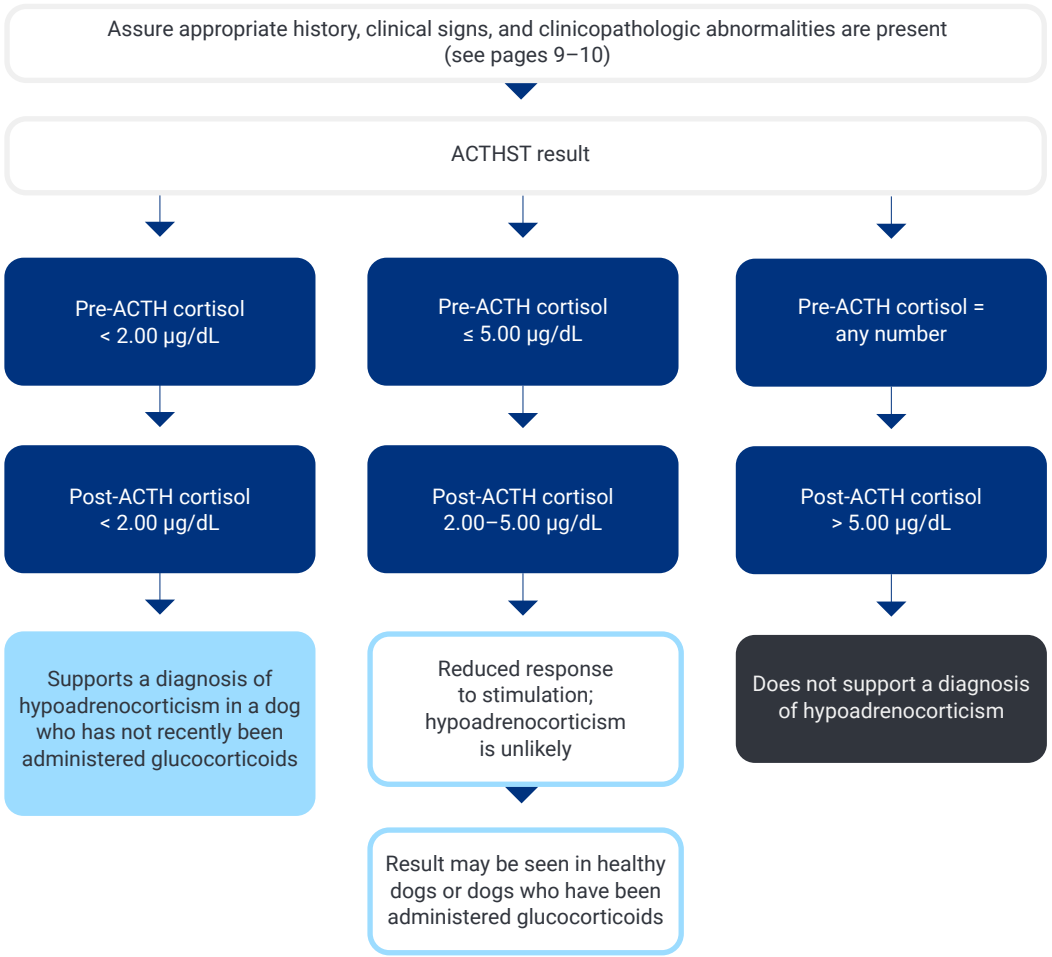
+ Relatively dilute urine in the face of dehydration

Screening for hypoadrenocorticism with resting cortisol

It is unlikely that a dog who has hypoadrencorticism will have a resting (baseline) cortisol concentration of ≥ 2.00 µg/dL. Therefore, resting cortisol is a very sensitive test for ruling out hypoadrenocorticism in dogs with clinical signs. However, resting cortisol is not a specific test for hypoadrenocorticism. Therefore, an ACTHST is required to confirm the diagnosis.[6]

Please note that a dog with hypoadrenocorticism that has been administered a glucocorticoid that cross-reacts with the assay (e.g., prednisone) may have results ≥ 2.00 µg/dL. Therefore, a full medication history is important.

Diagnosing Addison's disease with an ACTHST.



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References

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IDEXX