Addison’s Disease: Don’t Make a “Crisis” Out of Diagnosis and Management

Bill Saxon, DVM, DACVIM, DACVECC

Dechra

IDEXX

ALIVE: Agreeing Language in Veterinary Endocrinology

Only the names have been changed…

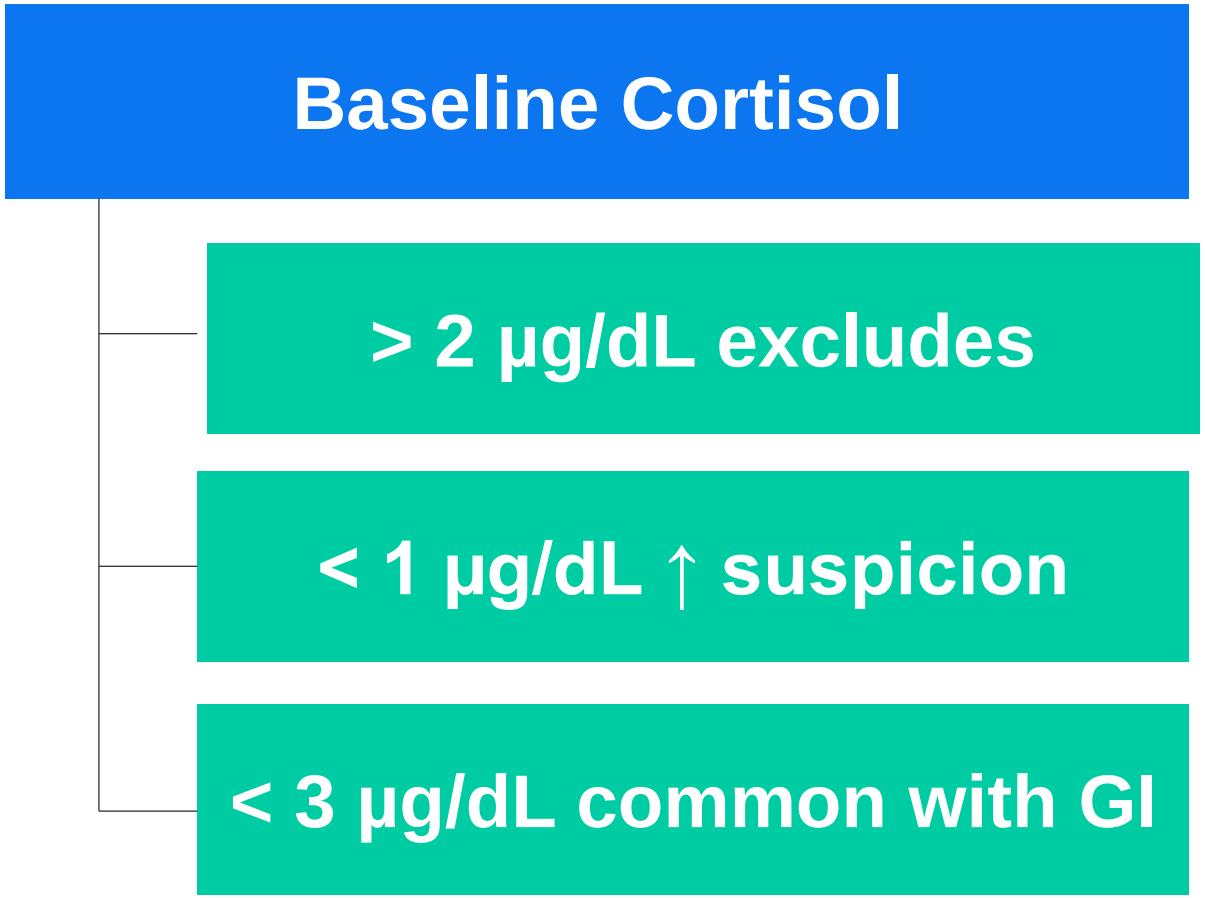
Addison’s disease	Primary hypoadrenocorticism
Atypical Addison’s disease	Eunatremic, eukalemic hypoadrenocorticism
Addisonian crisis	Adrenal crisis
Relative adrenal insufficiency	Critical illness-related corticosteroid insufficiency

Can I diagnose hypoadrenocorticism with resting cortisol?

No but you can rule it out.

ACTH stim test *required* to confirm the diagnosis.

Baseline cortisol can rule **out** hypoadrenocorticism



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Basal Serum Cortisol Concentration as a Screening Test for Hypoadrenocorticism in Dogs

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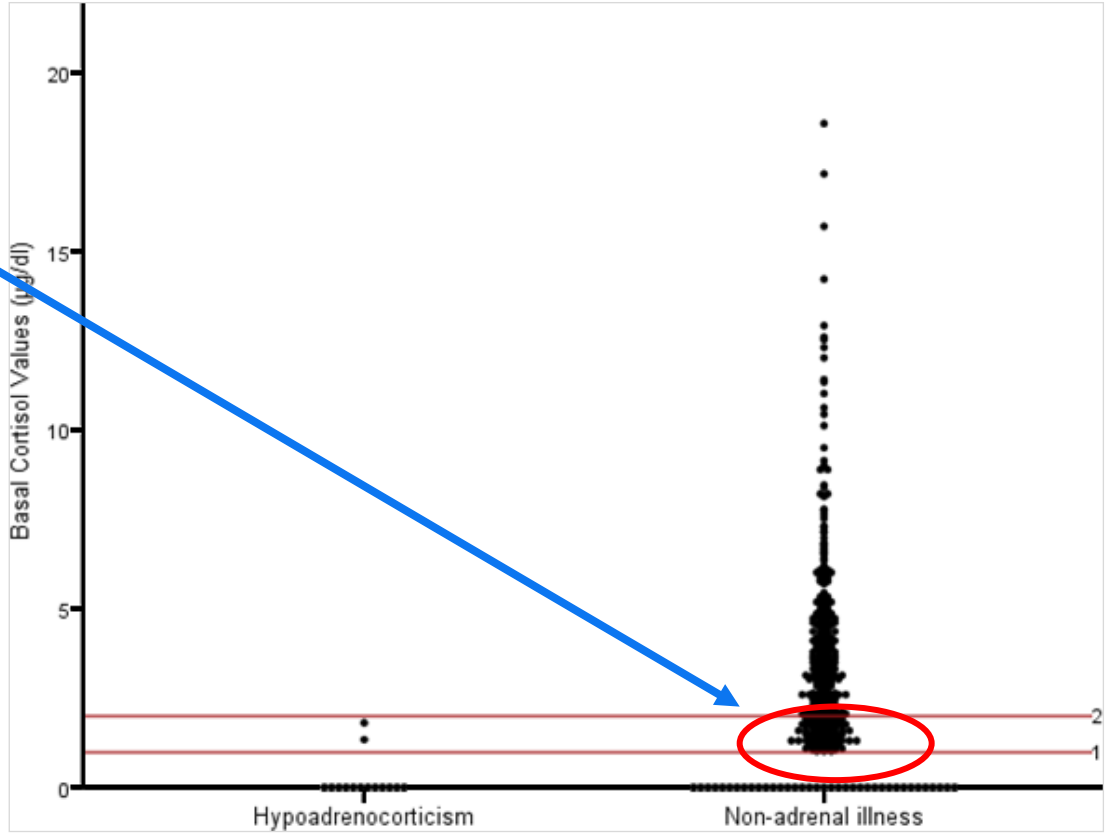
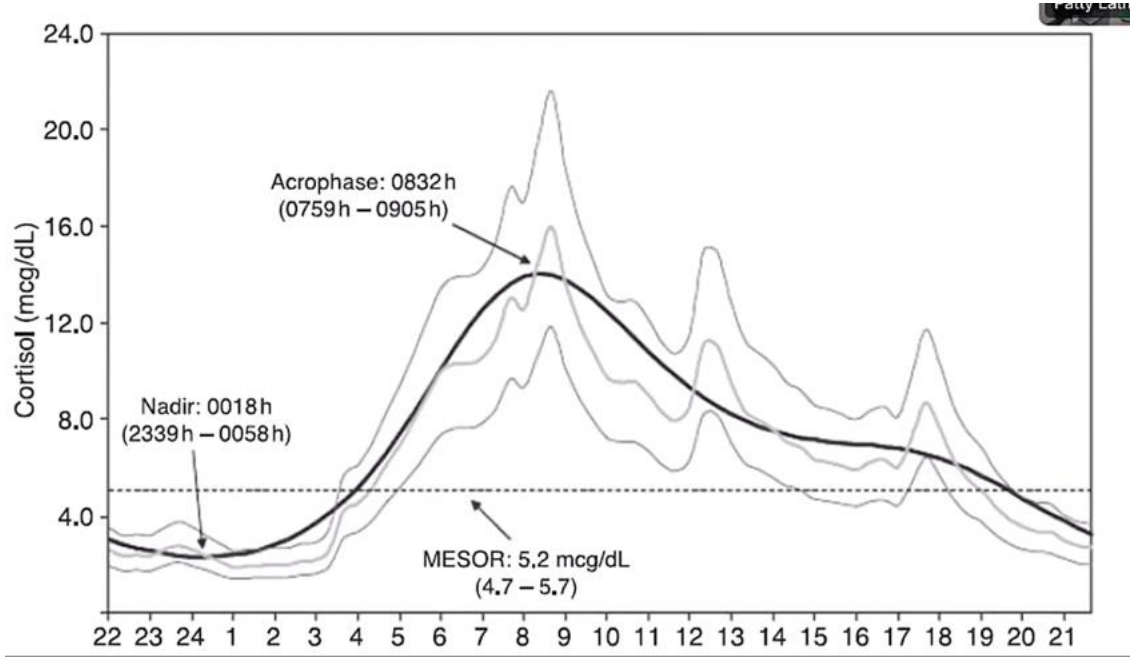
- 450 dogs, non-adrenal illness
- 14 dogs, hypoadrenocorticism

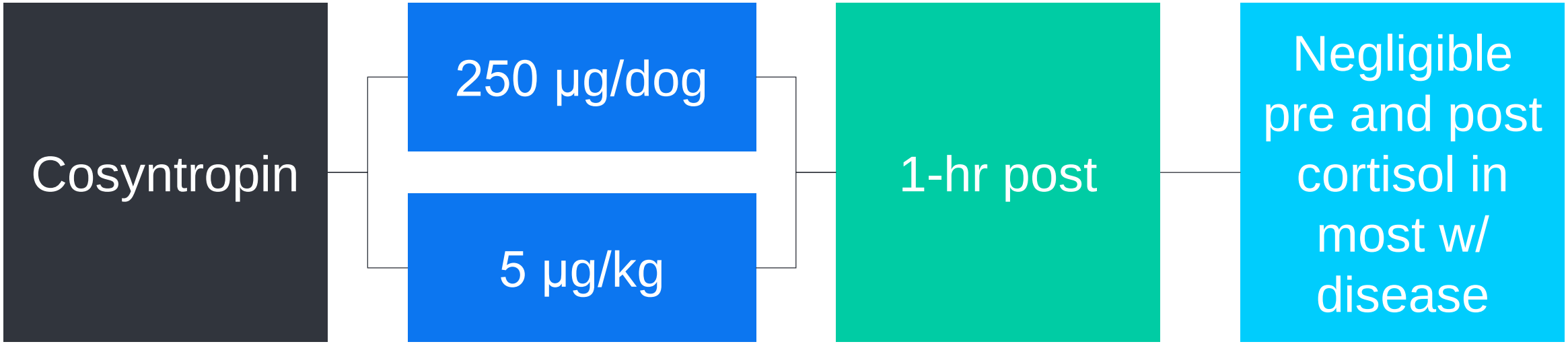


It’s different in people…

- AM cortisol <3.6 ug/dL WITH endogenous ACTH >2x upper limit = Addison’s



ACTH stimulation test to diagnose – only *once.*



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Journal of Veterinary Internal Medicine Open Access ACVIM American College of Veterinary Internal Medicine

STANDARD ARTICLE

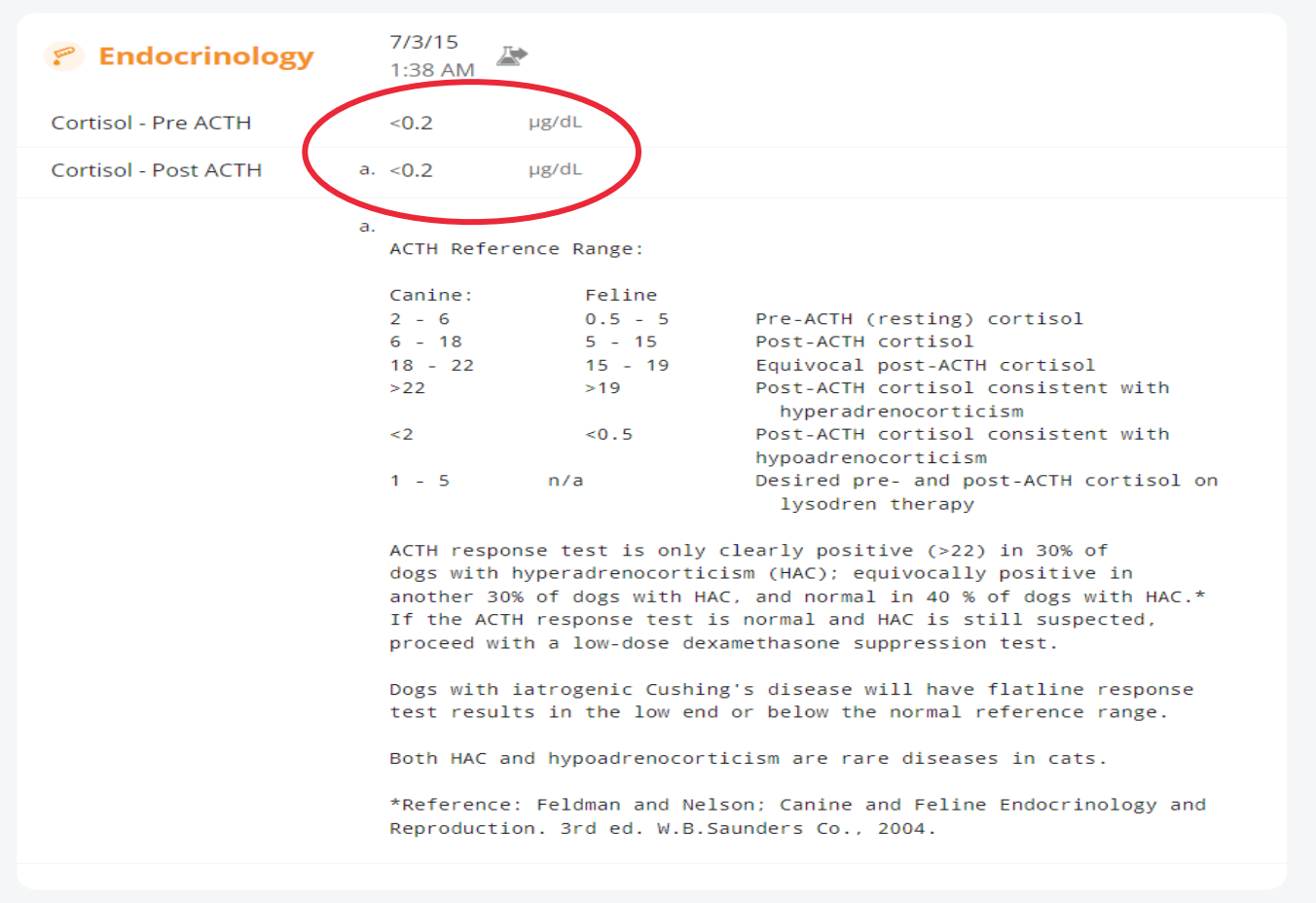
Low-dose ACTH stimulation testing in dogs suspected of hypoadrenocorticism

Annabel Botsford[1,4] | Ellen N. Behrend[1] | Robert J. Kemppainen[2] | Philippe R. Gaillard[3] | Frank Oprandy[3] | Hollie P. Lee[1]

- Low dose: **1 µg/kg cosyntropin, IV**
  - NOT FOR CUSHING'S DIAGNOSIS!!!
- Reconstitute with 1 mL sterile saline
  - 250 µg/mL
- To make 10 µg/mL
  - Add 1 mL of 250 µg/mL to 24 mL saline
- To make 50 µg/mL
  - Add 1 mL of 250 µg/mL to 4 mL saline
- Store at -20° C (-4° F) for up to 6 months

IDEXX

Typical ACTH stim test results…



Endocrinology 7/3/15 1:38 AM

Cortisol - Pre ACTH		<0.2	µg/dL
Cortisol - Post ACTH	a.	<0.2	µg/dL

a.

ACTH Reference Range:

Canine:	Feline	
2 - 6	0.5 - 5	Pre-ACTH (resting) cortisol
6 - 18	5 - 15	Post-ACTH cortisol
18 - 22	15 - 19	Equivocal post-ACTH cortisol
>22	>19	Post-ACTH cortisol consistent with hyperadrenocorticism
<2	<0.5	Post-ACTH cortisol consistent with hypoadrenocorticism
1 - 5	n/a	Desired pre- and post-ACTH cortisol on lysodren therapy

ACTH response test is only clearly positive (>22) in 30% of dogs with hyperadrenocorticism (HAC); equivocally positive in another 30% of dogs with HAC, and normal in 40 % of dogs with HAC.* If the ACTH response test is normal and HAC is still suspected, proceed with a low-dose dexamethasone suppression test.

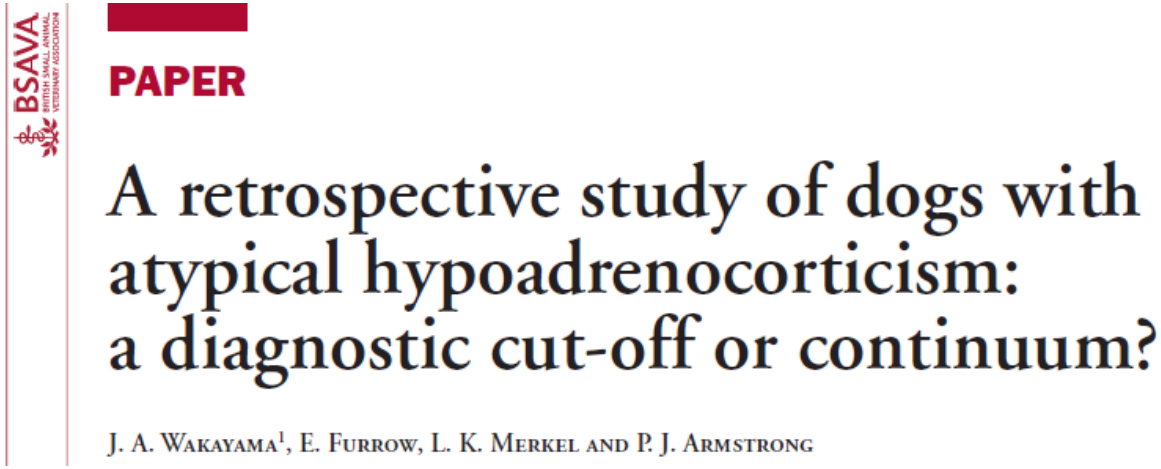
Dogs with iatrogenic Cushing's disease will have flatline response test results in the low end or below the normal reference range.

Both HAC and hypoadrenocorticism are rare diseases in cats.

*Reference: Feldman and Nelson; Canine and Feline Endocrinology and Reproduction. 3rd ed. W.B.Saunders Co., 2004.

What if stim results are borderline?
(Post ACTH cortisol 3-5ish…)

These are tricky…



PAPER

A retrospective study of dogs with atypical hypoadrenocorticism: a diagnostic cut-off or continuum?

J. A. Wakayama[1], E. Furrow, L. K. Merkel and P. J. Armstrong

- 9 dogs with stim results > 2 µg/dL (3.4 – 8.1 µg/dL)
  - "Equivocal"
  - Follow-up median 24 months (10-77 months)
  - 2 dogs lost to follow-up
  - 3 dogs were clinically well after d/c'd pred
  - 4 dogs—no improvement with pred
  - THESE DOGS DIDN'T HAVE ADDISON'S!!!

Can I give glucocorticoids prior to ACTH sim test?

It depends…

Glucocorticoids impact ACTH stim test in 2 ways:

- Cross-react with cortisol assay
  - Prednisone, prednisolone, methylprednisolone, etc.
  - NOT dexamethasone
- Suppress HPA Axis
  - Stim okay after single dose of dexamethasone (adrenal crisis)
  - Discontinue exogenous glucocorticoids minimum 2-3 wk before ACTH stim
    - All types – oral, topical otic/ocular, human skin creams
  - If signs occur as taper okay to perform stim
  - Post ACTH cortisol 2-8 µg/dL common, if stable repeat ACTH stim 2-3 wk

Does every sick dog have EEH?
(Addison’s aka the great pretender.)

Right?

EEH is indistinguishable from chronic GI disease

- 2 studies of dogs with chronic GI disease, resting cortisol <2 → ACTH stim
  - 4% final diagnosis hypoadrenocorticism (Hauck, et al. JVIM 2020)
  - 0.34% in a later study (Gallego, et al. JVIM 2022)

- Uncommon but life changing

- Repeat resting cortisol if first <2 µg/mL?
  - Repeat was normal in 67% with first < 2 µg/mL (Gallego, et al. JVIM 2022)

Suspect EEH when:

- Gastrointestinal signs
  - Megaesophagus?
- Albumin: globulin <1.08
  - Over 1/3 hyperglobulinemic
  - Hypoalbuminemia more common w EEH
- Low cholesterol (<3.43 mmol/L)
- Lack of stress leukogram in sick animal
  - Lymphocyte count >1500–1750cells/µL
  - Eosinophil count >500 cells/µL
- Reticulocytosis without anemia
- Increasing Ca, decreasing BG,regurgitation…

EEH in 30-40% of Addisonian dogs
Cats get it too.

EEH dogs older (8 yr) at dx than dogs with ‘regular’ Addison’s (5 yr)…

Reagan KL, McLarty E, Marks SL, et.. al. Characterization of clinicopathologic and abdominal ultrasound findings in dogs with glucocorticoid deficient hypoadrenocorticism. J Vet Intern Med. 2022;36(6):1947-1957. doi:10.1111/jvim.16564

What fluid should I use to treat an adrenal crisis?

Good old LRs.

Adrenal crisis: rethinking initial fluid choice

- LRs advantages
  - Contains buffer
  - Na^+ concentration lower than 0.9% NaCl
    - Lowest of isotonic crystalloids, 130 mEq/L
  - Trivial K (and Ca) concentration
- 0.9% NaCl concerns
  - Higher Na^+ concentration may raise serum Na too fast
    - Osmotic demyelination syndrome
  - Acidifying
  - Renal vasoconstriction due to high Cl^- concentration

Emergency treatment

- IV fluids
  - 10-20 ml/kg bolus (5-10 ml/kg cat) over 15-30 min, reassess, repeat prn
- IV dexamethasone
  - 0.1-0.2 mg/kg IV then 0.05 mg/kg q12h for 24-72 h
  - No prednis(ol)one or hydrocortisone until ACTH stim completed
  - No advantage to hydrocortisone CRI v dexamethasone injections
- Dextrose if hypoglycemic
  - 1 gm/kg 50% dextrose diluted 1:4 then add 2.5-5.0% to fluids
- Blood products if severe anemia (GI bleed)
- Remember whipworms → pseudohypoadrenocorticism

Maintenance treatment is **lifelong**

Prednisone

- 0.1–0.2 mg/kg/day
  - OFTEN LOWER
  - E.g., 0.03 mg/kg/day lg dogs
- 0.5 mg/kg initially
- 2–10X dose during stress or illness

DOCP (NEVER sole treatment)

- 1.1 mg/kg SQ/IM q28 days
- DOCP has no glucocorticoid activity
- Decrease dose 10-15% if hypokalemia or hypernatremia

Monitor

- Electrolytes at 14 days, then 28 days, eventually q3–6 months
- CBC, biochemical panel, urinalysis at least yearly once stable

Human dose adjustment guidelines…

Adrenal Insufficiency Patient Guide to Management of Illness and Stress-Related Medical Events

Updated 8/31/2020

	Event	Sub-Event	Dosage Recommendation*
Home Self-management	Illness with fever	Fever >100.4-102°F	Double hydrocortisone replacement dose until recovery (~2-3 days)
		Fever >102.2°F	Triple hydrocortisone replacement dose until recovery (~2-3 days)
	Circumstantial increased physical and/or emotional stress	Unusual work-related stress or increased hours, travel, overexertion, intensive exercise, positive or negative emotional stress	Dependent on individual and circumstance, but typically requires extra dose of 5-10 mg based on symptoms; proactively consult with endocrinologist at routine visit
	Dental work	Any	Extra hydrocortisone 10-20 mg can be given a few hours later depending on pain level from procedure
		Local anesthesia	Extra hydrocortisone 20 mg before procedure
	Unable to tolerate oral medications due to illness or trauma		Hydrocortisone 100 mg IM or SC and consider ER; see NADF Guide to Adrenal Crisis Care Medication Information
	Minor to moderate surgery stress		Hydrocortisone 25-75 mg per 24 hours in addition to maintenance dose (~1-2 days)
Healthcare Practitioner Administered	Dental work	General anesthesia	Extra hydrocortisone 50 mg IV before anesthesia
	Unable to tolerate oral medications due to illness or trauma	With dehydration or inability/ unwillingness to self-inject IM or SC	Hydrocortisone 100 mg IV
	Major surgery or major stress from severe infection, sepsis (hospitalized)		Hydrocortisone 100 mg IV and continuous infusion 200 mg/24 hours
Other	Cardiac stress test or angiogram	Consult your endocrinologist	
	Colonoscopy		
	Chemotherapy		

Do I need to use DOCP if electrolytes are normal?

Probably not at least initially but…

J Vet Intern Med 2014;28:154–159

Evaluation of Aldosterone Concentrations in Dogs with Hypoadrenocorticism

M.E. Baumstark, N.S. Sieber-Ruckstuhl, C. Müller, M. Wenger, F.S. Boretti, and C.E. Reusch

- Normal electrolytes does not mean normal aldosterone
- 4/70 dogs with HA were atypical
  - 3/70: Na^+ and K^+ within reference range
  - 1/70: K^+ decreased
  - ACTH-stimulated aldosterone undetectable in all
  - BUT do they need DOCP???
    - Perform aldosterone stimulation test?
- 1 developed hyperkalemia 6 months later
- (Another study: Approx 10% will develop e-lyte abnormalities and require mineralocorticoid…)

Is hypoadrenocorticism a thing in cats?

Rare but in the news lately.

STANDARD ARTICLE | Open Access

Clinical findings, treatment, and outcomes in cats with naturally occurring hypoadrenocorticism: 41 cases

Emma Roberts, Ian K. Ramsey, Ruth Gostelow, Anna Latysheva, Luca Battaglia, Paolo Silvestrini, Ghita Benchekroun, Karen Brenner, Bérénice Conversy, Riccardo Ferriani ... See all authors

First published: 11 December 2024 | https://doi.org/10.1111/jvim.17243

Hypoadrenocorticism in cats: a 40-year update

Magdalena J Glebocka and Alisdair Boag

Journal of Feline Medicine and Surgery
1–7

DOI: 10.1177/1098612X241248381
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Sage

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Clinical features and long-term management of cats with primary hypoadrenocorticism using desoxycorticosterone pivalate and prednisolone

Nadja S. Sieber-Ruckstuhl[1] | Livia Harburger[1] | Natalie Hofer[1] | Claudia Kümmerle[1] | Claudia Müller[1] | Barbara Riond[2] | Regina Hofmann-Lehmann[2] | Claudia E. Reusch[1] | Felicitas S. Boretti[1]

Hypoadrenocorticism cat style…

- Autoimmune, trauma, lymphoma, congenital (2 cats <12 mo)
- Clinical signs and lab findings like dogs (lack of stress leukogram)
- Hypercalcemia in 32% (iCa)
- EEH exists in cats (some zero aldosterone pre-, post stim)
- Low cobalamin, low TLI (EPI) in some
- ACTH stim 5 µg /kg, 125 µg/cat IV, IM, 30- and 60-min post samples
- Treatment similar to dog but caution re volume overload
- DOCP dose 2.2 mg/kg (higher than dog)
- Pred dose median 0.3 mg/kg

Thank you!

125 mcg

Do we *have* to do an ACTH stimulation test to diagnose Addison's?

Yes.

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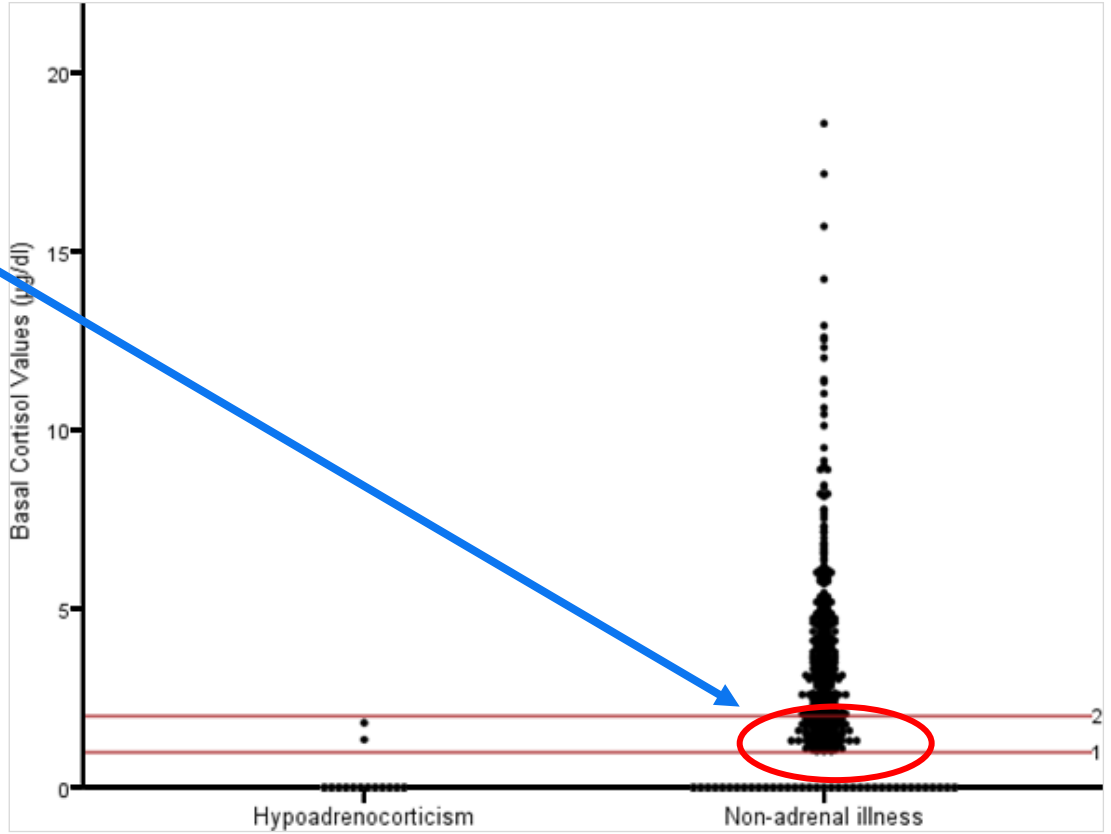
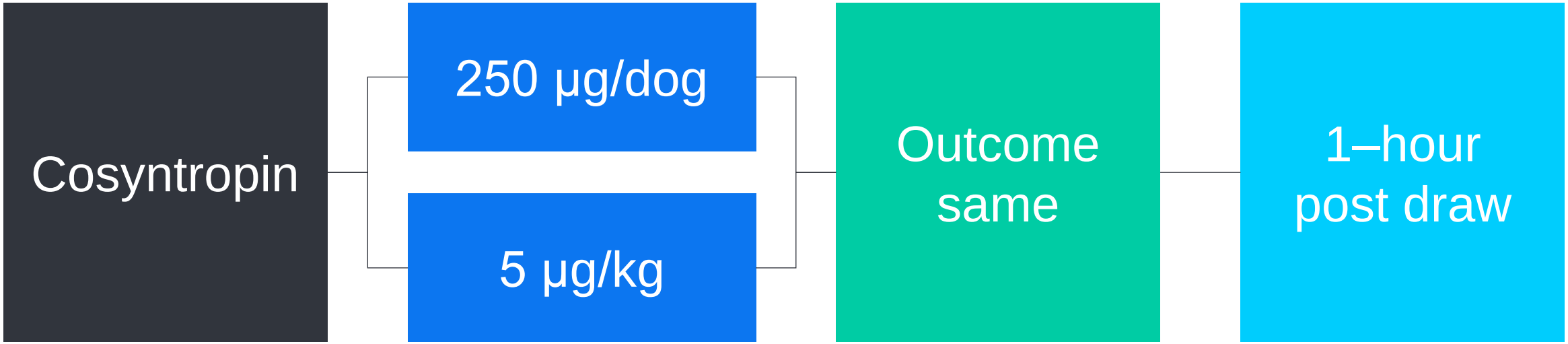


ACTH stimulation test (only once, to diagnose)



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Right?

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Prevalence and characterization of hypoadrenocorticism in dogs with signs of chronic gastrointestinal disease: A multicenter study

Christina Hauck[1] | Silke S. Schmitz[2] | Iwan A. Burgener[3] | Astrid Wehner[1] | Reto Neiger[4] | Barbara Kohn[5] | Thomas Rieker[6] | Sven Reese[7] | Stefan Unterer[1]

- Basal cortisol <2 µg/dL
  - 42/151 (28%) total dogs
    - 6/151 (6%) had Addison's
- Less common in another study (1/282) (Gallego, et al. JVIM 2022)
  - Repeat baseline cortisol >2 ug/dL in 19/28
- UNCOMMON but life changing

Suspect EEH when:

- Gastrointestinal signs
  - Megaesophagus?
- Albumin: globulin <1.08
  - Over 1/3 hyperglobulinemic
  - Hypoalbuminemia more common w EEH
- Low cholesterol (<133 mg/dL)
- Lack of stress leukogram in sick animal
  - Lymphocyte count >1500–1750cells/µL
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- Reticulocytosis without anemia
- Increasing Ca, decreasing BG, regurgitation…

EEH in 30-40% of Addisonians. Cats get it also.

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What fluid should I use in an adrenal crisis?

Good old LRs.
(or Hartmann's.)

Adrenal crisis: rethinking fluid choice

- LRs advantages
  - Contains buffer
  - Na concentration lower than 0.9% NaCl
  - Trivial K concentration
- 0.9% NaCl concerns
  - Acidifying
  - Higher Na concentration may raise serum Na too fast
    - Osmotic demyelination syndrome
  - Renal vasoconstriction due to high Cl concentration

Emergency treatment

- IV fluids
  - 10–20 ml/kg bolus over 15–30 min, reassess, repeat prn
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  - No prednis(ol)one or hydrocortisone until ACTH stim completed
  - No advantage to hydrocortisone CRI v dexamethasone injections
- Dextrose if hypoglycemic
  - 1 gm/kg 50% dextrose diluted 1:4 then add 2.5–5.0% to fluids
- Blood products if severe anemia (GI bleed)
- (Don’t forget about whipworms!)

What does of DOCP should I use?

Start with half of the traditional dose.

Maintenance treatment is **lifelong**

Prednisone

- 0.1–0.2 mg/kg/day
  - OFTEN LOWER
  - E.g., 0.03 mg/kg/day lg dogs
- 0.5 mg/kg initially
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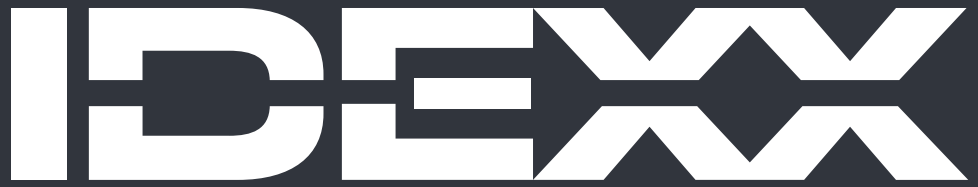
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