- Canine Hyperadrenocorticism

- Cushing's syndrome: umbrella term referring to the constellation of clinical and chemical abnormalitites that result from chronic exposure to excessive concentrations of glucocorticoids
- Cushing's disease: pituitary-dependent hyperadrenocorticism

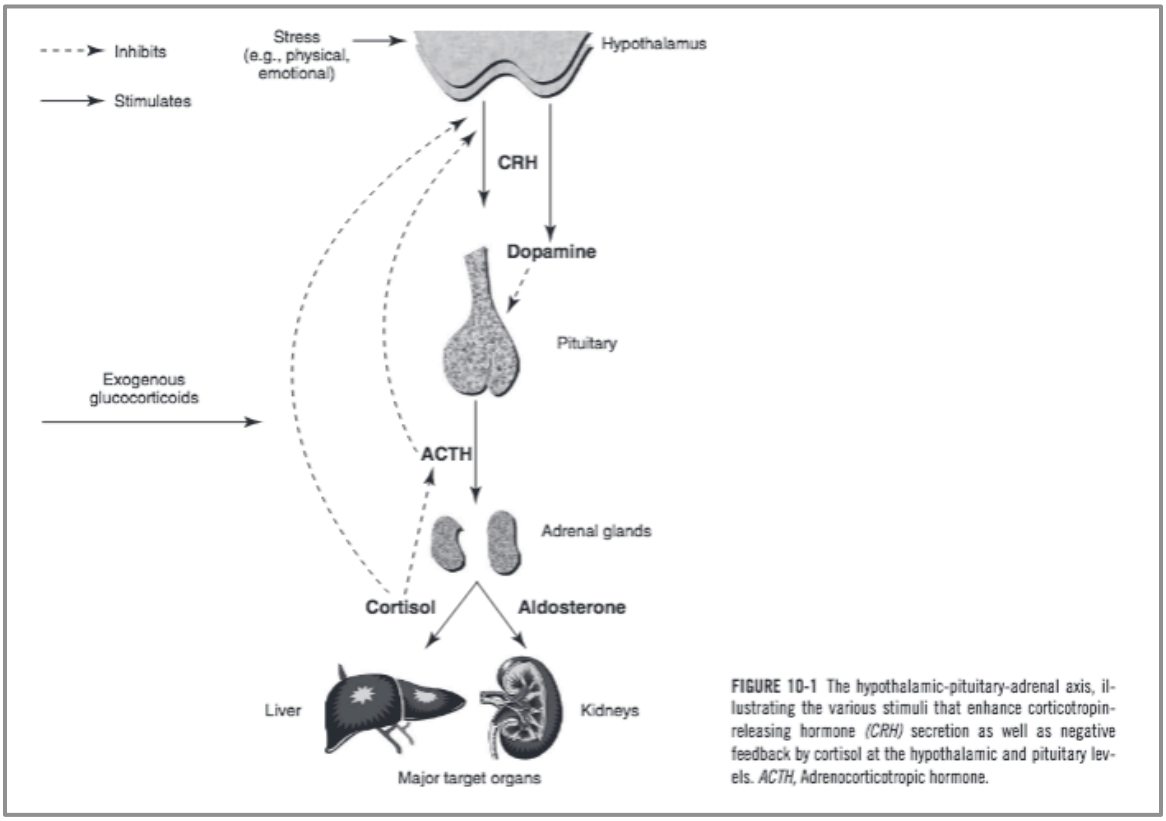
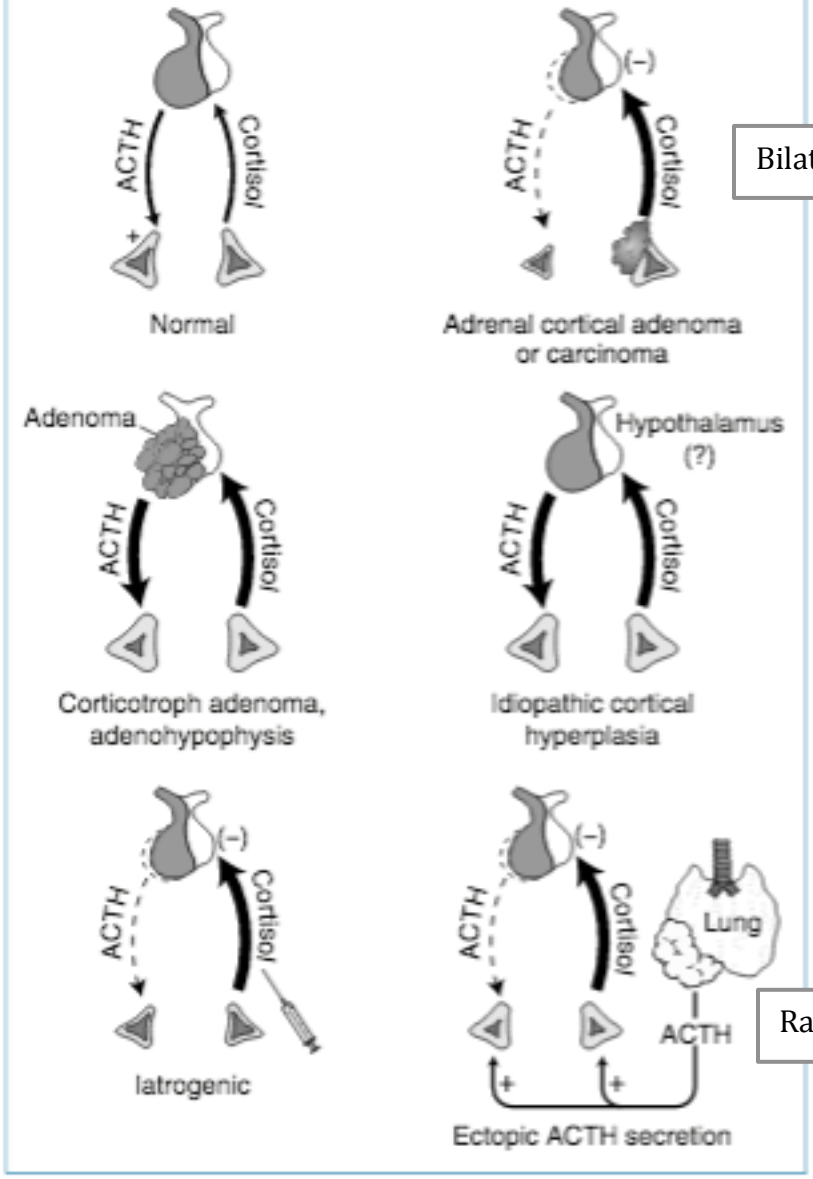


FIGURE 10-1 The hypothalamic-pituitary-adrenal axis, illustrating the various stimuli that enhance corticotropin-releasing hormone *(CRH)* secretion as well as negative feedback by cortisol at the hypothalamic and pituitary levels. *ACTH*, Adrenocorticotropic hormone.

- Adrenal cortex:
  - Glomerulosa: aldosterone production
  - Faciculata: glucocorticoid production
  - Reticularis: androgen production
- Cholesterol is the precursor for all steroids (80% LDLs)
- Pituitary-dependent hyperadrenocorticism (PDH)
  - 80-85% dogs with naturally occurring HAC
  - 20-100%: histologically recognized pituitary tumors
    - Variation may be due to 'persistence of pathologist' and other lab factors as some tumors can be very small
    - Author's experience: 'almost all' dogs with PDH have a pituitary tumor
  - Functioning pituitary carcinoma: rare
  - Pituitary adenoma**
- Microadenoma: <10mm
  - 31-48%: <3mm
- Macroadenoma: >10mm



Bilateral adenomas are possible

Rarely reported in dogs

FIGURE 10-6 Multiple pathogenic mechanisms of cortisol excess in dogs. (In Maxie MG, editor: *Jubb, Kennedy and Palmer's pathology of domestic animals*, Philadelphia, 2007, Saunders, p. 339.) *ACTH*, Adrenocorticotropic hormone.

- Signalment
  - Middle aged to older dogs
  - >89% are >6y
  - >75% are >9y
  - Female predisposition…?
  - Statistical predisposition: Poodles, Boxers, Dachshunds
    - Small dogs tend to get PDH
      - 75% dogs with PDH <20kg

- Large dogs tend to get AT
    - 50% dogs with AT >20kg

TABLE 10-4 CLINICAL MANIFESTATIONS OF CANINE HYPERADRENOCORTICISM*

COMMON	LESS COMMON	UNCOMMON
Polyuria/polydipsia	Lethargy	Bruising
Polyphagia	Hyperpigmentation	Thromboemboli
Panting	Comedones	Ligament rupture
Abdominal distention	Pyoderma	Facial nerve palsy
Endocrine alopecia	Thin skin	Calcinosis cutis
Hepatomegaly	Poor hair regrowth	Pseudomyotonia
Muscle weakness	Urine dribbling	Testicular atrophy
Muscle wasting	Insulin-resistant diabetes mellitus	Persistent anestrus
Systemic hypertension		

Modified from Behrend EN, et al.: Diagnosis of spontaneous canine hyperadrenocorticism: 2012 ACVIM consensus statement (Small animal), *J Vet Int Med* 27:1292, 2013.
*Categorization of frequency is based on identification at the time of initial presentation.

- Canine HAC is likely overdiagnosed
    - Multitude of clinical signs
    - False-positive results on screening tests
- Primary indication for pursuing a diagnosis of HAC is the presence of one or more of the common clinical signs and physical examination findings
- Vomiting, diarrhea, coughing, sneezing, pain, or bleeding is not caused by HAC
- Poor appetite and seizures are uncommon and
    - If related to HAC, are due to the presence of a pituitary macroadenoma
- Physical exam findings
    - Abdominal enlargement
    - Panting
    - Truncal obesity
    - Bilaterally symmetric alopecia
    - Hyperpigmentation
    - Skin infections
    - Comedones
    - Hepatomegaly
- Diagnostics

- Certain clinicopathalogic changes are consistent with HAC, though none are pathognomonic

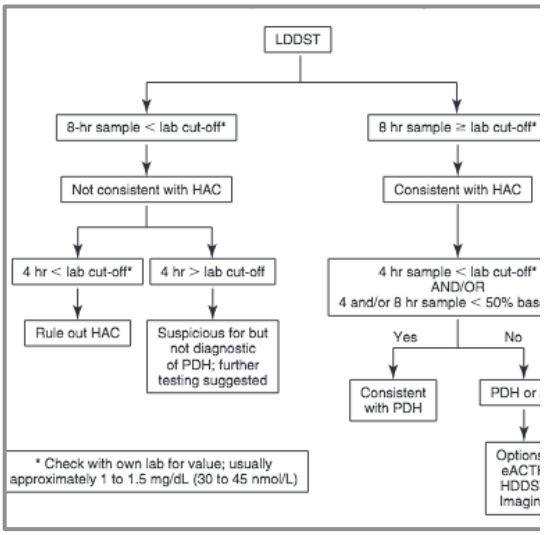
TABLE 10-5 HEMATOLOGIC, SERUM BIOCHEMICAL, URINE, AND RADIOGRAPHIC ABNORMALITIES THAT OCCUR WITH HYPERADRENOCORTICISM

TEST	ABNORMALITY
Complete blood count (CBC)	• Mature leukocytosis • Neutrophilia • Lymphopenia • Eosinopenia • Erythrocytosis; mild
Serum chemistries	• Increased alkaline phosphatase (ALP; sometimes extremely elevated) • Increased alanine aminotransferase (ALT) (usually mild) • Hypercholesterolemia • Hypertriglyceridemia • Hyperglycemia • Increased bile acids • Decreased blood urea nitrogen (BUN)
Urinalysis	• Urine specific gravity less than 1.015, often less than 1.008 • Proteinuria
Radiography/ultrasonography	• Hepatomegaly • Excellent abdominal contrast • Osteoporosis • Calcinosis cutis/dystrophic calcification • Adrenal calcification (usually adrenal tumor) • Pulmonary thromboembolism (PTE) (rare) • Calcified trachea and main stem bronchi • Pulmonary metastasis of adrenal carcinoma
Blood pressure	• Hypertension
Thyroid testing	• Low thyroxine (T_4) concentrations • Triiodothyronine (T_3) concentrations

- Complications associated with HAC
  - Urinary crystals and calculi: typically Ca-containing
  - Hypetension: activation of RAAS, enhanced vascular sensitivity to pressors?

- Hypothyroidism: hypercortisolemia causes secondary hypothyroidism
  - 40-60% dogs with HAC have decreased T3 and T4
  - If a patient is suspected to have both HAC and HypoT4, treat the HAC first then retest for HypoT4
- Diabetes mellitus
- Gallbladder mucocele: an association has ben postulated but not proven
- PTE: humns with HAC are 4x at risk for PTE
  - Increased levels of procoagulation factors
  - Decreased antithrombin

- Diagnosis
- A suspicion of HAC should be established from the history, physical examination findings, results of routine laboratory tests (CBC, serum biochemistry profile, and urinalysis), radiographs, and/or AUS
- Screening and differentiating tests
  - Screening tests: confirm or rule out the existence of HAC
    - Aim to demonstrate:
      - Increased cortisol production -or-
      - Decreased sensitivity of the hypothalamic-pituitary-adrenal axis to negative glucocorticoid feedback
    - None have 100% sensitivity or specificity
    - Low Dose Dexamethasone Suppression Test
      - Demonstrates decreased hypothalamic-pituitary-adrenal axis sensitivity to negative glucocorticoid feedback
      - Sensitivity for diagnosis of HAC is high (85-100%)
      - Differentiates between PDH and AT in approximately 40% of dogs with HAC
      - Considered safe
        - A single report exists of a dog that had a fatal anaphylactic reaction to dexamethasone
      - Relatively inexpensive
      - Lower specificity (44-73%)
      - Requires 8 hours to complete
      - Protocol:
        - Dexamethasone (0.01 to 0.015 mg/kg IV)
        - Blood drawn before and at 4 and 8 hours after injection



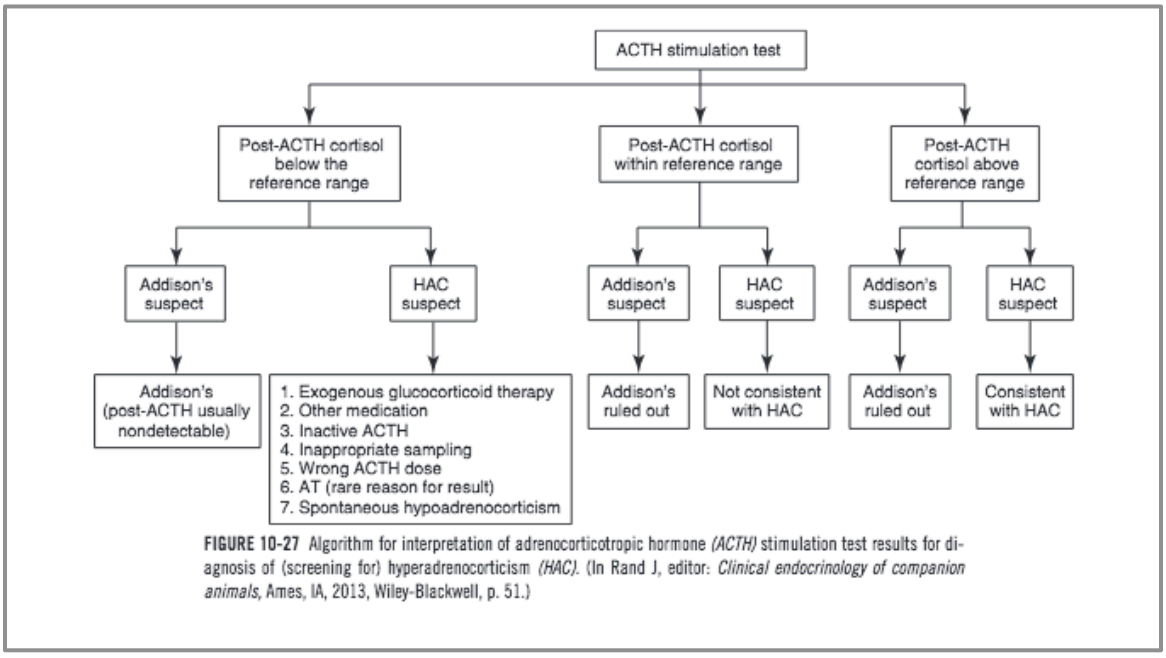
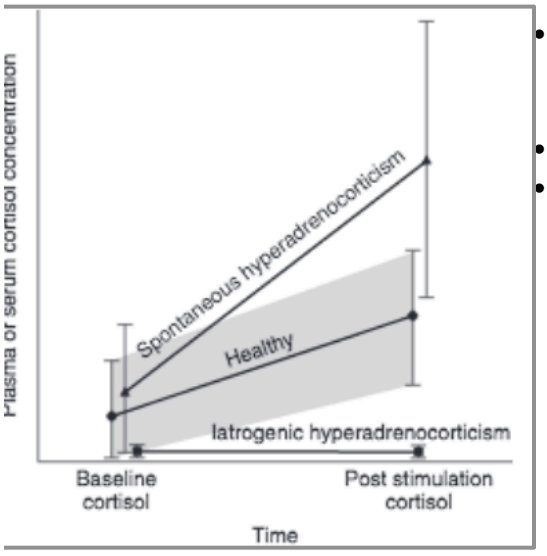
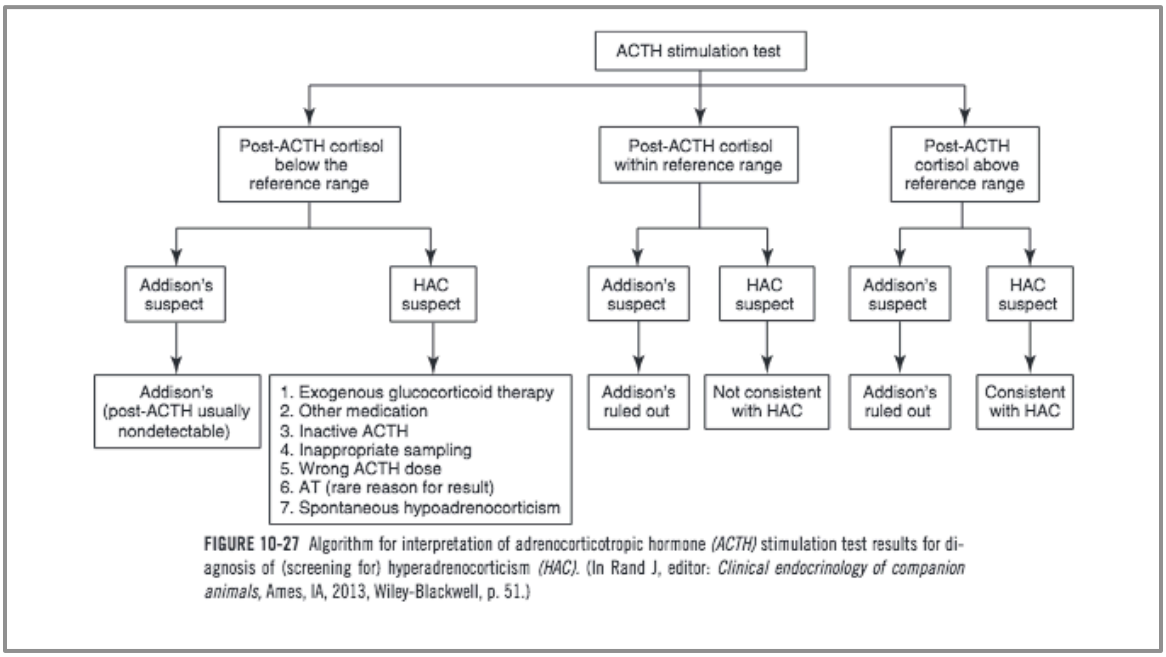


FIGURE 10-27 Algorithm for interpretation of adrenocorticotropic hormone *(ACTH)* stimulation test results for diagnosis of (screening for) hyperadrenocorticism *(HAC)*. (In Rand J, editor: *Clinical endocrinology of companion animals*, Ames, IA, 2013, Wiley-Blackwell, p. 51.)

- ACTH stimulation test
  - Assesses adrenocortical reserve
  - Gold standard for diagnosis of iatrogenic HAC
  - (The only test recommended for monitoring response to therapy for HAC)
  - Safe, simple, and not time-consuming
  - Lower sensitivity (57-95%) than the LDDST
    - Especially for dogs with an AT
    - Can never differentiate between PDH and AT
  - Specificity: 59%-93%
  - Protocol:
    - 5 µg/kg cosyntropin or tetracosactrin IV, maximum of 250 µg per dog
    - Samples for cortisol measurement drawn before and 1 hour after administration





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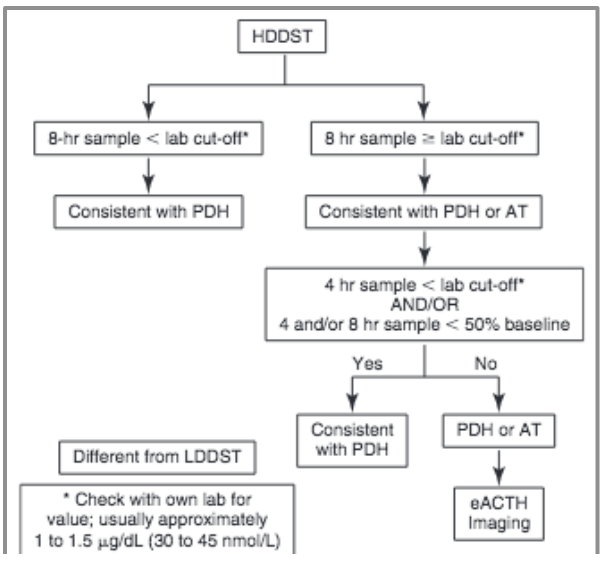
- Urine Creatinine to Cortisol measurement (UC:CR)
  - Safe and easy
  - High sensitivity (75-100%)
  - Relatively inexpensive
  - If combined with dexamethasone suppression testing, differentiation information can be provided
  - Low specificity (20-25%), depending on the laboratory performing the testing
  - Differentiating tests: if a diagnosis of HAC is confirmed, biochemical differentiating tests or imaging to distinguish between PDH and AT

- Differentiating tests
  - Should only be done after a screening test has confirmed the presence of HAC
  - It is important to differentiate PDH and AT because treatment and prognosis differ
  - HDDST



        - Measurement of eACTH concentration
            - PDH: eACTH concentration is normal to elevated due to secretion from the pituitary tumor
            - AT: eACTH concentration is low due to autonomous tumoral secretion of cortisol
        - In some cases, the LDDST may provide the differentiation as well as the diagnosis
            - (Review: If the 8-hour post-dexamethasone concentration is greater than the laboratory cutoff results are consistent with HAC)
            - Additionally, if the 4-hour post-dexamethasone concentration is below the laboratory cutoff –or- if one or both post-dexamethasone concentrations is less than 50% of baseline → PDH is present
                - Some suppression is occurring
            - If both post-dexamethasone concentrations are above the laboratory cutoff –and- neither is less than 50% of baseline, either PDH or AT is possible
        - Imaging
            - As with the screening tests, no test is 100% accurate
            - Radiographs
                - 53% dogs with ATs diagnosed by detection of calcification of visualization of a mass
                - Mineralization of the adrenals rarely occurs with PDH
            - AUS
                - Ultrasonography has more application as a differentiating tool (vs rad) because both adrenal glands are routinely visualized
                - Small or non-calcified ATs can be detected
                - Bilateral adrenal enlargement can be documented in dogs with PDH
                - Large variability in appearance of the adrenals
                - Potential to miss tumors, not visualize entire adrenal glands, or mistake bilateral ATs for PDH
            - CT with contrast and MRI: may provide differentiating information
- Treatment
    - Treatment typically greatly improves quality of life for both the owner and dog
    - However, not all dogs with positive tests for HAC need to be treated
        - The decision to treat should be made on a case-by-case basis
    - Important to test for damaging effects of HAC Iproteinuria, hypertension) in patients not receiving treatment because if

either/both are present and due to HAC, treatment may be more imperative

- PDH
  - Trilostane
    - Synthetic steroid analogue, suppresses production of progesterone and its end-products, including cortisol and aldosterone
    - High efficacy
    - Objective monitoring by use of an ACTH stim
    - Relatively high rate of adverse effects (though potentially less than that of mitotane)
    - Adverse effects for the most part are relatively mild, including lethargy, weakness, decreased appetite, vomiting, and diarrhea.
  - Mitotane
    - Adrenocorticolytic, causing selective necrosis of the zona fasciculata and zona reticularis
    - High efficacy, especially for PDH
    - Objective monitoring by use of an ACTH stimulation test
    - High cost
    - Therapy of HAC with mitotane occurs in two phases: induction (loading) and maintenance
    - Adverse effects are generally gastrointestinal or neurological
      - Include weakness, vomiting, anorexia, diarrhea, ataxia
    - If a dog does not respond to the induction protocol after 21 days, mitotane resistance should be considered
    - Maintenance therapy will be necessary for the remainder of the dog's life, although the dose and frequency varies between patients and can vary in an individual patient over time
  - Hypophysectomy
- AT
  - Adrenalectomy
  - Treatment of choice for a cortisol-secreting AT
  - Technically difficult, serious intra- and postoperative complications are common, and the reported mortality is variable but can exceed 25%
  - Should only be undertaken by experienced surgeons in a hospital with a well-equipped ICU and 24-hour observation and care
  - Preoperative variables significantly associated with shorter survival times included size of the AT, presence and extent of

vena caval invasion, concurrent azotemia, and presence of acute adrenal hemorrhage
- Intraoperative variables associated with shorter survival times included hemorrhage requiring a blood transfusion and concurrent nephrectomy
- Postoperative variables associated with shorter survival times included development of pancreatitis, PTE, acute renal failure, disseminated intravascular coagulation, hypotension, and hypoxemia
- ATs are challenging to manage following adrenalectomy, due to concurrent immunosuppression, impaired wound healing, systemic hypertension, and a hypercoagulative state; frequent tumoral infiltration into surrounding blood vessels and soft tissues; potential postoperative development of pancreatitis (especially with a right-sided adrenal mass); and existence of hypoadrenocorticism following removal of the mass
- Thromboembolism typically develops during or within 24 hours of surgery and carries a high mortality rate
- Trilostane/mitotane

Questions

1. Your patient is a 8y FS Labrador retriever who is being examined on ER for acute on chronic GI upset. Other than mild dehydration and BCS 6/9, your physical exam is unremarkable. Abdominal ultrasound reveals bilaterally plump adrenal glands, and no other abnormalities. The senior student accompanying you on the case asks about testing for HAC. Your response is:
2. What intraoperative AT adrenalectomy complications are associated with shorter survival times?
3. Identify the screening tests for HAC.

Answers

1. Your patient is a 8y FS Labrador retriever who is being examined on ER for acute on chronic GI upset. Other than mild dehydration and BCS 6/9, your physical exam is unremarkable. Abdominal ultrasound reveals bilaterally plump adrenal glands, and no other abnormalities. The senior student accompanying you on the case asks about testing for HAC. Your response is:
    a. Adrenal size is subjective, and there is much overlap between adrenal size of normal dogs and those with HAC
    b. In a patient not clinical for HAC, treatment is not warranted regardless of HAC diagnostics
    c. The false positive rate is likely to be high if testing for a patient without clinical suspicion of HAC
2. What intraoperative AT adrenalectomy complications are associated with shorter survival times?
    a. Bleeding requiring a transfusion
    b. Concurrent nephrectomy
3. Identify the screening tests for HAC.
    a. UC:Cr
    b. ACTH stim
    c. LDDST