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Endocrine Emergencies Online 'Mini Series'

Session 1: Adrenal Gland Disease In Dogs

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Endocrine Emergencies

Introduction

General indicators of adrenal endocrine emergencies
Crisis event may be acute or peracute in onset BUT
Usually prior history of waxing and waning vague illness

- Exercise intolerance
- Inappetence or polyphagia
- PU/PD
- Mild weight loss
- Intermittent GIT signs

Signs may indicate multisystemic disease
Weakness or collapse is a common presenting feature

Although an uncommon emergency, adrenal gland disease can result in sudden deterioration of the present. Despite their acute presentation, adrenal gland disease is insidious in onset and patients will have a history of other signs that precede the acute presentation.
The key to spotting adrenal emergencies is to have a good understanding of the historical clues to adrenal gland disease, remember the routine biochemical changes that are likely to occur and have adrenal gland disease somewhere on the differential list for emergencies presenting with collapse, acute onset blindness or neurologic signs.

Outline

Review of adrenal anatomy and function
Evaluating the adrenal glands in dogs
Adrenal gland emergencies in dogs

- Hyperadrenocorticism – presenting signs and biochemical changes
    - Bleeding
    - SARDS
    - Macroadenoma
    - Nelson's syndrome
    - Other acute presentations
- Hypoadrenocorticism - presenting signs and biochemical changes
- Addisonian crisis
    - Typical
        - IVFT
        - Managing hyperkalaemia
    - Atypical
    - Relative cortisol insufficiency
- Phaeochromocytoma
- Conn's syndrome

Review of anatomy and physiology

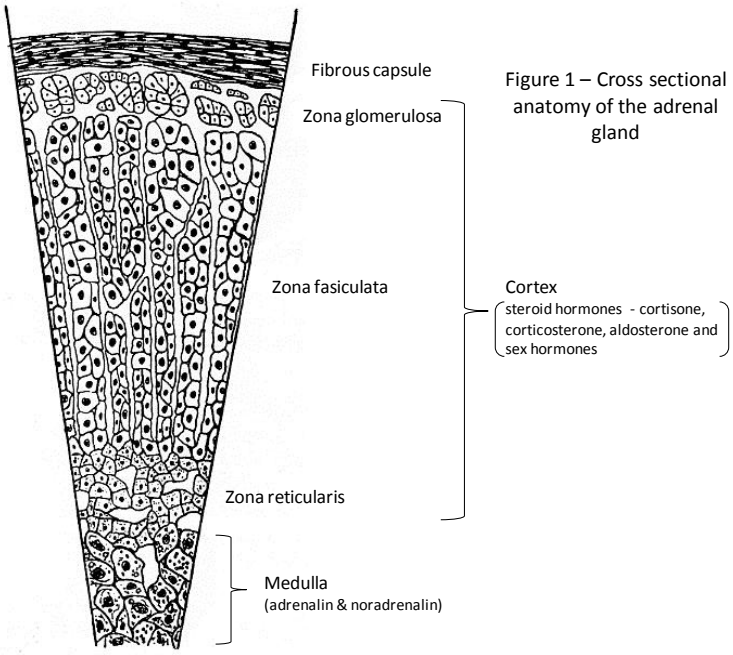


Figure 1 – Cross sectional anatomy of the adrenal gland

The adrenal gland is divided into a cortex and medulla (Fig. 1). The medulla produces catecholamines whilst the cortex produces steroid hormones. The cortex is divided into 3 regions with all 3 regions secreting cortisone but aldosterone secretion is limited to the zona glomerulosa and cortisol and sex hormones to the 2 inner zones.
Steroid hormones are derived from cholesterol via a series of metabolic pathways (Fig. 2) culminating in 5 secreted hormones – corticosterone, desoxycorticosterone (small biological effect), cortisol, aldosterone and dehydroepiandosterone (sex hormone precursor).

Cortisol is the most active of the glucocorticoids produced (Table 1). Synthesis of glucocorticoids is controlled by the feedback mechanism of the hypothalamic-pituitary-adrenal (HPA) axis (Fig. 2).

Table 1 – Relative activities of adrenally-secreted and synthetic corticosteroids

	Glucocorticoid activity	Mineralocorticoid activity
Cortisol	1	1
Corticosterone	0.3	15
Aldosterone	0.3	3000
Deoxycorticosterone	0.2	100
Cortisone	0.7	1
Prednisolone	4	0.8
Fludrocortisone	10	125
Dexamethasone	25	~0
Desoxycorticosterone pivalate	~0	High
Betamethasone	35	~0
Methylprednisolone	5	~0

Corticotrophin releasing hormone (CRH) is secreted by the hypothalamus resulting in ACTH release from the pars distalis. ACTH is also produced by the pas intermedia but this secretion is under dopaminergic control (Fig. 3). Aldosterone synthesis and secretion is less stimulated by adrenocorticotrophic hormone (ACTH) and is primarily controlled by the renin-angiotensin-aldosterone system (RAAS) (Fig. 4) and plasma potassium levels.

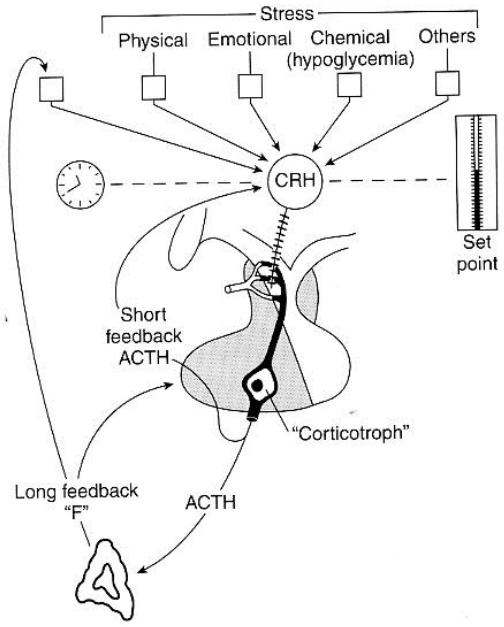
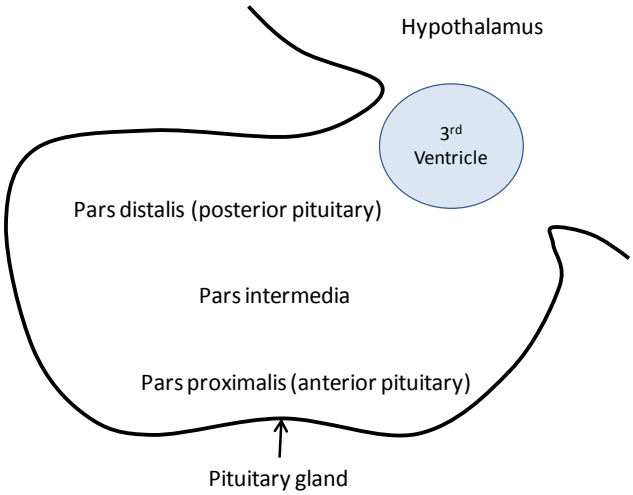


Figure 2 – HPA axis in the control of glucocorticoid production

Figure 3 – Pituitary gland anatomy



Disease can affect the adrenal gland either directly by hypertrophy/neoplasia of part or all of the gland or atrophy. The adrenal gland can also be affected by disease of the pituitary resulting in pituitary dependent hyperadrenocorticism (PDHAC).

Investigating adrenal function

Sample handling and test interpretation

- Measurement of cortisol and aldosterone should be performed by radioimmunoassay
- Cortisol and aldosterone are relatively robust small molecules and special handling is not specifically required – either serum or plasma can be used, preferably separated.
- Prednisolone and other exogenous steroids except dexamethasone will cross react with the cortisol assay.
- Cortisol levels are artificially lower in lipaemic samples but the effect is unlikely to cause a significant change in interpretation. They are unaffected by haemolysis or jaundice.
- ACTH is unstable and levels will fall rapidly unless the sample is properly handles – requires blood sample to be taken into chilled EDTA tubes, the EDTA plasma immediately separated and frozen in a plastic vial and transported to the laboratory to arrive frozen.

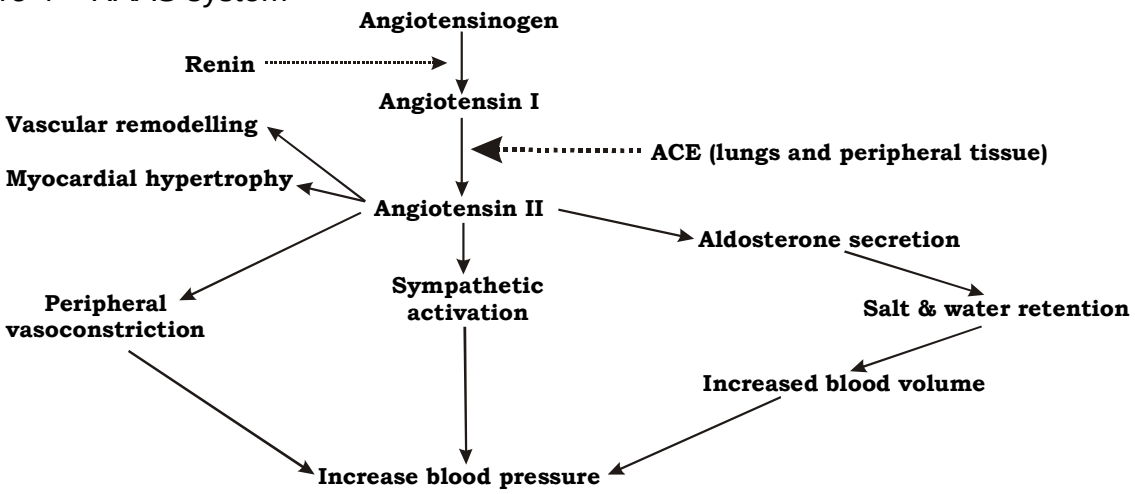
Adrenal function tests

Table 2 – sensitivity and specificity of adrenal function tests for HAC.

Test	Sensitivity	Specificity
LDDS	85-100	44-73
ACTH stimulation	80-95	82-91
UCCR	50-100	22-100

NB – none of the diagnostic tests below are 100% sensitive or specific for HAC. False positive and false negative occur with all of these tests. Performing multiple tests is not always helpful in establishing a clear diagnosis.

Figure 4 – RAAS system



ACTH stimulation test

Mainstay of adrenal function screening in dogs as it is a quick and easy test.

1. Baseline blood sample
2. Synthetic ACTH (Synacthen) injected IV or IM - use 1 vial (0.25mg) dogs >5kg and ½ vial in dogs <5kg
3. Second sample collected 45-60 minutes later.

PHHAC dogs usually have normal baseline cortisol but stimulate well above the reference range (>600nmol/L) but false positives and negatives occur

ADHAC dogs often have elevated basal levels (above 250nmol/L) with little or no stimulation.

Dogs with hypoadrenocorticism usually have undetectable cortisol levels pre- and post-ACTH

If in-house SNAP ELISA testing (Idexx) is used it is important to set the machine to the correct dynamic range (high for HAC) and low (for hypoadrenocorticism).

Low dose dexamethasone suppression test (LDDST)

Mainstay of adrenal function screening; takes longer to perform and requires 3 samples so is inappropriate for the majority of dogs presenting with a potential adrenal emergency.

Urine cortisol:creatinine ratio (UCCR)

Generally considered as a good negative indicator of HAC in dogs as 97-99% of HAC cases have a positive result i.e. if ratio < $30x10^{-6}$ then the dog is unlikely to have HAC.

Less work has been performed in cats but a level below $36x10^{-6}$ makes HAC unlikely although there is an equivocal range from 13-$36x10^{-6}$

<u>*Aldosterone*</u>

- Although not primarily controlled by ACTH, ACTH stimulation test will result in increased levels of aldosterone. Protocol is the same as for ACTH stimulation tests and helps to better define dogs with hypoadrenocorticism particularly in terms of their need for mineralocorticoid support.
- Aldosterone response to ACTH can also be used to confirm hypoadrenocorticism in dogs already receiving glucocorticoid therapy
- Baseline aldosterone levels should be measured in cats suspected of having hyperaldosteronism (Conn's syndrome).

<u>Imaging the adrenal gland</u>

Radiography

Rarely of value in the diagnosis of adrenal gland disease but can be supportive.

HAC - Most adrenal masses are not sufficiently large to be visible on radiographs but radiography can be useful to detect changes supportive of the diagnosis such as hepatomegaly and dystrophic calcification. 50% of adrenal masses are calcified. Large adrenal masses may displace the abdominal organs ventrally and caudally.

Hypoadrenocorticism – may see microcardia/small pulmonary vessels and/or microhepatica associated with hypovolaemia. Small percentage of cases have megaoesophagus

Ultrasound

Along with routine screening tests and adrenal function tests, ultrasound is widely used to try and detect adrenal gland change and differentiate PDHAC from ADHAC.

- Technically demanding especially in obese, uncooperative and panting patients
- Adrenal gland abnormalities are common findings in dogs without adrenal gland disease

- Measurement of adrenal gland width has proved most valuable but still has a relatively low sensitivity and specificity (70-80%) for HAC if the width of the left adrenal gland is > 7.4mm and right >8.1mm
- Small adrenal glands are seen in hypoadrenocorticism but there is significant overlap with normal dogs.

- Most valuable in differentiating PDHAC from ADHAC
  - Very experienced ultrasonographers can also give valuable information about the extent and invasion of adrenal masses
  - FNA of adrenal masses – NB care if phaeochromocytoma possible as this may cause sudden catecholamine release

TIPS

Non-specific change – hepatomegaly with rounded edge and increased echogenicity (relative to spleen)

- Left adrenal

  Longitudinal plane
  Cranial pole of the left kidney in the middle of screen
  Moderate amount of pressure on the transducer, move medially to image the aorta.
  Located between renal & cranial mesenteric arteries.
  Peanut-shaped hypoechoic structure

- Right adrenal

  More difficult to detect due to overlying gas shadows of GIT
  Longitudinal view of the right kidney (transducer should be subcostal)
  Then angle the transducer to the dorsal midline and move the transducer medially.
  Identify a large tubular vessel - aorta, caudal vena cava, or portal vein
  Identify CVC – compressibility or flow pattern on Doppler
  Right adrenal dorsal to CVC and just caudal to liver border
  Heart or slipper-shaped or arrowhead-like

Advanced imaging
Used to

1. Assess adrenal tumours as it is more sensitive in looking for invasion of surrounding structures in particular renal blood vessels and vena cava. Despite this increased sensitive it is not possible to give a definitive decision on whether complete surgical removal of an adrenal mass will be possible
2. Look for the presence of pituitary masses and differentiate macro- from microadenomas

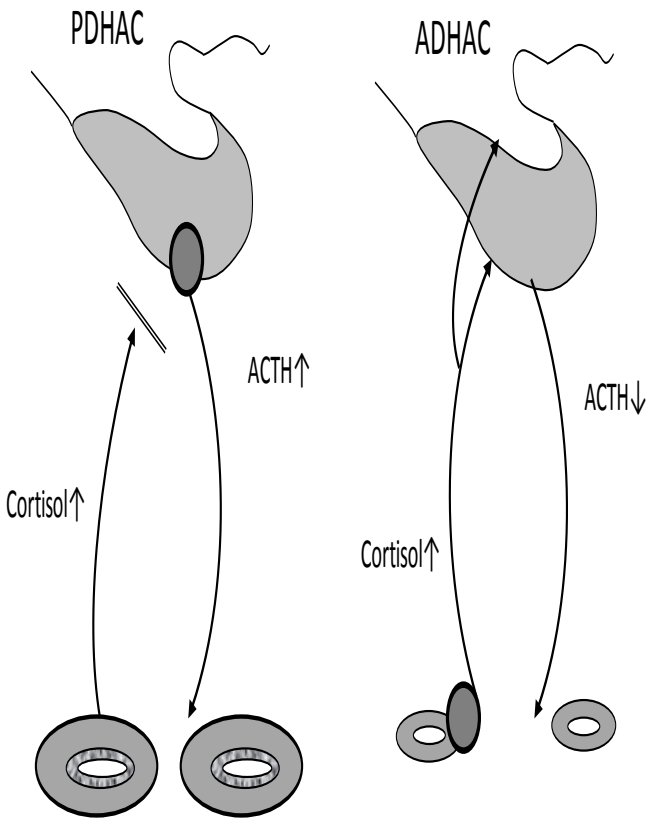
Hyperadrenocorticism

HAC is the 3rd most common endocrinopathy in dogs. The majority of cases, especially in small dogs, are pituitary dependent. 15-20% have adrenal neoplasia that is usually solitary and unilateral with a large breed and female bias (Figure 5)

Signalment

Middle → older aged dogs; rare in dogs <6 y.o.
Poodles, Dachshunds, terriers and Boxer dogs appear predisposed

Figure 5 – Types of HAC and their effect on ACTH levels and adrenal gland size



HAC is unlikely in dogs presenting with a history of …..

- Poor appetite/anorexia (except if there is a macroadenoma and other neurologic signs)
- Vomiting, diarrhoea
- Sneezing, coughing
- Icterus
- Pruritus
- Pain
- Seizures
- Bleeding
- Renal failure
- Pancreatitis
- Liver failure
- Immune-mediated disease
- Urine SG > 1.030
-

EXCEPTIONS DO OCCUR

Clinical presentation of HAC (Table 3)

Historical sign	Physical findings
PU/PD	
Abdominal enlargement	Abdominal enlargement – hepatomegaly and fat redistribution, catabolism of abdominal muscles
Alopecia	Alopecia
Anoestrous	
PP	
Lethargy & decreased exercise tolerance	Muscle weakness
Obesity	
Acne (skin infection, comedones)	Acne (skin infection, comedones)
Heat intolerance & panting	Panting – Pickwickian syndrome
Cutaneous hyperpigmentation	Cutaneous hyperpigmentation
Testicular atrophy	Testicular atrophy
Calcinosis cutis	Calcinosis cutis
Exophthalmus	Exophthalmus
	Myotonic muscle contraction

Prevalence	>75%	50-75%	25-50%	<25%

Indicators of HAC on routine haematology, biochemistry and urinalysis (Table 4)

CBC	Leucocytosis with mature neutrophilia, eosinopenia and lymphopenia
Glucose	Mild hyperglycaemia*
Liver enzymes	Mild increase in ALT, disproportionate increase in ALKP can be into the 1000s IU/L 90-95% HAC dogs have increased ALKP
BUN	Normal to decreased
Lipids	Hypercholesterolemia / triglyceridemia common Cholesterol – 10% < 6.5mmol/L; 15% 6.5-7.8mmol/L and 75% > 7.8mmol/L
Bile acids	30% dogs elevated results not associated with primary hepatic disease
Electrolytes	Hypophosphatemia in 30% of cases. Small percentage have $Na^+\uparrow$ and $K^+\downarrow$
Urinalysis	USG usually < 1.015 and often <1.008 Glycosuria in 10% cases Proteinuria common and can be moderately increased UTI in 40-50% of cases

* If severe hyperglycaemia consider diabetes mellitus (DM) alone or diabetic and HAC (rare)
** Significant percentage (75%) of HAC cats are also diabetic

Misdiagnosis of HAC
Metabolic stress can lead to a marked increase in cortisol response to ACTH potentially resulting in mis-diagnosis. The case below was being tested for possible hypoadrenocorticism. As above GIT signs would be an unusual presentation for HAC

- 'Ruby' 2.10 year old female, neutered Miniature Schnauzer

Presented with haemorrhagic diarrhoea
Mucous membranes were pink and tacky; HR 130bpm; RR 24/minute T37.4^{o}C
Abdomen tense but no focus of pain found
Appeared nauseous - belching and lip-smacking
ACTH stimulation test – pre - 118nmol/L; post - >1380nmol/L → THIS IS NOT HAC!

Acute presentations of HAC

The majority of HAC cases are unlikely to result in acute presentation as signs are usually insidious and slow moving. Most HAC cases will present due to PU/PD and/or dermatologic changes. Acute presentations are usually associated with secondary metabolic or mass effects

- Diabetes mellitus – approximately 5% of HAC cases

Potential for DKA

- Hypertension – >50% of dogs with uncontrolled HAC
- CHF especially if predisposing factors
- Pulmonary thromboembolism
- Sudden acquired retinal degeneration – link unclear
- Calcium oxalate calculi and acute LUT obstruction
- Non-traumatic ligamentous rupture
- Pyelonephritis and UTI
- Neurologic signs associated with macroadenoma
- Facial nerve paralysis

Hypertensive disease

BP should be measured in all dogs presenting as emergencies. In HAC hypertension can lead to acute onset blindness (haemorrhage, retinal detachment, SARD) or CNS signs

CNS haemorrhage (CVA)

- Clinically characterized by persistent, acute onset, focal intracranial neurologic deficits

Signs depend on site and extent of bleed

- Haemorrhagic stroke results from blood vessel wall rupture
- With supportive care, partial to complete recovery is
- Identification and treatment of the associated hypertension and HAC is of paramount importance, as the presence of coexistent disease is a negative prognostic indicator and important risk factor for recurrence.
- Emergency treatment should be directed towards the neurologic signs (controlling ICP) and preventing further expansion of the lesion

Ocular disease

Hypertensive haemorrhage or retinal detachment

Sudden Acquired Retinal Degeneration (SARD)

- Female dogs 6 to 11 years old.
- Rapid vision loss hours → weeks.
- May be an accompanying history of PU/PD
- Abnormalities in serum chemistries and urinalysis suggestive of hyperadrenocorticism
- Clinical examination consistent with peripheral blindness

Normal corneal and palpebral and oculocephalic reflexes

Absent/diminished PLR, following, menace, obstacle negotiation

Retinal examination in acute cases appears normal

Neurologic disease

Prognosis for most acute neurologic presentations of HAC is poor.

CVA

Nelson's syndrome

- Rapid expansion of an adenoma following bilateral adrenalectomy

Seen in dogs shortly after starting trilostane or mitotane treatment

Failure of cortisol feedback inhibition

- Presents as a space occupying mass with muscle weakness

Macroadenoma
Patients tend to be dull listlessness and inappetent progressing to anorexia, restlessness, reduced response to stimuli to stupor, ataxia and aimless pacing.

Hypoadrenocorticism

Typically cases present with waxing and waning clinical signs; Addisonian crises do occur and these are the most common adrenal-associated endocrine emergencies that present in 1st opinion practice.

Table 5 – Typical clinical presentation of hypoadrenocorticism

Historical concerns	Physical examination	
Poor appetite/anorexia		Dehydration
Lethargy/depression	Lethargy/depression	Bradycardia
Thin	Thin	Weak femoral pulse
Vomiting/regurgitation		Melaena/haematochezia
Weakness	Weakness	Hypothermia
Weight loss		
Diarrhoea		
Waxing and waning illness		
PU/PD		
Shaking/shivering		
Collapse	Shock/collapse	
Abdominal pain	Abdominal pain	

Table 6 – typical changes in routine blood tests in hypoadrenocorticism

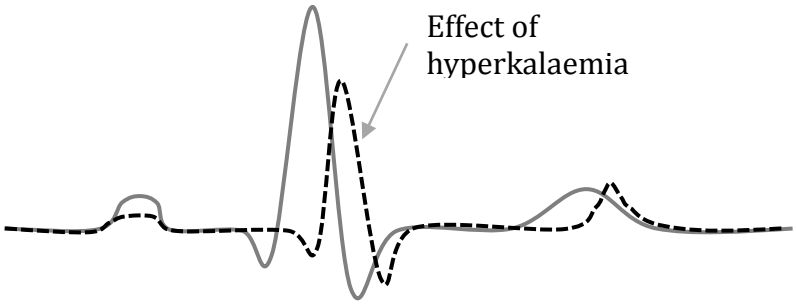
Haematology			Biochemistry	
Non-regenerative anaemia			Hyperkalaemia	
Eosinophilia			Hyponatraemia	
Neutrophilia			Hypochloraemia	
Lymphocytosis			Hypercalcaemia	
Lack of stress leucogram			Azotaemia	
			Hyperphosphatemia	
			Hypoglycaemia	
			Raised liver parameters	
			Metabolic acidosis	
			Hypoalbuminemia	
			Hypocholesterolemia	
Prevalence	>75%	50-75%	25-50%	<25%

Although frequently quoted, a low Na:K ratio below 27 is poorly specific for hypoadrenocorticism; hyponatraemia more useful indicator of possible hypoadrenocorticism.
Major differential diagnosis if electrolytes not measured is advanced renal failure; NB hyperkalaemia can also be present in acute kidney injury. The prognosis for hypoadrenocorticism is vastly better than for severe renal disease.
NB1 - hyperkalaemia can also be present in acute kidney injury.
NB2 – hypoadrenocorticism is one of the few disease states where using USG to distinguish between renal and pre-renal azotaemia will give a false result as USG in hypoadrenocorticism despite the azotaemia being pre-renal in origin.

ECG changes in hypoadrenocorticism

ECG changes will occur with hyperkalaemia but they are less predictable than are generally quoted as these changes were documented in normal dogs given IV potassium infusions. However, if electrolyte measurement are not available in a crisis situation then an estimate of severity of the hyperkalaemia can be gained from an ECG (Figure 6 below)

Figure 6 – Classic effects of hyperkalaemia on ECG morphology



Therapy

Fluid therapy in an Addisonian crisis

Potassium level (mmol/L)	ECG changes
5.5	Slowing of rate Peaked T wave Shortened Q-T interval
6.5-7.5	Widened QRS complex Small R waves
7.0-8.5	Small but wide P waves Increased P-Q interval
8.5-10.0	Loss of P wave S-T segment abnormalities Small R waves
>10.0	Death

Increasing severity of hyperkalaemia

In the majority of cases, dogs in crisis die from hypovolaemia rather than hyperkalaemia hence fluid therapy is essential. Appropriate fluid therapy will also serve to sort resolve the hyperkalaemia.

- Ideally 0.9% sodium chloride as

Has the most sodium

Does not contain potassium

BUT is acidifying

Marked acidosis may require bicarbonate – Immol/kg given over 20 minutes

- Hartmann's is OK if no saline available

Alkalinising an contains some calcium(2mmol/L)

BUT less sodium (0.6%) and some potassium (5mmol/L)

- 0.18% sodium and 4% glucose is absolutely contraindicated

Rate should be determined by physical examination and the status of the patient.

- Estimate from electrolyte disturbance
- Blood pressure
- Chest radiographs

Most cases 3-5 times maintenance is appropriate. However if there volume depletion is severe, shock rates can be used– 90ml/kg/hr BUT this can have a profound effect on electrolytes and acid base balance.

Dealing with hyperkalaemia

Hyperkalaemia can result from both whole body excess as well as cellular shift; most dogs in Addisonian crisis are acidotic and this leads to a movement of potassium ions out of the cell to try and mediate the acidosis by moving hydrogen ions into the cell. Correction of the acidosis with fluids can lead to a rapid movement of potassium back into the cell and a sudden fall in serum potassium. In the vast majority of cases let the kidneys sort the potassium problem out. Potassium

levels can change quickly in cases where there is a significant cellular shift so regular monitoring of clinical and biochemical response is important.
Severity of clinical signs of hyperkalaemia depends, in part, on the absolute level but also rate of increase

- Potassium up to 7-7.5mmol/L without evidence of significant bradycardia or arrhythmia – fluid alone
- Potassium 7.5-9.0mmol/L depends on clinical signs

Fluids
Address acid-base abnormalities
Calcium gluconate may reduce the risk of fatal arrhythmia
50-100mg of calcium gluconate over 10-20 minutes
Rarely necessary

- Potassium > 9.0mmol/L

Consider insulin and glucose
0.5g/kg glucose + 0.06-0.125iU/kg neutral insulin over 30-60min
NB Life threatening hypoglycaemia can occur so regular glucose monitoring essential. Duration of action of insulin exceeds persistence of glucose

- Potassium > 10mmol/L is usually fatal

<u>Corticosteroid treatment</u>

Patients stabilisation should precede administration of corticosteroids as IV corticosteroids can cause an initial fall in BP that could be potentially very serious in an already hypovolaemic, hypotensive patient. Further, although dexamethasone does not cross react with cortisol measurement it will make interpretation of ACTH stimulation test problematic.

- Baseline sample for cortisol then give Synacthen and resample at 45 minutes
- IV hydrocortisone TOC 2-4mg/kg q4-6 hr initially

Substantial mineralo and glucocorticoid activity
Otherwise
Methylprednisolone succinate 1-2mg/kg IV q2-6hr
Dexamethasone 0.2-0.5mg/kg initial dose then 0.1mg/kg q8hr
Less mineralocorticoid activity so start fludrocortisone when patient is able to accept oral medication

Atypical Hypoadrenocorticism

- Both purely cortisol deficient and aldosterone deficient cases
- Aldosterone deficiency will present with typical electrolyte disturbances but will have normal ACTH stimulation cortisol results
- Pre and post ACTH aldosterone should be measured
- Cortisol deficient cases present with normal electrolytes
- Secondary hypoadrenocorticism is very rare and implies a failure of pituitary secretion of ACTH.

Cortisol-only deficient hypoadrenocorticism

These dogs typically present with weakness, inappetence and GIT signs particularly diarrhoea with some haemorrhage. These dogs are often missed as being Addisonian.

- Study of 18 dogs

Most were young (< 7 years)
Larger breeds (> 20 kg)
Clinical signs were nonspecific
Lethargy, weight loss
Gastrointestinal disturbances including regurgitation
Laboratory changes
Hypocholesterolemia, hypoalbuminemia, hypoglycaemia, and a mild, non-regenerative anaemia were common
Ten of the 18 dogs responded well to glucocorticoid supplementation alone,
2 dogs went on to develop electrolyte abnormalities

Relative adrenal insufficiency

Poor adrenal function in the face of disease-associated demand – patients present with much more severe signs than would be expected for their level of disease.

- Cortisol requirement of an individual is dependent on their physiologic state

Can increase up to 10x in severe disease stress
'Physiologic' doses of prednisolone 0.1-0.2mg/kg

- Limited studies in veterinary patients

Evaluation of the response to ACTH stimulation in 14 dogs with sepsis
Decreased response to ACTH stimulation in 6 of the dogs
Survival of poor-responders was 40% vs.100% responders.

- Diagnosis is controversial in man

NOT AN EXCUSE TO GIVE EVERY SICK PATIENT GLUCOCORTICOIDS!

Phaeochromocytoma and hyperaldosteronism

Phaeochromocytoma

Clinical cases of phaeochromocytoma appear to be rare. Diagnosis is difficult as adrenal gland incidentalomas are common making the presence of an adrenal mass in a hypertensive patient difficult to evaluate.

- Can present as emergencies due to acute release of catecholamines

Hypertension, tachyarrhythmias, weakness, and collapse
Management with phenoxybenzamine (α) and β–adrenergic blockers
Surgery optimal long term treatment but vascular invasion can occur

- Diagnosis urinary and plasma metanephrine

Hyperaldosteronism

Hyperaldosteronism (Conn's syndrome) is a very rare disease in dogs compared to cats.

- Over secretion of aldosterone leading to profound hypokalaemia
- Primary signs are hypertension and muscle weakness and signs of hyperprogesteronism

Neck ventroflexion less likely than cats

- Can require high levels of potassium supplementation as potassium wastage so high
- Diagnosis elevated aldosterone in the face of low/normal renin

i.e. inappropriate aldosterone secretion

High aldosterone:renin ratio

Serum for aldosterone; frozen EDTA plasma for renin

- Long term spironolactone, potassium and BP control or surgery

Conclusions

Although uncommon adrenal gland emergencies do occur – recognition that adrenal gland disease is present, particularly with adrenal insufficiency states will lead to rapid patient improvement and a good long term prognosis.