8. HRVATSKI KONGRES VETERINARA MALE PRAKSE S MEĐUNARODNIM SUDJELOVANJEM

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Zajedno stvaramo
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Sažeci predavanja

ORGANIZATOR: ODJEL VETERINARA MALE PRAKSE HRVATSKE (OVMPH)

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GI drugs – useful or useless?

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Professor of General Practice

1

Antiemetic therapy

- Vomiting frequently occurs secondary to primary or secondary gastrointestinal disease
- Antiemetic therapy should only be considered as symptomatic therapy
- Determine and resolve the underlying disease process

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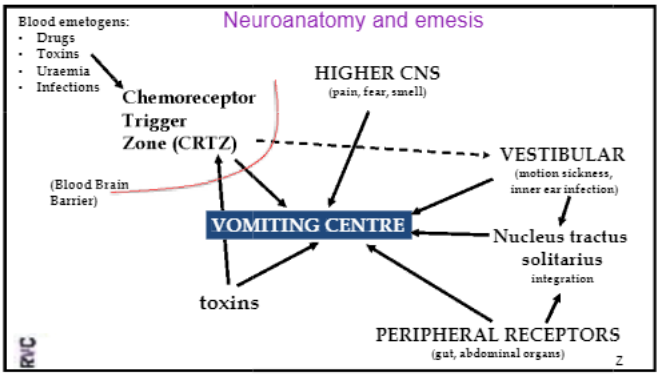
Neuroanatomy and emesis



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Causes of nausea and vomiting: some central / some peripheral…

- GI disturbances
- Chemotherapy induced nausea and vomiting (CINV):
  - cisplatin, carboplatin, doxorubicin, cyclophosphamide
  - acute, delayed or anticipatory
- Drugs, toxins
- Motion sickness and vestibular disease
- Fear and emotions

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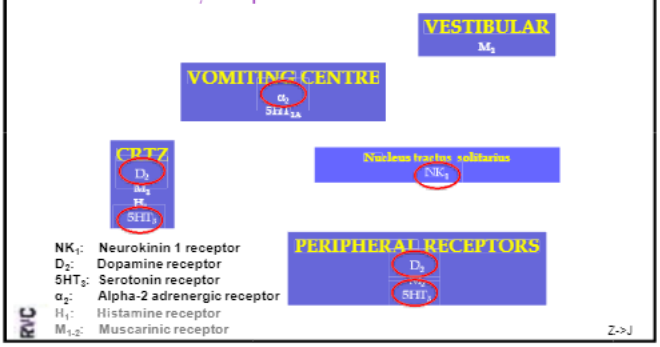
4

Neurotransmitters, receptors and emesis



NK_1: Neurokinin 1 receptor
D_2: Dopamine receptor
5HT$_3$: Serotonin receptor
α_2: Alpha-2 adrenergic receptor
H_1: Histamine receptor
M_{1-2}: Muscarinic receptor

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Neurotransmitters and emesis – species differences

- Cats and dogs may differ in importance of receptors in emesis
- D_2 receptors in CRTZ more important in dog
  - apomorphine, a D_2-dopamine receptor agonist is a potent emetic agent in the dog but not the cat

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Neurotransmitters and emesis – species differences

- α2-adrenergic receptors may be more important in cat emesis
  - Xylazine more potent emetic agent in the cat than the dog
  - Prochlorperazine (α_2 blocker as well as dopamine and histamine) might be more useful than metoclopramide (dopamine antagonist) in cats
- Histamine is a potent emetic in the dog but not the cat

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Neurotransmitters and emesis – species differences

- Cytotoxic drug-induced emesis
  - mediated by 5-HT_3 receptors in the CRTZ of the cat
  - visceral and vagal afferent 5-HT_3 receptors are activated in the dog

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Common antiemetics

- NK_1 antagonists
- Metoclopramide
- $5HT_3$ antagonists
- Phenothiazines

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Maropitant (Cerenia®)

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Neurotransmitters and emesis

VESTIBULAR
M_1
H_1

VOMITING CENTRE
α_2
$5HT_{1A}$

CRTZ
D_2
M_1
H_1
$5HT_3$

Nucleus tractus solitarius
NK_1

maropitant

PERIPHERAL RECEPTORS
D_2
M_1
$5HT_3$
Motilin

NK_1: Neurokinin 1 receptor
H_1: Histamine receptor
$5HT_3$: Serotonin receptor
D_2: Dopamine receptor
M_{1-3}: Muscarinic receptor

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Maropitant (Cerenia®)

- Pharmacology
  - selective antagonist of Substance P at the NK_1 receptor
  - inhibits the final common pathway involved in activating the vomiting reflex in the CNS
  - effective against emesis induced by both peripheral and central stimuli
  - oral dose (2-8mg/kg) is much higher than injectable dose (1mg/kg) : significant first pass metabolism
  - Long half-life (6h)

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Maropitant (Cerenia®)

- Effective antiemetic for dogs
  - Acute gastroenteritis
  - Cytotoxic-induced vomiting
  - Motion sickness
    - Higher dose required

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Maropitant (Cerenia®)

- Responsible use
  - Very effective antiemetic so take care
  - Use symptomatically not therapeutically
  - If vomiting persists or recurs, investigate rather than just repeating treatment
    - Unless reason for vomiting is known e.g. pancreatitis
  - Do not use if GI obstruction suspected

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Maropitant (Cerenia®)

- Possible additional properties
  - Perioperative use
    - Vomiting associated with premedication
    - Potential analgesic adjunct
      - reduction of sevoflurane requirement with visceral stimulus
    - Return to feeding: post-operative nausea (?)
  - May protect against neuro-inflammation

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Maropitant (Cerenia®)

- What does maropitant <u>not</u> do
  - Not a very effective anti-nausea drug
  - Not effective in preventing gastroesophageal reflux under an aesthesia
  - No evidence it is effective in management of respiratory disease
    - Feline asthma
    - Canine bronchitis

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Maropitant generic: Prevomax®

- Different formulation : benzyl alcohol
- Significantly less painful after subcutaneous administration in dogs
- No difference between injection temperatures (4°C vs 25°C)

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Metoclopramide

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Metoclopramide

Antagonises
- D_2 dopaminergic receptors
- $5HT_3$-serotonergic receptors (weak)

and
- has a peripheral pro-cholinergic effect

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Neurotransmitters and emesis

VESTIBULAR
M_1
H_1

VOMITING CENTRE
α_2
$5HT_{1A}$

CRTZ
D_2
M_1
H_1
$5HT_3$

Nucleus tractus solitarius
NK_1

metoclopramide

PERIPHERAL RECEPTORS
D_2
M_2
$5HT_3$
Motilin

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Metoclopramide

Indicated for:
- various emesis-inducing disorders which involve peripheral activation of vomiting
- cancer chemotherapy
- gastroesophageal reflux
- decreased gastric emptying
- also not very effective against nausea

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$5HT_3$ antagonists

e.g ondansatron *(Zofran®)*, dolasetron *(Anzemet ®)*
- Usually to control cytoxic drug induced emesis e.g. cisplatin
- No veterinary registered product so off label use in the UK
- Effectiveness as antiemetics is orders of magnitude better than metoclopramide e.g. 100 times better in the ferret

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Neurotransmitters and emesis

VESTIBULAR
M_1
H_1

VOMITING CENTRE
α_2
$5HT_{1A}$

CRTZ
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Nucleus tractus solitarius
NK_1

PERIPHERAL RECEPTORS
D_2
M_2
$5HT_3$
Motilin

$5HT_3$ antagonists

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Less well-known antiemetics

- Acepromazine
  - Useful with morphine premedication
- Mirtazapine (off label)
  - Appetite stimulant +/- antiemetic?
  - Anecdotal use in chronic kidney disease (CKD)
    - 1.88mg/cat
  - Side effects
    - vocalisation
    - increase in liver enzymes

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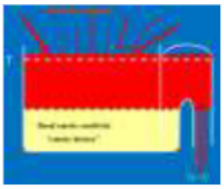
Nausea in animals

- Continuum: nausea precedes emesis (but not always)
- Emesis occurs when threshold level reached
- Subjective, perceptual experience
- Therefore difficult to recognise and remains undertreated



With thanks to Ludovic Pelligand, RVC

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Clinical signs of nausea

- Lethargy, depression
- Salivation, lip licking
- Exaggerated swallowing (gulping)
- Shivering, abnormal body posture
- Food aversion
- Elevated heart rate
- Ultimately: vomiting

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Consequences of nausea

- Debilitating
  - Prevention of emesis with persistent nausea is worse than the short nausea relief brought by vomiting
  - Hyporexia
    - negative caloric intake ➔ weight loss ➔ worse prognosis
    - dehydration, fluid imbalances
- May precipitate euthanasia
  - Lower quality of life perceived by owner

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Ranking of side effects in human patients receiving chemotherapy

- Nausea is number 1 feared side effect, worse than vomiting
- Reason for abandoning chemotherapy in people

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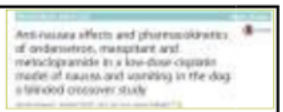
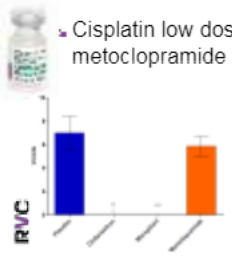
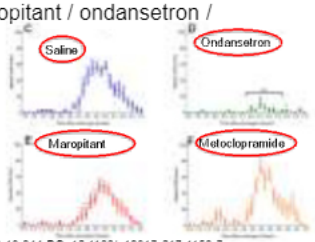
All antiemetics do not have the same anti-nausea effect !



- Cisplatin low dose + maropitant / ondansetron / metoclopramide / saline





Kenward et al. BMC Veterinary Research (2017) 13:244 DOI 10.1186/s12917-017-1156-7

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Is there a parallel between pain and nausea?

We have a lot to learn from historical progress in pain care to improve nausea care

With thanks to Ludovic Pelligand, RVC

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How good are they at treating nausea?

- NK_1 antagonists
  - Not very
- Metoclopramide
  - Not at all
- $5HT_3$ antagonists
  - Very good
- Phenothiazines
  - Not studied

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Anti-ulcer drugs

- H_2 receptor antagonists
- Sucralfate
- Misoprostol
- Omeprazole

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Anti-ulcer drugs - indications

- Treatment of confirmed gastric ulceration
  - Diseases causing ulceration
  - Nonsteroidal anti-inflammatory toxicity
- Management of diseases where gastric ulceration is a risk
  - Renal disease
  - Liver failure

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Anti-ulcer drugs - indications

- Used to prevent secondary oesophagitis in severe vomiting
- Or where reflux a concern
  - Post BOAS surgery
  - Brachycepahic anaesthetics
- They are not anti-emetics and are not needed for every dog or cat that is vomiting
- Gastritis does not = gastric ulceration

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H_2-receptor antagonists

- Cimetidine (Zitac), ranitidine (Zantac), famotidine (Pepcid)
- Effective in treating gastric ulceration caused by a variety of disorders including NSAIDs and uraemia
- Only Zitac is veterinary product (but only for oral use) thus use of others is off label

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H_2-receptor antagonists

- Cimetidine, ranitidine and famotidine differ in potency
  - But this just means amount of drug to achieve the effect
  - Does not mean "stronger"
- Equally effective at promoting ulcer healing if given at appropriate dose frequency
- Base drug choice on considerations of:
  - cost
  - client convenience (frequency of dosing)
  - concurrent drug therapy
  - justification for prescribing off label

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H_2-receptor antagonists – dosing frequency

- Cimetidine
  - every 6-8 hours
  - Only suppresses acid production for 3-5 hours
- Ranitidine
  - every 8-12 hours
- Famotidine
  - every 12-24 hours

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Sucralfate

- Indicated for symptomatic treatment of gastric ulceration from a variety of causes
- In humans as effective as antacids or H_2 receptor antagonists in healing ulcers

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Omeprazole (Losec)

- Proton pump inhibitor
- Slightly greater efficacy in healing ulcers in humans than H2 antagonists
- More expensive
- In small animal veterinary medicine
  - used increasingly commonly but is off label as not a veterinary registered product and rationale in many cases not strong
  - ulcers or oesophagitis refractory to other anti-ulcer drugs
  - ulcers associated with gastrinomas or mast cell tumours
  - pre-op for breeds at risk of reflux

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Omeprazole – if needed

- Inhibition of acid secretion is not immediate
  - Approximately 30% of the maximal is achieved on day 1 of administration
    - incomplete binding to all H+-K+-ATPases
    - degradation initially in an acid environment thus less reaching the intestine for absorption
      - as acid secretion diminishes, degradation less and intestinal absorption higher
    - possibly also inhibition of metabolising enzymes
- Maximal inhibitory effect is achieved within approximately 2-4 days
  - Use IV initially if more immediate effect required

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Conclusions

- Drugs can be very effective anti-emetics but not necessarily effective anti-nausea agents
- Poorly managed nausea has patient welfare implications just as poorly managed pain does
- Not every vomiting patient needs an **anti-ulcer** drug
- Be aware and take care

#Take Home message

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Royal Veterinary College
University of London

Anorexia and normal blood work - where's the disease?

Jill E Maddison
BVSc DipVetClinStud, PhD, FACVSc, SFHEA, MRCVS
Professor of General Practice

Saving pawsome, one tail at a time

1

My pet won't eat

Define the problem further

- Prehension difficulties?
- Painful mouth?
- Dysphagia?
- Loss of smell?
- Just "picky"?
- "True" anorexia?

2

What's the key question?

- Can't eat?

  Or

- Won't eat?

3

Dysphagia = can't eat

- Define as difficulties in:
  - Prehension

    And/or
  - Mastication

    And/or
  - Swallowing
- Prehension and mastication difficulties are most often associated with disorders of the mouth and pharynx

4

Dysphagia

- Dysphagia can also be due to:
  - Inflammation of the muscles of mastication (myositis)
  - Neuromuscular lesions resulting in paralysis of:
    - muscles of the jaw (cranial nerve V - trigeminal) or
    - tongue (cranial nerve X11 – hypoglossal)

5

Difficulties in swallowing

- Excessive, forceful attempts to swallow or regurgitation of food from the mouth or nostrils
- Causes include:
  - Local disorders in the pharynx
    - inflammation, foreign bodies, neoplasia.
  - Neurological disorders involving cranial nerve IX (glossopharyngeal) or cranial nerve X (vagus)

6

Difficulties in swallowing

- Causes include:
  - Cricopharyngeal achlasia
    - Rare congenital disorder
    - Cricopharyngeal sphincter fails to relax when animal swallows
    - Surgically correctable by a cricopharyngeal myotomy

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Difficulties in swallowing

- Oral/pharyngeal inflammation
- Key question?
- Is this due to local or systemic disease?

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Oral/pharyngeal inflammation

- Systemic
  - uraemia
  - viral infections (cats)
  - neutropenia
  - immune-mediated e.g. pemphigus
- Local
  - irritants (plant, chemical)
  - foreign bodies
  - dental disease (but must be severe)
  - lymphocytic/plasmacytic stomatitis
  - neoplasms

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9

10

11

Anorexia = won't eat

Appetite control

- Feeding-satiety centres - hypothalamus
- Influenced by:
  - blood glucose levels
  - body temperature
  - metabolic products
  - neural input from the gastrointestinal tract
  - substances released by neoplasia
  - psychic factors

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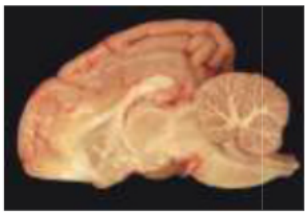
Anorexia

AND……..

- Direct CNS pathology



13

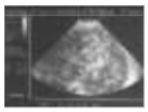
Search for a more specific sign

14

Anorexia – the hunt for a more specific sign

Physical examination

- Pyrexia?
- Masses?
- Severe constipation?
- Severe heart disease?
- Anaemia?
- Icterus?



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Anorexia – the hunt for clin path changes

- Anaemia
- White blood cell changes
- Electrolytes
  - Sodium, potassium, calcium
- Hepatic enzymes
- Renal parameters
- Pancreatic pathology
- Serum protein levels

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But before we get carried away

- Owner concern
- Perception vs reality
- Duration of anorexia/hyporexia?
- Any weight loss?


17

Is this patient stressed?

- Separation anxiety
- New baby/pet
- Change in environment or routine
- Loss of an owner or companion


18

Is this patient in pain?

19

Is this patient nauseous?

20

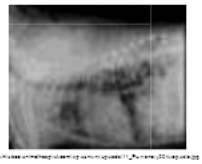
Clinical signs of nausea

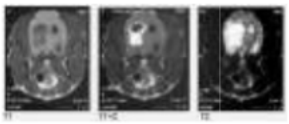
- Lethargy, depression
- Salivation, lip licking
- Exaggerated swallowing (gulping)
- Shivering, abnormal body posture
- Food aversion
- Elevated heart rate
- Ultimately: vomiting

21

I really can't find anything! Help!

- Consider:
  - Primary GI disease
  - Lead toxicity – especially cats
  - Pancreatitis – cats
  - Hepatic disease – especially cats
  - Atypical hypoadrenocorticism
  - "Hidden" infection e.g.
    - Pyelonephritis
  - Occult neoplasia
  - Primary CNS disease





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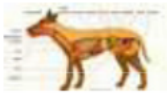
Primary vs secondary GI disease

- Primary GI disease
  - Pathology involves the gut directly
    - E.g. inflammation, neoplasia, foreign body, parasites
  - Usually present with GI signs
    - vomiting and/or diarrhoea
  - But anorexia may be the only sign due to neural input from the GI tract to the hypothalamus
  - Bloods often normal or reveal consequences not causes
- Secondary GI disease
  - Metabolic disease causing GI signs
  - Bloodwork usually helpful



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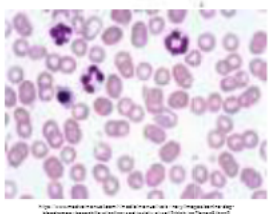
Lead toxicity

- Uncommon but can occur where lead paint has been used, lead sinkers used for fishing, lead mining
- In cats, clinical signs may be nothing more than anorexia
- Haematology can be normal especially if RBC morphology not reviewed



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Pancreatitis - cats

- Often due to low grade oedematous inflammation
  - Acute pancreatitis may also occur
- Has been reported in cats ranging in age from four weeks to 18 years
- Breed?
  - Siamese cats have been over-represented in some case series
  - Bengal cats over-represented in RVC study
- Dietary factors do not seem to be a trigger
- Some cases may have a bacterial aetiology and respond well to antibiotics

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Pancreatitis in cats - clinical signs

- Most common signs
  - Lethargy
  - Anorexia
  - Weight loss
- Vomiting reported in less than 50% of cats
- Overt abdominal pain uncommon
  - Discomfort on deep abdominal palpation?
- Other signs that may be seen
  - Icterus
  - Diarrhoea
  - Polyuria/polydipsia

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Pancreatic clin path – dogs vs cats

- In the dog, ALP usually increased due to impact on biliary tract
- ALT often increased due to effect of inflammatory mediators on liver parenchyma +/- cholestasis
- Usually have an inflammatory leukogram
- Often have lipaemic serum
- In the cat enzymes may or may not be increased

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Pancreatitis in cats - clinical pathology

- Unlike in the dog, amylase and lipase of virtually no diagnostic value
- Feline pancreas synthesises less than 10% of amylase in comparison to dogs
- Feline pancreatic lipase (fPLI) needs to be interpreted with care

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Hepatic disease – clinical pathology

- Any one or a combination of …….
  - Increased liver enzymes(ALT, ALP, GGT))
  - Increase bilirubin
  - Increased bile acids
  - Increased blood ammonia
  - Decreased blood glucose
  - Increased or decreased cholesterol
  - Increased protein (globulins)
  - Decreased protein (albumin)
  - Decreased clotting factors
  - Platelet dysfunction

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Hepatic disease – clinical pathology

- Or none!
- And especially in …….

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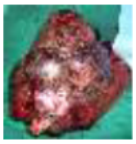
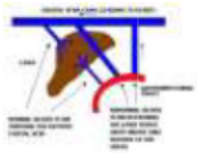
Hepatic disease

- Hepatic diseases in dogs that can have minimal or no liver enzyme increases
  - portacaval shunts
  - end stage cirrhosis
  - advanced neoplasia





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Hypoadrenocorticism: signalment

- A disease of young to middle aged dogs and much more uncommonly, middle aged cats
- In dogs the disease is approximately twice as common in females as males regardless of neutering status
- Particularly marked breed predispositions:
  - Standard poodles
  - Bearded collies
  - Leonburgers
  - Nova Scotia Duck Tolling Retrievers

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Hypoadrenocorticism

- Can present as:
  - An acute adrenal crisis

  OR
  - Waxing, waning clinical signs - "just ain't doing right"
- May have specific GI signs
  - Vomiting, diarrhoea, melaena, abdominal pain
- May have neuromuscular signs
  - weakness, muscle tremors
- Or may "just" have lethargy, anorexia

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"Typical" hypoadrenocorticism

- Cortisol and aldosterone deficiency
- Clinical pathology
  - Absence of a stress leukogram in an unwell dog
  - Plus either hyponatremia and/or hyperkalemia (⇓ Na:K ratio)
  - Often but not always:
    - Azotaemia
    - Hypoalbuminaemia
    - Hypoglycaemia
    - Hypercalcaemia

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"Atypical" hypoadrenocorticism

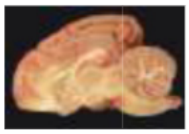
- Cortisol deficiency but not aldosterone deficiency
- Absence of a stress leukogram and normal Na and K levels
- Often but not always have:
  - Hypoalbuminaemia
- So this can be a diagnosis for our patient with anorexia and "normal" bloods
- Is it atypical or just underdiagnosed??
  - ~27% of cases of hypoadrenocorticism seen at RVC referrals (2012-2016)

36

37

Other "silent" causes of anorexia

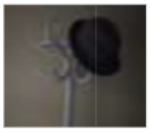
- "Hidden" infection e.g.
  - Pyelonephritis
- Occult neoplasia
- Primary CNS disease



38

In conclusion when there is anorexia and normal blood work

- Am I sure the anorexia/hyporexia is "real"
- Am I sure there is nothing stopping this patient from eating = can't eat?
- Is this patient stressed or in pain?
- Is this patient nauseous?
- Am I sure there isn't any other clinical sign to hang my diagnostic hat on



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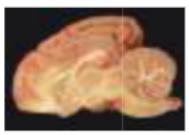
In conclusion when there is anorexia and normal blood work

- Is lead toxicity feasible?
- Does this cat have pancreatitis?
- Does this dog or cat have liver disease?
- Does this dog have atypical hypoadrenocorticism?
- Should I go on a tumour hunt?
- What's going on in the brain?
- Is there an occult infection somewhere e.g. pyelonephritis?



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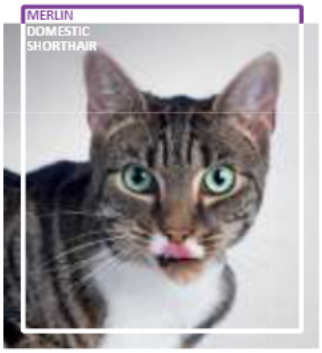
Inspiring,
relevant, practical

Online and onsite CPD from the RVC

www.rvc.ac.uk/cpd



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A rational approach to the patient with PU/PD or impaired urine concentrating ability

Jill E Maddison
BVSc DipVet Clin Stud PhD FACVSc SFHEA MRCVS
Professor of General Practice

1

Define the problem – polydipsia and/or polyuria

- Physiological
- Urinary incontinence
- Polyuria causing incontinence
- Pollakiuria/dysuria
- Pathological

2

Confirming polydipsia

- Dog > 100 mls/kg day
- Cat > 50 mls/kg/day
- Owner impressions
- Home monitoring
- Urine concentration?

3

Define the system

- Primary polydipsia – "want to drink"
  - Lesion is causing excessive water intake which → polyuria
- Primary polyuria – "need to drink"
  - Lesion is causing excessive urine production which is → polydipsia
  - Structural renal disease?
  - Or
  - Extra-renal disease causing renal dysfunction
    - kidney is structurally fine but function impaired extra-renal issues

4

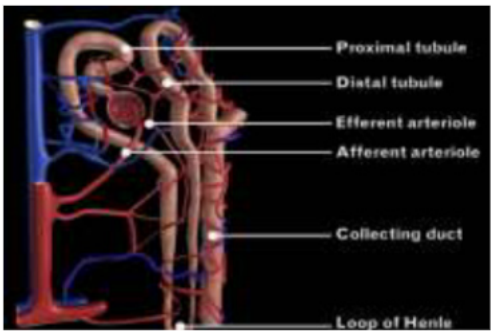
Primary polydipsia

- Psychogenic causes
- Hyperadrenocorticism
- Hepatic encephalopathy
- Hyperthyroidism
- Hypothalamic lesion affecting thirst receptors (rare)
- Drug effect on thirst centre (e.g. phenobarbitone)

5

Primary polyuria – we now have to consider renal physiology

6



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Primary polyuria – 4 mechanisms

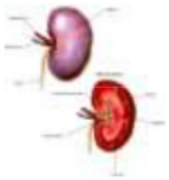
Primary renal
- Structural renal pathology

Extra renal
- Reduced medullary hypertonicity
- Absent or impaired ADH
- Osmotic diuresis

8

Primary polyuria - mechanism #1

Primary structural renal disease
- Chronic kidney disease (CKD)
- Pyelonephritis (reversible)
- Nephrocalcinosis
- Bilateral neoplasia



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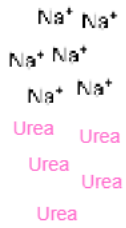
Primary polyuria - mechanism #2

Reduced medullary tonicity
- Hyponatraemia e.g.
  - Hypoadrenocorticism
  - Profound gut sodium loss
- Decreased urea concentration
  - ADH deficiency/dysfunction
  - Liver disease?
- Endotoxaemia
  - Disrupts the medullary osmotic gradient
- Hypercalcaemia and hypokalaemia
  - disrupts the Na-K pump in the ascending Loop of Henle resulting in increased sodium loss



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Primary polyuria – mechanism #3

Absent, reduced or dysfunctional ADH
- Diabetes insipidus
- Hyperadrenocorticism
- Hypercalcaemia
- Hypokalaemia
- Pyometra
- Pyelonephritis *especially if due to E.coli*

11

Primary polyuria – mechanism #4

Osmotic diuresis
- Glucosuria
  - Diabetes mellitus
  - Renal tubular defect

12

Urine SG

- **SG of < 1.008** (1.006 in cats) - actively diluted
- **SG of 1.008 - 1.012** has been neither been diluted nor concentrated
- **SG of >1.012** has been concentrated to some degree

But is it enough?

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When is urine SG inappropriate?

- If < 1.030 (1.045 in cats) in a dehydrated and/or azotaemic patient
- EVEN if > 1.012

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If the urine SG is inappropriate?

Primary polydipsia?

- Animal will often concentrate urine if placed in a different environment e.g. hospital
- Consider if no other clinical signs, bloods are unremarkable and patient is otherwise bright and happy
- Not a consideration if the patient is also unwell

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If the urine SG is inappropriate and primary polydipsia ruled out?

Structural or functional?

Either

- The kidney CANNOT concentrate because it is structurally damaged
  - CKD
  - Nephrocalcinosis
  - Pyelonephritis (reversible)
  - Bilateral neoplasia

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If the urine SG is inappropriate and primary polydipsia ruled out?

OR

- The kidney cannot concentrate because there is some extra-renal factor interfering with normal renal function
  - Reduced medullary hypertonicity
  - Impaired ADH function
  - Increased osmolarity of the filtrate

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Hyposthenuria

- Urine SG < 1.008 (< 1.006 in cats)
- Patient CANNOT have structural renal disease
  - CKD
  - Nephrocalcinosis
  - Bilateral neoplasia
- But can have pyelonephritis
  - Impaired urine concentration due to disruption of medullary osmotic gradient and impaired ADH function

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Why?

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Hyposthenuria – urine has been actively diluted

- Psychogenic polydipsia
- Diabetes insipidus
- Hypercalcaemia
- Hyperadrenocorticism
- Pyometra
- Pyelonephritis
- Hepatic disease
- Profound blood loss
- Hypokalaemia
- Hyperthyroidism
- Hyponatraemia

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Hyposthenuria – unwell animal

- Psychogenic polydipsia
- Diabetes insipidus
- Hypercalcaemia
- Hyperadrenocorticism – unless concurrent disorder
- Pyometra
- Pyelonephritis
- Hepatic disease
- Profound blood loss
- Hypokalaemia
- Hyperthyroidism
- Hyponatraemia

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Urine SG > 1.008-1.030

- Renal disease
- Diabetes mellitus
- Polycythaemia
- Pyelonephritis
- Hypercalcaemia
- Hyperadrenocorticism
- Hepatic disease
- Pyometra
- Hyponatraemia
- Hyperthyroidism
- Hypokalaemia

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Concentrated urine

- Diabetes mellitus
- Renal glucosuria

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Important!

- Impaired urine concentration and azotaemia can occur because of different and unrelated mechanisms
  - Except in structural renal disease (CKD, nephrocalcinosis, neoplasia)

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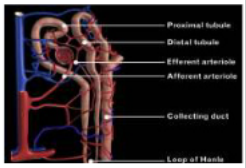
Azotaemia vs impaired urine concentration

- Azotaemia is about the rate of filtration through the glomerulus – determined by
  - Number of nephrons
  - Renal blood flow rate
  - Afferent arteriole blood flow rate
  - The glomerular "sieve"



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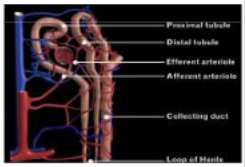
Azotaemia vs impaired urine concentration

- Urine concentration involves tubular function
  - Movement of water to and from the glomerular filtrate
  - Determined by
    - Number of nephrons
    - Medullary hyperosmolarity
    - ADH function
    - Filtrate osmolarity



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Azotaemia – summary of causes

- Structural renal disease
  - Loss of >75% of nephrons
- Reduced renal blood flow
  - Hypovolaemia
    - Dehydration
    - Hyponatraemia
  - Heart failure
  - Hypotension
  - Shock
- Constriction of afferent glomerular arteriole
  - Hypercalcaemia
- Severe glomerular damage

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Disorder	↓ GFR → Azotaemia	Impaired urine concentration
Structural renal disease	↓ nephrons	↓nephrons
Hypercalcaemia	Constricted afferent arteriole	ADH dysfunction
Hyponatraemia	Hypovolaemia	Decreased medullary hypertonicity
Dehydrated patient with normal renal function	Decreased renal perfusion	No
Dehydrated patient with polyuric disorder	Decreased renal perfusion	ADH dysfunction OR Osmotic diuresis OR Reduced medullary hypertonicity
Glomerular disease	↓ Flow through glomerulus	Not impaired until tubular pathology develops

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Take home messages for azotaemia

- MUST check urine SG if at all possible
- ALWAYS check Na^+ and Ca^{2+}
- Regardless (almost) of the degree of azotaemia
- Dogs vs cats ……

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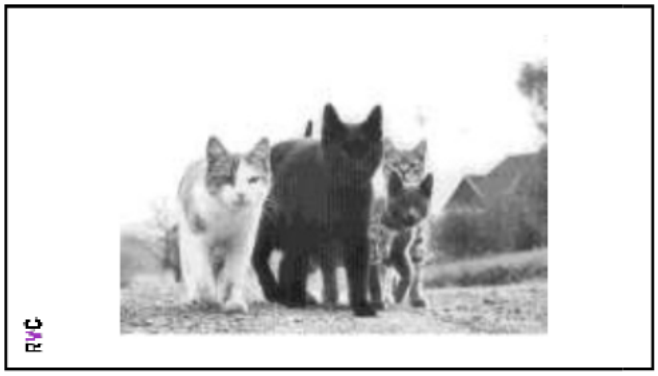

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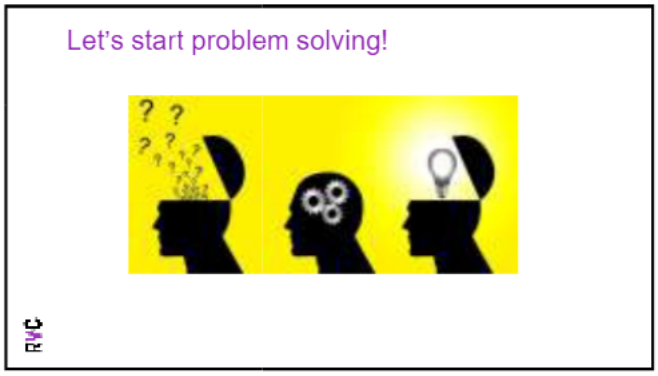
Royal Veterinary College
Jaundice and liver disease
Jill E Maddison
BVSc DipVetClinStud PhD FACVSc SFHEA MRCVS
Professor of General Practice

1


Let's start problem solving!
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"Basil"
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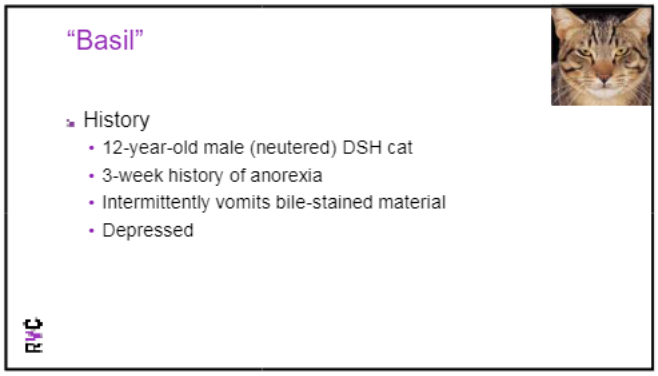
3


"Basil"
History
12-year-old male (neutered) DSH cat
3-week history of anorexia
Intermittently vomits bile-stained material
Depressed
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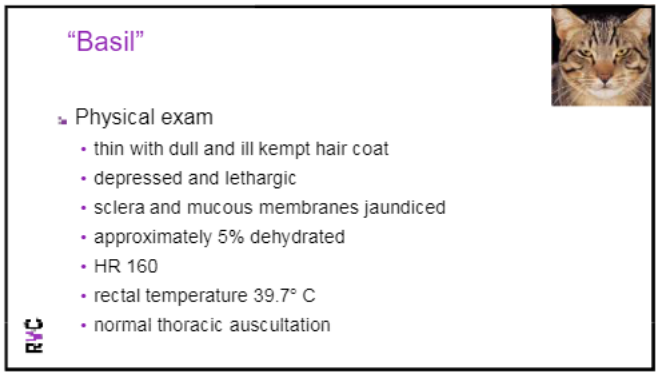
"Basil"
Physical exam
thin with dull and ill kempt hair coat
depressed and lethargic
sclera and mucous membranes jaundiced
approximately 5% dehydrated
HR 160
rectal temperature 39.7° C
normal thoracic auscultation
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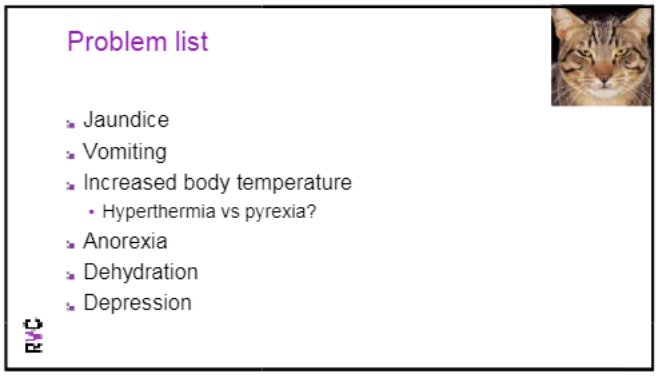
Problem list
Jaundice
Vomiting
Increased body temperature
Hyperthermia vs pyrexia?
Anorexia
Dehydration
Depression
RVC

6

Problem list – what are the specific problems?

- Jaundice
- Vomiting
- Increased body temperature
  - Hyperthermia vs pyrexia?
- Anorexia
- Dehydration
- Depression

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Problem list - specific

- Jaundice
- Vomiting
- Pyrexia
- Anorexia
- Dehydration
- Depression

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Problem list – the most specific?

- Jaundice
- Vomiting
- Pyrexia
- Anorexia
- Dehydration
- Depression

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Define the system and location

- Haemopoietic vs hepatobiliary

OR

- Prehepatic vs hepatic/posthepatic

AND

- Sepsis/severe inflammation

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Define the system

- Differentiating haematopoietic (pre-hepatic) jaundice from hepatobiliary jaundice is easy
  - Animals with red cell haemolysis that is severe enough to result in jaundice will always have a significant anaemia that is usually, but not always, regenerative

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Haemolytic anaemia – causes dogs/cats

- Immune mediated
  - Primary
  - Secondary
- Microangiopathic/physical turbulence
  - Splenic torsion
  - Haemangiosarcoma
  - Caval syndrome
  - Disseminated intravascular coagulation (DIC)
- Metabolic
  - E.g. hypophosphataemia in diabetes mellitus

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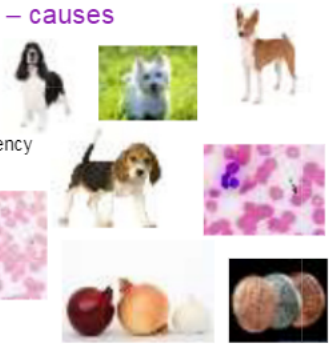
Haemolytic anaemia – causes dogs/cats

- Congenital e.g.
  - pyruvate kinase deficiency
  - phosphofructokinase deficiency
- Infectious
  - E.g. Babesia
- Drugs/toxins
  - Look for Heinz bodies
    - garlic, onions
    - zinc



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Define the location

- But it is more difficult to differentiate hepatic and post hepatic jaundice in dogs and cats

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Define the lesion – dogs/cats

- Thus, we often just consider causes of hepatic and post hepatic jaundice together
  - Note species differences

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Hepatic jaundice

Most common causes - dogs

- Chronic inflammatory hepatitis
- Neoplasia (diffuse e.g. lymphoma)
- Toxic hepatitis
- Infectious hepatitis
  - Leptospirosis
  - Adenovirus

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Hepatic icterus

Most common causes - cats

- Cholangitis (also referred to as cholangiohepatitis)
  - Acute neutrophilic
  - Chronic neutrophilic
  - Chronic lymphocytic
- FIP
- Neoplasia
- Hepatic lipidosis?
  - Prevalence depends on geographic location

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Post-hepatic jaundice - causes

- Toxic or infectious cholangitis (if only involving the common bile duct)
- Pancreatic disease
  - pancreatitis
  - pancreatic abscess
  - pancreatic carcinoma
- Infiltrating or space-occupying biliary lesions
  - abscess
  - neoplasm
  - mucocoele
  - chololethiasis
  - cholecystitis

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Post-hepatic jaundice - causes

- Bile duct rupture/leakage
- Intestinal pathology
  - causing obstruction of bile flow at the entrance of the common bile duct into the duodenum

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Non-hepatic/anaemic causes of increased bilirubin

- May cause increased bilirubin but not necessarily visible jaundice
  - E.g. reference range of bilirubin in the dog is up to 15μmol/L but overt jaundice does not occur until the level is around 45 μmol/L
- Fever (humans, animals?)
- Anorexia (horses, cats – to a small degree)
- Sepsis or significant inflammation (dogs, cats,)
  - can cause jaundice (though this is uncommon)
  - especially in cats

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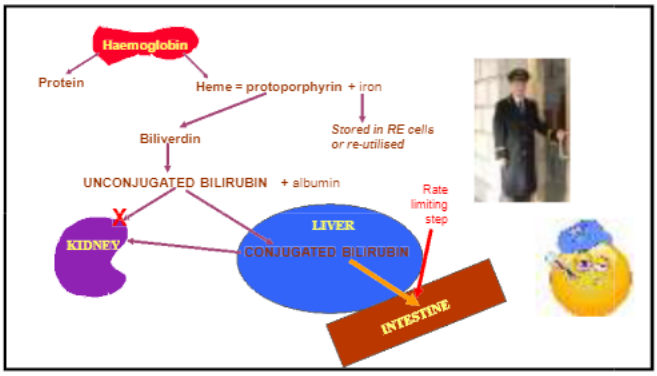

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Back to Basil

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Path results

- PCV 25%
  - Mild anaemia once rehydrated
  - Pre-hepatic jaundice ruled out
- Moderately inflammatory but not septic leukogram

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Path results

- Increased:
  - ALT - 300 U/L
  - Bilirubinaemia
- Normal
  - ALP
  - Spec Feline Pancreatic Lipase (fPLI)
  - Amylase
  - Bile acids were not requested

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Diagnostic imaging

- No ultrasonographic abnormalities reported

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Final diagnosis

- Biopsy confirmed neutrophilic (suppurative) cholangitis and pancreatitis

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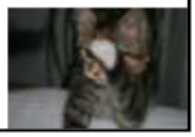
Key questions

- Why were the liver and pancreas so shy about telling the blood there was something wrong?
- Would it have been helpful to do bile acids?
- What are the key things to note about interpreting key clinical pathology tests related to the liver and pancreas in cats vs dogs?
  - PLI, amylase, ALP, bile acids
- Was the ultrasonographer blind?



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Why was the fPLI negative?

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Spec fPL

- Reference range is < 3.5 µg/L
- Values > 5.3 µg/L
  - consistent with pancreatitis
- Values between 3.5 and 5.3 µg/L
  - grey zone
- Note that cats produce much less PLI than dogs

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Feline Spec fPLI

- Difficult to validate sensitivity and specificity
- No gold standard for diagnosis
  - Pancreatic biopsy?
- Unlike dogs few other clinical pathology tests of potential value
- Clinical signs of pancreatitis often non specific
  - Malaise
  - Weight loss

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Spec fPL - sensitivity

- 67% sensitivity (33% false negatives) reported in the literature
  - Small cohort of 28 cats with biopsy confirmed pancreatitis
- RVC study* – 275 cats
- Dx based on ultrasound +/- histology/cytology
- 24% false negatives
  - Cats without US changes excluded so value may be higher

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* Lee, C, Kathrani, A and Maddison, JE JVIM 2020

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Spec fPL - specificity

- 97% specificity initially reported
  - Thus if PLI increased cat almost certainly has pancreatitis?
  - No false positives?
- In the literature specificity reported to be 67-100%
  - Thus up to 1/3 false positives
- RVC study of 275 cats* = 10% false positives
  - Value could be lower at least as a co-morbidity
- No good data on specificity in cats with GI disease other than pancreatitis

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* Lee, C, Kathrani, A and Maddison, JE JVIM 2020

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SNAP fPL™(cats)

- Similarly to dogs, SNAP® fPL™ in comparison with Spec fPL is thought to have:
  - higher sensitivity (fewer false negatives)
  - lower specificity (more false positives)

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In cats ….

- If the Spec fPLI is positive then good chance cat has pancreatitis
  - Though this may not be their primary pathology if associated with IBD etc
- If it is negative it means nothing – keep hunting
- Why is this important?
  - Feline pancreatitis is commonly chronic and relapsing and may have a bacterial aetiology in some cases

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Why was the amylase not increased?

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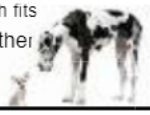
Interpreting amylase in dogs vs cats

- In dogs ……
- Interpret with care but still can be useful
- Moderate increases (2-3 times) can occur in many disorders

- Increases > 3 times normal often = pancreatitis in dogs if clinical signs consistent
  - Especially if lipaemic serum and other clin path fits
- Normal or moderately increased levels neither confirm nor rule out pancreatitis



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Amylase and lipase in cats

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Amylase and lipase in cats

- Amylase and lipase of virtually no diagnostic value in cats
- Feline pancreas synthesises less than 10% of amylase in comparison to dogs

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Why was the ALP not increased?

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ALP in cats and dogs differs

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ALP

- Bound to membranes of bile canaliculi and bile ducts
- Increased by any condition causing cholestasis
  - intra- or extra-hepatic
  - increased synthesis and regurgitation

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ALP

- Increased by….
  - glucocorticoids
    - dog not cat
  - anticonvulsant therapy (phenobarbitone)
    - dog not cat
  - hyperthyroidism
    - possible bone ALP isoenzyme

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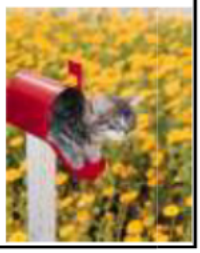
ALP in cats

- Shorter half life
  - 6 vs 72 hrs
- Feline bile canaliculi excrete less ALP than dogs



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ALP in cats

- Cholestasis and jaundice will occur often without an elevation in ALP
- Thus any increase above the reference range is of concern

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ALP in cats

- The only non-primary hepatobilary disease of importance that causes elevated ALP in cats is hyperthyroidism
  - Pancreatitis included as an hepatobiliary disease
  - Diabetes mellitus can cause hepatic lipidosis and increased ALP

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Should bile acids have been measured in Basil?

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Let's talk about bile acids – why do they increase?

- Decreased clearance from portal blood
  - Diffuse hepatocellular disease
  - Portacaval shunting
- Decreased excretion in bile
  - Obstructive cholestasis – intrahepatic
  - Posthepatic cholestasis

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Bile acids are not liver function tests

- Reflect hepatobiliary or hepatic vascular dysfunction
- Elevation may roughly correlate with severity of lesion
- But does not correlate with….
  - reversibility of lesion
  - prognosis
  - degree of shunting in portosystemic encephalopathy

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Bile acids – helpful but not infallible

- If hepatobiliary disease confirmed by other tests, bile acids tell you no more than you already know
  - i.e. the patient has hepatobiliary disease
- Does not quantify degree of dysfunction any further
- Non-hepatic disorders can increase bile acids
  - Hyperadrenocorticism
  - Intestinal bacterial overgrowth

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Bile acids - when are they useful?

- Confirm hepatobiliary disease if liver enzyme increases not explained or not sufficiently high to confirm liver disease
- Diagnosis of portacaval shunts
- But beware of asymptomatic portal vein hypoplasia
  - Common
  - Breeds include Yorkies, Cairns, Maltese, Bichon Frise

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Bile acids - when are they not useful?

- Jaundiced patient
  - Except IMHA or sepsis
- Where liver enzymes unequivocally indicate hepatobiliary pathology

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RVC study – bile acids (BAs) in dogs*

- Hepatic biopsies and pre and/or post prandial BAs in 206 dogs
  - 99 normal liver
  - 107 confirmed liver pathology
    - Parenchymal
    - Vascular
    - Biliary
- Reference range at RVC is 0-5µmol/L
  - 0-25 µmol/L most commonly used as cut-off

* Brooke, CT and Maddison, JE 2019

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Dogs with confirmed liver pathology – the false negatives

- 40 dogs with confirmed liver disease (37%) had **pre**-prandial BAs < 25 µmol/L
- 16 dogs with confirmed liver disease (15%) had **post**-prandial BAs < 25 µmol/L
- 9 (0.8%) dogs with confirmed liver disease had both **pre** & **post** BAs < 25 µmol/L
  - 4 parenchymal
  - 4 vascular
  - 1 biliary

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Dogs with confirmed liver pathology – the false negatives

- 14 (13%) dogs with confirmed liver disease had **pre** and/or **post**-prandial BAs < 5 µmol/L
- 3 dogs with confirmed liver disease had both **pre** and **post** prandial BAs < 5 µmol/L
  - 2 parenchymal
  - 1 vascular

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Dogs with no liver pathology – the false positives

- 9 (9%) dogs had **pre**-prandial BA > 25µmol/L
  - Highest was 59
- 19 (19%) dogs had **post**-prandial bile acids > 25µmol/L
  - Highest was 287 in a dog with a meningioma!

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RVC study – bile acids (BAs) in cats*

- Hepatic biopsies and **pre** and/or **post** prandial BAs in 39 cats
  - 18 normal liver
  - 21 confirmed hepatic disease
    - Parenchymal
    - Vascular (most)
    - Biliary
- Reference range at RVC is 0-5 µmol/L
  - but 0-25 µmol/L is more common

* Brook, CT and Maddison, JE 2019

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Cats with confirmed liver pathology – the false negatives

- 11 cats with confirmed liver disease (52%) had **pre**-prandial BAs < 25 µmol/L
- 7 cats with confirmed liver disease (33%) had **post**-prandial BAs < 25 µmol/L
- 5 (24%) cats with confirmed liver disease had both **pre** and **post** BAs < 25 µmol/L
  - 2 parenchymal +/- biliary
  - 3 vascular

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Cats with no liver pathology – the false positives

- 1 cat with no liver pathology had **pre**-prandial and **post** prandial BA > 25 µmol/L

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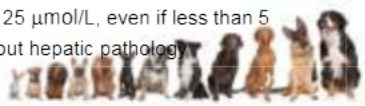
Take home message?

- In dogs…….
  - Increased bile acids above the reference range do not confirm hepatic disease
  - But once they reach around 60 (pre-prandial) you can be more confident
  - Bile acids less than 25 µmol/L, even if less than 5 µmol/L do not rule out hepatic pathology



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Take home message?

- In cats .....
  - Bile acids less than 25 µmol/L do not rule out hepatic pathology
  - But increased pre-prandial (above 25 µmol/L) bile acids usually indicate pathology
- But r

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Summary

- If hepatobiliary disease confirmed by other tests, bile acids tell you no more than you already know
  - i.e. the patient has hepatobiliary disease
- Does not quantify degree of dysfunction any further
- A normal bile acid level even if post-prandial does not rule out hepatic pathology
- Interpret increased bile acid levels with care

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Was the ultrasonographer blind?

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Appreciate what ultrasound can and cannot tell you

- Sensitive to the presence of lesions
- But usually cannot give a histological diagnosis
- And cannot rule out pathology

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Ultrasound sensitivity – RVC studies

- Patients with hepatic biopsies and specialist ultrasonography
- False negative – no abnormality detected on ultrasound, but biopsy confirmed pathology present
- False positive – no abnormality detected on biopsy, but abnormalities reported on ultrasound

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Ultrasound sensitivity – RVC studies

Dogs

- 371 dogs with US and biopsy results
- % of cases with abnormal US signs recorded for the range of pathology types
- Sensitivity range
  - 86% (14% false negatives) for steroid hepatopathy
  - 48% for hepatitis (52% false negatives)

Warren-Smith et al, JSAP 2012

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Ultrasound sensitivity – RVC studies

Cats (53)

- 53 cats with US and biopsy results
- All pathologies
- 20% false negatives
- 2% false positives

Different pathology types

- Neoplasia 6% false negatives
- Inflammatory disease 40% false negatives

Mascaro & Maddison, 2022

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Without a biopsy

- Recognise that in most cases you may have confirmed liver disease based on clin path and diagnostic imaging but this is not a final diagnosis
- Is it bacterial, viral, neoplastic, toxic, immune mediated, fibrotic etc?

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Without a biopsy

- Sometimes evidence will allow good guess
- For Basil other Dx options
  - Hepatic lymphoma
  - Lymphocytic cholangitis
  - Pancreatic carcinoma
  - FIP
- May have to treat the treatable but first do no harm
- Note that most "liver" drugs may be "supportive" but do not treat the lesion

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Portfolio of evidence

- Assessing the liver and pancreas requires a portfolio of evidence
- It is rare that one test (clinical pathology or diagnostic imaging) can rule in or out the presence of hepatic or pancreatitis disease
- Balance of probabilities

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Interpreting the numbers – assessing the anaemic or bleeding patient

Jill Maddison
BVSc, DipVetClinStud, PhD, FACVSc, SFHEA, MRCVS
Professor of General Practice

Excellence in veterinary education

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A tale of three dogs

Excellence in veterinary education

2

"Guinness"

- Eight year old male (N) Labrador

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History

- Acute history of collapse several hours ago
- Passed large amount of melaenic faeces
- Vomited once
- Active and normal the preceding day
- Had eaten well the preceding afternoon

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Physical examination

- Very weak
- Very pale mucous membranes
- HR = 160 = PR
- Splenomegaly
- Rectal temperature 37.6° C

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Problem list

- Collapse
- Pale mucous membranes
- Melaena
- Vomiting
- Splenomegaly

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Prioritised list – what will get us to the diagnosis?

- Pale mucous membranes
- Melaena
- Splenomegaly
- Collapse
- Vomiting

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Define the problem and system

Pale mucous membranes

- Poor peripheral perfusion?

  or
- Anaemia?

Why is this the leading question?

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Why is this the leading question?

Anaemia
- Haemorrhage
- Haemolysis
- Bone marrow failure

Poor peripheral perfusion
- Heart failure
- Shock
- Dehydration

Pale mucous membranes

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Assessment of melaena – define the problem

- Swallowed blood
  - Diet
  - Bleeding in oral cavity or respiratory cavity
  - Licking bleeding wound
- GI bleeding

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Assessment – define the system

- Melaena
  - **Primary GI disease**
    - Neoplasia
    - Parasites
    - Foreign body
    - Inflammatory

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Assessment – define the system

- Melaena
  - **Systemic disease**
    - Coagulopathy
    - Systemic vasculitis
    - Systemic disease causing ulceration
      - Hypoadrenocorticism
      - Mast cell tumours - anywhere
      - Liver disease
      - Uraemia
      - Drugs

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Leading questions that will change the direction of the case

- Are the pale mm due to anaemia or poor peripheral perfusion?
- Is the melaena due to GI ulceration or coagulopathy?

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Minimum data that will answer these questions

- PCV
  - 18% (37-55)
- Total plasma protein
  - 76 g/L (55-75)
- Platelet count
  - 10 x 10^9 (200-500)

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Leading questions that will change the direction

- Are the pale mm due to anaemia or poor peripheral perfusion?
  - anaemia
- Is the melaena due to GI ulceration or coagulopathy?
  - thrombocytopenia
- Is the systolic murmur due to cardiac disease or anaemia?
  - anaemia

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Acute anaemia – key question

Haemorrhage or haemolysis?

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So we look for clues

- Clinical signs
  - external haemorrhage?
  - internal haemorrhage?
- Plasma protein
- Autoagglutination?
- Plasma appearance
  - haemolysed?
  - icteric?
- Degree of regeneration
- RBC morphology
  - spherocytosis
  - shistocytosis
  - Heinz bodies
  - infectious agents
- Urine
  - haemoglobinuria?
  - bilirubinuria?

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Plasma protein

- Acute haemorrhage
  - Often associated with decreased plasma protein concentrations
- Chronic external haemorrhage
  - Plasma protein will usually be decreased
- Haemolysis
  - Plasma protein high normal or often increased
- Internal haemorrhage
  - Plasma protein normal

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"Guinness"

- Haemorrhage or haemolysis?
- Why is it very unlikely that the major cause of his anaemia is the melaena?
  - Plasma protein is slightly high
  - If gut blood loss had been sufficiently severe to cause this degree of anaemia plasma protein should be at lower end of reference range

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"Guinness"

- Key question now?
- Haemolysis or abdominal haemorrhage?

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"Guinness"

- Avoid abdominocentesis due to thrombocytopenia ➔ risk of more bleeding
- Abdominal imaging showed
  - Splenomegaly
  - No evidence for free fluid
- Thus abdominal haemorrhage unlikely
- Anaemia is due to haemolysis

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Haemolysis – next key question

Intravascular or extravascular?

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Intravascular haemolysis

- Easily demonstrated
  - centrifuged plasma
- Haemoglobinuria is often also present
  - differentiate from haematuria
- Jaundice much more common than in extravascular haemolysis

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"Guinness"

- No detectable intra-abdominal haemorrhage
- Urinalysis – no haemoglobinuria
- Plasma is clear
- Thus extravascular haemolysis is occurring
- Melaena is contributing to the anaemia but not the sole cause

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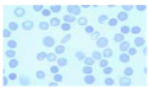
Haemolytic anaemia – causes

- Immune mediated
  - Primary
  - Secondary
- Microangiopathic/turbulent damage e.g.
  - Splenic torsion
  - Haemangiosarcoma
  - Caval syndrome
  - Look for damaged RBCs
    - Shistocytes, acanthocytes
- Metabolic
  - E.g. hypophosphataemia in diabetes mellitus



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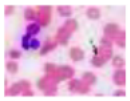
Haemolytic anaemia – causes

- Congenital e.g.
  - pyruvate kinase deficiency
  - phosphofructokinase deficiency
- Infectious
- Drugs/toxins
  - Look for Heinz bodies
    - garlic, onions
    - zinc



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Now I do need some information from a full haemogram

- And not just the numbers!

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Haematology

PCV	18%	37-55%
MCV	72	60-74
Reticulocyte count	4.4% (uncorrected) 1.98% (corrected)	<1.5%
Nucleated RBC/100 WBC	19/100 WBC	0
Red cell morphology 1+ anisocytosis, 2+ polychromasia No evidence for autoagglutination		
Platelet count	10 x 10^9/L	200-500
Total plasma protein	76.0 g/L	55-75

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Haematology

WBC count - all cells x 10^9/L	30.0	7.0-12.0
Neutrophils (seg)	18.0	4.0-9.4
Band neutrophils	9.0	0 - 0.24
Lymphocytes	0.6	0.9-3.6
Monocytes	2.4	0.2-1.0
Eosinophils	0.0	0.1-1.2

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Biochemistry

- All biochemistry OK except mild increase in ALT
  - 100 U/L – ref range up to 60

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Summary of clin path

- Anaemia
  - regenerative
- Significant normoblastaemia
- Stress & inflammatory leukogram with significant left shift
- Thrombocytopenia
- Slightly increased plasma protein

Images courtesy of Prof. Paul Canfield

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Assessment of anaemia

- Corrected reticulocyte count is 1.98% - just above the reference range (<1.5%)
- Thus only mildly regenerative anaemia
  - because has occurred acutely
  - full marrow response will take 2-4 days
- ++ NRBCs due to peracute nature of the anaemia
- Possibly also some splenic pathology

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RBC morphology

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RBC morphology

- Vitally important in assessing cause of haemolysis
- In particular look for:
  - Spherocytes
  - Shistocytes (fragmented RBCs)
  - Heinz bodies
  - Infectious causes

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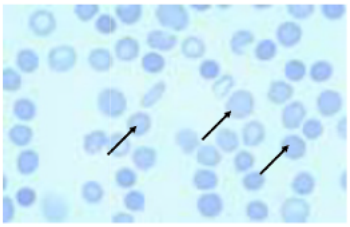
Spherocytes



Images courtesy of Prof. Paul Canfield

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"Guinness"

- No spherocytes observed
- No autoagglutination
- Can IMHA be ruled out?
- No

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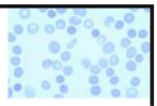
IMHA?



- Spherocytes
  - Commonly but **not** invariably present in IMHA
  - Antibodies can be directed against RBC precursors
- Autoagglutination
  - Absence does not rule out IMHA – most common with intravascular haemolysis due to IgM

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Damaged RBCs

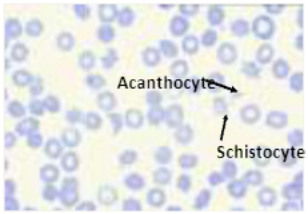

Image courtesy of Prof. Paul Canfield

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Shistocytosis – identify the lesion

- Blood has been forced through narrow passages (microangiopathy)
  - Splenic torsion
  - Haemangiosarcoma
  - DIC
  - Vascular neoplasm/abscess
- Or physically damaged
  - Severe valvular pathology
    - endocarditis
  - Caval syndrome

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"Guinness"

- No shistocytes or any other type of damaged RBC observed
- Can microangiopathy be ruled out?
- No – but less likely
  - Evidence of damage would be present for anaemia this severe
  - and/or
  - No evidence for intravascular haemolysis

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Assessment of leukogram

- Neutrophils (segmented) =18.0
- Band neutrophils = 9.0
- Serious left shift
  - Sepsis
  - Huge inflammatory process
  - Haemolysis

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Thrombocytopenia

- Inadequate **production**
  - Bone marrow disorders
  - Drugs
- Excessive **consumption**
  - DIC (disseminated intravascular coagulation)
  - Blood loss

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Thrombocytopenia

- Excessive **destruction**
  - Immune mediated thrombocytopenia (IMT)
- **Infectious** (variable mechanisms)
  - *Erlichia*
  - *Babesia*
  - *Angiostrongylus*
  - *Anaplasma*

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Thrombocytopenia

- Effect of bleeding on platelet numbers?
- Haemorrhage will not result in platelet count less than 50 x 10^9
- Spontaneous haemorrhage will not occur unless platelet count less than 30 x 10^9
  - Unless platelet dysfunction present

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"Guinness"

- Thrombocytopenia
  - ~~Decreased production~~?
    - Other cell lines fine
  - Consumption?
    - ~~Haemorrhage~~?
    - DIC is possible
      - Complication of IMHA
    - ~~Infectious?~~
      - Not in an endemic area and no travel history
  - Destruction?
    - Immune-mediated thrombocytopenia (IMT) definitely possible

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Immune mediated disease

- Primary
  - No underlying cause
- Secondary e.g.
  - Lymphoma
  - Haemangiosarcoma
  - Drugs

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Further plans?

- Ensure no relevant drug history
- Carefully evaluate again – especially lymph nodes etc
- Coombes test?
- Check for DIC (disseminated intravascular coagulation)
  - Clotting times, D-dimer
- Ultrasound spleen

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Final diagnosis

- Immune mediated haemolytic anaemia and thrombocytopenia (Evans Syndrome)
- Successfully treated:
  - Prednisolone
    - 2-3 mg/kg for a dog of his size then tapered
  - If available
    - Azathioprine
    - Vincristine

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James
2 year old male neutered Pomeranian

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History and physical examination

- Presented for black tarry diarrhoea and reduced appetite for 1 week
- Physical exam difficult ….highly aggressive!
- Mucous membranes (through muzzle) pale
- Rest of physical exam unremarkable

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Problem list

- Melaena
- Pale mucous membranes
- Not a very nice dog!

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Key questions that will change the direction of the case

- Is the melaena due to
  - Swallowed blood?
  - Primary GI disease?
  - Secondary GI disease causing GI ulceration?
  - Coagulopathy?
- Are the pale mm due to decreased perfusion or anaemia?

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Pathology results (in house)

- PCV = 18% (35-55)
- MCV (mean corpuscular volume) 78 (60-74)
- Reticulocyte count (corrected) = 4.4%
- Platelet count = 100 x 10^9 (200-500)
- Total protein = 50g/L (55-75)
- All biochemistry normal
- Faecal flotation negative
- Plain abdominal radiographs unremarkable

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Problem list

- Melaena
- Pale mucous membranes = regenerative anaemia
- Hypoproteinaemia
- Thrombocytopenia

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Key questions that will change the direction of the case

- Is the melaena due to primary GI disease, secondary GI disease or a coagulopathy?
  - No evidence for swallowed blood
  - Not thrombocytopenic
  - Need to fully assess coagulation
- Are the pale mm due to decreased perfusion or anaemia?
  - Anaemia
  - Now I need to know more than the numbers

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Pathology results (laboratory)

- Coagulation profile = normal
- Blood film review
  - *Platelets are clumped and decreased*
  - *Mild anisocytosis, mild polychromasia, mild hypochromasia, mild macrocytosis =consistent with regenerative anaemia*
  - *There are occasional mast cells present*

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Problem list

- Melaena
- Regenerative anaemia
- Hypoproteinaemia
- Thrombocytopenia
- Circulating mast cells
  - Inflammation (uncommon)
  - Neoplasia (most likely)

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Final outcome

- Owner declined further diagnostics
  - Ultrasound
  - Exploratory surgery
- Post mortem confirmed infiltrative GI mast cell neoplasia

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"Robert"

10 year old male (N)
English Pointer

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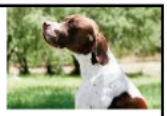
History



- Had appeared ok first thing in the morning
- Had eaten normally
- Was walked outside to car this evening and collapsed
- Standing again when presented at the vet

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Physical examination

- Reasonably alert
- Very pale mucous membranes
- HR 120
- Chest auscultation unremarkable,
- Abdominal palpation unremarkable
- Temperature 38.1
- No petechiae evident

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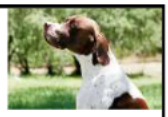
Problem list



- Collapse
- Pale mucous membranes

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Haematology – the relevant numbers

PCV	12%	37-55
MCV	60	64-76
Reticulocyte count	1.65% (corrected)	<1.0%
Total plasma protein	66	55-75 g/L
Mild neutrophilia with lymphopenia and eosinopenia		

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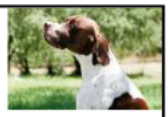
"Robert"



- Mild regenerative anaemia
- Microcytosis
- Stress leukogram

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Microcytosis

- Iron deficiency due to external blood loss
- Most commonly from chronic GI bleeding
  - Local disease
  - Systemic disease causing ulceration
  - Coagulopathy
- Portacaval shunt
  - → Microcytosis in ~ 50% cases but anaemia not usually a feature

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"Robert"

- Anaemia too severe for portacaval shunt
- Coagulation profile was normal
- Check drug history for NSAIDs
  - none
- Check for urine blood
- Check for faecal occult blood
  - +ve but dinner yesterday was raw kangaroo meat
- Check for parasites
  - Negative

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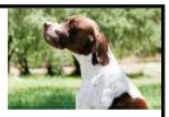
"Robert"



- Strong suspicion for GI bleeding due to a focal lesion causing microcytic anaemia
- Owner declined further diagnostics
- Treated symptomatically
  - Carafate and cimetidine
- PCV increased to 22%

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"Robert" – progress

2 weeks later
- PCV 18%
- Passing very dark faeces
- Owner declined further diagnostics

4 weeks later
- PCV 15%
- Owner consented to referral ultrasonography

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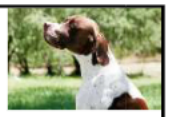
"Robert" – progress



- Ultrasonography – showed small mid-abdominal mass
- Exploratory laparotomy
  - Ulcerated jejunal mass
  - Histopathology = stromal tumour – leiomyoma
- 6 month follow up – still doing well

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Take home message?

- The final assessment of patients with anaemia and bleeding requires understanding of what the haemogram is telling you
- When the patient is anaemic you need more than the PCV
- And you must assess plasma protein, RBC size and RBC morphology
  - Guinness – TPP and NRBCs
  - James – blood smear ➔ mast cells
  - Robert – MCV = microcytosis

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And finally – beware of diagnostic bias

Availability bias	A tendency to favour a diagnosis because of a case the clinician has been seen recently.
Anchoring bias	Where a prior diagnosis is favoured but is misleading. The clinician persists with the initial diagnosis and is unwilling to change his or her mind
Framing bias	Features that do not fit with the favoured diagnosis are ignored
Confirmation bias	When information is selectively chosen to confirm, not refute a hypothesis. The clinician only seeks or takes note of information that will confirm his or her diagnosis, and does not seek or ignore information that will challenge it.
Premature closure	Narrowing the choice of diagnostic hypotheses too early

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Vomiting in small animals - *a logical diagnostic approach to "vomiting"*

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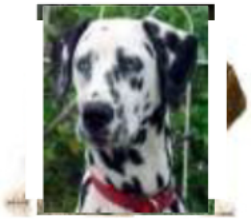
Professor of General Practice
BVetMed Course Director

Shaping passions, shaping futures

1

My dog or cat is "vomiting"



2

Diagnostic approach to the "vomiting" patient

- Define the problem
- Define the system
- Define the location
- Define the lesion

3

Define the problem

- Vomiting
- Regurgitation
- Gagging
- Coughing
- Reflux

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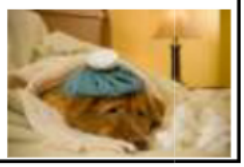
Stages of vomiting

- **Nausea**
  - reduced gastric tone
  - duodenal and proximal jejunal tone is increased
  - duodenal contents reflux into the stomach
  - depression, hypersalivation, repeated swallowing
- **Retching**



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Stages of vomiting

- **Vomiting**
  - glottis closed
    soft palate pressed up against nasopharynx
    - protects against aspiration

    abdominal muscles and diaphragm contract
  - cardia opens, pyloris contracts
    reverse peristalsis
  - cardiac rhythm disturbances
  - changes in colonic motility

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6

Regurgitation

- Passive process
  - no coordinated movements
- Beware of gag reflex
- Often induced or exacerbated by alterations in food consistency and exercise
- Facilitated by gravity when the head and neck are held down and extended

RVC

7

Vomiting v regurgitation vs reflux - clues?

- Behaviour?
- Bile?
- pH?
- Appearance of food?
- Mucous?
- Cough?
- May need to observe
- Both vomiting and regurgitation can be occurring

RVC

8

Why is important to define the problem?

- Investigations totally different
- Lesions totally different
- Management totally different

RVC

9

For example –vomiting?

- Often can be treated symptomatically
- If need to investigate various tests can be useful
  - Biochemistry
  - Haematology
  - Urinalysis
  - Abdominal imaging
  - Endoscopy
  - Exploratory laparotomy

RVC

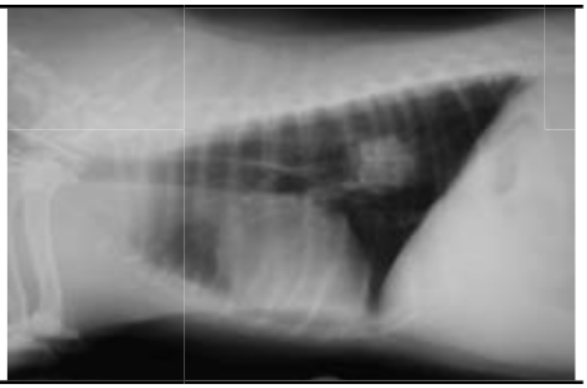
10

Regurgitation?

- Rarely responds to symptomatic treatment
- If persistent is usually a "bad" disease
- To investigate?
  - Imaging of the oesophagus
    - plain rads
    - contrast
    - fluoroscopy
  - Endoscopy

RVC

11



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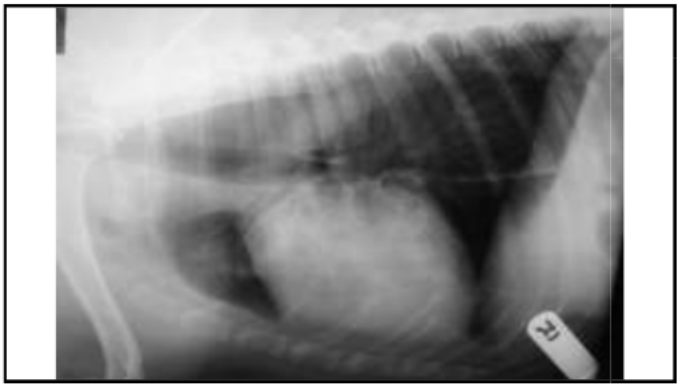

13

To investigate regurgitation?

- But not haematology, biochemistry, exploratory laparotomy
- Some are a waste of money
- Some are downright dangerous in a patient with oesophageal disease

RVC

14

Why have a systematic approach to defining the problem?

- Incorrect definition of problem can lead to:
  - potentially endangering patient by delayed or incorrect diagnosis
  - wasted time
  - wasted money
  - impair vet/client relationship and trust

RVC

15

Why does it matter?

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16

Vomiting is confirmed

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17

Define the system

- Primary GI disease
- Secondary GI disease

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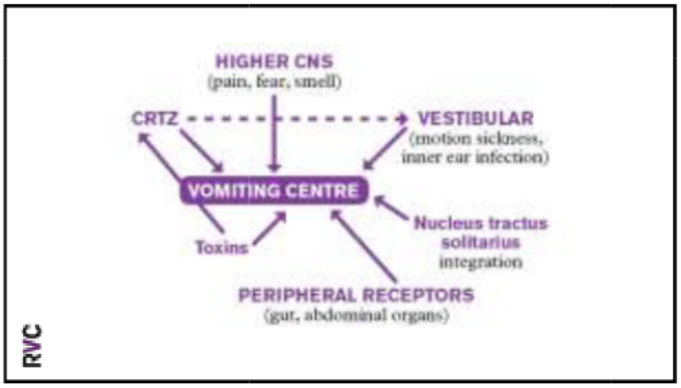
18

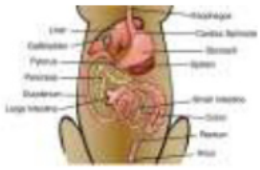


19

Define the system

Primary GI (structural)

- Stomach to the large bowel



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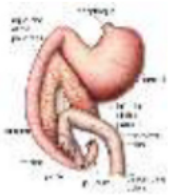
20

Define the system

Secondary GI (functional)

- Accessory digestive organ
  - Pancreas
- Electrolyte imbalance
  - Na^+
  - K^+
  - Ca^{2+}



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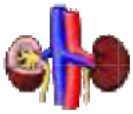
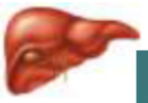
Define the system

Secondary GI (functional)

- Endogenous toxins
  - Kidney
  - Liver
  - Ketoacidosis
  - Infection
- Exogenous toxins
  - Primary CNS





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Why is this important?

- Investigations totally different
- Lesions totally different

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To investigate **secondary** GI disease?

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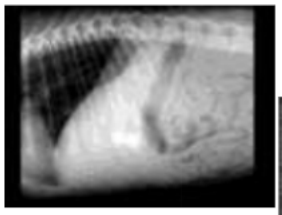
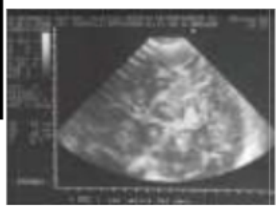
To investigate **secondary** GI disease?





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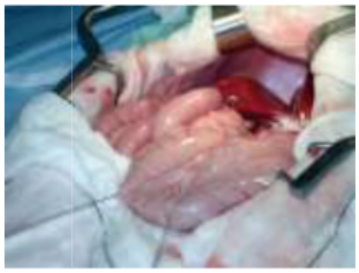
To investigate **secondary** GI disease?



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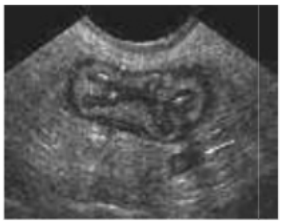
26

To investigate **primary** GI disease?



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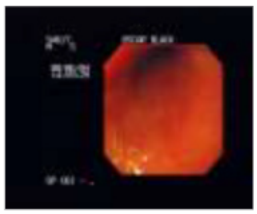
27

To investigate **primary** GI disease?



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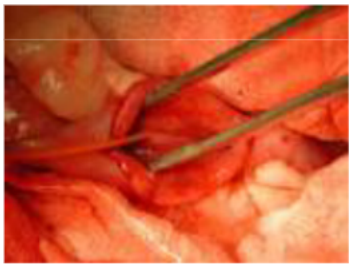
To investigate **primary** GI disease?



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To investigate primary GI

May give information about the clinical status of the patient but rarely the cause of the vomiting

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Why does it matter?

- Incorrect definition of the system can lead to:
  - wasted time
  - wasted money
  - potentially endanger patient by delayed or incorrect diagnosis

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Why does it matter?

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32

Why does it matter?

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33

Why is this important?

- Rational use of diagnostic aids to achieve maximum benefit and value for the client's investment

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Why is this important?

- Better communication with client

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35

Primary vs secondary clues?

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Primary GI

- Vomiting will often (but not always) relate in time to eating
- Vomiting may be delayed for some hours in animals with non-inflammatory gastric disorders
- Animals with foreign bodies or secretory disorders of the bowel often vomit despite not eating
- Vomiting more commonly occurs at variable times after eating in lower bowel disorders

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Primary GI

- Animal may be normal in all respects, including appetite
- Or they may be depressed and inappetant due to:
  - the particular lesion
  - the secondary effects of prolonged vomiting

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Primary GI

Should be strongly suspected if:

- An abnormality is palpable in the gut, e.g. foreign body, intussusception
- The vomiting is associated with significant diarrhoea
- The patient is clinically and historically normal in all other respects
- The onset of vomiting significantly preceded any development of signs of malaise – depression and/or anorexia
- The vomiting is consistently related in time to eating

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Secondary GI

Should be strongly suspected if the vomiting:

- Occurred subsequent to the onset of other signs of malaise – inappetance and/or depression
- Other clinical signs present e.g. jaundice, PU/PD

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Secondary GI

- Patients usually metabolically ill
- Exceptions
  - Early pancreatitis
  - Hyperthyroid cats

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Can't tell?

- Patient started vomiting and became metabolically ill at around the same time
- No clues strongly suggesting primary or secondary GI

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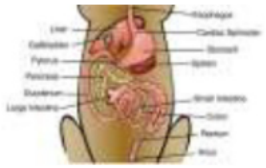
Define the location – primary GI

- Stomach to the colon



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Define the location

Primary GI disease

- Assessment of likely location/s important in determining what diagnostic method is appropriate
  - barium meal
  - barium enema
  - endoscopy
  - proctoscopy
  - laparotomy

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"Common" primary GI causes of vomiting

- Gastritis
  - Spoiled food
  - Dietary indiscretion
  - Food intolerance
- Viral infection (dog)
  - Parvo
  - Corona
  - Rota
- Foreign body
- GI neoplasm

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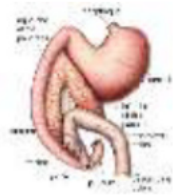
Define the location – secondary GI

- Accessory digestive organ
  - Pancreas
- Electrolyte imbalance
  - Na^+
  - K^+
  - Ca^{2+}



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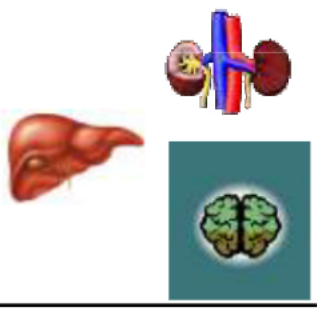
46

Define the location – secondary GI

- Endogenous toxins
  - Kidney
  - Liver
  - Ketoacidosis
  - Infection
  - Neoplasia
- Exogenous toxins
- Primary CNS



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47

"Common" secondary GI causes of vomiting

- Pancreatitis
- Liver disease
- Renal disease
- Endocrine disease
  - Diabetic ketoacidosis
  - Hypoadrenocorticism
  - Hypercalcaemia

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Diagnostic approach to the "vomiting" patient - summary

- Careful evaluation of the history and physical examination
  - Vomiting or regurgitating?
  - Or possibly reflux
  - If vomiting - Primary or secondary GI or can't tell?
  - It doesn't matter if you can't answer the question as long as you ask it!

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Diagnostic approach to the vomiting patient - summary

- Investigate secondary GI if appropriate
  - to eliminate secondary GI if not sure
  - to identify organ/pathology
  - to assess underlying disease that may influence management/prognosis
  - to assess metabolic effects of vomiting

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Diagnostic approach to the vomiting patient- summary

- If history, physical examination and/or clinical pathology rules out 2° GI disease:
- Investigate primary GI disease
  - plain & contrast radiographs
  - ultrasound
  - endoscopy
  - exploratory laparotomy

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Questions?

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RVC Royal Veterinary College University of London

Logical approach to diarrhoea in dogs and cats

Jill E Maddison
BVSc, DipVetClinStud, PhD, FACVSc, SFHEA, MRCVS
Professor of General Practice

Shaping passions, advancing futures

1

Problem based approach – most problems

- Define the problem
- Define the system
- Define the location
- Define the lesion

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Problem based approach – diarrhoea

- Define the problem
- Define the location
- Define the system
- Define the lesion

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3

Define the problem

- Alteration in normal pattern of defaecation
  - soft, unformed stools
  - increased faecal water content
  - and/or
  - increased frequency of defaecation

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Define the problem

- Usually no problem with definition
- Some owners may confuse
  - Vaginal discharge
  - Anal sac discharge
- Beware of constipation

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Classification of diarrhoea

- Relatively mild or more severe with the presence of secondary systemic effects?
- Acute or chronic?
- Acute
  - usually treat symptomatically
- Chronic
  - requires investigation
  - only a small proportion of cases in general practice

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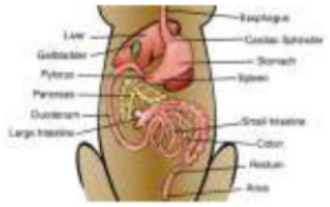
Classification of diarrhoea

Define location

- Small bowel
- Large bowel
- Mixed

Can also think of this as refining the problem



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Why is this important?

- Can help clarify if primary or secondary GI disease
- Different causes – small vs large bowel
- Some differences in useful diagnostic tools
  - Trypsin like immunoreactivity that tests for exocrine pancreatic insufficiency (TLI)
  - Endoscopy (small bowel) vs proctoscopy (large bowel)
- Different treatments

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Classification of diarrhoea

- A thorough history is……..?

ESSENTIAL!!!

- Physical exam often unremarkable

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Classification of diarrhoea

AVOID FRUSTRATION AND WASTED CLIENT FUNDS!!

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Classification of diarrhoea

- Small vs large bowel

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Small bowel diarrhoea

- Consistency
- Pattern
- Blood
- Colour
- Weight loss?
- Vomiting?
- Borborygmus and flatulence
- Appetite?
- Water balance
- Physical examination?

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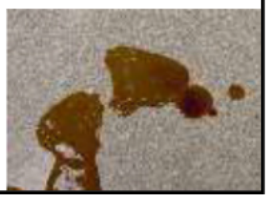
Large bowel diarrhoea

- Amount and frequency
- Mucus
- Fresh blood
- Tenesmus
- Weight loss?
- Appetite?
- Vomiting?
- Physical examination?



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Define the system

- **Small bowel** diarrhoea can be due to primary or secondary GI disease

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14

Define the system

- Primary GI disorders
- Secondary GI disorders
  - hepatic disease
  - pancreatic insufficiency
  - pancreatitis
  - hyperthyroidism
  - hypoadrenocorticism (Addison's disease)
  - renal disease

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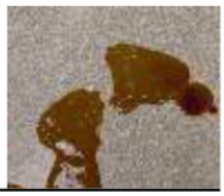
Define the system

- Overt **large bowel diarrhoea** as the major presenting sign almost always indicates there is a primary GI lesion
- **Mixed bowel diarrhoea** (signs of both small and large bowel) also usually due to primary GI disease
  - If it is the major clinical sign



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Secondary GI disease

This diarrhoea associated with secondary GI disease

- Most frequently has the characteristics of small bowel disease
- Diarrhoea is not usually the primary presenting complaint (except exocrine pancreatic insufficiency)

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Where is the stumbling block?

- Defining the problem?
- Defining the location?
- Defining the system?
- Defining the lesion
  - There aren't THAT many options!
  - But there are no easy blood tests to help!
  - Investigation requires mixture of:
    - faecal exam
    - therapeutic trial
    - perhaps more invasive tests

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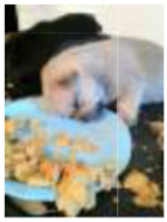
18

Acute small bowel diarrhoea - Define the lesion



- Diet related
  - overeating (especially pups)
  - dietary change
  - spoiled food
  - garbage
- Parasites
  - ascarids
  - hookworms

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Acute small bowel diarrhoea - Define the lesion

- Protozoa
  - *Giardia* sp.
  - *Coccidia*
- Infection
  - viral enteritis
    - Parvo
    - Corona
    - Rota
  - bacterial
    - Campylobacter (young animals only, mixed bowel diarrhoea, potential zoonotic)
    - Salmonella (uncommon but consider if fed raw food or a hunter, potential zoonotic)
    - Clostridium difficile (uncommon)
    - *E. coli*

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Acute small bowel diarrhoea - Define the lesion

- Acute haemorrhagic diarrhoea syndrome (AHDS)
  - Also called Haemorrhagic Gastroenteritis (HGE)
  - Acute onset of vomiting and bloody diarrhoea
  - Significant haemoconcentration (increased PCV) with a normal or low plasma protein
  - Typically described in small breed dogs but any size/breed can be affected
  - Cause may be novel necrotising toxin produced by Type A *Clostridia perfringens*
  - However, antimicrobial therapy does not improve outcome unless the patient is septic

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Chronic small bowel diarrhoea - Define the lesion

- Toxins
- Parasites
  - *Toxocara* (round worms)
  - *Ancylostoma* (hookworms)
  - Note that have pubic health implications (visceral larval migrans)
- Diet related
  - lactose intolerance (relatively common)
  - gluten intolerance (uncommon)
  - dietary hypersensitivity/intolerance (common)

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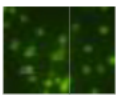
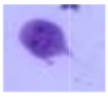
Chronic small bowel diarrhoea - Define the lesion





- Bacteria and protozoa
  - *Campylobacter* (rarely clinically significant in adults, zoonotic potential)
  - *Clostridium* (many false positive on faecal panels)
  - *Giardia* (zoonotic potential very low)
  - *Cryptosporidium* (zoonotic potential low – reported in immunocompromised patients)
  - *Coccidia* (*Cystoisospora* spp.) not zoonotic
- Deep mycoses
  - In some geographic areas e.g. Asia, part of USA
  - E.g. Prototheocosis

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Dietary hypersensitivity

- Chronic intermittent diarrhoea vomiting, pruritus
  - Cat: ears, face
  - Dog: axillary region, feet
- Allergens
  - Dog: beef, lamb, chicken, wheat (gluten)
  - Cat: fish, milk and dairy

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Chronic small bowel diarrhoea

- Inflammatory bowel disease (IBD)
- Now called Chronic Enteropathy (CE)
  - Diet responsive CE (most common)
  - Immunosuppressive responsive CE
    - Probably *real* IBD
  - Antibiotic responsive CE (very uncommon)
    - abnormal/unbalanced bacterial population
    - abnormal gut reaction to normal bacterial population
    - combination of both
  - Non-responsive CE

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Chronic enteropathy (CE)

- Not a single disease
- Detection of gut inflammation does not = IBD requiring immunosuppressive therapy
- A good proportion of patients will respond to dietary change
- A small number need immunosuppressive therapy
- A very small number to antibiotics
  - Young, large breed dogs most likely

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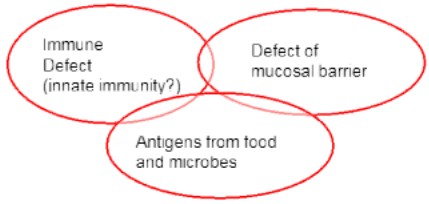
Chronic enteropathy



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Chronic enteropathy – treatment trials - diet

- Dietary trial
  - Novel protein or hydrolysed
  - If one doesn't work try another
  - MUST ensure total compliance – NO other food or treats of any sort

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Dietary trials

- Full response may take 6-10 weeks
- But reasonable response should be seen within 2 weeks
- Much harder in cats
- Keep cats on elimination diets indoors
  - Mice/birds are not hypoallergenic!

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Chronic enteropathy – treatment trials - antibiotics

- Smallest cohort of dogs
  - Diet related chronic enteropathy much, much more common
  - Often large breed, young
- If no response to a properly conducted dietary trial
- ➔ metronidazole or tylosin
  - For dysbiosis
  - Often require recurrent treatment
  - Increased fibre in diet may help
- No response to either diet or antibiotics?

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Chronic enteropathy – IBD

- Genetic immune defect?
- Some respond to immunosuppressive treatment
  - Prednisolone
  - Azathioprine
  - Cyclosporin
  - Chlorambucil
- For small group no Rx is effective

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Chronic small bowel diarrhoea

- Neoplastic
  - diffuse lymphosarcoma
  - adenocarcinoma
  - mastocytoma
  - other
- Lymphangiectasia (primary or secondary)
- Brush border enzyme biochemical defects

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Chronic small bowel diarrhoea – secondary GI causes

- Hypoadrenocorticism (dogs, rarely cats)
- Hyperthyroidism (cats)
- Exocrine pancreatic insufficiency - EPI (dogs, occasionally cats)
- Chronic pancreatitis (dogs & cats)
- Liver disease (dogs and cats)
- There will usually be clinical signs in addition to diarrhoea except for EPI

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Protein losing enteropathy (PLE)

- Protein-losing enteropathy (PLE) is a syndrome rather than a specific disease
- Occurs when diffuse small intestinal disease results in excessive loss of serum proteins into the gut causing hypoproteinaemia

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Protein losing enteropathy (PLE)

- Main causes are:
  - Immunosuppressive-responsive or non-responsive chronic enteropathy (aka IBD)
  - Lymphangiectasia
  - Lymphoma
- Most common clinical signs:
  - GI signs
    - diarrhoea +/- vomiting
  - Weight loss
  - Effects of hypoproteinaemia
    - ascites, pleural effusion, peripheral oedema

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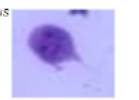
35

Large bowel diarrhoea - Define the lesion

- Parasites
  - *Trichuris vulpis (dogs)*
  - *Ancylostoma caninum*
    - *Potential public health issue – cutaneous larval migrans*
- Protozoa
  - *Giardia*
  - *Entamoeba* sp
  - *Tritrichomonas foetus* (cats)



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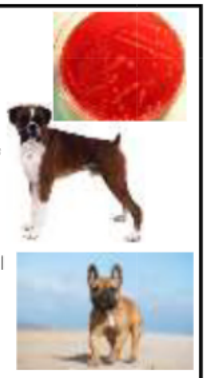
Large bowel diarrhoea - Define the lesion

- Bacteria
  - *Campylobacter* *(rarely clinically significant in adults but is zoonotic)*
  - *Clostridium* *(many false positive on faecal panels)*
  - *Salmonella* sp. *(very uncommon but consider if fed raw food or a hunter; potential zoonotic)*
  - Granulomatous colitis (Boxers, French Bull dogs)
    - Enteropathogenic invasive *E.coli*



RVC

37

Large bowel diarrhoea - Define the lesion

- Diet related
  - Toxicity (garbage etc)
  - "Fibre-responsive"
  - Dietary hypersensitivity/intolerance
- Inflammatory
  - Idiopathic ulcerative
  - Eosinophilic
  - Granulomatous
- Neoplasia
- Stress
- Strictures

RVC

38

Mixed bowel diarrhoea

- Various aetiologies can affect the small and large bowel so may cause mixed bowel signs e.g.
  - *Giardia*
  - *Campylobacter*
  - Dietary indiscretion/intolerance/hypersensitivity
  - Acute haemorrhagic diarrhoea syndrome (AHDS)
  - Inflammatory

RVC

39

Thus

- Work logically through the possibilities

PATIENCE!

RVC

40

Diagnostic tools - chronic small and large bowel diarrhoea

- Faecal flotation for helminths +/- treatment with a broad spectrum anthelmintic
- Fresh faecal examination for Giardia or antigen test or treat with fenbendazole
- Full blood count and total plasma protein
- Faecal culture?
- Faecal panels?

RVC

41

Diagnostic approach – small bowel only

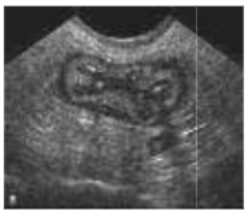
- Serum trypsin like immunoreactivity (TLI)
  - If exocrine pancreatic insufficiency (EPI) a realistic differential diagnosis
- Cobalamin (B_{12}) and folate?
  - Too non-specific to help with diagnosis in most cases
  - Useful to asses if cobalamin supplementation needed – gut disease and almost always EPI
  - If low at diagnosis, may be poor prognostic marker for IBD

RVC

42

Diagnostic tools - chronic small and large bowel diarrhoea

- Ultrasound
  - Duodenal wall should be < 3mm
  - Jejunum/ileum < 2mm
  - Assess if mucosa or muscularis thickened as will influence biopsy method
  - Assess if there is loss of layering indicating infiltrative disease



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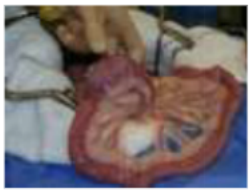
43

Diagnostic tools - chronic small and large bowel diarrhoea

- Biopsy
  - endoscopy
  - laparotomy



RVC

44

Trials vs biopsy

- The healthier the patient the more consideration should be given to therapeutic trials instead of biopsy
  - Modest to no weight loss
  - Relatively good body condition score
  - Normal serum albumin concentration
  - Not lethargic
  - Not anorexic
  - No ultrasonographic evidence of infiltrative disease
  - Normal B12

RVC

45

When should I biopsy?

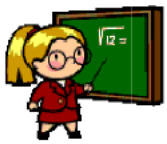
- Thus consider earlier rather than later if there is:
  - hypoproteinaemia
  - significantly thickened intestinal wall and/or loss of wall layering
  - significant weight loss
  - hypercalcaemia
  - low B12
  - neoplasia strongly suspected
  - owner unable/unwilling to follow diagnostic plan
- But ….questionable value in differentiating IBD from small cell lymphoma in cats

RVC

46

Jill's "rules"

- In general practice, you will not usually need to biopsy an animal with chronic small or large bowel diarrhoea who is otherwise well and has no clues that there may be infiltrative disease (neoplasia, fungal, lymphangiectasia) until they have been……



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Jill's "rules" for assessing chronic diarrhoea

- Treated for parasites
  - Helminths and *Giardia*
- Proper dietary trial
  - Single novel protein source or hydrolysed diet
    - If one doesn't work, try another one
  - Increased fibre diet – especially large bowel diarrhoea

- If that's not successful ……..
- Treat with metronidazole or tylosin for antibiotic responsive enteropathy (only needed for a very few number of cases)

RVC

48

Jill's "rules"

- If small bowel diarrhoea present ensure secondary GI disease ruled out before biopsy
  (noting species difference previously discussed)
  - Exocrine pancreatic insufficiency
  - Hyperthyroidism
  - Liver disease
  - Hypoadrenocorticism (Addison's disease)

RVC

49

Diagnostic approach - chronic diarrhoea

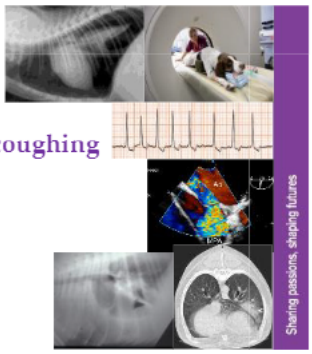
Overall aims of diagnostic approach

- Non-invasive → invasive
- Inexpensive → expensive
- Therapeutic or dietary trial – if at all possible only change one element
  - So you know what worked!

RVC

50

RVC Royal Veterinary College University of London



Logical approach to coughing and dyspnea

Croatia, 2023

David B Church

Sharing passions, shaping futures

1

Cardiorespiratory disease

Define the problem

What are the likely problems that make us feel we might be dealing with cardiorespiratory disease ??

RVC

2

Cardiorespiratory disease: problems ??

- sneezing/nasal discharge
- coughing
- dyspnea
- coughing and dyspnea
- ascites
- syncope

RVC

3

A logical approach to clinical problem solving

Define the problem

Define the system

Define the location

Define the lesion

RVC

4

Cardiorespiratory disease

Problem	System
sneezing/discharge	Respiratory
coughing	
dyspnea	
coughing & dyspnea	
ascites	Cardiovascular/oncotic pressure
syncope	Neurological

RVC

5

Respiratory disease

Problem	Location
sneezing/discharge	???
coughing	???
dyspnea	???
coughing & dyspnea	???

Can the clinical signs help us with localization?

RVC

6

Maxie 7 yr M Lab

System?respiratory

- decreased exercise tolerance
- marked dyspnea
- no coughing
- mitral murmur III/VI, HR=140
- increased respiratory sounds
- presented collapsed and cyanotic

What part of the respiratory system?

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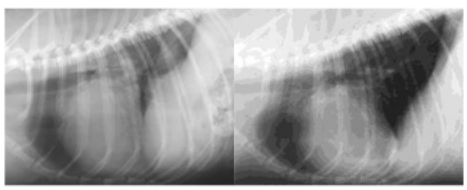
7



On admission 4 hr later

RVC

8

I think the most likely treatment was:

1. Aminophylline
2. Enalapril
3. Furosemide
4. Pimobenden
5. Intubation

RVC

9

Tetley 7 year M JRT

RVC

10

Tetley 7 year M JRT

History

- coughing:
  - started approximately 3 months ago
  - progressively worsening
  - normal respiratory effort
- left systolic murmur 5th ICS (heard previously)

RVC

11

Tetley 7 year M JRT

Physical examination

- coughing which is unproductive
- normal cardiac impulse and respiratory rate (28)
- markedly increased thoracic sounds
- left systolic murmur PMI 5th ICS, HR 110
- otherwise unremarkable

RVC

12

Tetley 7 year M JRT

Assessment

??????

RVC

13

Tetley 7 year M JRT

Problem list

What system(s) is/are involved ?

1. coughing
2. increased thoracic respiratory sounds
3. systolic murmur over the mitral valve region

RVC

14

Tetley 7 year M JRT

Problem list

What system(s) is/are involved ?

1. coughing - respiratory
   What part of the respiratory system?
2. increased thoracic respiratory sounds - respiratory
3. systolic murmur over the mitral valve region – cardiac

RVC

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Respiratory disease

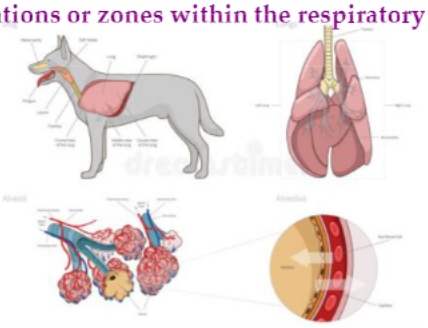
Problem	Location
sneezing/discharge	???
coughing with minimal dyspnea	???
dyspnea with minimal coughing	???
coughing *and* dyspnea	???

Now can the clinical signs help us with localization?

RVC

16

Locations or zones within the respiratory tract



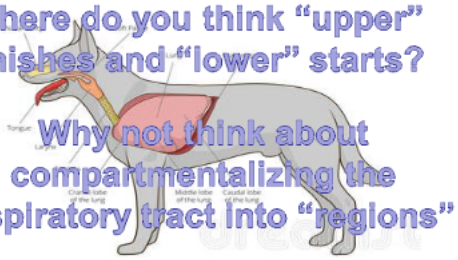
RVC

17

Locations or zones within the respiratory tract

Where do you think "upper" finishes and "lower" starts?

Why not think about compartmentalizing the respiratory tract into "regions"



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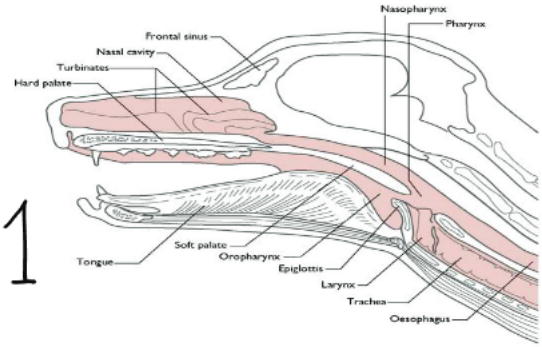

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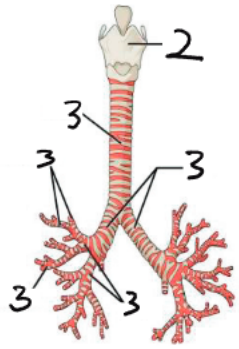

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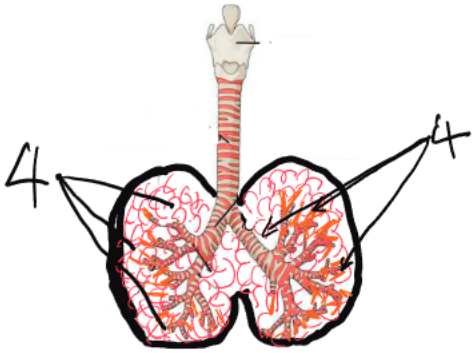

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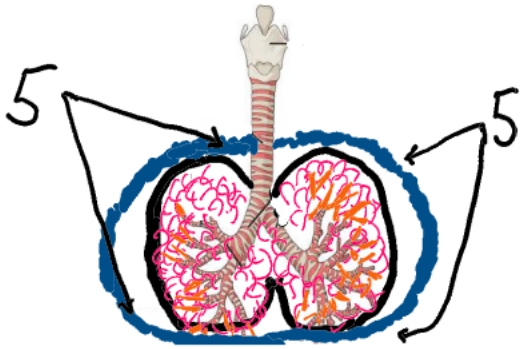

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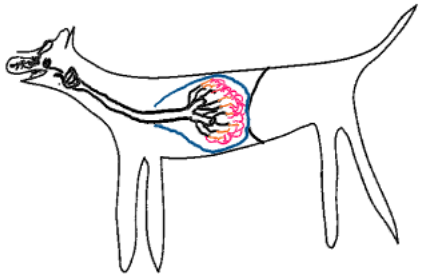
Locations or zones within the respiratory tract



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23

Locations or zones within the respiratory tract

1. Nasal cavity and cranial oro-pharynx
2. Larynx and caudal oro-pharynx
3. Trachea and larger airways (bronchi)
4. Alveoli and bronchioles
5. Pleural space and mediastinal space

RVC

24

Respiratory disease

Problem	Location
sneezing/discharge	nasal cavity/oropharynx
coughing with minimal dyspnea	???
dyspnea with minimal coughing	???
coughing *and* dyspnea	???

RVC **Can the clinical signs help us with localization?**

25

Tetley 7 year M JRT

RVC

26

Tetley 7 year M JRT

History

- coughing:
  - started approximately 3 months ago
  - progressively worsening
  - no dyspnea
- left systolic murmur 5th ICS (heard previously)

RVC

27

Tetley 7 year M JRT

Physical examination

- coughing which is unproductive
- normal cardiac impulse and respiratory rate (28)
- markedly increased thoracic sounds
- left systolic murmur PMI 5th ICS, HR 110
- otherwise unremarkable

RVC

28

Tetley 7 year M JRT

Problem list

What part of the respiratory system?

1. coughing - respiratory
2. increased thoracic respiratory sounds - respiratory
3. systolic murmur over the mitral valve region – cardiac

RVC

29

Tetley 7 year M JRT

Problem list

What part of the respiratory system?

1. coughing with minimal dyspnea- respiratory
2. increased thoracic respiratory sounds - respiratory
3. systolic murmur over the mitral valve region – cardiac

RVC

30

Tetley 7 year M JRT

Assessment

- respiratory disease
  - the location of the respiratory disease ??
  - is it primary or secondary ??
- cardiac disease
  - is it primary or secondary ??

RVC

31

Coughing with *minimal* dyspnoea

Define the system

- respiratory tract

Define the location

- what parts are most likely to be involved ?

RVC

32

Coughing with *minimal* dyspnoea

Define the system

- respiratory tract

Define the location

- what parts are most likely to be involved ?
- where in the respiratory tract are the cough receptors located ?

RVC

33

Locations or zones within the respiratory tract

1. Nasal cavity and cranial oro-pharynx
2. Larynx and caudal oro-pharynx
3. Trachea and larger airways (bronchi)
4. Alveoli and bronchioles
5. Pleural space and mediastinal space

RVC

34

Coughing with *minimal* dyspnoea

Define the system

- respiratory tract

Define the location

- tracheal disease
- bronchial disease

Can we focus on anything that might help determine if it is more likely to be tracheal or bronchial ?

What part of the respiratory tract are making the respiratory sounds we can auscultate over the thorax ?

RVC

35

Coughing with *minimal* dyspnoea

Define the system

- respiratory tract

Define the location

- tracheal disease
- bronchial disease

Can we focus on anything that might help determine if it is more likely to be tracheal or bronchial ?

With increased thoracic respiratory sounds we are likely to be dealing with bronchial disease

RVC

36

Tetley 7 year M JRT

Problem list

1. coughing with minimal dyspnea- respiratory
2. increased thoracic respiratory sounds - respiratory
3. systolic murmur over the mitral valve region – cardiac

RVC

37

Tetley 7 year M JRT

Assessment

- respiratory disease
  - the location of the respiratory disease ??
  - is it primary or secondary ??
- cardiac disease
  - is it primary or secondary ??

RVC

38

Tetley 7 year M JRT

Assessment

- respiratory disease
  - bronchial disease +/- trachea
  - is it primary or secondary ??
- cardiac disease
  - is it primary or secondary ??

RVC

39

Tetley 7 year M JRT

Assessment

- respiratory disease
  - bronchial disease +/- trachea
  - is it primary or secondary ??
- left AV insufficiency
  - is it primary or secondary ??

RVC

40

Tetley 7 year M JRT

Assessment

- respiratory disease
  - bronchial disease +/- trachea
  - is it primary or secondary ??
- left AV insufficiency
  - primary structural cardiac disease

RVC

41

Is the dog coughing & dyspneic because of cardiac disease ?

- the respiratory tract is unarguably involved but the important question is:
  - is it secondary involvement to the equally clearly present cardiac disease?
  - remember secondary involvement can result in structural changes in the affected organ producing the clinical signs
- there is a rather large clue we can *all* utilize, regardless of available facilities, to help decide if the cardiac disease is likely to be causing the coughing and dyspnea..

RVC

42

Tetley 7 year M JRT

Assessment

Two crucial questions ...
Is he dyspneic/tachypneic?
Is he tachycardic?

- respiratory disease
  - bronchial disease +/- trachea
  - is it primary or secondary ??
- left AV insufficiency
  - primary structural cardiac disease

RVC

43

Tetley 7 year M JRT

Physical examination

- coughing which is unproductive
- normal cardiac impulse and respiratory rate (28)
- markedly increased thoracic sounds
- left systolic murmur PMI 5th ICS, HR 110
- otherwise unremarkable

RVC

44

Tetley 7 year M JRT

Assessment

Two crucial questions ...
Is he dyspneic/tachypneic?
Is he tachycardic?

- respiratory disease
  - bronchial disease +/- trachea
  - more likely to be primary
- left AV insufficiency
  - primary structural cardiac disease

RVC

45

Tetley 7 year M JRT

Diagnostic tests

- chest radiographs
- cine-radiography (fluoroscopy)
- electrocardiography
- echocardiography
- routine clinical pathology

RVC

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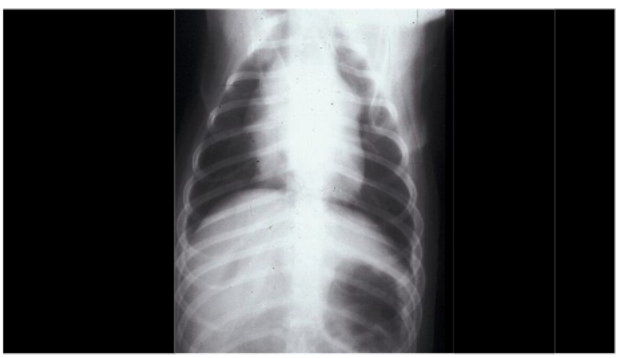

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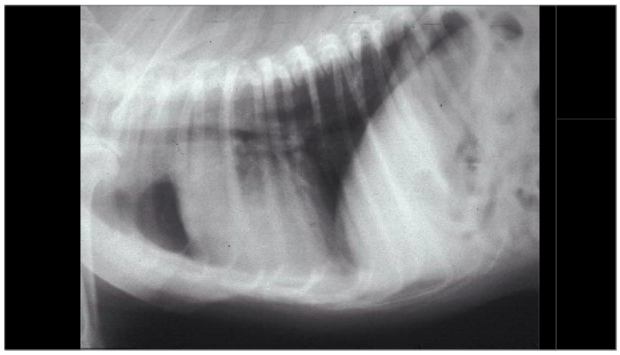

48

Coughing with *minimal* dyspnoea

Define the system

- respiratory tract

Define the location

- bronchial disease +/- tracheal disease

Define the lesion

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49

Tracheal disease: possible lesions

- malformations
- degenerative disease (collapsing airways)
- inflammation – exudative ?
- neoplasia

RVC

50

Bronchial disease: possible lesions

- malformations
- degenerative disease (collapsing airways)
- exudative inflammation
- constrictive inflammation
- neoplasia

increased thoracic respiratory sounds

RVC

51

Coughing with *minimal* dyspnea: bronchial lesions

1. malformations
2. degenerative disease
3. exudative inflammation
4. constrictive inflammation
5. neoplasia

RVC

52

Tracheal disease: possible lesions

1. malformations
2. degenerative disease (collapsing airways)
3. inflammation – exudative ?
4. neoplasia

RVC

53

Coughing with *minimal* dyspnea: bronchial lesions

1. malformations
2. degenerative disease
3. exudative inflammation
4. constrictive inflammation
5. neoplasia

RVC

54

Coughing with minimal dyspnea

Tracheobronchial disease: possible lesions

- malformations
- degenerative disease (collapsing airways)
- inflammation
  - exudative
- neoplasia

RVC

55

Tetley 7 year M JRT

Assessment

- **respiratory disease**
  - **bronchial disease +/- trachea**
  - **more likely to be primary**
- **left AV insufficiency**
  - **primary structural cardiac disease**

RVC

56

Tetley 7 year M JRT

Assessment

- **respiratory disease**
  - **bronchial disease +/- trachea**
  - **more likely to be primary and not "structural"**
- **left AV insufficiency**
  - **primary structural cardiac disease**

RVC

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Tracheobronchial disease: optimal diagnostic aids

- tracheobronchoscopy
- cine-radiography (fluoroscopy)
- thoracic radiography or CT scan
- transtracheal aspirate or bronchial wash ……

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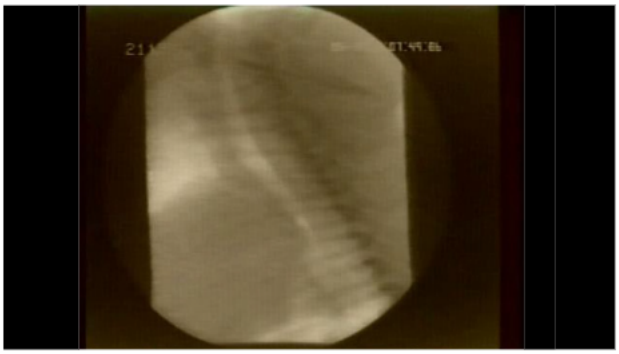
58



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Tracheobronchial disease: optimal diagnostic aids

- tracheobronchoscopy
- cine-radiography (fluoroscopy)
- thoracic radiography or CT scan
- transtracheal aspirate or bronchial wash ……

collapsing trachea/bronchi can NOT be diagnosed with thoracic radiography

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60

Respiratory disease

Problem	Location
sneezing/discharge	nasal cavity/oropharynx
coughing with minimal dyspnea	tracheobronchial
dyspnea with minimal coughing	???
coughing *and* dyspnea	???

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61

Dyspnea with *minimal* coughing

Define the system

- respiratory tract

Define the location

- laryngeal dysfunction
- intrathoracic disease

RVC

62

Dyspnea with *minimal* coughing

Define the system

- respiratory tract

Define the location

- laryngeal dysfunction
- intrathoracic disease

auscultation

RVC

63

Laryngeal disease

RVC

64

Laryngeal disease

Define the lesion

???????

RVC

65

Laryngeal disease: lesions

- malformations
  - everting lateral saccules
  - disproportionate rima glottis
- degenerative disorders
  - chondromalacic lesions
- inflammation
- neoplasia
- paresis
  - primary and secondary neuromuscular diseases
  - idiopathic neuromuscular disorders

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Laryngeal disease: diagnosis

- auscultation
  - laryngeal
  - thoracic
- laryngoscopy
  - sedation: acepromazine
  - anesthesia: propofol to effect
  - pre-examination doxapram ??
- preparation for recovery or …

RVC

67

Dyspnea with *minimal* coughing

Define the system

- respiratory tract

Define the location

- laryngeal dysfunction
- intrathoracic disease

RVC

68

Dyspnea with *minimal* coughing

Define the system

- respiratory tract

Define the location

- laryngeal dysfunction
- intrathoracic disease

auscultation

RVC

69

Dyspnea with *minimal* coughing: intrathoracic locations

- pleural diseases
- bronchial diseases

auscultation

- alveolar diseases without bronchial involvement

RVC

70

Pleural disease: possible explanations or lesions

- effusions
  - transudate
  - exudate
  - blood or chyle
- air
- abnormal tissue (neoplasia)
- ectopic normal tissue (abdominal)

RVC

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Pleural disease: optimal diagnostic aids

- thoracic radiography or CT scan
- ultrasonography
- thoracocentesis
- thoracic drainage
- echocardiography

RVC

72

Pleural disease: possible explanations or lesions

- effusions
  - transudate
  - exudate
  - blood or chyle
- air
- abnormal tissue (neoplasia)
- ectopic normal tissue (abdominal)

RVC

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Pleural effusions that are transudates

- this will always be due to one of either:
  - increased hydrostatic pressure
  - reduced osmotic pressure
- if the raised hydrostatic pressure is due to heart failure
  - in the dog due to right heart failure
  - in the cat more likely due to left heart failure

RVC

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Pleural disease: possible explanations or lesions

- effusions
  - transudate
  - exudate
  - blood or chyle
- air
- abnormal tissue (neoplasia)
- ectopic normal tissue (abdominal)

RVC

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Dyspnea with *minimal* coughing: intrathoracic locations

- pleural diseases
- bronchial diseases

auscultation

- alveolar diseases without bronchial involvement

RVC

76

Bronchial disease: possible lesions

- malformations
- degenerative disease (collapsing airways)
- exudative inflammation
- constrictive inflammation
- neoplasia

increased thoracic respiratory sounds

RVC

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Coughing with *minimal* dyspnea: bronchial lesions

1. malformations
2. degenerative disease
3. exudative inflammation
4. [redacted]on
5. neoplasia

RVC

78

Dyspnea with *minimal* coughing: bronchial lesions

- [redacted]
- degenerative disease (collapsing airways) + emphysema
- [redacted]
- constrictive inflammation
- [redacted]

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Bronchial disease

Dyspnea with minimal coughing ☑

Coughing with minimal dyspnea ☑

Cough with significant dyspnea ☑

RVC

80

Bronchial disease: optimal diagnostic aids

- thoracic radiography or CT scan
- transtracheal aspirate or bronchial wash ……
- tracheobronchoscopy
- cine-radiography (fluoroscopy)
- hematology ??????

RVC

81

Sterile bronchial inflammation in cats

- immune mediated inflammation or "autoimmune disease"
- mixed clinical picture that can vary between two extremes:
  - bonchoconstriction with minimal exudate
  - exudative inflammation with minimal bronchoconstriction

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Bronchial disease

Dyspnea with minimal coughing ☑

Coughing with minimal dyspnea ☑

Cough with significant dyspnea ☑

RVC

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Dyspnea with *minimal* coughing: intrathoracic locations

- pleural diseases
- bronchial diseases

} **auscultation**

- alveolar diseases without bronchial involvement

RVC

84

Dyspnea with *minimal* coughing: alveolar lesions

- emphysema
- pulmonary fibrosis and degeneration
- early phases of pulmonary edema
- anything that produces fluid accumulation in the alveoli will usually ultimately involve the bronchi

RVC

85

Respiratory disease

Problem	Location
sneezing/discharge	nasal cavity/oropharynx
coughing with minimal dyspnea	tracheobronchial
dyspnea with minimal coughing	???
coughing *and* dyspnea	???

RVC

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Respiratory disease

Problem	Location
sneezing/discharge	nasal cavity/oropharynx
coughing with minimal dyspnea	tracheobronchial
dyspnea with minimal coughing	laryngeal/intrathoracic
coughing *and* dyspnea	???

RVC

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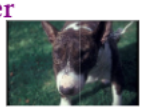
Arthur 5 year M Bull Terrier



History

- coughing and dyspnea for 5-6 days
- retching regularly
- progressive depression, lethargy and inappetance over the last 4 days

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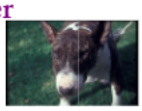
Arthur 5 year M Bull Terrier



Physical examination

- tachypnea and dyspnea (respiratory rate approximately 40/min)
- increased generalised thoracic respiratory sounds
- systolic murmur loudest over the mitral valve region (5th left ICS) with tachycardia (HR~180)

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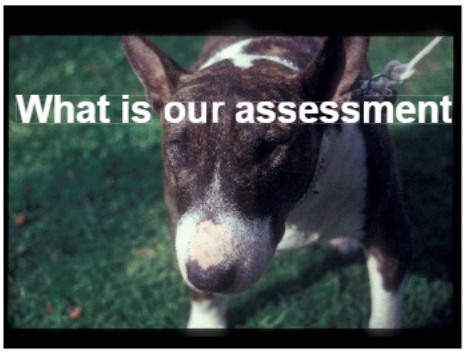
90



91

Arthur 5 year M Bull Terrier

Problem list

1. coughing and dyspnea
2. systolic murmur loudest 5th left ICS
3. depression & lethargy

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92

Respiratory disease

Problem	Location
sneezing/discharge	nasal cavity/oropharynx
coughing with minimal dyspnea	tracheobronchial
dyspnea with minimal coughing	laryngeal/pleural/bronchial
coughing *and* dyspnea	???

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93

Coughing *and* dyspnoea

Define the system

- respiratory tract

Define the location

- bronchial disease
- bronchoalveolar disease

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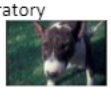
94

Arthur 5 year M Bull Terrier

Assessment

What to do now ?

- bronchoalveolar disease and mitral valve disease
- the bronchoalveolar disease could be *secondary* to heart failure resulting in pulmonary edema or…..
- there could be *primary* bronchoalveolar disease with a concurrent heart disorder that is *not* causing respiratory dysfunction
- he is tachycardic and tachypneic…



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Bronchoalveolar disease: optimal diagnostic aids

- thoracic radiography
- transtracheal aspirate
- bronchoscopy +/- washings
- fine needle aspirate or biopsy
- serology and fecal analysis
- hematology

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Arthur is most likely to have …..

1. pulmonary edema secondary to heart failure caused by dilated cardiomyopathy
2. pulmonary edema secondary to heart failure caused by mitral valve disease
3. bacterial bronchoalveolar inflammation
4. parasitic bronchial inflammation
5. bronchoalveolar neoplasia

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Arthur 5 year M Bull Terrier

Reassessment

- bronchoalveolar disease *and* mitral valve disease
- bronchoalveolar disease is most likely due to aspiration pneumonia
- concurrent heart disease that is *not* causing respiratory dysfunction
- what do we do now….
- establish cause of 'presumed' inflammation

RVC

98

Pulmonary parenchymal disease: thoracic radiography

Can it help identify the cause ?

on occasions, certainly

RVC

99

Respiratory disease

Problem	Location
sneezing/discharge	nasal cavity/oropharynx
coughing with minimal dyspnea	tracheobronchial
dyspnea with minimal coughing	laryngeal/pleural/bronchial
coughing *and* dyspnea	bronchoalveolar

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100

Chronic coughing & dyspnea in an older dog with MVD

- clinical dilemma …..
- what is happening with this dog ??
- is it primary respiratory disease or is it…
- heart failure causing secondary respiratory disease …

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101

Chronic coughing & dyspnea in an older dog with MVD

Typical heart failure patients

- a 'soft' cough, more at night
- sleep poorly
- have tachycardia
- will tend to be underweight
- *subtle* increases in thoracic respiratory sounds

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102

Chronic coughing & dyspnea in an older dog with MVD

Primary respiratory patients

- a 'harsh' cough, with excitement
- sleep well
- sinus arrhythmia
- will tend to be overweight
- markedly increased thoracic respiratory sounds

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Locations or zones within the respiratory tract

1. Nasal cavity and cranial oro-pharynx
2. Larynx and caudal oro-pharynx
3. Trachea and larger airways (bronchi)
4. Alveoli and bronchioles
5. Pleural space and mediastinal space

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Respiratory disease

Problem	Location
sneezing/discharge	nasal cavity/oropharynx
coughing with minimal dyspnea	tracheobronchial
dyspnea with minimal coughing	laryngeal/pleural/bronchial
coughing *and* dyspnea	bronchoalveolar

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105

Royal Veterinary College
University of London

Problems with calcium: what should we be prioritising ?

Croatia Vet Association, 2023

David Church
Professor of Small Animal Studies
The Royal Veterinary College
University of London

1

Calcium problems - what are we going to cover !!

- Factors to think about with hypercalcemia
  - a logical approach using an understanding of the physiology
  - the clinical consequences and how they can help diagnosing likely explanations
  - treatment priorities
- What we need to focus on when confronted with documented hypocalcemia

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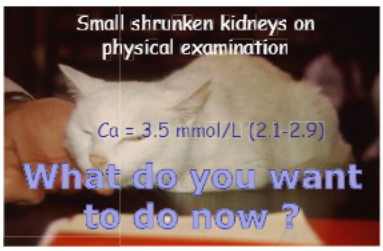
2

Tigger 12y FN DSH



Creatinine = 590umol/l, urine sg 1.019

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3

What would you like to do now ?

1 Obtain an ionised serum calcium?

2 Perform abdominal ultrasound ?

3 Obtain hematology & biochemistry?

4 Perform full urinalysis and urine culture?

5 Check the phosphate ?

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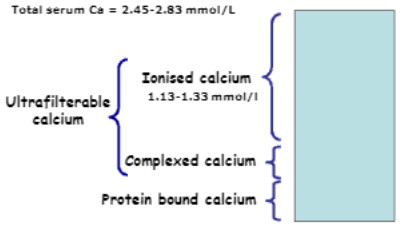
4

Measurement of calcium



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5

Measurement of serum calcium

- principally interested in ionised calcium
- so when you look at the calcium always also look at the albumin.....
- numerous devices that can measure ionised calcium "at bedside" but remember ...
- ionised calcium measurements are prone to artefacts
  - increases in pH increases protein binding & decreases ionised calcium
  - increases in pH can occur through exposure to air, agitation, variation in heparin conc. Etc
  - lipemia increases serum ionised calcium concentrations

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Interpretation of serum calcium

- principally interested in disruption of calcium metabolism
- this means abnormalities in the two hormone systems that control calcium or...
- abnormalities in the organs that absorb, store and excrete calcium

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7

Interpretation of serum calcium

- principally interested in disruption of calcium metabolism
- this means abnormalities in the two hormone systems that control calcium:
  - parathyroid hormone
  - metabolites of vitamin D specifically the most active being 1,25 dihydroxycholecalciferol or calcitriol

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8

Interpretation of serum calcium

- principally interested in disruption of calcium metabolism
- this means abnormalities in the two hormone systems that control calcium:
  - parathyroid hormone
  - metabolites of vitamin D specifically the most active being 1,25 dihydroxycholecalciferol or calcitriol
- why is that important to us as clinicians?
- PTH increases calcium and *decreases* PO_4
- 1,25 D_3 increases calcium and *increases* PO_4
- the serum phosphate can help us decide whether PTH elevation is the likely cause of the hypercalcemia

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9

Interpretation of serum calcium

- principally interested in disruption of calcium metabolism
- this means abnormalities in the two hormone systems that control calcium or...
- abnormalities in the organs that absorb, store and excrete calcium
- so when you look at the calcium don't just look at the albumin but also ALWAYS look at the phosphate !!!
- because it provides a clue as to whether the problem relates to PTH and...

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10

Interpretation of serum calcium

- principally interested in disruption of calcium metabolism
- this means abnormalities in the two hormone systems that control calcium or...
- abnormalities in the organs that absorb, store and excrete calcium
- so when you look at the calcium don't just look at the albumin but also ALWAYS look at the phosphate !!!
- we need to be acutely aware of the calcium phosphate product because ....

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11

Interpretation of serum calcium

- principally interested in disruption of calcium metabolism
- this means abnormalities in the two hormone systems that control calcium or...
- abnormalities in the organs that absorb, store and excrete calcium
- so when you look at the calcium don't just look at the albumin but also ALWAYS look at the phosphate !!!
- it is the calcium phosphate product that results in irreversible soft tissue calcification
  - if the product of the serum concentrations of Ca and PO_4 is greater than 5.5/55 this *will* be resulting in soft tissue calcification

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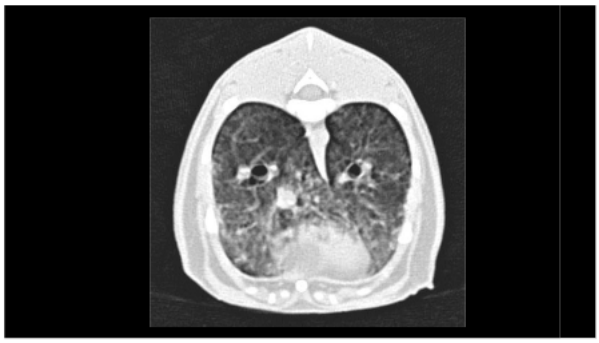

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Hypercalcemia

- hypercalcemia should NEVER be ignored
- repeatable hypercalcemia should always be investigated, even in the absence of obvious clinical signs
- prolonged untreated hypercalcaemia, especially with normal or increased phosphate, can lead to irreversible damage to many organs especially kidneys
- it is however NOT a diagnosis in itself

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Hypercalcemia

Clinical signs

- polydipsia and polyuria
- weakness, lethargy, depression
- inappetence, vomiting, diarrhea, constipation
- facial pruritis and oral discomfort
- muscle twitching and fasciculations
- cardiac tachydysrhythmias
- sudden death
- or no detectable clinical signs at all !!!

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Hypercalcemia

Clinical pathology

- clearly hypercalcemia..
- with or without disruption to serum phosphate concentration
- with or without evidence of disruption to renal function...

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Hypercalcemia

Multiple effects on renal function

- interferes with ADH action in the collecting tubule
- impairs Na and Cl resorption in the loop of Henle decreasing medullary hypertonicity
- if accompanied by sufficiently high phosphate will cause nephron destruction through deposition of calcium phosphate ($[Ca] \times [PO_4] > 5.5$) and .....
- causes vasoconstriction of the afferent glomerular arterioles resulting in ....
- azotemia

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Hypercalcemia

Effect on renal function

Hypercalcemia tends to result in *both* azotemia AND inadequately concentrated urine

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Hypercalcemia

Clinical pathology

- clearly hypercalcemia will be present..
- with or without disruption to serum phosphate concentration
- with or without evidence of disruption to renal function characterised by azotemia & inadequately concentrated urine
- but we need to remember...
- impaired renal function can result in alterations to calcium & phosphate metabolism resulting in ...
- hypercalcemia and most importantly ...
- *hyper*phosphatemia

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19

Chronic kidney disease

CKD will result in *both* azotemia *and* inadequately concentrated urine

And potentially..

hypercalcemia

But this will *always* be accompanied by ..

hyperphosphatemia

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20

Hypercalcemia

Reasons for it's existence

- non-pathological reasons
  - rapidly growing young dogs
  - laboratory error
- transient or interpretative
  - hemoconcentration
  - hyperalbuminemia
- pathological
  - due to increased PTH or PTH-like activity
  - unrelated to increased PTH activity

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Hypercalcemia

Pathological causes

- increased PTH activity
  - primary hyperparathyroidism
- increased PTH-like activity
  - humoral hypercalcemia of malignancy
  - lymphosarcoma, anal sac adenocarcinomas, multiple myelomas, etc, etc
- unrelated to increased PTH or 'PTH-like activity'
  - non-parathyroid hormone dependent causes of hypercalcemia

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Hypercalcemia

Increased PTH & PTH-like activity

- ionised hypercalcemia AND low or non-elevated phosphate are typically present
- serum PTH likely to be "inappropriately not suppressed" or there may be an elevation in serum PTHrP or some other PTH-like compound
- PTHrP is measureable, others are not
  - PTHrP is an important PTH-like factor identified in 1982
  - plays a central role in mediating humoral hypercalcaemia of malignancy
  - commercial assays readily available

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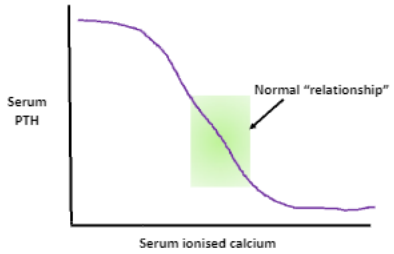
Parathyroid hormone v Ca



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Hypercalcemia

Causes *not* related to "PTH-ish" activity

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Hypercalcemia

Causes *not* related to "PTH-ish" activity

- vitamin D toxicity
  - excessive supplementation
  - rodenticides
  - psoriasis creams
- granulomatous inflammation
- hypoadrenocorticism
- chronic kidney disease
  - various factors: low phosphate renal diets, desensitised CaSR, etc
- idiopathic hypercalcemia of cats
- significant osteolysis

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Idiopathic hypercalcemia

- perhaps the most common cause of hypercalcaemia in cats
- as it is idiopathic it is indeed a diagnosis of exclusion...
- generally middle aged cats on commercial diets
- commonly develop Ca oxalate uroliths throughout the urinary tract
- monitor calcium, urine SG, renal function
- management – try dietary management first ...
- meat only diet for around 4 weeks and then you MUST revert to a balanced (home-prepared?) diet

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Boris

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Boris

History

A 9 year-old, male neutered, labradoodle who presented with a history of mild but persistent polydipsia and polyuria for the last 2-3 months.

On closer questioning the owner thinks that perhaps he has become a little lethargic and less keen on going for walks over the last 6 months but this is an impression more than a clear problem.

Physical Examination

Boris's physical examination is unremarkable apart from a systolic murmur most audible over the mitral valve region with a heart rate of ~90 bpm and BCS of ~3/9.

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Boris
Problem list

1. Polydipsia and polyuria
2. Lethargy
3. Degenerative mitral valve disease (compensated)
4. Poor BCS

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Boris
In house diagnostic tests

PCV	0.42 L/L	(0.37-0.55)
TPP	78 g/L	(55-75)
Azostix	>22 mmol/L	(2-10)
Dextrostix	6 mmol/L	(3-7)

Urinalysis: pH 6, SG 1.018, glucose -ve, ketones-ve, protein -ve, blood -ve

What to do next ?

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Boris
Clinical pathology

PCV	0.43 L/L	(0.37-0.55)
TPP	79 g/L	(55-75)
WBC count - all cells x 10^9/L		
Neutrophils (seg)	12.7	(4.0-9.4)
Neutrophils (bnd)	0.2	(0 – 0.2)
Lymphocytes	2.3	(0.9 - 3.6)
Monocytes	0.4	(0.2 – 1.0)
Eosinophils	1.0	(0.1-1.2)

Urinalysis: pH 6.5, SG 1.015, protein +, all others -ve

TSP	71 g/L	(53-74)
Alb	30g/L	(22-35)
Glob	41 g/L	(22-45)
ALT	78 U/L	(<60)
ALP	210 U/L	(<110)
Urea	27 mmol/L	(2-15)
Creat	178 µmol/L	(40-140)
Glucose	6 mmol/L	(3.3-7.0)
Amylase	4000 U/L	(<2,800)
Calcium	4.0 mmol/L	(2.1-2.9)
PO_4	0.7 mmol/L	(0.8-1.6)
Sodium	144 mmol/L	(137-150)
K	5.4 mmol/L	(3.3-4.8)
Chloride	119mmol/L	(105-120)

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Boris
Results of diagnostic procedures

Interpret the results and decide on what tests if any you want upto a maximum of £400 ...

- Repeat Ca and PO_4 estimations (£45)
- Plain abdominal radiographs (£90)
- Thoracic radiographs (£90 or an extra £45 with the abdominal radiographs)
- Abdominal ultrasound (£145)
- Cervical ultrasound (£125)
- Cardiac ultrasound (£185)
- Serum PTH and PTH-rp estimation (£315)
- Fine needle aspirates of liver (£135)
- Fine needle aspirates of lymph nodes (£135)
- Estimate of urinary calcium excretion (£105)
- Therapy with l-asparginase (£298)

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Boris

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Hypercalcemia

Clinical signs

- polydipsia and polyuria
- weakness, lethargy, depression
- inappetence, vomiting, diarrhea, constipation
- facial pruritis and oral discomfort
- muscle twitching and fasciculations
- cardiac tachydysrhythmias
- sudden death
- or no detectable clinical signs at all !!!

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Primary hyperparathyroidism

- Keeshunds markedly over-represented in developing primary hyperparathyroidism:
  - autosomal dominant
  - with age-related penetrance
- increased & autonomous PTH production by a functional neoplasm (usually a solitary adenoma)
- a disease of older dogs, generally over six years and uncommon in cats
- calcium negative feedback is lost

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Primary hyperparathyroidism

- these dogs are often well – the hypercalcaemia may be an incidental finding
- often an unremarkable physical exam
- may develop urolithiasis and then show lower urinary tract signs – dysuria, pollakiuria, haematuria
- uncommon for other signs of hypercalcaemia to be present

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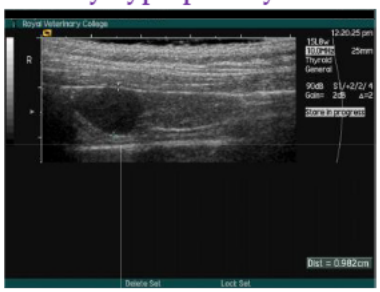
Primary hyperparathyroidism



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38

Boris
Results of diagnostic procedures

Interpret the results and decide on what tests if any you want upto a maximum of £400 ...

- Repeat Ca and P estimations (£45)
- Plain abdominal radiographs (£90)
- Thoracic radiographs (£90 or an extra £45 with the abdominal radiographs)
- Abdominal ultrasound (£145)
- Cervical ultrasound (£125)
- Cardiac ultrasound (£185)
- Serum PTH and PTH-rp estimation (£295)
- Fine needle aspirates of liver (£135)
- Fine needle aspirates of lymph nodes (£135)
- Estimate of urinary calcium excretion (£105)
- Therapy with l-asparginase (£298)

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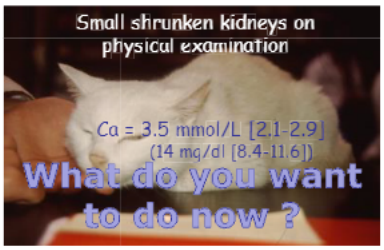
Tigger 12y FN DSH



Creatinine = 590umol/l, urine sg 1.019

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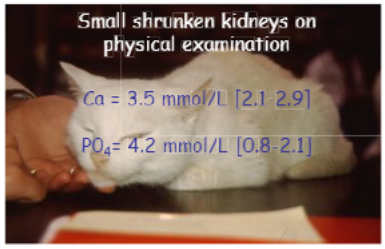
40

Tigger 12y FN DSH



Creatinine = 590umol/l, urine sg 1.019

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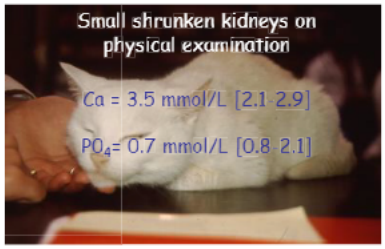
Tigger 12y FN DSH



Creatinine = 590umol/l, urine sg 1.019

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Hypercalcemia
Management

- correct underlying cause or causes has to be the principal goal
- of course this is not always possible
- additionally can consider treatment to reduce the degree of hypercalcemia
  - fluid therapy
  - furosemide
  - bisphosphonates
    - pamidronate: 150mg vials
    - alendronate: 10mg caplets

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Hypercalcemia

- principally interested in disruption of calcium metabolism and ionised calcium is "preferable"
- don't just look at the calcium, ALWAYS look at the phosphate...and also the level of azotemia
- pathological causes of hypercalcemia relate to excess PTH/PTH-like activity OR various other problems not related to elevated PTH activity
- the phosphate level helps "steer" your decisions
- all hypercalcemias should be investigated but ....
- it is the calcium phosphate product that is producing irreversible soft-tissue calcification (>5.5)
- you may need to treat "symptomatically"

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44

Hypercalcemia

- in *cats* hypercalcemia seems to be more commonly "caused by" or associated with:
  - chronic kidney disease
  - "idiopathic" hypercalcemia
  - the rest ...
- in dogs hypercalcemia seems to be more commonly caused by:
  - neoplasia
  - primary hyperparathyroidism
  - the rest .....

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45

Hypocalcemia

- not an uncommon finding as a clinically insignificant result of hypoalbuminemia
- however, ionised hypocalcemia is not uncommonly associated with (dogs ~30%, cats ~ 50%).....
- chronic kidney disease AND we'll also see ...
- other causes include
  - pancreatitis
  - primary hypoparathyroidism
  - iatrogenic hypoparathyroidism after thyroidectomy
  - eclampsia
- NOT; *TRULY, REALLY* NOT; dietary ...
- what does it look like clinically .....

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Hypocalcemia

Clinical signs

- abnormal neurological, neuromuscular and gastrointestinal function or combinations of all of these....
  - panting, anxiety & behavioural changes
  - weakness with a stiff & stilted gait
  - inappetance through to vomiting
  - hyperthermia
  - muscle tremors & cramps, muscle pain
  - seizures

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Chloe

Clinical pathology

PCV = 0.47 L/L (0.37 - 0.50)			Protein	77	(54 - 75)
TPP = 78 g/L (55 - 78)			Alb	30	(22 - 35)
Leuk =	16.4	(7 - 15)	Glob	47	(27 - 45)
Neut =	14.8	(3.3 - 9)	ALT	789	(< 60)
Lymp=	0.7	(0.9 - 3.2)	ALP	109	(<110)
Mono=	0.9	(0.2 - 1.0)	Amylase	4434	(<2800)
Eos =	0.0	(0.2 - 1.2)	Urea	25	(2 - 10)
urine sg = 1.045			Creat	175	(40 - 150)
Na	149	(137 - 150)	Glucose	3.8	(3.3 - 6.0)
K	4.5	(3.7 - 4.8)	Ca	1.3	(2.1 - 2.9)
Cl	119	(105 - 120)	PO_4	2.45	(0.8 - 1.6)
cPLI	300	(<185; <400*)	Bilirubin	11	(0 - 15)

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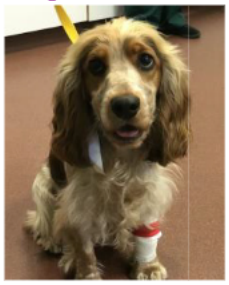
Chloe 4 year FN Cocker Spaniel

- hypocalcemia
- along with marked hyperphosphatemia tells us ...
- she is very likely to have ....
- hypoparathyroidism



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Hypocalcemia

Clinical signs

- abnormal neurological, neuromuscular and gastrointestinal function or combinations of all of these....
  - panting, anxiety & behavioural changes
  - weakness with a stiff & stilted gait
  - inappetance through to vomiting
  - hyperthermia
  - muscle tremors & cramps, muscle pain
  - seizures

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Hypocalcemia

- is frequently an unimportant problem clinically as it can be a result of a number of other abnormalities
- however when it is the *cause* of clinical signs it ABSOLUTELY needs managing as it is life-threatening
- consequently whenever detected it should ALWAYS be investigated to a level that makes you comfortable you understand the reasons for its presence....

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Hypocalcemia

Management

- once you have determined the hypocalcemia is clinically significant and have corrected a potential underlying cause then the hypocalcemia needs to be managed with:
- if necessary intravenous 10% calcium gluconate
  - 0.5-1ml/kg to effect followed by
  - 6.5-10ml/kg/24h as a continuous rate infusion
- subacutely oral medication..
  - calcitriol: 20-30 ng/kg/24h tapering to 5-15ng/kg/24h
  - AT-10: 20-30 µg/kg/24h tapering to 10-15 µg/kg/24-48h
- calcium carbonate adjusted with the dose of calcitriol or AT-10

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Hypocalcemia

Management

Monitoring requires checking the calcium but also the ... phosphate !!!

Adding $CaCO_3$ can help keep the calcium at acceptable levels without creating hyperphosphatemia

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Hypercalcemia

Causes *not* related to "PTH-ish" activity

- vitamin D toxicity
  - excessive supplementation
  - rodenticides
  - psoriasis creams
- granulomatous inflammation
- hypoadrenocorticism
- chronic kidney disease
  - grape intoxications
- Idiopathic hypercalcemia of cats
- significant osteolysis

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RVC Royal Veterinary College University of London

Diagnosis and management of canine Cushing's syndrome in 2023

Croatia, 2023

David Church
Professor of Small Animal Studies
The Royal Veterinary College
University of London

Sharing passions, shaping futures

2

Cushing's syndrome

Overview

- what do we mean by the term Cushing's syndrome ?
- how do we diagnose this disease effectively and efficiently ?
- how do we optimise management effectively?
- effective management will include:
  - establishing aetiology
    - clinical signs don't indicate causality
    - pituitary-dependent (PDH): 85% - 90%
    - adrenal dependent (ADH): 10 – 15%
    - Iatrogenic causes: less common ?
  - ensuring treatment is effective enough to significantly improve quality of life
  - a cost-benefit analysis is essential

RVC

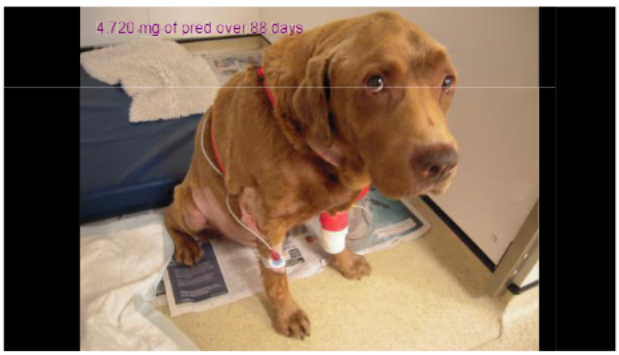
3

Cushing's syndrome

- clinical problem brought about by chronic over exposure to glucocorticoids:
  - naturally occurring
    - pituitary-dependent (PDH): 85% - 90%
    - adrenal dependent (ADH): 10 – 15%
  - iatrogenic causes
    - usually chronically administered underdosage
- relatively characteristic clinical picture ??
  - insidious onset means presentation occurs at variable stages
  - changes can be subtle, especially early in the disease
  - death usually caused by secondary problems rather than from Cushing's directly
  - is 'not treating' an option ??

RVC

4



5

Cushing's syndrome

- clinical problem brought about by sub-acute over exposure to glucocorticoids:
  - naturally occurring
    - pituitary-dependent (PDH): 85% - 90%
    - adrenal dependent (ADH): 10 – 15%
  - iatrogenic causes
    - usually chronically administered underdosage
- relatively characteristic clinical picture ??
  - insidious onset means presentation occurs at variable stages
  - changes [illegible]
  - death usually caused by secondary problems rather than from HyperA directly
  - is 'not treating' an option ?

Not really – but it MUST be effective !

RVC

6

Cushing's syndrome

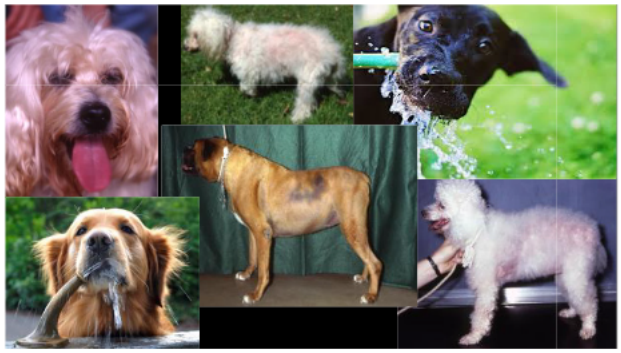
Cost considerations

- need to bear in mind what we are trying to achieve
- we have to diagnose this disease effectively and efficiently
- what do we really need to diagnose it effectively ?
  - a consistent set of clinical signs for 2023 ? £55
  - a consistent set of clinical pathology £200
  - endocrine test results which 'confirm' the diagnosis ?
    - ~~urine cortisol:creatinine ratio~~ £48
    - ACTH stimulation test ? £82
    - low dose dexamethasone suppression test ? £112

£337 to £367

RVC

7

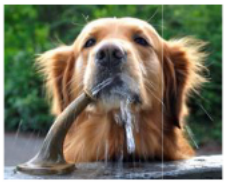


8

Cushing's syndrome

Clinical picture in the dog - 2023

- polydipsia and polyuria
  - why ?
  - what does that tell us ??



RVC

9

Cushing's syndrome

Clinical picture in the dog - 2023

- polydipsia and polyuria
  - why ?
  - what does that tell us ??
- panting excessively ...?

RVC

10

Cushing's syndrome

Clinical picture in the dog - 2023

- polydipsia and polyuria
  - why ?
  - what does that tell us ??
- panting excessively ...?
- relatively inactive dog although many owners won't have noticed

RVC

11

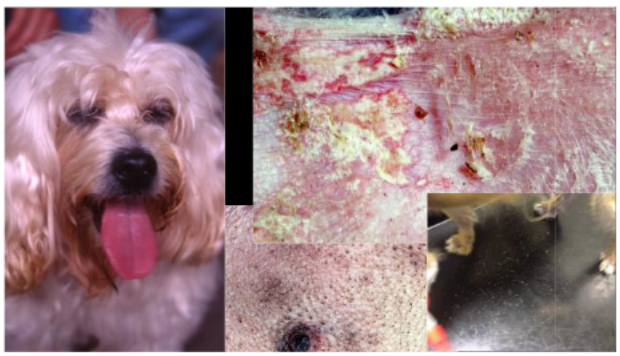
Cushing's syndrome

Clinical picture in the dog - 2023

- polydipsia and polyuria
  - why ?
  - what does that tell us ??
- panting excessively ...?
- relatively inactive dog although many owners won't have noticed
- "old for their age"
  - epaxial muscle wasting

RVC

12



13

Cushing's syndrome

Clinical picture in the dog - 2023

- polydipsia and polyuria
  - why ?
  - what does that tell us ??
- panting excessively ...?
- relatively inactive dog although many owners won't have noticed
- "old for their age"
  - epaxial muscle wasting

Abnormal becomes the "new normal"

RVC

14

Cushing's syndrome

Clinical picture in the cat - 2023

- a cat with diabetes mellitus that is difficult to manage ....
- varying degrees of insulin resistance
- present for varying periods of time
- usually no other signs increasing your index of suspicion
- an uncommon problem

RVC

15

Cushing's syndrome

Clinical picture in the dog - 2023

- polydipsia and polyuria
  - why are they polydipsic ?
  - there is no value in measuring urine specific gravity
- panting excessively and a variably poor hair coat
- relatively inactive dog although many owners won't have noticed
- "old for their age"
  - epaxial muscle wasting

What is NOT a feature of the clinical picture?

Inappetence and of course pruritis

RVC

16

Cushing's syndrome

Cost considerations

- need to bear in mind what we are trying to achieve
- we have to diagnose this disease effectively and efficiently
- what do we really need to diagnose it effectively ?
  - a consistent clinical picture adjusted for 2023 ? £55
  - a consistent set of clinical pathology ? £200
  - endocrine test results which confirm the diagnosis ?
    - ~~Endogen cortisol overload ? £45~~
    - ACTH stimulation test ? £82
    - low dose dexamethasone suppression test ? £112

£337 to £367

RVC

17

Cushing's syndrome

Diagnosis

- haematology and biochemistry
  - stress leukogram; liver enzyme elevations, ALP >>ALT
  - urine specific gravity & micro-urine generally unhelpful

£142

- dynamic testing is generally required ...
  - ACTH stimulation test £82
  - Low dose dexamethasone suppression test £112

which test is best ??

RVC

18

Endocrine disorders:
diagnosing with certainty ...

When basal hormone values are poor discriminators ...

- dynamic testing has to be considered a viable alternative
  - which dynamic test is best for which types of disorder ?
- as a general rule we use suppression tests for evaluating disorders resulting from "overactive endocrine problems" and stimulation tests for clarifying "underactive endocrinopathies"

RVC

19

Cushing's syndrome

ACTH stimulation test

- poorly diagnostic in a proportion of cases:
  - post ACTH cortisols less than upper limit of the normal range
  - post ACTH cortisols between 500 to 750 nmol/L
- extremely accurate when post ACTH cortisols > 1000 nmol/L
- virtually *never* discriminatory for PDH verses ADH
- so it works in a % of cases and its convenient but.....
- it's sensitivity is generally reported as around 80%

RVC

20

Test results	Disorder present	Disorder absent	Totals	Predictive value & prevalence
Positive	16	18	34	PPV = 47%
Negative	4	162	166	NPV = 97.6%
Totals	20	180	200	
Sensitivity and Specificity	Se = 80%	Sp = 90%		Prevalence 10%

Test results	Disorder present	Disorder absent	Totals	Predictive value & prevalence
Positive	96	8	104	PPV = 92%
Negative	24	72	96	NPV = 75%
Totals	120	80	200	
Sensitivity and Specificity	Se = 80%	Sp = 90%		Prevalence 60%

RVC

21

Test results	Disorder present	Disorder absent	Totals	Predictive value & prevalence
Positive	16	18	34	PPV = 47%
Negative	4	162	166	NPV = 97.6%
Totals	20	180	200	
Sensitivity and Specificity	Se = 80%	Sp = 90%		Prevalence 10%

Test results	Disorder present	Disorder absent	Totals	Predictive value & prevalence
Positive	128	4	132	PPV = 97%
Negative	32	36	68	NPV = 53%
Totals	160	40	200	
Sensitivity and Specificity	Se = 80%	Sp = 90%		Prevalence 80%

RVC

22

Cushing's syndrome

ACTH stimulation test

Results in a 'negative predictive value' of 53% if the prevalence in the tested population is approximately 80%

RVC

23

Cushing's syndrome

Low dose dexamethasone suppression test

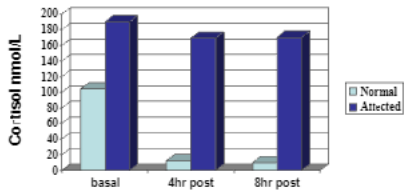
- more appropriate test for what we are trying to investigate:
  - demonstrates *impaired capacity to reduce* cortisol production
  - lack of suppression for a given level of glucocorticoid activity
- samples taken over an 8 hour period:
  - must have an intermediate sample at 3 or 4 hours
  - dose of dexamethasone (0.01mg/kgIV) is small & must be delivered accurately
- lack of suppression has to "contextualised"

RVC

24

Cushing's syndrome

Low dose Dexamethasone suppression



RVC

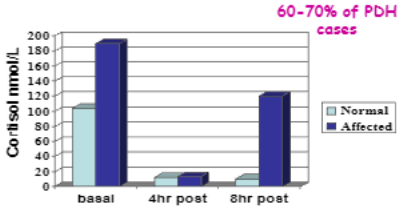
25

Cushing's syndrome

Low dose Dexamethasone suppression

Pituitary dependent

60-70% of PDH cases



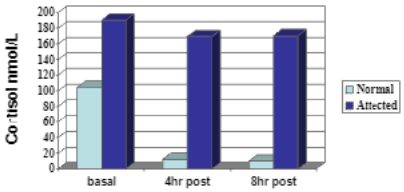
RVC

26

Cushing's syndrome

Low dose Dexamethasone suppression

~100% of adrenal dependent hyperadrenocorticism and ~30% of cases with PDH



RVC

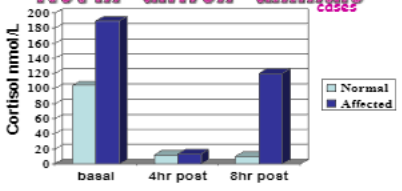
27

Cushing's syndrome

Low dose Dexamethasone suppression

Not in "unwell" animals

PDH cases



RVC

28

Cushing's syndrome

Diagnosis – to confirm Cushing's syndrome

- ACTH stimulation test
  - convenient
  - less expensive
  - concern regarding false negatives
- Low dose dexamethasone suppression
  - less convenient
  - more expensive
  - concern regarding false positives
  - but we can control this relatively easily and...
  - in a proportion of cases it can help us discriminate aetiologies

RVC

29

Cushing's syndrome

How do we discriminate

- when appropriate with our LDDST results:
  - suppression at 4h with rebound at 8h
- adrenal ultrasonography
- at least two estimations of basal ACTH levels
  - plasma must be separated and frozen within 30 minutes
  - values are not subnormal but not necessarily elevated
- high dose dexamethasone suppression test

RVC

30

Cushing's syndrome

How do we discriminate

- when appropriate with our LDDST results:
  - suppression at 4h with rebound at 8h
- adrenal ultrasonography

RVC

31

Cushing's syndrome

How do we discriminate

- when appropriate with our LDDST results:
  - suppression at 4h with rebound at 8h
- adrenal ultrasonography
  - asking is their a difference between left & right AND

RVC

32

Cushing's syndrome

How do we discriminate

- when appropriate with our LDDST results:
  - suppression at 4h with rebound at 8h
- adrenal ultrasonography
  - asking is their a difference between left & right AND
  - is the smaller adrenal 'smaller than normal'?
  - *should* be <3-4.5mm

RVC

33

ULPGC Universidad de Las Palmas de Gran Canaria | Hospital Clínico Veterinario

Slide courtesy of Carlos Melian

Reference range (upper limit, median and lower limit) in mm for the maximal adrenal gland thickness in 86 healthy dogs

	≥2.5-5 kg		5-10 kg		10-20 kg		20-40 kg	
	Left	Right	Left	Right	Left	Right	Left	Right
upper	4.8	5.5	5.6	6.0	6.2	7.7	7.4	9.4
median	4.2	4.1	4.3	5.2	5.0	5.6	6.1	7.1
lower	3.4	3.2	3.4	3.8	3.9	4.2	5.2	5.4

n: 86 clinically healthy dogs; ≥2.5-5 kg: 21 dogs, >5-10 kg: 22 dogs, >10-20 kg: 22 dogs, >20-40 kg: 21 dogs
Reference range based on the 10 to 90th percentile

ECVIM-CA

Pérez-López L., Ibáñez JR, Rosado A, Santos Y, Melián C. Ultrasonographic evaluation of adrenal gland thickness in healthy dogs and in dogs with hyperadrenocorticism. Proceeding of the 29th ECVIM Congress.

34

Cushing's syndrome

How do we discriminate

- when appropriate with our LDDST results:
  - suppression at 4h with rebound at 8h
- adrenal ultrasonography
  - is there an adrenal that is smaller than normal (<3-4.5mm)

RVC

35

Cushing's syndrome

How do we discriminate

- when appropriate with our LDDST results: £0
  - suppression at 4h with rebound at 8h
- adrenal ultrasonography £200
  - is there an adrenal that is smaller than normal (<3-4.5mm)
- at *least* two basal plasma ACTH levels £188
  - plasma must be separated and frozen within 30 minutes
  - values are not subnormal but not necessarily elevated
- with a high dose dexamethasone suppression test ? £112

RVC

36

Cushing's syndrome

Diagnosis – to confirm hyperadrenocorticism

- ACTH stimulation test £82
  - convenient
  - less expensive
  - concern regarding false negatives
- Low dose dexamethasone suppression £112
  - less convenient
  - more expensive
  - concern regarding false positives
  - but we can control this relatively easily and...
  - in a proportion of cases it can help us discriminate aetiologies

clinically contextualised

RVC

37

Cushing's syndrome

How do we discriminate

- when appropriate with our LDDST results: £0
  - suppression at 4h with rebound at 8h
- adrenal ultrasonography £200
  - is there an adrenal that is smaller than normal (<3-4.5mm)
- at *least* two basal plasma ACTH levels £188
  - plasma must be separated and frozen within 30 minutes
  - values are not subnormal but not necessarily elevated
- with a high dose dexamethasone suppression test ? £112

RVC

38

Cushing's syndrome

Overview

- what do we mean by the term hyperadrenocorticism ?
- how do we diagnose this disease effectively and efficiently ?
- how do we optimise management effectively?
- effective management will include:
  - establishing aetiology
    - clinical signs don't indicate causality
    - pituitary-dependent (PDH): 85% - 90%
    - adrenal dependent (ADH): 10 – 15%
    - iatrogenic causes: less common ?
  - ensuring treatment is effective enough to significantly improve quality of life
  - a cost-benefit analysis is essential

RVC

39

Cushing's syndrome

Cost considerations

- need to bear in mind what we are trying to achieve
- we have to diagnose this disease effectively and efficiently
- what do we really need to diagnose it effectively ?
  - a consistent clinical picture adjusted for 2022? £55
  - a consistent set of clinical pathology ? £142
  - endocrine test results which confirm the diagnosis ?
    - low dose dexamethasone suppression test ? £112

£309

RVC

40

Cushing's syndrome

Cost considerations

- need to bear in mind what we are trying to achieve
- we have to diagnose this disease effectively and efficiently
- what do we really need to diagnose it effectively ?
  - a consistent clinical picture adjusted for 2022 ? £55
  - a consistent set of clinical pathology ? £142
  - endocrine test results which confirm the diagnosis ?
    - low dose dexamethasone suppression test ? £112

£309

- what do we really need to differentiate it effectively ?
  - a low dose dexamethasone suppression test £0
  - abdominal ultrasonography £200

Total = £309 - £509

RVC

41

Cushing's syndrome

Overview

- what do we mean by the term Cushing's syndrome ?
- how do we diagnose this disease effectively and efficiently ?
- how do we optimise management effectively?
- effective management will include:
  - establishing aetiology
    - clinical signs don't indicate causality
    - pituitary-dependent (PDH): 85% - 90%
    - adrenal dependent (ADH): 10 – 15%
    - iatrogenic causes: less common ?
  - ensuring treatment is effective enough to significantly improve quality of life
  - a cost-benefit analysis is essential

RVC

42

Cushing's syndrome

Treatment options

- pituitary dependent hyperadrenocorticism:
  - medically
    - trilostane
    - mitotane
  - surgically
- adrenal dependent hyperadrenocorticism:
  - surgically
  - medically
    - trilostane

Remembering we are being driven by enhancing quality of life so it *has* to be *effective*

RVC

43

Cushing's syndrome

Effective treatment should ....

- modify clinical signs to ...
  - 50% of normal ?
  - effectively back to normal ?
- modify clinical pathology to...
  - 50% of normal ?
  - effectively back to normal ?
- modify serum cortisol to...
  - less than say 150nmol/L ?
  - less than the upper limit of the basal reference range ?
  - to within the bottom 25th percentile of the basal reference range ?

RVC

44

Cushing's syndrome

Treatment options

- pituitary dependent hyperadrenocorticism:
  - medically
    - trilostane
    - mitotane
  - surgically
- adrenal dependent hyperadrenocorticism:
  - surgically
  - medically
    - trilostane

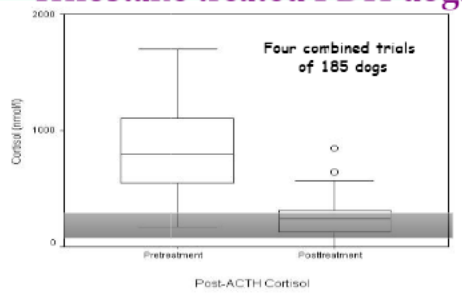
Remembering we are being driven by enhancing quality of life so it *has* to be *effective*

We want to "normalise" the patient; not make it "less Cushingoid"

RVC

45

Trilostane treated PDH dogs



RVC

46

Cushing's syndrome

Trilostane

- how does it work ?
- reduces glucocorticoid activity through inhibition of cortisol synthesis

RVC

47

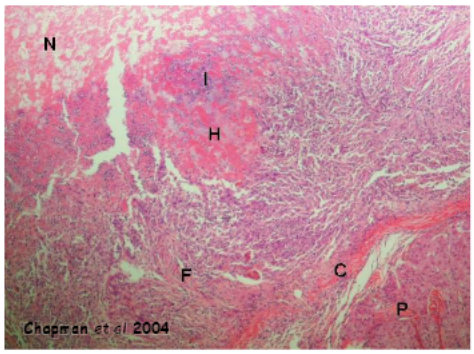
Cushing's syndrome

Trilostane – a dilemma

- inhibits cortisol production for less than 24 hours.....
- how is it possible for dogs to get hypoadrenocorticism ??
  - 7-15% developed hypoadrenocorticism

RVC

48



RVC

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Treating pituitary dependent hyperadrenocorticism

Trilostane

- inhibits cortisol synthesis & increases ACTH production
- ⇑⇑ ACTH production ⇒ ⇑⇑ adrenocortical blood flow
- adrenocortical blood supply is very fragile (rats, dogs, man)
- ⇑⇑ adrenocortical blood flow ⇒ adrenocortical hemorrhage
- adrenocortical hemorrhage ⇒ acute reduction in cortisol production which can be clinically significant

Wibur & Rich 1953, Hinson *et al* 1991

RVC

50

Cushing's syndrome

Trilostane

- inhibits 3 β hydroxysteroid dehydrogenase
- also induces adrenal hemorrhage through creating increased ACTH levels
- the adrenal hemorrhage is far more profound in PDH than in ADH
  - "efficacy" reduced in ADH compared to PDH as
  - in trilostane-treated PDH the rises in ACTH directly damage the adrenal glands
  - hypoadrenocorticism is ***absolutely*** still a concern

RVC

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Cushing's syndrome

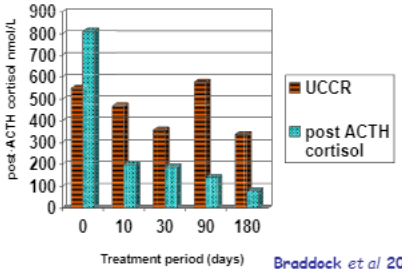
Trilostane – another dilemma..

- inhibits cortisol production for < 24 hours
- urinary corticoid levels remain elevated
  - relative to well controlled mitotane treated dogs
  - UCCR can't be used for monitoring treatment
- on occasions the clinical response can be excellent despite apparently inconsistent plasma cortisol levels

RVC

52

Post-ACTH cortisol & UCCR in PDH dogs treated with trilostane



Braddock *et al* 2006

RVC

53

Cushing's syndrome

Trilostane – another dilemma..

- inhibits cortisol production for < 24 hours
- urinary corticoid levels remain elevated
  - relative to well controlled mitotane treated dogs
  - UCCR can't be used for monitoring treatment
- clinical response can be excellent despite apparently inconsistent plasma cortisol levels
- something is not making sense..
  - not the adrenal hemorrhage effect
  - potentially peripheral effects?

RVC

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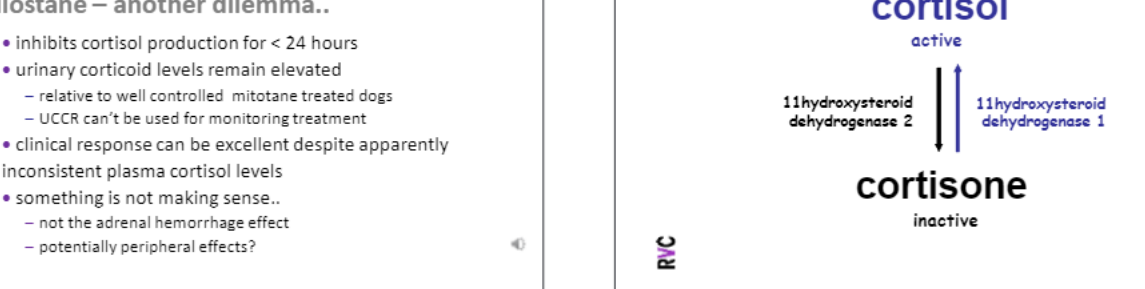
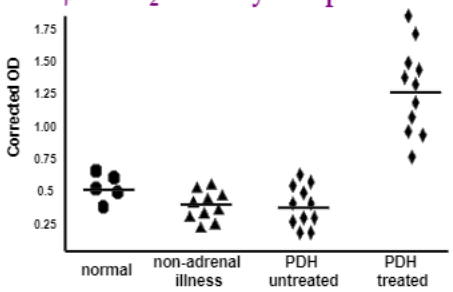


RVC

55

11 β HSD_2 leukocyte expression



RVC

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Cushing's syndrome

Trilostane

- reduces glucocorticoid activity through a *number of different* mechanisms including:
  - inhibition of cortisol synthesis
  - adrenocortical destruction in PDH patients but not ADH patients
  - peripheral up-regulation of enzymes deactivating cortisol – thereby inducing cortisol resistance

Trilostane's 'true colours' only revealed after broader clinical usage

RVC

57

Cushing's syndrome

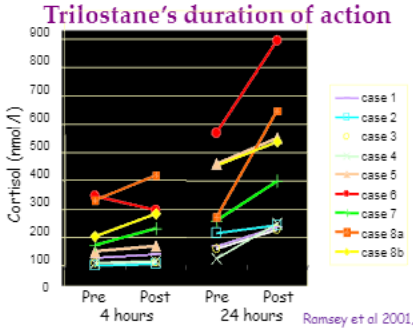
Trilostane

- reduces glucocorticoid activity through a number of different mechanisms
- start at 2– 4 mg/kg/24h (and adjust over time)

RVC

58

Trilostane's duration of action



Ramsey et al 2001, ESVIM congress

RVC

59

Cushing's syndrome

Trilostane

- reduces glucocorticoid activity through a number of different mechanisms
- start at 2– 4 mg/kg/24h (and adjust over time)
- given 12 hourly with food

RVC

60

Cushing's syndrome

Trilostane

- reduces glucocorticoid activity through a number of different mechanisms
- start at 1–2 mg/kg/12h with food (and adjust over time)
- monitoring ?

RVC

61

Cushing's syndrome

Trilostane

- reduces glucocorticoid activity through a number of different mechanisms
- start at 1–2 mg/kg/12h with food (and adjust over time)
- ACTH test 2-6 hr post-dose **focused on overdosing**
  - post-ACTH cortisol in the reference range for basal cortisol
  - is it the best means of assessing adequacy of trilostane's effect ?
  - pre tablet basal cortisol (2 hr window) have been suggested to be superior .....however.... **an owner based questionnaire**

RVC

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Cushing's syndrome

Trilostane in 2022

- reduces glucocorticoid activity through a number of different mechanisms
- start at 1–2 mg/kg/12h with food (and adjust over time)
- monitor efficacy utilising "biomarkers" for cortisol including an objective assessment of the clinical response

RVC

63

Cushing's syndrome

Trilostane in 2022

- reduces glucocorticoid activity through a number of different mechanisms
- start at 1–2 mg/kg/12h with food (and adjust over time)
- monitoring with:
  - Cush QoL clinical scoring system
  - serum ALP, cholesterol, leukogram
  - post ACTH cortisol
  - eACTH

RVC

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Cushing's syndrome

Trilostane

- reduces glucocorticoid activity through a number of different mechanisms
- start at 1–2 mg/kg/12h with food (and adjust over time)
- regular testing of dose adequacy
- fine to worry about overdosing but equally as important to *ensure we do NOT underdose* !!!

RVC

65

Cushing's syndrome

Trilostane

- reduces glucocorticoid activity through a number of different mechanisms
- start at 1–2 mg/kg/12h with food (and adjust over time)
- regular testing of dose adequacy
- underdosing results in unsatisfactory quality of life

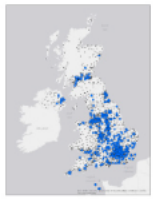
Vetcompass study: O'Neill *et al* BSAVA (2017)

RVC

66

What happens in general practice

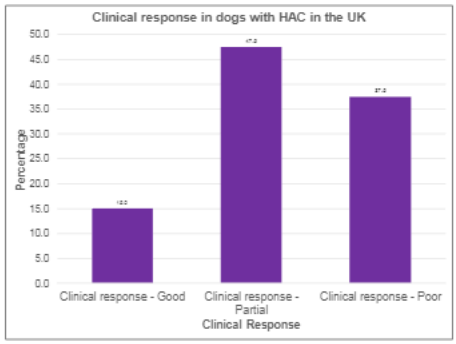

Epidemiology of hyperadrenocorticism among 210,824 dogs attending primary-care veterinary practices in the UK from 2009 to 2014



O'NEILL, D. G., SCUDDER, C., FAIRE, J. M., CHURCH, D. B., MCGREEVY, P. D., THOMSON, P. C. & BRODBELT, D. C. 2016. Epidemiology of hyperadrenocorticism among 210,824 dogs attending primary-care veterinary practices in the UK from 2009 to 2014. *Journal of Small Animal Practice*, 57, 365-373.

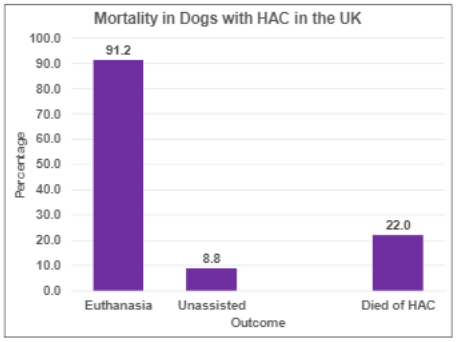
RVC

67



RVC

68



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Cushing's syndrome

Trilostane

- reduces glucocorticoid activity through a number of different mechanisms
- start at 1–2 mg/kg/12h with food (and adjust over time)
- regular testing of dose adequacy
- underdosing results in unsatisfactory quality of life
  - more than 80% of owners were unsatisfied with the response to treatment

£117 per visit Vetcompass study: O'Neill *et al* BSAVA (2017)

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70

Is the Cushing's syndrome adequately controlled?

8 / 15

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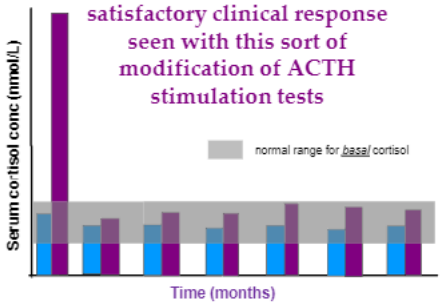
Trilostane treatment: satisfactory clinical response seen with this sort of modification of ACTH stimulation tests



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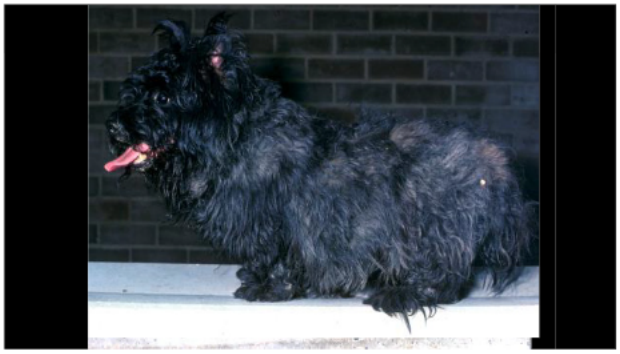

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Satisfactory trilostane treatment

Our understanding in 2022

- reduces glucocorticoid activity through a number of different mechanisms
- start at 1–2 mg/kg/12h with food (and adjust over time)
- monitoring with:
  - Cush QoI clinical scoring system
  - leukogram, serum ALP and cholesterol
  - post-ACTH cortisol in the reference range for basal cortisol (4-6h)

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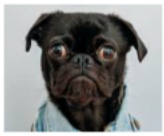
Satisfactory trilostane treatment

Our understanding in 2022

Do NOT be frightened to dose to achieve normality!!



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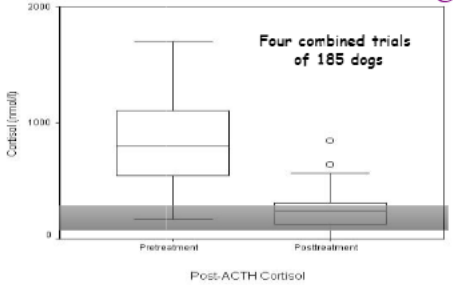
Trilostane treated PDH dogs



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Cushing's syndrome

Trilostane

- in a proportion of cases (20-25%) efficacy/clinical response are going to be variably poor
- what can we do ?
- review dose rate recommendations and consider increasing dose precision?

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Cushing's syndrome

Trilostane

- in a proportion of cases (20-25%) clinical response is poor
- review dose rate recommendations and dose precision
- consider more than twice daily dosing

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Cushing's syndrome

Trilostane

- in a proportion of cases (20-25%) clinical response is poor
- review dose rate recommendations and dose precision
- consider more than twice daily dosing
- compliance may become an issue
- however cost very definitely might be …

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Cushing's syndrome

Trilostane: once verses twice daily dosing

- Vetoryl® comparative prices:
  - 10mg caps: 23p per 1mg
  - 30mg caps: 9.5p per 1mg
  - 60mg caps: 5.9p per 1mg
  - 120mg caps: 4.5p per 1mg

- considering twice daily dosing is likely to almost double the price

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Cushing's syndrome

Trilostane

- in a proportion of cases (20-25%) efficacy or clinical response is variably poor
- review dose rate recommendations and dose precision
- consider twice/thrice daily dosing although price can be a real issue
  - minimum annual costs of £2308 (10kg), £2804 (20kg) to £4662 (30kg)
- we simply have to consider alternatives, but what?

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Cushing's syndrome

Surgical managements for PDH

- our two options are:
- to remove the source of the problem:
  - the whole pituitary, adenohypohysis & posterior pituitary
- or to remove the response end-organ:
  - both whole adrenals, cortex & medulla

Which would you prefer ?

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Cushing's syndrome

Surgical managements for PDH

- the problem is invariably a pituitary adenoma so maybe we should lean towards hypophysectomy….
- but, the vast majority of dogs with PDH do not show any signs referable to their intracranial mass lesion
- so removing it might be curative but..
- it is likely to have a greater risk of complications

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Cushing's syndrome

Bilateral adrenalectomy

- 22 dogs with confirmed PDH
- poorly controlled on medical therapy or..
- long term costs prohibitive
- hydrocortisone infusion implemented at the time of surgery
- post surgical hydrocortisone infusion with transfer to oral medication.

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Cushing's syndrome

Hydrocortisone infusion

- hydrocortisone sodium succinate
- 1 mg/ml solution
- 0.5 mg/kg/hr for 24 hours
- 0.25 mg/kg/hr for 24 to 48 hours
- introduce oral medication:
  - cortisone acetate 0.5mg/kg/12h - 24h
  - deoxycortisone pivalate 1 - 1.5 mg/kg/28 days

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Cushing's syndrome

Summary

- there are three main treatment options and all are expensive
- in the UK at least, assuming a two year survival period, the cheapest of the three is bilateral adrenalectomy:
  - especially in dogs of ~20kg or more
- bilateral adrenalectomy certainly needs to be considered with maintenance on deoxycortisone pivalate and maintenance doses of either cortisone (<20kg body weight) or prednisolone

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Monitoring treatment of Cushing's syndrome

Optimising management

- need to bear in mind what we are trying to achieve
- reliable reduction of clinical signs
- need to achieve a balance between ensuring there is:
- real and clear "normalisation" of the dog
- no fear about "overdoing it" and creating hypoadrenocorticism
- consider using "biomarkers" as well as serum cortisol levels
  - normal serum ALP and cholesterol
  - presence of a stress leukogram
  - normal serum Na and K concentrations

CushQoL-pet

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Royal Veterinary College
University of London

Managing diabetic patients in 2023

Croatia, March 2023

David Church

1

Diabetes mellitus

Where are we in 2023 ?

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Diabetes mellitus

Where are we in 2023?

- An increasing recognition that quality of life and owner–pet interactions are a *really* under-emphasised area
- A need to implement consistent principles *without* rigid protocols
- An improved understanding of what "remission" means in diabetic cats
- Value or otherwise of different monitoring techniques
- An increasing recognition of the prevalence & impact of co-morbidities in both cats and to a lesser extent dogs

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Diabetes mellitus - definition

Clinically significant deficiency of insulin secreting capacity

Absolute or relative & irreversible in dogs

Absolute or relative and potentially "reversible" in cats

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Diabetic management

Should think about adhering to four basic principles

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Diabetic management

- where possible correct underlying causes and/or factors that interfere with insulin's actions
- reduce hyperglycemia to <270mg/dl *and* minimise clinical hypoglycaemia
  - longer acting insulin or more frequent doses of shorter acting insulin
- reduce the hyperglycemic impact of meals using the most palatable food with the lowest glycemic index
- adapt management of the patient to the needs of the owner and the patient
  - utilise the whole veterinary team, *especially* the nurses

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Diabetic management

- first and foremost remember we are dealing with a major interaction between owner and patient

(www.rvc.ac.uk/diabetesvet)

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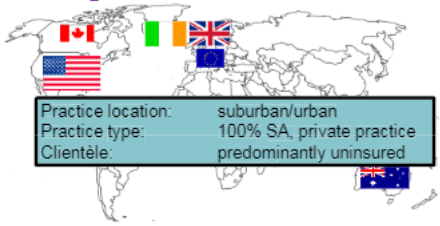
Population: 1192 clincians



Practice location:	suburban/urban
Practice type:	100% SA, private practice
Clientèle:	predominantly uninsured

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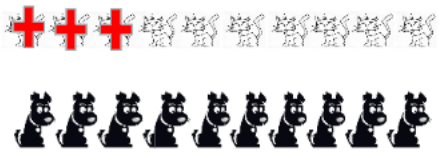
Total "loss" within one year



The Big Pet Diabetes Survey: Perceived Frequency and Triggers for Euthanasia

Would you be happy with a cruciate repair failure rate of 30%?

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If it's not country, type or location of practice, what is it that is killing diabetic dogs ????

It is the owners!

They don't like what we are asking them to do

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Diabetic management

- first and foremost remember we are dealing with a major interaction between owner and patient
- data we are getting would suggest the following
  - around 10% of dogs and ~15% of cats are euthanased at the time of diagnosis
  - within the first year, treatment is stopped in 15% - 20%
  - a total "loss" of around 30%-35% within the first year
- causes of "loss" fall into two broad categories
  - impact on the *owner's* quality of life directly
  - impact on the *owner's* quality of life indirectly

(www.rvc.ac.uk/diabetesvet)

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What about those that stay alive?

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Evaluation of a Quality-of-Life Tool for Dogs with Diabetes Mellitus

S.J.M. Niessen, S. Powney, J. Guitian, A.P.M. Niessen, P.D. Pion, J.A.M. Shaw, and D.B. Church

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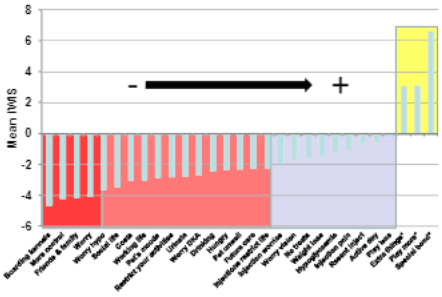

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Top 10 negative QoL score in the dog

Item	QoL score
1. Worry	-6
2. Friends and family	-6
3. Worry vision	-6
4. Boarding	-5
5. Worry hypo	-5
6. Social life	-5
7. Costs	-4
8. Future care	-4
9. Working	-4
10. Restrict activities	-4

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Diabetic management

- this really is a *major* interaction between patient and owner....
- will most of our patients be the same ?
- will most of our owners and their priorities be the same ??

What do you think is the most important key to success?

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Diabetic management

- this really is a *major* interaction between patient and owner....

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Diabetic management

- this really is a *major* interaction between owner and patient....
- then *flexibility* is a *key component* to success

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Diabetic management

- this really is a *major* interaction between owner and patient....
- then *flexibility* is a *key component* to success
- protocols tend to result in 'rigidity' which is totally at variance with flexibility ....

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Diabetic management

- this really is a *major* interaction between owner and patient....
- then *flexibility* is a *key component* to success
- protocols tend to result in 'rigidity' which is totally at variance with flexibility ....
- hence *principles* are what we want to look at, not so much protocols

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Diabetic management

1. where possible correct underlying causes and/or factors that interfere with insulin's actions
2. reduce hyperglycemia to <15mmol/L, minimise clinical hypoglycaemia
   - longer acting insulin or more frequent doses of shorter acting insulin
3. reduce the hyperglycemic impact of meals using the most palatable food with the lowest glycemic index
4. adapt management of the patient to the needs of the owner and the patient
   - utilise the whole veterinary team, *especially* the nurses

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Diabetic management

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Diabetic management

- Creating an environment where clinical signs are minimal and the Quality of Life of the patient *and* the owner are acceptable
- However, despite the above we often focus on test results such as:
  - blood glucose levels: "spot tests" or "curves"
  - urine glucose
  - fructosamine

A bit problematic as we know these parameters don't necessarily correlate well with clinical signs

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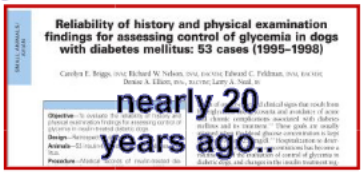
Always integrate any test results with the clinical picture

Various monitoring tools available

All with different pitfalls

Any result interpreted in the context of the clinical signs


Reliability of history and physical examination findings for assessing control of glycemia in dogs with diabetes mellitus: 53 cases (1995–1998)

nearly 20 years ago...

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How many different staff see your diabetic patients ?

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Reliable & consistent clinical evaluation

- clinical history can prove unreliable due to:
  - inter-person variation
  - variable methods of asking and answering questions
  - interpreting non-standard language
  - forgetting questions or inconsistant interrogation techniques
  - lack of quantification
- **RVC Diabetic Clinical Score:** a validated and standardised guide to mitigate some of these concerns

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RVC Diabetic Clinical Score

Factor	Score
Unintended Weight Loss 0 = None, or gained since last examined 1 = Mild (<5% loss) 2 = Moderate (5-10% loss) 3 = Severe (>10% loss)	2
Polyuria and Polydipsia 0 = Normal 1 = Mild (Some increase noted by owner) 2 = Moderate (Increased filling of water bowl) 3 = Severe (Constantly at bowl)	1
Appetite 0 = Normal or decreased appetite 1 = Mild polyphagia (Finishes eagerly) 2 = Moderate polyphagia (Finished eagerly and begs for more) 3 = Severe polyphagia (Obsessed with food)	1
Attitude/activity 0 = Normal 1 = Mild decrease (a bit less running and jumping) 2 = Moderate decrease (a bit less running and jumping) 3 = Severe decrease (lying about all the time)	2
Total Score =	6

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RVC Pet Diabetes App

- Diabetic management tool developed with & for diabetic pet owners
- The app incorporates a variety of components about the animal's diabetes including:
  - owner's objectivised clinical impressions (DCS & QoL)
  - blood glucose curves
  - urinalysis data
  - injection site reminder
  - caloric calculator

www.facebook.com/RVC Diabetic Remission Clinic

- The pet owner shares information with the vet nursing team at the practice – empowering & involving the owner
- Collective data can be used for diabetic research

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Diabetes mellitus – monitoring

- clinical signs:
  - reduced polydipsia and polyuria
  - normalised body condition score
  - consistency between vets & vet nurses ...
  - achieved using the Diabetic Clincial Score
- and then what ....?

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Diabetes mellitus – monitoring

- clinical signs:
  - reduced polydipsia and polyuria
  - normalised body condition score
  - consistency between vets & vet nurses ...
  - achieved using the Diabetic Clincial Score
- estimating glucose levels using "curves" & average daily blood or interstitial glucose
  - home glucose monitoring

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Diabetes mellitus – monitoring

- clinical signs:
  - reduced polydipsia and polyuria
  - normalised body condition score
  - consistency between vets & vet nurses ...
  - achieved using the Diabetic Clincial Score
- estimating glucose levels using "curves" & average daily blood or interstitial glucose
  - home glucose monitoring
- glycoalbumin/fructosamine (or glycosylated haemoglobin)

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Diabetes mellitus – home glucose monitoring

- suitable process for the majority of animals & owners
- around 80% of cases appear suitable
- marked differences in > 50% of cases between "in-hospital" v "out-patient" derived results
- complimentary to fructosamine
- various home-glucose monitoring devices available using <25µl of blood

Cost-benefit appraisal ?

Casella et al, JFMS 2005; Alt et al, JAVMA 2007

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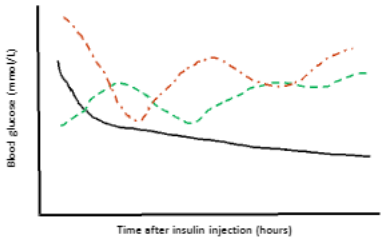
Reliability of blood glucose curves



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Reliability of blood glucose curves

- blood glucose curves produce "variable" results whether performed in hosptial or at home
- comparing day 1 & day 2 values resulted in different decisions in 27% of situations (hospital)
- paired curves were significantly different:
  - in 14/28 animals tested in hospital
  - in 6/14 animals tested at home
  - in 4/6 (66%) with good control and 2/8 (25%) with poor control

Better controlled patients have more variable blood glucose curves

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Continuous glucose monitoring

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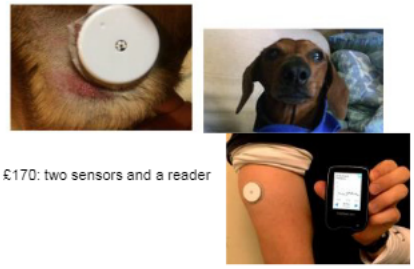
Free style Libre®



£170: two sensors and a reader

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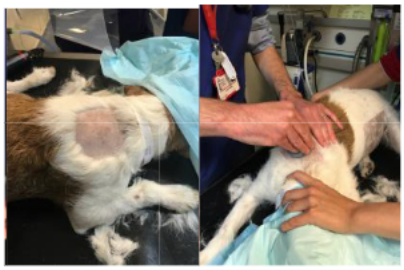
Libre:
continuous home glucose monitoring



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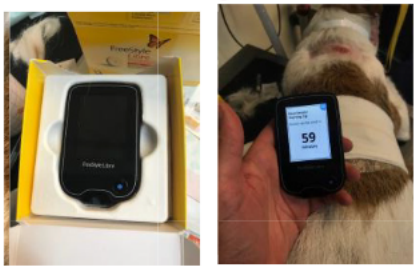
Libre:
continuous home glucose monitoring



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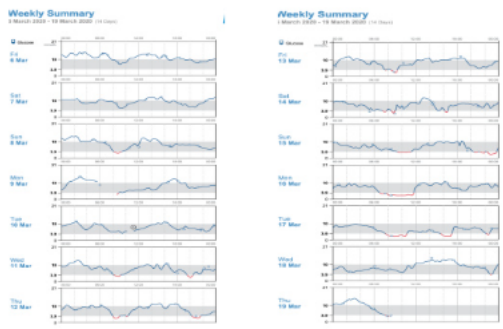

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Diabetes mellitus – home glucose monitoring

- Home glucose monitoring resulted in a significantly increased DIAQoL score
- In essence owners were happier, as they were less worried about things that might go wrong
- They felt more in control
- However .....
- The improvement in diabetic control was less convincing

Casella et al, JFMS 2005; Alt et al, JAVMA 2007, Hazuchova et al 2017

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Diabetes mellitus – monitoring

- clinical signs:
  - reduced polydipsia and polyuria
  - normalised body condition score
  - consistency between vets & vet nurses ...
  - achieved using the Diabetic Clincial Score

Value for money ??

- estimating glucose levels using "curves" & average daily blood or interstitial glucose
  - home glucose monitoring with blood or Libre®
- glycoalbumin/fructosamine (or glycosylated haemoglobin)

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Diabetes mellitus – "optimal" monitoring

- varies with different cases however:
  - essential we see improved clincial signs
  - continuous glucose monitoring should be our preference in 2023
  - home glucose monitoring helps overall owner quality of life
  - urine glucose can also be helpful in cats if they are transitioning off insulin
- hard to justify any form of close monitoring for the first few days after diagnosis
- use the nursing team's talents !!!

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Diabetic management

1. where possible correct underlying causes and/or factors that interfere with insulin's actions
2. adapt management of the patient to the needs of the owner and the patient
   - utilise the whole veterinary team, *especially* the nurses
3. reduce hyperglycemia to <15mmol/L, minimise clinical hypoglycaemia
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4. reduce the hyperglycemic impact of meals using the most palatable food with the lowest glycemic index

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Diabetic management

- Creating an environment where clinical signs are minimal and the Quality of Life of the patient *and* the owner are acceptable
- In the cat perhaps best achieved by the cat "coming off insulin"
- What should we expect in terms of achieving off insulin and how can we best achieve these expectations?

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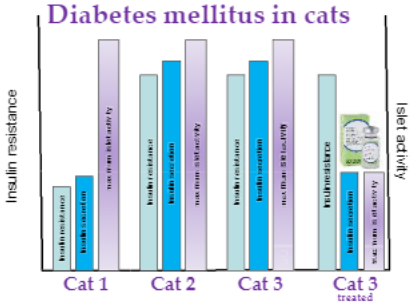
Diabetes mellitus in cats



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Diabetic management

- Creating an environment where clinical signs are minimal and the Quality of Life of the patient *and* the owner are acceptable
- In the cat perhaps best achieved by the cat "coming off insulin"
- What should we expect in terms of achieving off insulin and how can we best achieve these expectations?

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Diabetic management

- Creating an environment where clinical signs are minimal and the Quality of Life of the cat *and* the owner are acceptable
- In the cat perhaps best achieved by the cat "coming off insulin"

This is where we need to focus on improved "glycemic parameters"

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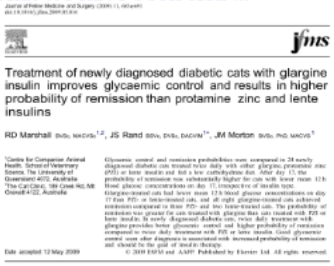
Diabetes "remission rates" in cats – what we have been told ...



Treatment of newly diagnosed diabetic cats with glargine insulin improves glycaemic control and results in higher probability of remission than protamine zinc and lente insulins

RD Marshall, JS Rand, JM Morton

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Diabetes "remission rates" in cats – what we have been told ...

Evaluation of detemir in diabetic cats managed with a protocol for intensive blood glucose control

Kirsten Roomp and Jacquie Rand

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Diabetes "remission rates" in cats – what we have been told ...

- Based on these studies, with much larger numbers of cats, the "remission rates" with glargine or determir are still around 81% - 84%
- Again however, there are a number of noteworthy features....
- Patients were recruited 'on line' with neither author examining recruited cases or involved in establishing the diagnosis and ...
- Of the cases recruited 58% of glargine and 70% of determir cases were *excluded* !!
- More accurately then a remission rate of 34% & 25% with glargine and determir respectively

Roomp & Rand 2008, Roomp & Rand 2012

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Diabetic management

- Creating an environment where clinical signs are minimal and the Quality of Life of the patient *and* the owner are acceptable
- Is the type of insulin we use important ?
- Is the type of food we feed important ?
- Is when we feed the patient important ?
- Is there any evidence to indicate characteristics that might suggest which cats are more or less likely to be able to come off insulin ?

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Improving glycemic control

- Is it likely the type of insulin we use will make a difference ?

Remind ourselves about some basic principles regarding insulin use

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Diabetic management

- Creating an environment where clinical signs are minimal and the Quality of Life of the patient *and* the owner are acceptable
- Is the type of insulin we use important ?
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Improving glycemic control

- Is it likely the type of insulin we use will make a difference ?

Remind ourselves about some basic principles regarding insulin use

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Dosing frequency using delayed acting insulins

- Traditional delayed insulins intermediate insulins - tend to last longer in dogs than in cats and longer in people than in dogs
- As a result it is difficult to achieve effective control of diabetes in dogs or cats on anything less than twice daily dosing...
- Especailly if they are being fed more than once daily
- Furthermore it is highly unlikely a diabetic cat will be able to come off insulin if it's not receiving an intermediate insulin *at least* twice daily

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Insulin: more than twice daily!

Intermediate acting insulins can certainly be used more than twice daily; in some cases and with suitable owners three or even four times daily

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Management of diabetes

- Is it likely the type of traditional (intermediate) insulin we use will make a difference ?

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Which traditional insulin should we be using ??

- in dogs this is probably still *either* a lente insulin zinc suspension or NPH insulin or possibly PZI
- there are not major differences in efficacy so cost is a consideration
- in cats it is a little more controversial....
- some strong suggestions by certain experts that glargine is the clear insulin of choice ...
- although previous evidence has not been all that clear....

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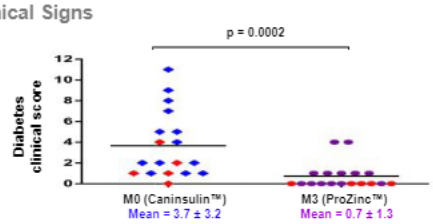
Comparison of Caninsulin® vs Protamine zinc

Clinical Signs



Significant decrease in diabetes clinical score

Gostelow et al 2015

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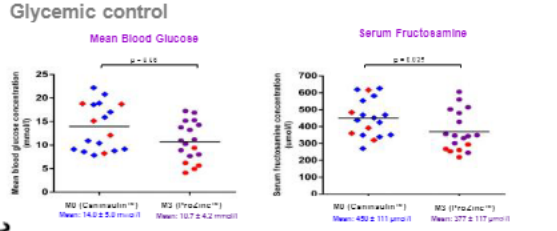
Comparison of Caninsulin® vs Protamine zinc

Glycemic control



Significant decrease in blood glucose and frustosamine

Gostelow et al 2015

RVC

61

Comparison of PZI vs glargine

Diabetic control at entry

Variable	PZIR	Glargine	p-value
Time from diagnosis to enrolment (days)	71 (49 – 93)	58 (49 – 82)	0.84
BID insulin dose (U/kg)	0.5 (0.3 – 0.7)	0.5 (0.4 – 0.8)	0.48
Average blood glucose during Month 0 24-hr curve	13.2 (9.0 – 15.8)	12.6 (10.7 -17.4)	0.80
Fructosamine (µmol/l)	469 (366 - 715)	483 (374 – 575)	0.78
DIAbetes-pet Score	-1.73 (-2.37 to – 1.01)	-1.43 (-2.07 to – 0.77)	0.13
Diabetic Clinical Score	3 (1 – 6)	4 (1 – 5)	0.99
Total insulin starting dose (U/kg BID)	0.5 (0.3 – 0.7)	0.5 (0.3 – 0.6)	0.76

17/22 (77%) PZIR cats and 20/24 (78%) glargine cats used home glucose monitoring

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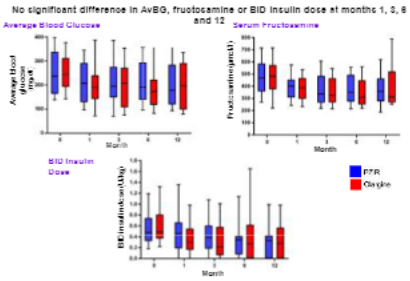
62

Comparison of PZI vs glargine

No significant difference in AvBG, fructosamine or BID insulin dose at months 1, 3, 6 and 12



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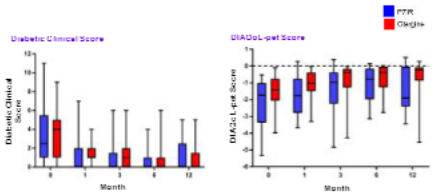
63

Comparison of PZI vs glargine

No significant difference in DC 8 or DIAQoL-pet scores at months 1, 3, 6 and 12



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64

Summarising: which traditional insulin in dogs and which in cats ?

- in dogs this is probably still *either* a lente insulin zinc suspension (caninsulin/vetsulin®) or NPH insulin or possibly PZI
- not lots of differences in efficacy so cost is a consideration
- in cats it is a little more controversial but in essence protamine zinc insulin is as good as any and better than most, including Caninsulin/Vetsulin
- insulin glargine is also adequate although certainly not worth the increased cost it incurs over PZI in many countries

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65

Summarising: what is the current situation about remission rates in cats

- While the proportion of 'diabetic' cats coming off insulin has been reported as being as high as 81% - 100% this might not be particularly representative of most situations
- The evidence supporting the benefits of glargine or determir over other longer acting insulins is not particularly robust
- Some evidence that porcine lente insulin is not as effective as PZI or glargine or determir
- PZI appears to be as effective as glargine

Roomp & Rand 2008, Marshall *et al* 2009, Roomp & Rand 2012, Gostelow *et al* 2014

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66

Improving glycemic control

- Is it likely the type of insulin we use will make a difference ?
- Is it likely the type of food used and when we feed patients will make a difference ?
- Is there any evidence to indicate characteristics that might suggest which cats are more or less likely to be able to come off insulin ?

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67

Diabetes mellitus – principles of insulin therapy

Who prescribes a prescription diabetic diet on every newly diagnosed diabetic patient you manage?

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68

Top 10 negative QoL score in the dog

Item	QoL score
1. Worry	-6
2. Friends and family	-6
3. Worry vision	-6
4. Boarding	-5
5. Worry hypo	-5
6. Social life	-5
7. Costs	-4
8. Future care	-4
9. Working	-4
10. Restrict activities	-4

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Diabetes mellitus – feeding

- caloric content needs to be standardised
  - intake regulated to body weight
  - 50 - 60 kcal/kg body weight
- composition should be standardised
  - carbohydrate content
  - fibre content ?
  - fat content ?
- significant difference between species.....

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70

Cats as carnivores – evolutionary development

- cats are relatively insensitive to insulin
  - adapted for an obligate carnivore (low carbohydrate) diet ?
- however *normal* cats can certainly adapt to variable levels of dietary carbohydrate but.....
- *diabetic* cats appear to have trouble adapting to diets which are NOT low in carbohydrate
  - when controlled for different insulin regimes, there seems to be improved diabetic control in cats fed low carbohydrate diets
- but what is a low carbohydrate diet ??

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71

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75

Cats as carnivores – evolutionary development

- cats are relatively insensitive to insulin
  - adapted for an obligate carnivore (low carbohydrate) diet ?
- however *normal* cats can certainly adapt to variable levels of dietary carbohydrate but.....
- *diabetic* cats appear to have trouble adapting to diets which are NOT low in carbohydrate
  - when controlled for different insulin regimes, there seems to be improved diabetic control in cats fed low carbohydrate diets
- but what is a low carbohydrate diet:
  - essentially any "wet food" or specifically formulated dry food...

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76

Diabetes mellitus – feeding

- caloric content needs to be standardised
  - intake regulated to body weight
  - 50 - 60 kcal/kg body weight
- composition needs to be standardised
  - low carbohydrate diet in diabetic cats (any "wet food")
  - feed as set meals although some animals will 'graze' (ideally then a low CHO formulated "dry food")
- in dogs, feeding a diet high in dietary fibre has *no* benefit in improving diabetic control

Fleeman *et al*, JSAP 2009

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77

Improving glycemic control

- Is it likely that the type of insulin we use will make a difference in most dogs?
- Is it likely that the type of food used and when we feed patients will make a difference?
- Is there any evidence to indicate characteristics that might suggest which cats are more or less likely to be able to come off insulin ?

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Improving glycemic control

I usually feed my diabetics before, or at the time of, insulin injection.

Is this optimal management ?

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79

Improving glycemic control

- insulin will lower the blood glucose for a period of 8-14hr
- each meal will raise the blood glucose
- more dramatic effect if meals are given at 12 hour intervals rather than more frequently
- ideally we want to match the opposing effects of the insulin and the meal to .....
- minimise "malutilisation" and achieve relatively stable blood glucose levels over the twelve hour period without developing hypoglycemia

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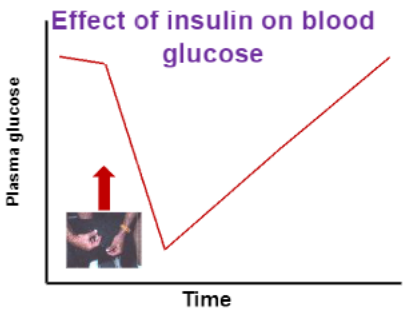
80

Effect of insulin on blood glucose



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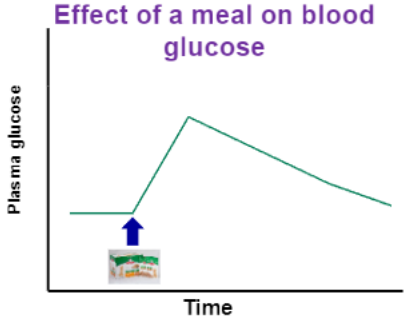
81

Effect of a meal on blood glucose



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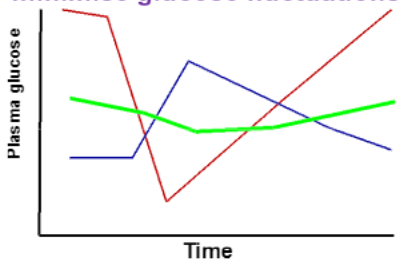
82

Matching the effects of insulin and meals to minimise glucose fluctuations



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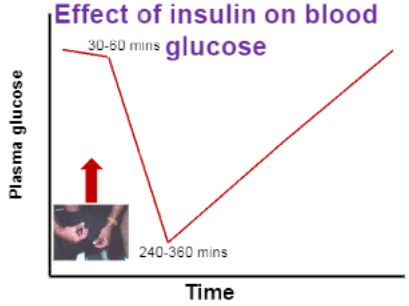
83

Effect of insulin on blood glucose



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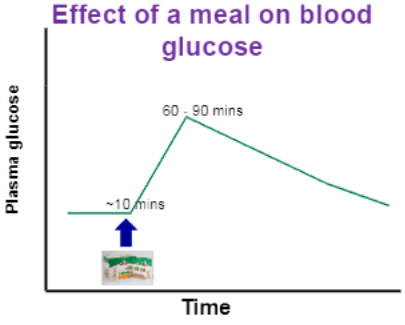
84

Effect of a meal on blood glucose



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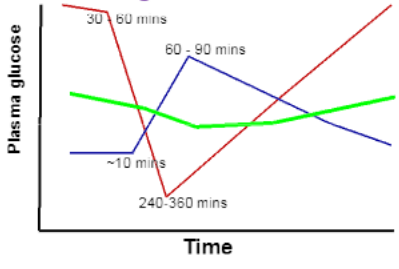
85

Matching the effects of insulin and meals to minimise glucose fluctuations



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86

Matching the effects of insulin and meals to minimise glucose fluctuations

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87

Matching the effects of insulin and meals to minimise glucose fluctuations

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88

Diabetes mellitus – principles of insulin therapy

I usually feed my diabetics before, or at the time of, insulin injection.

Is this optimal management ?

Nope, we aren't getting the most from our insulin

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89

Frustration of the canine diabetic cataract

- We want to try and avoid both the degree of hyperglycemia and how long it lasts as both are likely to be accelerating cataract development ..
- While at the same time doing our best to avoid any clinically significant periods of hypoglycemia
- And also not imposing so many restrictions on the owners that they give up on the whole exercise as being too stressful, too expensive or both!

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90

Top 10 negative QoL score in the dog

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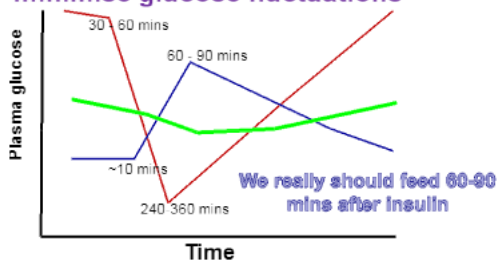
91

Matching the effects of insulin and meals to minimise glucose fluctuations



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92

Summarising: feeding my diabetic patients

- when using traditional insulins whenever possible try and match the effects of insulin and a meal by feeding approximately 60-90 mins *after* administering insulin
- always try and feed meals with standardised caloric and constitutive content regardless of whether it is a dog or a cat
- in cats ideally use a diet that is low (<12%) in carbohydrate
  - this can be *any* commercial "wet" food or if it is dry food then a prescription diabetic diet
- in grazing diabetic cats, consider more frequent injections of possibly shorter acting insulin or ultralong acting peakless insulin such as ???
  - and in "grazers" definitely preferable to use a prescription dry cat food diet
- in diabetic dogs there is no benefit in feeding low carbohydrate or high fibre diabetic diets
  - so feed them what they have been fed before and are comfortable with or find most palatable

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Improving glycemic control

- what if I am really uncomfortable about not feeding sometime after giving insulin, are there alternatives ?
- obviously if your patients are not having any sort of major fluctuations in their 12 hourly glucose levels then change nothing
  - glucose levels between 4mmol/l and 15 - 20mmol/L
- but if fluctuations are greater is there anything else I can do ?
- consider using a "basal" or "flat-line insulin" regime using an ultra-long acting, "peakless" insulin such as ...
- insulin Toujeo® or Lantus® XR

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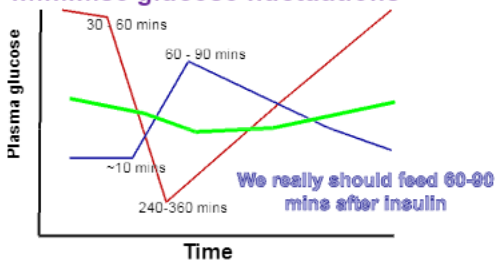
94

Matching the effects of insulin and meals to minimise glucose fluctuations



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93

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- insulin Toujeo® or Lantus® XR

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Insulin Toujeo® or Lantus® XR

- Starting dose of ~0.5U/kg/24h or 130% of the 12 hour dose of standard insulin the diabetic has been receiving
- Insulin dosage and meals can be independent
- May need to go to 12 hourly dosing but only after trying 24 hourly dosing and .....
- MUST, MUST, MUST be undertaken with concurrent continuous glucose monitoring

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95

Management of feline diabetes

- Is it likely that the type of insulin we use will make a difference ?
- Is it likely that the type of food used and when we feed patients will make a difference?
- Is there any evidence to indicate characteristics that might suggest which cats are more or less likely to be able to come off insulin ?

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96

Management of feline diabetes

- Are there any robust studies suggesting what might predict an increased likely hood of cat coming off insulin ?
- Gostelow et al 2017:
  - 46 cats enrolled on a one year study comparing glargine & PZI
  - Multivariate analysis determined the only characteristic that predicted remission was:
  - A greater than 2% loss in body weight within the first one month of treatment with either insulin

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97

Diabetic management

1. where possible correct underlying causes and/or factors that interfere with insulin's actions
2. adapt management of the patient to the needs of the owner and the patient
   - utilise the whole veterinary team, *especially* the nurses
3. reduce hyperglycemia to <15mmol/L, minimise hypoglycaemia
   - longer acting insulin or more frequent doses of shorter acting insulin
4. reduce the hyperglycemic impact of meals using the most palatable food with the lowest glycemic index

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98

Complicated diabetes

Increasing dose with an inadequate response

- either a rebound hyperglycemia or..
- the presence of a concurrent disease inducing consistent insulin resistance:
  - non-endocrine diseases
    - virtually any disorder that may or may not be producing *other* clinical signs
  - endocrinopathies
    - Cushing's syndrome
    - acromegaly

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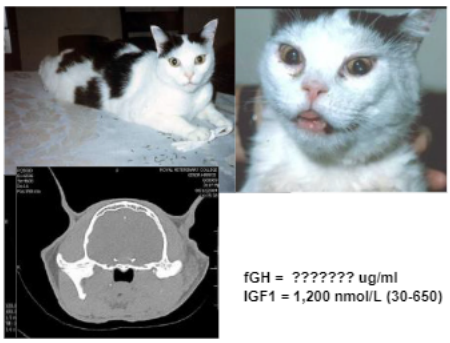
99



fGH = ??????? ug/ml
IGF1 = 1,200 nmol/L (30-650)

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100

Update on prevalence

- Schaefer abstract ECVIM Congress, JVIM, 2013
- N= 225 cats **1 in 5 !**
- [IGF-1]: 15–2471 ng/ml
  - median 584
  - 17.8% IGF-1 > 1000

- Niessen *et al* PLOS One (2015)
- N=1221 **1 in 4 !!**
- [IGF-1]: 39-2000 ng/ml
  - mean 787 (+/-563)
  - 26.1% IGF-1 > 1000
  - CT/MRI/necropsy
  - 95% +ve if IGF-1> 1000

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101

Can we trust IGF-1?

	Fruct	Insulin	BW	IGF-1
Month 0	680	1	3.95	212

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102

Complicated diabetes mellitus

Management of acromegaly

- aggressive insulin treatment
  - prepare everyone for long term instability
- radiotherapy
  - disappointingly inconsistent ...
- hypophysectomy
  - replacement hormone treatment required
- pasireotide injections
  - multi-receptor somatotroph antagonist

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Feline hypersomatotrophism

- more common than we thought
- In the UK currently around 1 in 4.5 diabetic cats
- < 10% had so-called "typical" phenotype
- index of suspicion based on serum IGF
- "confirmation" with demonstration of pituitary mass
- currently we suggest sampling all diabetics once they are on insulin (>4 weeks) and keep the separated serum in the freezer to be analysed if the cat's diabetes is not readily controlled

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104

Complicated diabetes

Increasing dose with an inadequate response

- either a rebound hyperglycemia or..
- the presence of a concurrent disease inducing consistent insulin resistance:
  - non-endocrine diseases
    - virtually any disorder that may or may not be producing *other* clinical signs
  - endocrinopathies
    - Cushing's syndrome
    - acromegaly

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105

Complicated diabetes

Increasing dose with an inadequate response

- Cushing's syndrome in the diabetic dog:
  - Cushing's syndrome is *not* the likely cause of the diabetes

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106

Complicated diabetes

Diabetes & Cushing's syndrome

- management principles should include:
  - an aspirational *ultimate* insulin dose trending to around 1.5U/kg/24h (divided)
- with 'standard' trilostane dosing the insulin dose tends to decline over 2-4 weeks
- consider enhanced glucose monitoring:
  - HBG verses urine glucose ?

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Diabetes mellitus

Where are we in 2023?

- Recognition that quality of life & owner–pet interactions must be our principal priority. Thus:
  - a need to implement consistent principles without rigid protocols
  - aim to minimise clinical signs through a degree of improved glycemic control
  - aim to minimise costs for many of our punters
- Diabetes mellitus is not really the same in dogs and cats because our management goals can be different
- Regardless, the emphasis HAS to be on clinical response and ...

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108

Royal Veterinary College
University of London

Hypoadrenocorticism:
diagnosis and management – what drugs and what doses.....

Vet Vault, 2022

David Church

Sharing passions, shaping futures

1

Hypoadrenocorticism:
pathophyiology

- a disorder resulting in clinically significant adrenocorticolysis
  - immune-mediated
  - adrenal haemorrhage due to ⇑⇑ ACTH
- reduced capacity to produce the two key adrenocortical hormones: cortisol and aldosterone
  - cortisol has equipotent glucocorticoid and mineralocorticoid activity
  - aldosterone has predominantly mineralocorticoid activity

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2

Hypoadrenocorticism:
pathophyiology

- a disorder resulting in clinically significant adrenocorticolysis
  - immune-mediated
  - adrenal haemorrhage due to ⇑⇑ ACTH
- reduced capacity to produce the two key adrenocortical hormones: cortisol and aldosterone
  - reduced capacity to produce cortisol ***and*** aldosterone : ***typical*** hypoadrenocorticism
  - a proportion of cases with ***no*** electrolyte abnormalities: ***atypical*** hypoadrenocorticism **Do these progress to "typical" ?**

Less than 15% progress to "typical" ?

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3

Hypoadrenocorticism: the two broad clinical pictures

- one clinical picture is of the acutely collapsed severely compromised patient:
  - may be sudden onset or maybe after a relapsing, more subtle set of problems
  - usually hypovolemic and/or dehydrated
  - poor circulatory integrity ("in-shock")
  - may be tachycardic, bradycardic or neither...
- a second clinical picture is of a variably subtle, "unwell" animal, that has a waxing and waning presence; it "comes and goes"

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4

Hypoadrenocorticism: the non-acute clinical picture

- waxing and waning "not doing well " type signs
- lethargy, depression, under-responsive
- reduced enthusiasm for exercise
- weakness
- inappetence
- vomiting and/or diarrhoea
- melena
- heart rate usually unaffected although on occasions may be bradycardic (<25 % of cases)

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5

Hypoadrenocorticism: the two broad clinical pictures

We can't recognise it reliably on clinical signs so can we rely on routine clinical pathology to make a diagnosis or to significantly increase our index of suspicion ??

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Hypoadrenocorticism: is there a suggestive clinical pathology "picture"

- mild to moderate anemia
  - non-regenerative and/or regenerative
- hypoproteinemic or...
  - normoproteinemic in a hypovolemic patient
- eosinophilia and/or lymphocytosis or ...
  - lack of a "stress leukogram"
- azotemia and inadequately concentrated urine
- hyponatremia and/or hyperkalemia
- hypercalcemia (total and ionised)
- hypoglycaemia

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7

Collapsed dog 1

Clinical pathology

PCV	0.35 L/L	(0.37-0.55)	TSP	63.0 g/L	(53-74)
TPP	65 g/L	(55-75)	Alb	30 g/L	(22-35)
			Glob	33 g/L	(22-45)
WBC count - all cells x 10^9/l			ALT	316 U/L	(<50)
			ALP	223 U/L	(<110)
Neutrophils (seg)	20.2	(4.0-8.4)	Urea	110 mmol/L	(2-10)
Neutrophils (band)	0.4	(0 – 0.2)	Creat	1113 µmol/L	(40-120)
Lymphocytes	0.3	(1.2 - 3.6)	Glucose	6.9 mmol/L	(3.3-7.0)
Monocytes	1.3	(0.2 – 1.0)	Amylase	5,041 U/L	(<2,500)
Eosinophils	0.0	(0.2-1.2)	Lipase	471 U/L	(<500)
			Calcium	2.6 mmol/L	(2.1-2.9)
Urinalysis : pH 6, SG 1.025, glucose -ve, ketones –ve, protein ++, blood –ve			PO_4	1.2 mmol/L	(0.8-1.8)
			Sodium	148 mmol/L	(137-160)
			K	3.9 mmol/L	(3.3-4.8)
			Chloride	118 mmol/L	(105-120)
			Chol.	7.9 mmol/L	(1.4 – 7.6)
			Bilirubin	13 mmol/L	(0 – 16)

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Collapsed dog 2

Clinical pathology

PCV	0.33 L/L	(0.37-0.55)	TSP	64.0 g/L	(53-74)
TPP	53 g/L	(55-75)	Alb	25 g/L	(22-35)
			Glob	29 g/L	(22-45)
WBC count - all cells x 10^9/l			ALT	85 U/L	(<50)
			ALP	123 U/L	(<110)
Neutrophils (seg)	9.2	(4.0-8.4)	Urea	90 mmol/L	(2-10)
Neutrophils (band)	0.2	(0 – 0.2)	Creat	718 µmol/L	(40-120)
Lymphocytes	3.6	(1.2 - 3.6)	Glucose	6.8 mmol/L	(3.3-7.0)
Monocytes	1.0	(0.2 – 1.0)	Amylase	5,041 U/L	(<2,500)
Eosinophils	1.1	(0.2-1.2)	Lipase	471 U/L	(<500)
			Calcium	3.1 mmol/L	(2.1-2.9)
Urinalysis : pH 6, SG 1.016, glucose -ve, ketones –ve, protein ++, blood –ve			PO_4	1.2 mmol/L	(0.8-1.8)
			Sodium	133 mmol/L	(137-160)
			K	4.8 mmol/L	(3.3-4.8)
			Chloride	112 mmol/L	(105-120)
			Chol.	7.8 mmol/L	(1.4 – 7.6)
			Bilirubin	13 mmol/L	(0 – 16)

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9

Hypoadrenocorticism: what is the story about the electrolytes ...

- hypoadrenocorticism tends to result in low serum sodium & high serum potassium but ...
  - not all cases with low sodium and/or high potassium are going to have hypoadrenocorticism
- animals* with a Na/K ratio of < 25:1:
  - 28% were hypoadrenocorticoid
  - 12% were on trilostane
- animals* with a Na/K ratio of < 20:1:
  - 64% were hypoadrenocorticoid
  - 22% artefacts

* RVC laboratory data, 2015

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Hypoadrenocorticism: is there a suggestive clinical pathology "picture"

- mild to moderate anemia
  - non-regenerative and/or regenerative
- hypoproteinemic or...
  - normoproteinemic in a hypovolemic patient
- eosinophilia and/or lymphocytosis or ...
  - lack of a "stress leukogram"
- azotemia and inadequately concentrated urine
- hyponatremia and/or hyperkalemia
- hypercalcemia (total and ionised)
- hypoglycaemia

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11

Hypoadrenocorticism: pathophyiology

- *typical* hypoadrencoroticoid patients: an absence of a stress leukogram *and* either hyponatremia or hyperkalemia or both (↓ Na:K ratio)
- *atypical* hypoadrenocorticism have an absence of a stress leukogram and normal Na and K levels
- most recently tested atypical patients also have normal aldosterone levels
- "atypical" ??
- ~27% of cases seen at RVC referrals (2012-2016)

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12

Hypoadrenocorticism: the two broad clinical pictures

We can't recognise it reliably on clinical signs so can we rely on routine clinical pathology to make a diagnosis or to significantly increase our index of suspicion ??

I certainly don't think so !!!

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13

Hypoadrenocorticism: the two broad clinical pictures

So how are we going to diagnose this condition with a level of confidence appropriate for the consequences of this disease – both in terms of missing a diagnosis and what is entailed in managing hypoadrenocorticism

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14

Hypoadrenocorticism: the two broad clinical pictures

- remember untreated hypoadrenocorticism is almost always fatal .....a tragedy as:
  - young dogs with a fatal disease for which..
  - there are effective management strategies
- however over diagnosing can also have serious and significant consequences...
  - exacerbation of already compromised organs
  - a protracted period of administration of inappropriate meds with adverse effects
  - once on these meds it is VERY difficult to investigate things further

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15

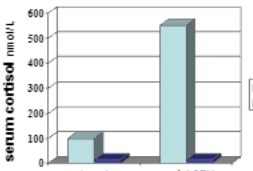
Hypoadrenocorticism

We confirm a diagnosis by an ACTH stimulation test

If the basal cortisol reference range is 25-125nmol/l then less than .. 60nmol/L

A post-ACTH cortisol within the bottom 25th percentile of the reference range for basal cortisol

ALIVE consensus statement 2020



If the basal cortisol reference range is 30-150nmol/l then less than .. 60nmol/L

RVC

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Hypoadrenocorticism: diagnosing the two broad clinical pictures

A diagnosis of hypoadrenocorticism requires an ACTH stimulation test with demonstration of subnormal levels of cortisol before and after ACTH as well as..

confidence that no prior glucocorticoid therapy could be interfering with the test results

RVC

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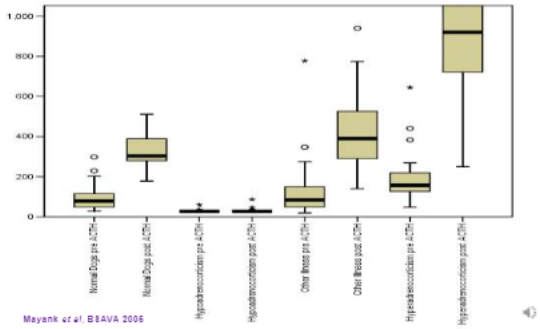

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Hypoadrenocorticism

We can reliably diagnose it with an ACTH stimulation test but how are we going to treat it ?

RVC

19

Hypoadrenocorticism: treating the two broad clinical pictures...

- acute patient with hypovolemia and varying degrees of compromised circulatory function including ultimately circulatory collapse
- the less dramatic, but equally unstable, subacute patient with non-specific, waxing and waning clinical signs, frequently manifesting itself through GIT disturbances

RVC

20

Hypoadrenocorticism: treating the acute clinical picture

- acute patient with hypovolemia and potential circulatory collapse.. what would optimum treatment look like ?
- supportive fluid therapy
  - but not too much as they are particularly "fluid sensitive"
- hormone supplementation that will be:
  - able to be parenterally administered
  - have similar degrees of both glucocorticoid *and* mineralocorticoid activity

Is that likely to be dexamethasone ?

RVC

21

Acute hypoadrenocorticism

Treatment

- parenterally administered medications
- intravenous fluids:
  - 0.9% NaCl
  - *absolutely* no more than 7-8ml/kg/hr
- adrenocortical hormone replacement
  - short acting and equally glucocorticoid and mineralocorticoid active
- hydrocortisone sodium succinate

RVC

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Acute hypoadrenocorticism

When hydrocortisone is infused IV at 0.5mg/kg/h the amount of cortisol present in the circulation provides adequate amounts of glucocorticoid and mineralocorticoid activity for a seriously stressed dog

RVC

23

Acute hypoadrenocorticism

Treatment protocol

- intravenous fluids:
  - 0.9% NaCl
  - 8 ml/kg/hr
- hydrocortisone sodium succinate
  - 0.5mg/kg/hr
  - 1-2 mg/ml

RVC

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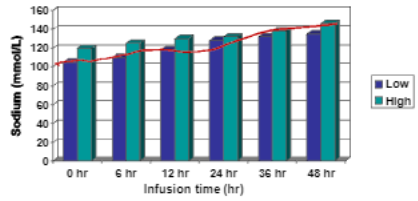
Acute hypoadrenocorticism

Sodium changes



RVC

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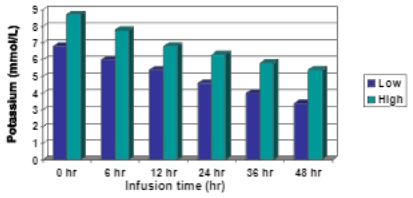
Acute hypoadrenocorticism

Potassium changes



RVC

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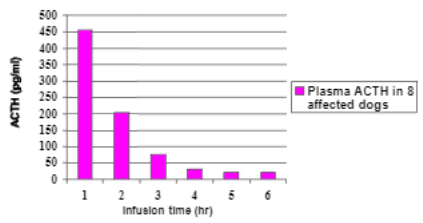
Acute hypoadrenocorticism



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Acute hypoadrenocorticism

Hydrocortisone

- parenterally administered agent
- dose rate of 0.5 mg/kg/h IV infusion
- equal levels of glucocorticoid *and* mineralocorticoid bioactivity
- short half-life
- simple, physiological
- effective

RVC

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Acute hypoadrenocorticism

Therapy

- start and maintain on IV fluids:
  - parenteral NaCl at 8ml/kg/hr
- start on hormone supplementation
  - hydrocortisone infusion at 0.5 mg/kg/h
- start on oral treatment once they start eating and drinking (usually within 36 hours)
- reduce infusion rate to 0.25 mg/kg/h IV
- stop after further 24 – 48 hours

RVC

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Hypoadrenocorticism: treating the chronic clinical picture

- sub-acute patient with varyingly severe clinical signs featuring a number of different body systems including but not limited to:
  - the gastrointestinal tract
    - structural gut disease
    - inflammatory bowel disease biopsies
  - the neuromuscular systems
    - weakness and lethargy
  - indicators of renal dysfunction
    - azotemia & inappropriately dilute urine
- medication with *appropriately balanced* glucocorticoid and mineralocorticoid activity

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Hypoadrenocorticism: treating the chronic clinical picture

Chronic Therapy

- a glucocorticoid:
  - cortisone acetate
  - prednisolone
- a mineralocorticoid:
  - deoxycorticosterone pivalate
  - florinef
- dietary considerations

Not controversial...

..but how much ??

RVC

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What dose would you use for a 15 kg dog

A. 0.2mg/kg/24h prednisolone?

B. 0.1mg/kg/24h prednisolone?

C. 0.07 mg/kg/24h prednisolone?

D. 0.5mg/kg/24hr cortisone?

E. 0.5mg/kg/24h prednisolone?

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Hypoadrenocorticism: treating the chronic clinical picture

What is the correct glucocorticoid dose ??

What is the correct glucocorticoid dose that will allow us to be comfortable that an Addisonian crisis will be very unlikely and that won't create sub-clinical Cushing's syndrome ??

RVC

33

Hypoadrenocorticism: treating the chronic clinical picture

What is the correct glucocorticoid dose ??

- normal adrenal production in the dog:
  - 0.2mg/kg/24h of cortisol
- prednisolone has:
  - 5 x the glucocorticoid activity of cortisol
- so a 10 kg dog "requires".....
- 0.4 mg per day of prednisolone
- in total !!!!

RVC

34

- £16/pack
- 28.5p/tablet

- £60/pack
- £2/tablet

RVC

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Hypoadrenocorticism

Take home messages

once stable, in dogs under 20kg, think about minimising glucocorticoid excess by using cortisone acetate rather than prednisolone

maintenance glucocorticoid doses are no more than 0.3-0.5 mg/kg/24h of cortisone which is about 0.04-0.07 mg/kg/24h of prednisone

RVC

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Hypoadrenocorticism: treating the chronic clinical picture

Chronic Therapy

- in managing stable patients we *really* need to avoid potential overdosing with glucocorticoids
- when specific glucocortioicid replacement is required then consider:
  - DOCP +/- cortisone < 20kg
  - DOCP +/- prednisolone (0.07mg/kg/24h)
- NaCl supplementation

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Hypoadrenocorticism: treating the chronic clinical picture

With DOCP do I need a glucocorticoid ??

- 1.8 - 2.2mg/kg via subcutaneous injection
- injection frequency varies but is generally around 4 weekly
- multi-dose vial: stable for 120 days
- the *label* says it has *no* glucocorticoid potency so you *must* use a glucocorticoid with it

However ....

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Hypoadrenocorticism: treating the chronic clinical picture

With DOCP do I need a glucocorticoid ??

- 1.8 - 2.2mg/kg via subcutaneous injection
- injection frequency varies but is generally around 4 weekly
- multi-dose vial: stable for 120 days
- DOCP *unarguably* has glucocorticoid potency although how much is still an actively debated question
- DOCP also has some progestin bioactivity (10-30%)
- consider a longer term DOCP dose of:
  - 1.0 - 1.5 mg/kg every 31 days
  - given current recommendations, expect to reduce to the above dose

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Hypoadrenocorticism

What if the electrolytes are normal?

- perform aldosterone estimations on the ACTH test samples but ....
- assay and cost considerations
- usually you will end up treating them with just a glucocorticoid

RVC

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Hypoadrenocorticism

Monitoring treatment efficacy

- clinical response as an overall indicator is paramount ✓
- glucocorticoid activity evaluated by:
  - leukogram ✓
- mineralocorticoid activity evaluated by:
  - sodium & potassium levels ✓
- ACTH stimulation test ✗
- basal ACTH level ✗

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Hypoadrenocorticism

Summarising

- if possible, confirm a diagnosis with an ACTH stimulation test *before* use of cross-reacting glucocorticoids
- use hydrocortisone parenterally in critical patients
- once stable, minimise glucocorticoid excess using cortisone in small dogs and..
- reduced DOCP dosing when clinically indicated
- do NOT consider a prednisone dose of 0.2-0.4 mg/kg/24h as anything even approximating "maintenance"
- if you use prednisone, use it at around 0.07 mg/kg/24h

RVC

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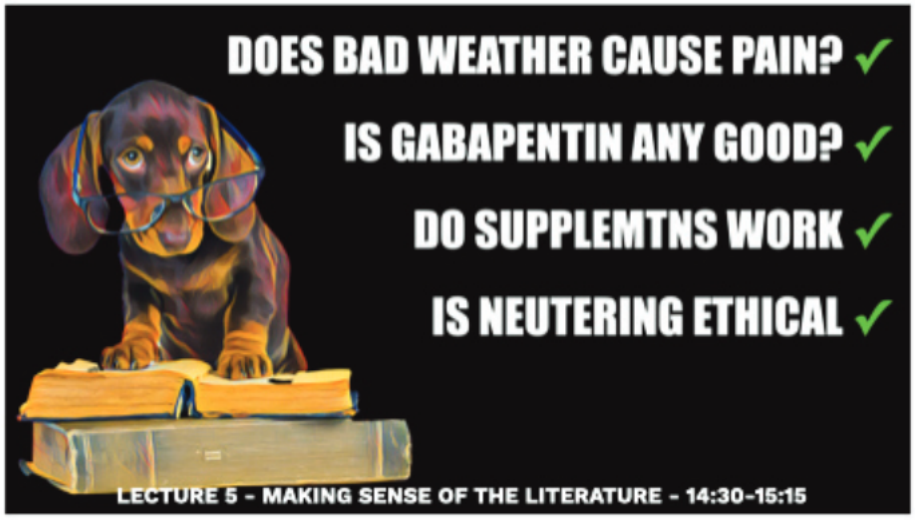
ORTHOPAEDICS PROCEEDINGS - 8TH CROATIAN NATIONAL CONGRESS, ZADAR - MARCH 31

ORTHOPAEDICS PROCEEDINGS - 8TH CROATIAN NATIONAL CONGRESS, ZADAR - MARCH 31



ORTHOPAEDICS PROCEEDINGS - 8TH CROATIAN NATIONAL CONGRESS, ZADAR - MARCH 31

BASIC CLINICAL PROCEDURES IN SMALL MAMMALS

Vladimír Jekl

It was found, that pet small mammal (exotic companion mammal) owners had, in general, limited knowledge of the needs of the animal species, particularly their diet and social needs. It is why practitioners should advise the owners to take all reasonable steps to maintain the animal's health, optimal housing, and diet and to avoid injury, illness, or behaviour frustration of the animal.

A clinical approach to the exotic companion mammals together with optimal restraint and clinical techniques (blood sampling, intravenous catheter placement, urethral catheter placement) will be presented. Many diagnostic methods are available to the clinician and veterinary nurses to help identify and describe the type of disease. It is imperative with small mammals that in emergency cases, the potential hazard of any diagnostic test needs to be considered, as minor stress can lead to the patient's collapse.

History and clinical examination

The history of exotic companion mammals can be problematic to obtain, as some owners can have a difficulty in recognizing abnormalities in behaviour, intake of food and urine, and faecal production. Weight loss, anorexia, and the presence and rate of progression of the disease or exercise intolerance should be ascertained.

- Animals should be observed while talking to the owner.
- The clinical examination is extremely important in assessing overall health and includes:
  - Assessment of behaviour, gait, and movement
  - Adspection of respiration
    - o Rabbits and commonly kept rodents are obligatory nasal breathers, so any obstructive disease of the nasal cavity could be life-threatening and lead to open-mouth breathing.
  - Auscultation
    - o Auscultate the thoracic cavity from more than 5 places, as heart murmurs or harsh lung sounds could be pronounced only from one particular place
    - o It is possible to palpate the pulse wave at a. femoralis a evaluate its function with the heartbeat, especially in ferrets and rabbits
    - o Heart diseases are very common in ferrets, guinea pigs, rats, and chinchillas
  - Mucosal surface
  - Eye and nose
    - o Rats, mice, and gerbils are commonly presented with chromodacryorrhoea (excessive porphyrin secretion) associated with conjunctivitis, rhinitis, stress, or any systemic disease
    - o Due to regular grooming, signs of discharge could be seen only as the presence of wet hair on the front paws
    - o Cataracts can be in caviomorph rodents associated with a high carbohydrate diet or diabetes mellitus
  - Skin elasticity, hair quality
    - o perineal area
    - o sex determination
    - o os penis (e.g. ferrets, guinea pigs) palpation, prepucial, scrotal and testicular palpation
    - o vagina
      - in rodents is "closed" during anestrus as the epithelial membrane is present (guinea pigs, chinchillas, and degus)
  - Ear pinna, external ear canal
    - o Ferrets - ear mites (Otodectes cynotis) are very common
  - Superficial lymph node palpation (submandibular, prescapular, axillary, inguinal, popliteal) - if you feel them - enlargement, easily mixed up with fat
  - Abdominal cavity palpation
    - o Thorax elevation
    - o Testicles in rodents could be present inside the abdominal cavity
  - Musculoskeletal system palpation
    - o Knee joint arthrosis very common in guinea pigs
    - o Pododermatitis is common in rabbits, guinea pigs, chinchillas, and rats
  - Facial symmetry, jaw palpation
    - o Apical cheek teeth elongation - common esp. in chinchillas, degus, and rabbits
  - Oral cavity evaluation
  - Rectal temperature
    - o Hypothermia at the time of hospital admission is a significant predictor of death not only in pet rabbits but also in other exotic companion mammals

Basic clinical procedures

- Faeces examinations - coprology
  - o Recommended in all young rabbits, ferrets, and guinea pigs
- Urinalysis
  - o Urinary tom cat catheters - size 1.0 or 1.3 mm work very well
  - o pH of herbivore exotic companion mammals is between 7.5-8.5
  - o in case of lower urine pH

- consider acidosis and look for blood acidobasic parameters
- poor prognostic factor

- Basic dermatological test
- Drug administration
- Blood sampling
  - o Haematology
  - o Plasma chemistry
  - o Acid-base balance
  - o Serology (e.g. E.cuniculi antibodies in rabbits)
- Imaging methods
  - o Radiography
  - o Ultrasonography
  - o Endoscopy
  - o Computed tomography
  - o Magnetic resonance
- Biopsy/Surgery
  - o Cytology
  - o Histopathological examination
- Other tests
  - o e.g. faeces PCR in ferrets for FECV

Acknowledgments

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RESPIRATORY DISEASES

Vladimir Jekl

Several challenges arise when evaluating a rabbit with respiratory disease. Rabbits are obligate nasal breathers, so "simple" rhinitis can cause severe respiratory distress and patient collapse. Causes of dyspnoea could be of the primary origin or secondary, where diseases primarily affecting other organs can result in respiratory embarrassment even if the respiratory system is healthy (e.g., anaemia, cardiac disease). Once the diagnosis has been completed, treatment options should be discussed with the owner.

Physiology

Rabbits are obligate nasal breathers, which means that the normal anatomical position of the epiglottis causes it to be engaged over the caudal rim of the soft palate, sealing the oral pharynx from the lower airways. Therefore, rabbits with advanced upper airway disease will attempt to breathe through their mouths, which prevents feeding and drinking and could be quickly fatal. Also, inadvertent occlusion of the nasal passages during any procedure, including oral cavity examination, can lead to respiratory compromise due to the ineffectiveness of mouth breathing.

Diagnostics

Diagnosis is based on thorough clinical examination, radiography, ultrasonography, endoscopy, echocardiography, computed tomography, and/or cytology and/or pathogen isolation or on a combination of the above-described imaging methods.

Treatment

Treatment is based on aetiology and consists of patient stabilization and supportive care; conservative treatment and/or surgery. Readers are redirected to read the author's publication dealing with respiratory diseases of small herbivorous rodents for a full review of possible diseases and treatment options.

Selected diseases, which may be associated with respiratory disorders.

- Viral infections
  - o Rabbit hemorrhagic disease
  - o Myxomatosis
  - o Leporid-4 Herpes virus
  - o SARS-CoV (under experimental conditions)
- Bacterial infections
  - o Pasteurella multocida infection
  - o Bordetella bronchiseptica and Staphylococcus aureus infections
  - o Cilia-Associated Respiratory (CAR) Bacillus infection

- Streptococcus spp. infection
- Treponematosis
- Mycobacterial infections

- Mycotic infection
  - Aspergillosis
- Parasitic disease
  - aberrant larva migrans (Cuterebra sp.)
  - verminous pneumonia (Protostrongylus sp.)
- Neoplastic and pseu-doneoplastic lesions
  - Intranasal adenocarcinoma
  - Various oral cavity and dental tumors in rabbits
  - Laryngeal and tracheal tumors.
  - Lung tumors (metastases - uterine carcinoma, mammary gland adenocarcinoma, lymphoma)
  - Thymoma
- Other diseases
  - Foreign body
  - Nasal septum deformation
  - Laryngeal paralysis
  - Tracheal stenosis
- Organomegaly, abdominal distension
- Pleural effusions
  - Chylothorax
  - Hydrothorax
- Brain disorders
- Metabolic acidosis
- Status ante finem

Acknowledgments

This article was supported by the grant of the University of Veterinary Sciences Brno IGA 105/2023/FVL and 105/2023/FVL.

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URINARY TRACT DISEASES

Vladimir Jekl

Urinary tract disorders in exotic companion mammals are seen very frequently, especially in rabbits, guinea pigs, rats, and ferrets. Urolithiasis is one of the most common diseases requiring surgical intervention. Both the formation and growth of uroliths may be influenced by urine pH, matrix availability, the degree of crystalluria, and the presence or absence of crystalline inhibitors. Urinary infection can be a predisposal factor or a sequela of urolithiasis. Based on the author's experience, uroliths in rabbits are mostly found in the urinary bladder and kidneys. In guinea pigs, it's the urethra, urinary bladder, and ureters; in ferrets, it is the urinary bladder. Struvites and calcium phosphate uroliths are usually formed in alkaline urine, cystine uroliths in acid, and calcium–oxalate and urate stones in acid-to-neutral urine. The genesis of very large urethral stones is presumably the result of a nidus of the calculi formed in the urinary bladder and then passing into the urethra, where it lodges and accumulates. As a result, the urethral lumen becomes slightly enlarged and thus allows a continuous flow of urine around the stone.

Predisposing factors for urinary calculi formation can be urinary tract inflammation, musculoskeletal pain (arthrosis, fractures, spondylosis, and trauma), metabolic disorders, obesity, dehydration, urinary neoplasia, or any previous surgery. The urine alkaline pH of herbivorous small mammals also increases the risk of forming insoluble calcium precipitates.

Diagnosis

The presence of urinary tract disease may be associated with inflammatory changes in the urinary system, renal dysfunction, urinary tract obstruction, and pain. The patient with a urinary obstruction secondary to urolithiasis has a life-threatening condition that must be solved as soon as possible. Animals are presented with anorexia, dysuria, haematuria, frequent urination, and perineal urine scald. Guinea pigs may vocalize during urination. However, in some cases, obvious clinical signs are unapparent.

Haematology and plasma/serum biochemistry are very important regarding the follow-up medical approach and prognosis determination.

Urinalysis could reveal the presence of erythrocytes, inflammatory cells, mucosal cells, and crystals. Urinary pH is influenced by the specific species' metabolism, feeding, actual metabolic status, inflammatory changes, or previous drug administration. Finding calcium crystals in the urine does not necessarily indicate that urolithiasis is present, especially in rabbits, guinea pigs, and degus, where calcium is excreted via urine under normal circumstances. However, if any signs of urinary disease or abdominal pain are present, further investigation is advisable. Low urinary pH and ketonuria bear guarded to poor prognosis.

Radiography and ultrasonography should always be performed. Compared to soft tissue density, most uroliths (struvite, calcium oxalate, calcium phosphate, cystine) are radiopaque (Figure 1), while urates may be radiolucent. Contrast studies (intravenous excretory radiography, positive contrast, double contrast, urethrogram) may help locate uroliths. Retrograde double contrast cystography may provide the clinician with valuable diagnostic and prognostic information about the bladder disease in question. This contrast study is particularly helpful in males and females with separate urinary papilla (rats, chinchillas, guinea pigs, degus, etc.). Abdominal ultrasound allows a non-invasive evaluation of the urinary tract. It is helpful in the detection of anatomical abnormalities, neoplasia, and urolithiasis.

Conservative treatment of calcium oxalate and calcium phosphate urolithiasis

Dietary therapy consists of reducing calcium and oxalate, moderate protein, and sodium restriction. Reducing dietary calcium, however, is not advisable by the author (VJ) as the induction of calcium metabolic disturbances. Treatment of all the aetiological factors, supporting urination and movement is the author's choice of management of the urinary tract disorders. Administration of potassium citrate enhances the calcium reabsorption in kidneys and inhibits urolith formation in the urinary bladder and may be of some help. Other drugs, which relax the urinary bladder (oxybutynin, altrenogest) and analgesics (metamizole, gabapentin) are preferable. In guinea pigs, one of the causes of cystitis, overload with nitrate was suggested, so lowering the dietary nitrogen is recommended.

The antibiotic therapy should be based on urine/urinary calculi bacteriology. Antibiotics of choice are nitrofurantoin or tetracycline for herbivorous rodent species, except when facing a urinary tract obstruction. In the case of rabbits and ferrets, beta-lactams can be an alternative. Sulphonamides should be avoided due to possible urolith formation, associated with their administration. Moreover, pre-existing uroliths might be surrounded by drug metabolites, making them resistant to dissolution.

Urinary bladder/urethral catheterization

Catheterization of the male urinary bladder is usually easy. The anatomy of the female mouse, rats, chinchillas, and guinea pigs is unique in that the urinary orifice is external and just anterior to the vaginal opening. This characteristic makes the bladder of these animals easier to catheterize than that of other species. The urethral orifice in female ferrets is located approximately 1-1.5 cm cranial to the blind clitoral fossa, which is situated on the ventral floor of the vestibule, just immediately cranial to the mucocutaneous junction. In female rabbits, the external urethral opening lies 4-6 cm cranial to the vulva inside the vagina.

Urethral catheters or tomcat catheters of size 1.8-5 French with guidewire can be used. Care should be taken so that the tip of the guide wire does not extend past the end of the catheter. Atraumatic and aseptic techniques should be used during all procedures. The animal is placed in ventral recum-

bency, with a rolled towel beneath the abdomen to elevate the hind quarters (females), or in dorsal recumbency (males). Before the insertion of the catheter, the external urethral opening should be cleansed by using an antiseptic solution. The distance from the external urinary orifice to the neck of the bladder should be estimated, and small amounts of water-soluble lubricant and analgesic gel is placed on the external urethral orifice. Minimal to moderate resistance is usually noted during catheterization. If resistance is encountered, withdraw the catheter for a short distance and apply 0.2-0.5 ml of saline (amount according to animal size) to enlarge the urethral lumen and then reinsert while gently rotating the catheter.

Cystotomy

A standard caudal laparotomy is performed. In males, one must assure not to damage the prepuce and the penis. The caudal ureters, urinary bladders, and proximal urethra are reached by this approach. Moistened pads or gauze are placed beneath the urinary bladder and a stay suture is applied on the bladder apex to facilitate manipulation. Urine should be aspirated via intraoperative cystocentesis (samples are used for bacteriology and antibiotic sensitivity testing), before entering the urinary bladder. An incision is performed on the ventral or dorsal bladder surface while keeping a distance from large veins and ureters. Urinary calculi are removed, part of the bladder wall excised for histopathological examination, and the bladder flushed with saline. The mucosal surface is checked for any pathological changes. The catheter is then passed into the uretra for additional flushing. Retrograde and/or normograde urohydropropulsion must be performed in all cases to remove any possible obstructions. The bladder wall is closed in two layers with absorbable material by two continuous inverting sutures. Polydioxanone, polyglyconate or polyglactin 910, poliglecaprone 25 are preferred suture materials.

Lithotripsy

Lithotripsy is a minimally invasive technique that provides an alternative to surgical urolith extraction. Intracorporeal laser lithotripsy and extracorporeal shock wave lithotripsy have been described as successful methods to treat urolithiasis in dogs. Lithotripsy may be particularly beneficial for patients with renoliths and marginal renal function and has already been used in rabbits and guinea pigs under experimental settings.

Acknowledgments

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DENTISTRY IN GUINEA PIGS

Vladimir Jekl

As a result of the increasing numbers of guinea pigs, being kept as private pets, dental disease is diagnosed frequently in veterinary clinics. The incidence of oral cavity disease is approximately 30-80 %; it varies both between species and within a species with age, with older animals affected more frequently. In the recent two decades, the number of articles and books describing the dental disease and its therapy has increased. However, there are still oral cavity disorders, which are not exactly described, and therapeutic approaches, which need to be verified by clinical practice. The article describes an approach to the guinea pig with dental disease and therapy of selected oral cavity disorders.

Oral cavity Anatomy and physiology

Guinea pigs have completely elodont dentition. The permanent guinea pig dental formula is I (1/1), C (0/0), P (1/1), and M (1/1). Dentition is diphyodont (deciduous and permanent teeth) and heterodont. Guinea pigs, chinchillas, and degus belong to the Simplicidenta due to the presence of a single set of maxillary incisors. Premolars and molars have a similar structure and in each quadrant of the oral cavity, they form a uniform functional grinding unit. Each mandibular cheek tooth is in occlusion with the corresponding maxillary cheek tooth. The occlusal plane is oblique (approximately 30° degrees). The mandibular arcade is wider than the maxillary arcade.

Pathophysiology of dental disease

Diseases of the oral cavity, particularly the syndrome of acquired dental disease, are the most common disorder in pet guinea pigs. Dental disease is multifactorial and many local and systemic conditions that affect the mouth and oral cavity have been described, including hereditary, infectious, metabolic, and traumatic conditions (including foreign bodies), electrical accidents, and neoplasms.

If the cheek teeth are not worn adequately and elongate intraorally, the mouth is held more open, stretching the masseter muscles and increasing the resting occlusal pressure on the teeth. As a result, the incisors elongate and lose the normal chisel-like wear pattern and animals have problems with bolus formation. As a result of metabolic bone disease, even physiological chewing forces may cause apical intrusion (retrograde elongation) and loss of alveolar supporting bone. Loss of supporting alveolar bone, forces generated during chewing, and tooth growth affect the curvature of the cheek teeth. Widening of the interproximal coronal surfaces, presence of sharp spurs, coronal elongation, and abnormal cheek teeth occlusal surfaces are common findings at this stage. In addition, occlusal pressure could prevent the eruption of cheek teeth, so that the apices intrude and induce bony remodeling of adjacent tissues. Mandibular cheek teeth apices also elongate and, in more severe cases, penetrate through the ventral mandibular cortex. As the condition progresses, mastication becomes more uncomfortable and only soft foods may be selectively eaten, resulting in further tooth growth due to lack of wear.

Horizontal enamel ridges and pigmentation which can be seen on the labial part of the incisors are the results of apical germinative tissue pathology. Such enamel dysplastic changes are commonly associated with calcium metabolism disorders and/or apical tooth inflammatory changes.

As all the teeth erupt continuously, many factors may harm tooth substance (dentin, cementum, enamel) formation. This may lead to improper periodontal alignments, macrodont teeth development, and the presence of more than one tooth in the alveolar sockets, which is commonly seen in guinea pigs.

Periodontitis, dental caries, and dental resorptive lesions are commonly present in guinea pigs.

Clinical signs

An accurate history should be obtained from the owner and a routine clinical examination should be performed on all patients presented for dental procedures. Animals suffering from systemic disease require special attention and life-threatening conditions should be addressed immediately. Clinical signs are associated with hypersalivation, anorexia, chewing disturbances, changes in food preferences (soft and palatable feed particles), and poor body condition. In some cases, dental disease can also be accompanied by the development of facial/odontogenic abscesses, wet dermatitis, epiphora, exophthalmia, and damage to the temporomandibular joint.

Diagnostics

Diagnosis of incisor, premolar, and molar pathology is based on clinical examination, intraoral examination under anaesthesia, and radiography/or computed tomography. A combination of oral cavity endoscopy and computed tomography is the most beneficial for optimal diagnostic diagnostics and treatment planning.

Therapy

All the procedures, treatment plans, and prognoses should be explained precisely and consulted again with the client at any point in the therapy. The conservative approach is possible only in cases where no inflammation is present, or periodontitis or other inflammatory process does not affect the tooth to the level, where surgical extraction is the best option for the treatment.

Analgesia

Perioperative analgesia (metamizole (dipyrone), NSAID such as meloxicam or carprofen, buprenorphine/methadone intramuscular; or lidocaine, fentanyl, ketamine in CRI) and long-term chronic pain management is commonly necessary as an adjunct therapy to the surgical treatment. Some of the general rules which prevent painful stimuli during clinical crown reduction and occlusal surface adjustment are 1) prevention of heating injury during teeth drilling (to not spend more than 3 sec. on one tooth at one time); prevention of soft tissue (skin and gingiva) injury when using dental burr; and 3) using a minimal pressure with the burr when reducing clinical crown.

Chronic pain management may be provided using nonsteroidal anti-inflammatory drugs (meloxicam 1.5 mg/kg PO q8-12h), gabapentin (5-30 mg/kg PO q12h), opioids (buprenorphine, long-acting buprenorphine) and/or their combinations. Other drugs can be also used (e.g., tramadol, cannabinoids); however, their efficacy has not yet, in these species, been scientifically described.

Peri- and postoperative care

Peri and postoperative care may include fluid therapy, thermal support, gastrointestinal motility drugs (e.g., metoclopramide, ranitidine, cisapride, itopride), and analgesics. The author may use the motility medications on a case-by-case basis. Animals should be closely monitored till full recovery. If the animal refuses to eat, convalescent diets for herbivorous small mammals are offered, preferably orally via syringe (Supreme Science® Selective Recovery, Oxbow Critical Care Supreme Science® Selective Recovery, Emeraid Intensive Care Herbivore®, Supreme Science® Selective Recovery).

Clinical crown reduction and occlusal surface adjustment

The aim of intraoral incisor, premolar, and molar clinical crown reduction and occlusal surface adjustments is to establish as much physiological occlusion as possible. In old rabbits, some teeth may erupt slowly and have arrested

growth, so the therapy aims to allow the rabbit to chew and not correct all the teeth to the normal clinic crown height. The author uses carbide and steel drills for the clinical crown reduction and then finer diamond drills for occlusal surface adjustment and finalizing the procedure. In cases of guinea pigs, chinchillas and degus, occlusal plane and clinical crown reduction should be as physiological as possible as the chewing pattern is different from rabbits.

Apicoectomy in guinea pigs

Macrodontia in guinea pigs is, in comparison with other pet herbivorous rodents and with rabbits, a relatively common disorder. The aetiology is not yet exactly described but structural changes of the continuously growing tooth seem to be responsible for chronic infection/irritation of the germinative tissue of the affected tooth. The macrodontia is commonly present with other disorders associated with dental disease syndrome such as apical and coronal elongation of the incisors and/or premolars, and or molars; changes in tooth curvature; occlusal surface changes; periodontitis; dental caries and other dental and soft tissue pathologies.

In guinea pigs, teeth in the mandibular arcade are, based on the author's experience, the most commonly affected. Diagnostics are based on thorough oral cavity examination, radiography, and/or computed tomography. Macrodont premolars and molars can be easily identified with the use of the radiographic technique described by Minarikova23 or by techniques described by Crossley and Böhmer. Nevertheless, computed tomography can show a more detailed picture of the overall tooth quality and is the author 's preferred imaging method.

Therapy includes treatment of the primary disorder and affected tooth extraction, which can be done intraorally, extraoral, or by their combination. The author's preferred method is an apicoectomy, where the apical part of the tooth is removed by an extraoral approach using a dental burr. After the tooth substance is removed, the use of antibiotic-impregnated beads or marsupialization (used by the author) - in case of bacterial infection - with simple skin closure is recommended. The coronal part (the tooth remnant) acts as a natural plug and prevents feed impaction into the wound after the extraction. This remnant is then worn down by natural chewing and then released into the mouth cavity. In the meantime, the wound is healing from the apical part of the alveolus and preventing further complications.

Odontogenic abscesses

Appropriate treatment of osteomyelitis includes surgical intervention in combination with antibiotic therapy, analgesia, and supportive care. Marsupialization, thorough debridement, affected tooth extraction, and affected bone removal are critical in the primary control of the source of infection. Other treatments include a combination of surgical debridement and tooth extraction with local use of AIPMMA beads, long-lasting doxycycline gel or manuka honey, and wound closure.

Systemic antibiotic treatment for a minimum of 7-14 days after surgery is also recommended. The choice of anti-infective agents for the treatment of osteomyelitis is based on cytological and microbiological findings and antimicrobial susceptibilities. Antimicrobial agents demonstrate variable penetration into bone. However, agents with poor bone penetration can achieve bone tissue concentration above the minimum inhibitory concentration for target pathogens.

In cases where surgical treatment of osteomyelitis is not feasible, suppressive oral antibiotic therapy has been described to control the disease. The potential benefit from chronic antibiotic suppressive therapy exists; however, it is not an effective alternative to surgical treatment of bone infection.

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INCISOR EXTRACTION IN RABBITS

Vladimir Jekl

Incisor malocclusion is a common dental disorder in pet rabbits but can be also seen in guinea pigs, hamsters, rats, and other exotic companion mammals. In dwarf rabbit breeds with hereditary incisor malocclusion are clinical signs seen already at the age of 3-4 months. However, most commonly, incisor malocclusion develops secondarily due to trauma or premolar and molar disorders. Enamel and dentin hypoplasia, infection and apical incisor elongation associated with epiphora may be detected.

The only definitive and completely effective treatment for severe malocclusion and acquired dental disease of incisors is extraction. Rabbits adapt easily to lack incisors, much better than when teeth are short or maloccluded, and they can eat normally using the lips and tongue to prehend food.

If only one incisor is affected, extraction of one tooth is recommended, if more than one tooth is affected, all six incisors should be extracted. Incisor extraction is performed all the time with animals under general anaesthesia.

Indications

- abnormally elongated incisor teeth
- aberrant growth of one of the incisors
- incisor infection
- severe cases of nasolacrimal duct infection

Incisor extraction

- Extraction should be considered only when there will be definite benefits for the animal.
- Pre-extraction radiographs are optimal to establish the tooth morphology, curvature, fractures, or adjacent tissue disease.
- All the instruments should be manipulated with controlled force to prevent any iatrogenic injury.
- Local regional anesthesia should be applied (VJ prefers to use a combination of the mandibular nerve and infraorbital nerve block).
- Adjacent tissue and the tooth itself should be cleaned and the gingival incision is made, which separates the gingival tissues from the tooth.
- Fine dental luxators and elevators (Crossly incisor luxator, Fahrenkrug luxator, adjusted hypodermic needles) are used to sever the periodontal ligament, compress alveolar bone and deliver the tooth. When the tooth/alveolar bone curvature is more curved or the animal is too small, the hypodermic needles could be used to break down periodontal ligaments. Gentle rotation forces should be used to dislodge the tooth.
- Fine extraction forceps or needle holders are used for tooth or tooth root extraction.
- After extraction, the alveolar socket should be cleaned and flushed with saline.
- To prevent tooth regrowth, ensure that the tooth is entire with dental pulp inside. If not, the pulp needs to be removed from the alveolar socket as well.
- After extraction, the alveolar socket should be cleaned and flushed with saline.
- Wound is then closed with absorbable suture material (VJ preference). Another option is to leave the wound open.

Complications

A possible complication of the incisor extraction includes tooth fracture or the eruption of the "new" tooth. Because of the previous alveolar bone remodeling, the incisors mostly erupt in the same manner as before or show various degrees of malposition and deformity. For this reason, it is recommended to damage apical germinative tissue. When the pulp does not remain in extracted teeth, various techniques for the tooth pulp damage or their combinations should be used: apical curettage, the use of intrusive pressure of the corresponding teeth, or alveolar socket flushing with saline.

If the tooth breaks, some authors recommend waiting till the tooth once re-grows and then extract. Based on the author's (VJ) experience, all teeth removal during one anaesthetic and surgery session is a better option. In that case, a lateral transgingival approach for incisor extraction is recommended.

Practical tips:

- Before the extraction, clinical crown height adjustment is recommended, and the procedure is booked approximately 7 days in advance. In a due time, the animal gains weight and will be at less anesthetic risk. Moreover, the incisors start to erupt/grow more quickly (up to 5 mm a week), which means that the dentoalveolar junction will be more fragile so tooth luxation will be easier.
- Local analgesia is of great use. Injection directly into the periodontal space is, based on the author's experience very helpful.
- Smooth the surface of the incisive bone with a fine dental burr.
- All teeth should be extracted. If one is broken, surgical extraction should be performed.

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NEUTERING OF EXOTIC COMPANION MAMMALS

Vladimir Jekl

Desexing of male exotic companion mammals belongs to routine surgical procedures. Before the surgery, the animal should be clinically examined and if any health issue is found, it needs to be addressed and the patient stabilized before the surgery. In older animals, screening tests for other such are endocrine, cardiac, and dental diseases in ferrets; dental, kidney, liver, and cardiac diseases in rabbits; dental, kidney, liver, and cystitis in guinea pigs; kidney and respiratory diseases in rats should be performed before the surgery.

Animals are anaesthetized, placed on a heating pad (thermal support management), and monitored during surgery. Preoperative and postoperative analgesia administration is implemented as a standard part of any surgical procedure.

Indications

Indications for male desexing are commonly prevention of breeding, prevention of courtship behaviour, prevention of territorial behaviour, and scent gland marking in ferrets. Medical reasons for desexing include traumatic scrotal injury, scrotal hernia, or testicular tumour.

Approach

A scrotal, pre-scrotal, or abdominal approach may be performed in male desexing. An open or a closed technique can be used, and the spermatic cord can be ligated closed with an overhand tie, open with a “self-tie” technique, or ligated with 4-0 absorbable sutures.

In the case of the scrotal approach, the skin incisions are left open to heal by secondary intention; in other techniques, the wound is closed routinely. The author (VJ) preferably uses the scrotal approach in ferrets.

The pre-scrotal approach is commonly used in rabbits. The author (VJ) is using the combined technique, where the tunica vaginalis and m. cremasters are incised through the small median skin incision 1-2 cm from the scrotal skin junction. Testicle and epididymis are exteriorized from the vaginal tunica, epididymitis is bluntly dissected from the ligaments, and vessels, and ductus epididymitis is ligated and then excised. A small incisional opening in the vaginal tunica is then closed. Skin suture is performed in all cases.

The intraabdominal approach is mainly used in rodents and hedgehogs. As rodents’ testicles are freely movable within the scrotum and could move into the abdominal cavity due to a large inguinal canal, it is easy to gently manipulate them into the abdominal cavity using slight pressure on the parascrotal sacs. Caudal laparotomy is performed, and testicles are located and gently exteriorized from the body. All the tissue is ligated and excised. The abdominal wall and skin are then sutured separately.

Complications

Complications are rare but may include bleeding scrotal oedema, and gastrointestinal stasis. Secondary infection or adverse reaction to suture material was also described.

Chemical castration

So-called "chemical" or "hormonal" castration is commonly used in ferret hobs using deslorelin implants. The successful effect was also described in male rats and hamsters.

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OVARIECTOMY AND OVARIOHYSTERECTOMY

Vladimir Jekl

Ovariectomy and ovariohysterectomy in pet ferrets, rabbits, and rodents are one of the most common surgical procedures performed in the first line and also in the second opinion/specialized veterinary clinics. Before each surgery, the animal should be clinically examined and if any health issue is found, it needs to be addressed and the patient stabilized before the surgery. In older animals, screening tests for other such are endocrine, cardiac, and dental diseases in ferrets; dental, kidney, liver, and cardiac diseases in rabbits; dental, kidney, liver, and cystitis in guinea pigs; kidney and respiratory diseases in rats should be performed before the surgery. This approach is similar to all surgical interventions.

Blood sampling with subsequent haematological and plasma chemistry analyses is, at the author's practice, a standard part of the preoperative examination.

Animals are anaesthetized, placed on a heating pad (thermal support management), and monitored during surgery till full recovery. Preoperative and postoperative analgesia administration is implemented as a standard part of any surgical procedure.

Indications

Indications for the ovariectomy or ovariohysterectomy are commonly prevention of breeding, prevention of territorial behaviour, and scent gland marking in ferrets. Medical reasons for desexing include the presence of uterine tumours in rabbits, the prevention of ovarian cystic disease and uterine tumours in rats, the prevention of prolonged oestrus in ferrets, the prevention of uterine pathologies, and mammary gland tumours in rats.

Anatomy of a female ferret and rabbit reproductive tract

Reproductive anatomy of a female ferret

Paired ovaries are ovoid structures located caudal to the particular kidney. The left ovary, oviduct, and uterine horns are located between the colon descendens and abdominal wall. The left ovary is located approximately 0.5-1cm caudal to the left kidney and the right ovary is located approximately 1.0-1.5 cm caudal to the right kidney. The oviduct is present between the particular ovary and uterine horn in the mesosalpinx. Ovaries are cranially attached by the suspensory ligament, which attaches to the body wall at the level of the last rib. Due to the very short ligament between the ovary and the uterine horn is ovary fixed in the immediate proximity of the uterotubal junction. Ferrets have two long uterine horns which fuse close to the cervix and form a relatively short body. The cervix is more pale and whitish in colour and firmer on palpation when compared with the uterine body.

The ovaries, oviduct, and uterine horns are supplied with arterial blood via ovarian and uterine arteries. These two vessels anastomose near the cranial part of the uterine horn. Ovarian arteries rise from the aorta. The uterine artery is the main branch of the vaginal artery. It enters the mesometrium at the level of the cervix and runs cranially along the border of the uterine horn.

Reproductive anatomy of a female rabbit

The ovaries of a rabbit are elongated and ovoid in shape organs. Due to the longer ligament between the ovary and uterine horn is ovary located at a distance of approximately 1-2 cm from the uterotubal junction.

Rabbits have a uterus duplex, which means that they have two separate uteri which have their own cervices. These cervices enter the vagina separately. The vagina is, compared with other small mammals, very large.

Approach

For ovariohysterectomy or ovariectomy, a standard midline approach may be used in all animals. In guinea pigs, a flank approach is recommended, especially in young animals. The uterus is identified and then ovarian pedicles, ovarian and uterine vessels, and the uterus is ligated. In rabbits, both

ovaries and uteruses are excised, and also the cranial part of the vagina, which is ligated.

Always completely ligate the ovarian pedicles and uterine body with 4-0 absorbable suture material. Vessels in broad uterine ligament should be also ligated or cauterized. Gentle organ manipulation is essential because small organs could easily tear and bleed.

Complications

Complications may include bleeding, ligation of different structures, ovarian remnant tissue, and gastrointestinal stasis. Secondary infection or adverse reaction to suture material was also described.

Chemical castration

The successful effect of hormonal castration was described in female ferrets, rats, and rabbits.

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MANAGEMENT OF GASTROINTESTINAL DISORDERS IN RABBITS

Vladimir Jekl

The most common disorder of the gastrointestinal tract in herbivorous exotic companion mammals is gastrointestinal (GI) stasis. GI stasis is defined as disruption of the normal propulsive GI motor activity from non-mechanical mechanisms (synonyms: paralytic ileus, functional ileus, paralytic ileus) or because of bowel obstruction (synonyms: mechanical ileus, mechanical obstructions). The cause of the obstruction may be external to the bowel (extrinsic), within the wall of the bowel (intrinsic), or due to a luminal defect/foreign body that prevents the passage of gastrointestinal contents. Obstruction of the intestine can be partial or complete. The most common cause of bowel obstruction in exotic companion mammals is the presence of an intraluminal foreign body.

In rabbits, the term gastrointestinal syndrome or rabbit gastrointestinal syndrome was recently used to define a complex of clinical signs, symptoms, and concurrent pathologic conditions affecting the digestive apparatus of the rabbit. The following pathologic conditions can be included, and often occur in combination: gastric impaction, gastric gas accumulation, intestinal impaction, intestinal gas accumulation, intestinal obstruction, primary gastroenteritis, adhesions, neoplasia, pancreatitis, and liver disease. The pathophysiology of the primary GI stasis and secondary diseases is indeed in exotic companion mammals even more complex than already described.

GI stasis

Gastrointestinal stasis in rabbits, guinea pigs, and chinchillas is commonly associated with an inappropriate diet (low fiber, high in digestible carbohydrates). However, gastrointestinal stasis could be associated with any stressful situation or condition that stimulates the sympathetic nervous system including pain, systemic disease, or surgery.

The GI motility decrease, the digesta retention is prolonged and the normal balanced ecosystem in the bowel (especially the caecum) is disrupted. Caecal pH is altered and allows potentially pathogenic bacteria to overgrow (Clostridium sp., E. coli). Above described bacterial overload may lead to clinical enteritis/typhlitis or enterotoxemia.

In case of prolonged digesta retention in the stomach, there is a risk of gastric ulcer development, which leads to another source of pain.

Gastrointestinal hypomotility results in gas formation in the intestines (mostly caecum) or stomach. Gas distension is painful and stimulates the sympathetic nervous system and deteriorates the situation.

Secondary impaction can be produced by over-accumulation of normal gastrointestinal contents due to alterations in motility, or desiccation of normal contents due to dehydration.

Metabolic acidosis is a common sequela of negative energetic balance due to anorexia esp. in rabbits and herbivorous rodents.

Mechanical obstruction

Primary mechanical obstruction of the stomach is commonly seen by the author in ferrets. Various foreign bodies of different origins (mostly rubber, foam, and earplugs) are located within the stomach of the ferret. Foreign bodies are causing permanent or temporary pyloric obstruction or can be passed distally into the duodenum or jejunoileum, which can cause permanent obstruction.

In rabbits, the most common site of GI obstruction is the proximal duodenum, distal to the pylorus. Caecal or colonic obstruction in rabbits is commonly secondary due to caecal content dehydration and caecolite formation. In guinea pigs, signs associated with GI obstruction are present in case of gastric dilatation/torsion. It was stated that the pellets of impacted hair that acutely obstruct the small intestine of rabbits are a completely different condition from the hairballs (gastric trichobezoars) or impacted stomach contents that develop during periods of gastric hypomotility. It seems, that the pellets are formed by compression of ingested hair during passage through the large intestine, and the excreted pellets containing the compressed hair are accidentally reingested during caecotrophy. This would explain why the pellets are similar in size to hard faeces and are so compressed. Small hair pellets can pass through the digestive tract whereas larger pellets may obstruct the intestine causing pain, which slows gut motility and further reduces the chance of the pellet moving along the intestinal tract. In some cases, the obstruction does move through the small intestine, resulting in a spontaneous recovery as it passes into the hindgut.

Obstruction leads to progressive dilation of the GI tract proximal to the blockage. Swallowed air, and gas from bacterial fermentation, can accumulate, adding to stomach or intestine distention. As the process continues, the stomach/intestine wall becomes oedematous, normal absorptive function is lost, and fluid is sequestered into the bowel lumen. In severe cases, the perfusion to the GI wall is reduced and obstructions lead to ischemia, which will eventually lead to necrosis and perforation. In ferrets, with pyloric or duodenal obstruction, ongoing emesis leads to additional loss of fluid containing sodium, potassium, chlorides, and hydrogen ions and to metabolic alkalosis. In rabbits and rodents which cannot vomit, the gas and fluid accumulation leads quickly to stomach dilatation and cardiovascular collapse. In rabbits and guinea pigs, stomach dilation readily leads to metabolic acidosis. These fluid losses (vomiting or into the GI tract) can result in hypovolemia. Bacterial overgrowth can also occur in the proximal duodenum, which is normally nearly sterile. Gastric mucosa erosions and/or ulcerations can develop due to reduced vascular supply of the stomach.

Optimal management of RGIS needs to be determined based on a clinical case. Dosages and therapeutical protocols used in this paper are recommended and used in the author's practice, however, need to be adjusted when indicated or not used at all.

Management of gastrointestinal disorders in rabbits

- Recognizing the pain (inactivity, anorexia, staring, reduced comfort behaviour, pressing of the belly against the ground, changes of the facial mimic, other behaviour changes)
- Try to find out the primary (or secondary) disease (aetiology)
- Anxiolytics, first-line analgesia/sedation (rabbits)
  - Midazolam (0.2-0.5 mg/kg IM)
    - § Opioids
    - § Butorfanol 0.2-0.5 mg/kg IM
    - § Buprenorphine 0.01-0.05 mg/kg SC
    - § Methadon 0,3-0,5 mg/kg IM
  - Midazolam (0.2-0.5 mg/kg IM)
  - Metamizole 50 mg/kg IM
  - Fentanyl/fluanisone 0.2-0.3 mg/kg SC
- Oxygen
- Thermal support
  - Body temperature measurement
- IV access and IV fluids
  - No saphenous or femoral veins
  - e.g. Ringerfundin®
- Diagnostics
  - Abdominal radiography

    Observation on gastric size, small intestinal dilatation, and gas within the large intestine and caecum aid in radiological diagnosis of small intestinal obstruction large intestine.
  - Abdominal ultrasound
  - Haematology
  - Blood chemistry
    - § Pain is in rabbits associated with marked hyperglycemia (above 350 mg/dl)
  - Urinalysis (esp. pH)
  - Acid-base balance
- Treat the primary disease/diseases
- Pain medication
  - NSAIDs (can be controversial)
    - § Meloxicam 0.1-0.3 mg/kg SC q12h (use with care in ferrets)
  - Opioids
    - § Buprenorphine 0.01-0.05 mg/kg SC q8-12h

§ or CRI - Fentanyl 5–10 mg/kg/min, ketamine 1–2 mcg/kg/h

§ Hydromorphone 0.1 mg/kg SC, IV

§ (Tramadol 10 mg/kg PO q8h)

- Prevention of gastric ulceration
  - o Ranitidine 5 mg/kg IM q12h
  - o Famotidine 1–3 mg/kg PO q12-24h
- Prokinetics (only in case of non-obstructive ileus or post-operatively)
  - o Metoclopramide 0.5-1 mg/kg IM q8h
  - o Ranitidine 5 mg/kg IM q12h
  - o Itopride 10 mg/kg PO q12h
  - o Trimebutine 1-2 mg/kg PO q12h
  - o (CRI lidocaine 0.01 mg/kg/min IV)
- Simethicone, dimethicone (not effective due to different aetiology)
- Feeding (only in case of non-obstructive ileus or post-operatively)
  - o Recovery diet (force-feeding - syringe, nasogastric tube)
  - o Herbivores - fresh grass, vegetables, and fruits
- Surgery
  - o Gastroscopy in ferrets
  - o Gastrotomy/enterotomy
  - o Foreign body "milking" distally
- Stress release/anxiolysis
  - o Hospitalization
  - o Client bonding
  - o Benzodiazepines (see above)
  - o Pheromones
- Antibiotics
  - o When indicated (not used by the author routinely)
- Probiotics
  - o No exact effect is described.

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