# Masterclass

# Common medical challenges with ageing horses

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**Programma Masterclass**

# Common medical challenges with ageing horses

## Wetenschappelijke Vereniging voor de Gezondheid van het Paard vzw

| | |
|---|---|
| 9h00 | Ontvangst en registratie |
| 9u30-12h30 | *Common medical challenges with ageing horses* |
| | Prof. Dr Andy Durham, Liphook Equine Hospital, UK |

# Common medical challenges with ageing horses

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## Clinical Approach to Liver disease in horses

Liver disease is commonly encountered in equine practice although the correct clinical approach to liver disease cases is frequently unclear, resulting in many speculative empirical therapies being applied in many cases. Frequently such approaches are ineffective and may even delay recognition and appropriate treatment and management of a deteriorating case. A clear and logical approach to any clinical scenario facilitates success and satisfaction and there are a few key fundamental facts pertaining to equine liver disease which should influence and guide the approach when cases are encountered (see table 1).

| KEY CLINICAL FACTS RELATING TO EQUINE LIVER DISEASE |
|---|
| 1. Owing to the large functional reserve capacity of the liver, most cases of liver disease are subclinical or show only subtle clinical signs.<br>2. Most cases of liver disease seen in practice appear to persist for long periods of time.<br>3. Most cases of liver disease in horses occur as an outbreak rather than as single cases.<br>4. Diagnosis, prognosis and selection of appropriate therapy for liver disease cases is rarely ever possible without examining biopsy specimens. |

*TABLE 1. Important considerations when planning the clinical approach to equine liver disease cases.*

### Why is reserve capacity important?

It has been estimated that at least 70% of the functional capacity of the liver must be damaged before function is seriously compromised. Thus, the clinical signs that we often associate with liver disease (severe weight loss, hepatic encephalopathy, jaundice etc…) will only arise when horses have suffered considerable amounts of liver damage and consequently indicate a poor prognosis (Figure 1). Thus, when increased concentrations of

liver enzymes are found in a horse showing no serious clinical signs of liver disease, there may still be quite significant damage present (e.g. b) or c) in figure 1) and further investigation is important at this stage. In short, we should be mindful that ***horses hide liver disease very well*** and that the best clinical success will be achieved with liver disease cases investigated while they are at a relatively early stage. Fewer than a third of cases will survive long term when investigated following development of signs liver failure, compared with more than 90% of those cases with liver disease seen at earlier subclinical or mild clinical stages (Durham et al., 2003a).

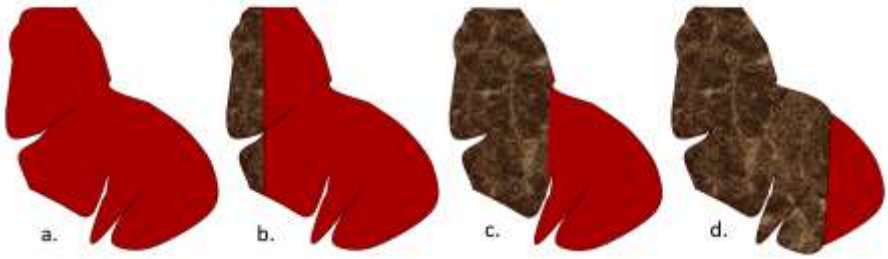


*Figure 1. Diagrammatic representation of progressive liver disease: a) healthy, b) 10% damage, c) 50% damage, d) 75% damage. Only d) is likely to be showing classical signs of hepatic failure; the other 3 may appear externally healthy.*

**What is the relevance of a prolonged clinical course?**

Many of us will have encountered cases of liver disease where increased serum liver enzymes are found to remain abnormal for many months or even years. This may or may not be associated with clinical deterioration for the reasons outlined above. Fundamentally this can be for 2 reasons: either the liver disease is self-perpetuating, or the cause of liver disease remains present and is exerting persistent or repetitive liver insult. Either or both of these explanations is plausible. For example, conditions such as pyrrolizidine alkaloid toxicity (ragwort poisoning) tends to be progressive even after removal of the source of ragwort (Figure 2). Neoplasia (Figure 3) clearly is also progressive as are suspected immune-dysregulated disease processes such as chronic active hepatitis. Thankfully all of these 3 prime examples tend to demonstrate characteristic liver pathology enabling their specific diagnosis following liver biopsy. However, we should also be mindful of scenarios where continual exposure to low grade hepatotoxins may be present, or even chronic infections that explain the prolonged duration of apparent liver disease (see below). Indeed, where known causes of self-perpetuating hepatic disease (as listed above) are ruled out by biopsy, then it is logical to assume that the cause of the liver disease remains present and should therefore be sought.

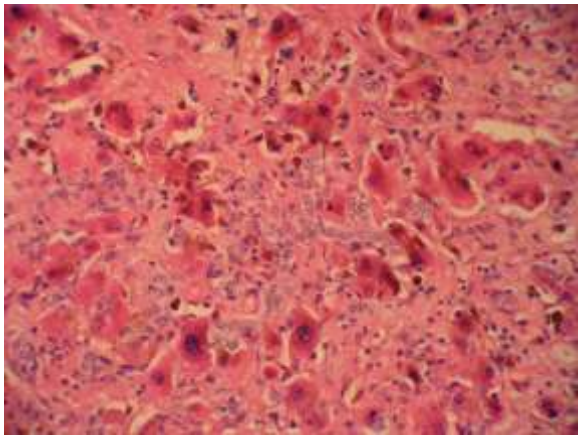

*Figure 2. The classic signs of progressive megalocytosis, fibroplasia and biliary hyperplasia in a case of pyrrolizidine alkaloid toxicity. Such diagnostic changes are seen relatively rarely in horses examined for liver disease in the UK despite the common suspicion that ragwort is causative.*

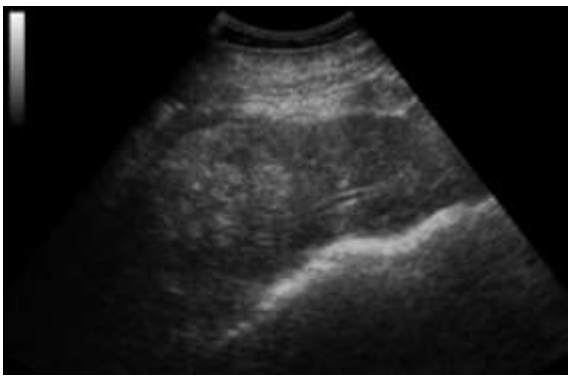

*Figure 3. Ultrasonographic image of biliary carcinoma in the right liver lobe of an elderly horse.*

## Outbreaks of liver disease

There is an increasing awareness that liver disease in horses most commonly occurs as an outbreak amongst several horses. We might often fail to notice this because, as mentioned above, many horses affected as part of the outbreak will have subclinical disease and may appear to be clinically healthy. Therefore, when a case of liver disease is encountered in a horse (often based on increased serum concentrations of liver enzymes), it is very important that stablemates become part of the investigation. Simply checking serum GGT concentration in some or all of the horse's associates will usually reveal the problem to be far more widespread than first suspected. Awareness of this will clearly influence considerations of causality. When liver disease occurs as an outbreak we should primarily consider toxic and infectious causes.

### *Hepatotoxicity*

Perhaps the best-known cause of liver disease in UK horses is pyrrolizidine alkaloid toxicity resulting from ragwort ingestion. Clearly this might be expected to occur as an outbreak in horses sharing pasture or forage sources. So well-known is this disease that there has been a strong temptation to speculatively attribute causation of many liver disease cases to ragwort in the absence of specific evidence of such; creating a self-fulfilling belief that it is a common cause of liver disease. Recent surveys of horse owners, veterinary surgeons and pathologists

however indicate that genuinely confirmed ragwort toxicity is actually not at all common in UK horses (Durham, 2015), and we should all be prepared to think "outside the ragwort box" when considering causation of liver disease in horses in the UK. Other toxins should be considered such as excessive iron ingestion associated with supplements or high concentrations in water, soil or forage. The equine liver is clearly susceptible to iron toxicity although a degree of iron accumulation within the liver also appears to be a normal feature in many UK horses and donkeys (Durham et al., 2003b, Brown et al., 2011). Mycotoxins have also come under recent scrutiny. A recent survey compared hay samples from yards with liver disease outbreaks with those where horses had no liver disease. Fumonisin B1, a known hepatotoxin, was found in over 30% of hay samples from premises suffering outbreaks of liver disease but not from any of the control premises (unpublished data, Durham, 2017). Aflatoxins were also occasionally suspected although appeared far less common and less clearly associated with the liver disease outbreaks.

*Infectious hepatitis*

Liver fluke (*Fasciola hepatica*) might be considered as a possible cause of outbreaks of hepatic disease especially in areas known to experience the problem in cattle and sheep. Firm antemortem diagnosis relies on detection of Fasciola eggs in faeces but is hampered by the frequent existence of non-patent infections and also insensitivity even in cases where eggs are shed. Other tests such as coproantigen assays and serologic assays are available but have extremely poor diagnostic value. For example, in a recent Irish study (Quigley et al., 2017) most fluke-infected horses were seronegative (sensitivity 42%) and a positive serologic test result performed similarly to tossing a coin (PPV 50%)! Therapeutic problems also exist with clear evidence of resistance to triclabendazole, the only trematodicide known to be safe in horses.

Viral hepatitis is well recognised in many other species but appears to be rarely investigated in horses. However, a recently discovered virus known as non-primate hepacivirus (NPHV) is coming under increasing scrutiny as a possible cause of contagious liver disease in horses. The virus is a very close relative of human hepatitis C virus and clearly shows hepatotrophism in horses. Although first discovered in USA (Burbelo et al., 2012), the virus is now recognised to be commonly present in equine populations in many countries around the world including the UK (Lyons et al., 2014). Clinical studies of the effects of the virus are thus far sparse, although interestingly chronic viraemia for weeks or months appears common and mild to moderate increases in liver enzymes are reported following infection (Figueiredo et al., 2015, Pfaender et al., 2015). Currently we do not know the precise importance or relevance of this virus to equine liver health in the UK but further studies into this, and other viruses, are ongoing.

## **Why bother to biopsy**?

Although many more of us are familiar with equine liver biopsy than once was the case, it is still far from commonly employed when liver disease cases are encountered in practice (Figure 4). Clearly owner consent and budget play a role here, but there is also reticence by many veterinary surgeons to undertake what they believe to be a difficult and risky

procedure without obvious benefits. The risks of liver biopsy have been massively overstated over many years. The technique is, in fact, remarkably safe with a negligible risk of serious complications. Tales of severe haemorrhage in the past were almost invariably in cases of severe hepatic failure where compromise of clotting function was present. As mentioned above, such cases of hepatic failure will invariably have a poor prognosis in any case and we should be aiming to investigate cases at a far earlier stage (i.e. diseased but not failing livers) when clotting dysfunction is not a concern. Liver biopsy is also a remarkably simple procedure especially when aided by what may be fairly low-tech portable ultrasound machines. When contemplating liver biopsy and discussing with the client, we must be clear about why we are doing it and what we want to achieve. Liver biopsy should aim to answer 4 specific questions and it is the only investigative method that can consistently and successfully do so:

1. Is liver disease genuinely present or not?
2. Is a specific diagnosis possible from the biopsy, including conditions such as pyrrolizidine alkaloid toxicity, neoplasia, septic cholangitis, chronic active hepatitis and haemosiderosis?
3. What is the prognosis for the horse?
4. What is the appropriate and specific treatment for the liver condition?

*Figure 4. Collection of a liver biopsy under local anaesthetic in a lightly sedated horse.*

**<u>Putting it all together into a logical clinical approach</u>**

So, when we have first identified a case of suspected liver disease in a horse, usually based on blood work, what should we do? (also see figure 5)

1. Test herdmates – is this an individual case or an outbreak? *(Usually the answer is an outbreak).*
2. Is there a specific cause identified or suggested by biopsy such as ragwort poisoning, bacterial hepatitis, neoplasia etc…? *(Usually the answer is no).*
3. The pattern and severity of pathology in the biopsy should be used to offer a prognosis and to guide choice of therapy (and how aggressive therapy needs to be).
4. Consider changing forage source in case of mycotoxins in hay.

5. Consider testing blood (or biopsy specimens) for the presence of non-primate hepacivirus (NPHV).
6. Where a good response to logical treatment is not seen over 1-3 months then consider:
    a. Re-evaluating the case including re-biopsy
    b. That the inciting cause is probably still present so re-evaluate the possibilities of chronic hepatotoxicity or chronic hepatotrophic viral infection.

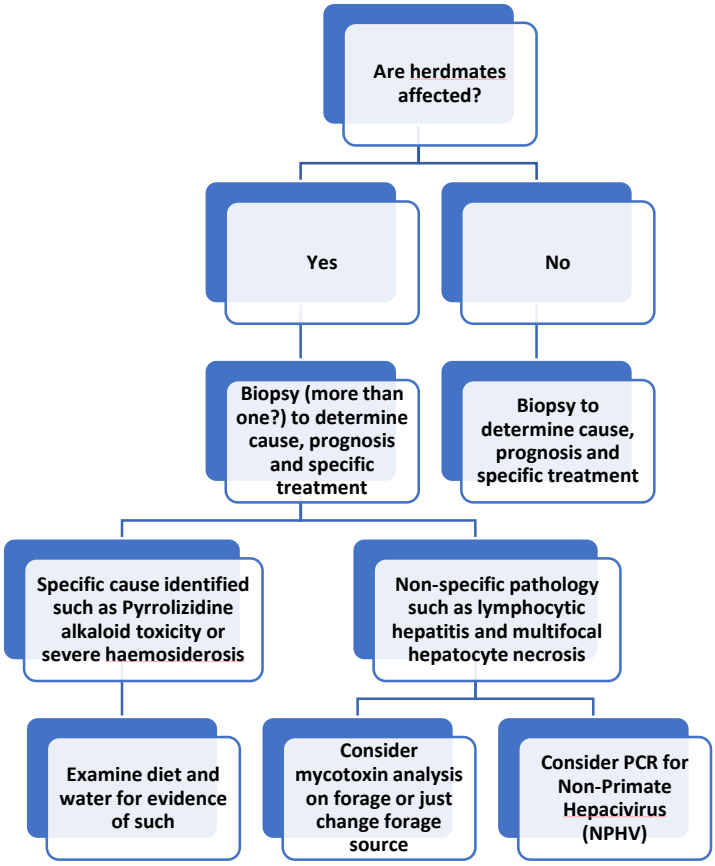


*Figure 5. Algorhythm following the main clinical decisions during the investigation of suspected liver disease cases.*

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# MAKING BEST USE OF LABORATORY TESTS IN THE INVESTIGATION OF OBSCURE WEIGHT LOSS

## INTRODUCTION

Weight loss implies an ***imbalance between energy supply and use*** and it is often helpful to consider the differential diagnoses for a weight loss case in the context of such fundamentals:

**Energy Supply**

a) inadequate dietary provision (eg poor diet)
b) incomplete consumption of the diet (eg dental disease)
c) incomplete digestion and absorption of the diet (eg small intestinal inflammatory bowel disease)
d) dysfunctional metabolic processing and delivery of the absorbed nutrients (eg hepatic disease)

**Use/Loss**

a) exercise, lactation, pregnancy
b) protein losing conditions (parasitism, enteropathy, effusion, blood loss, renal disease)
c) chronic inflammation
d) neoplasia
e) diabetes mellitus

The object of the investigation of weight loss in the horse is firstly to distinguish horses that have an underlying medical cause for the weight loss from those that have a managemental/dietary cause from those that perhaps actually have no weight problem at all. In practice, the 3 key initial questions to address at the first clinical examination of the horse are:

1. Is the individual actually underweight, and if so,
2. Is the individual is *consuming* an *appropriate diet* for its expected *physiologic requirements*?
3. Are there any clinical signs suggestive of a specific disease process? (eg diarrhoea, quidding, halitosis, nasal discharge, cough).

This may then direct the initial approach towards, for example, increasing dietary energy supply (eg vegetable oil 0.1-1.0 ml/kg BWT daily), dental examination or investigation of the intestinal or respiratory tract. However, there are a significant number of cases that appear to have an appropriate dietary intake and furthermore show no localising clinical signs of disease – perhaps clinically normal or showing no more than mild dullness/vague lethargy. It is this latter group that will require a more considered diagnostic approach and the selection of clinicopathological aids is a vital part of their investigation. Although this discussion is directed at the clinicopathologic investigation of these cases, the value of a detailed, systematic clinical examination cannot be overemphasised. Vague and non-specific weight loss cases are a significant diagnostic challenge and no opportunity should be missed to gather what may prove to be subtle but vital clinical diagnostic information (eg retinal degeneration as an early sign of motor neuron disease, enlarged mesenteric lymph nodes in

alimentary lymphoma, mild distal limb thickening in thoracic lymphoma [hypertrophic osteopathy]).

In practice, cases of vague weight loss that have a medical cause without localising signs are predominantly ***enteropathies*** (small bowel) with ***hepatopathies*** also being reasonably common and occasional internal ***neoplasms*** (especially multicentric lymphoma and gastric squamous cell carcinoma) also being recognised. Other potential causes of weight loss in the absence of specific clinical signs include ***chronic infection*** (eg parasitism, abscessation), ***grass sickness, renal disease***, and ***equine motor neuron disease***.

Many cases will remain without a specific *ante mortem* diagnosis due to the limitations of many tests used. Many may also have causes which are difficult or impossible to define – such as temperament, age or perhaps subcellular biochemical pathology for which we don't yet possess diagnostic techniques.

**INITIAL CLINICAL PATHOLOGY** (perhaps at the same visit as the first examination)

HAEMATOLOGY *(requires EDTA or citrated samples)*

**a) Anaemia -** commonly seen in weight loss cases - if marked (eg PCV <22%; RBC < 5.0 x $10^{12}$/l) this should be considered in conjunction with a bone marrow aspirate to differentiate regenerative and non-regenerative.

- **Non-regenerative anaemia** is a very common, non-specific finding in chronic weight loss cases and is not often very helpful in the differential diagnosis. This mild anaemia may result from chronic inflammatory conditions such as abscessation or infiltrative bowel diseases, chronic renal failure (occ. severe anaemia) or many forms of neoplasia especially lymphoma or simply malnutrition.
- **Regenerative anaemia** is more helpful and is suggestive of a chronic source of blood loss (eg. parasitism, gastric squamous cell carcinoma, splenic haemangiosarcoma) or haemolysis (eg immune mediated anaemia secondary to lymphoma, emerging infections such as Equine Infectious Anaemia or Piroplasmosis).

**b) Leucocytic changes –** common but rarely definitive

- **Neutrophilia** - can be a feature of septic and non-septic conditions such as infiltrative bowel diseases, cyathostominosis, neoplasia (especially lymphoma), immune-mediated diseases, Cushing's disease, chronic bacterial infections or simply a result of stress. A **band neutrophilia** (left shift) is more suggestive of septic than non-septic conditions.
- **Neutropaenia -** common in acute sepsis (eg. acute septic effusion such as peritonitis) but uncommon in chronic bacterial diseases or neoplasia which have more relevance to this discussion.
- **Monocytosis** - monocytes are not simply an indicator of chronicity as they can be raised very promptly in various inflammatory and neoplastic conditions.
- **Eosinophilia** - contrary to popular belief is not at all suggestive of intestinal parasitism or even generalised eosinophilic disease syndromes – little specific help. Often high in allergic diseases, respiratory disease, skin and intestinal disease.

PROTEINS *(requires plain serum for total protein, albumin and globulins; EDTA or citrated samples for fibrinogen)*

Proteins show a circadian rhythm and may vary by as much as 10-15 g/L total protein over the day (high evening, low noon). Horses' total protein values tend to increase significantly post feeding due to loss of GI secretions. Monitoring should take this into account and standard timing of sampling with respect to feeding is important.

- **Albumin** – is one of the first things to look at in weight loss cases. Normally albumin should be in the 30's. Marked hypoalbuminaemia (eg. <20g/L and as low as 6) strongly indicates protein losing enteropathy of various types. Mild to moderate hypoalbuminaemia (eg. 20-25 g/L) also usually reflects enteropathy although more realistic alternative explanations exist including hepatopathy, effusion, chronic blood loss (eg. gastric squamous cell carcinoma) and chronic inflammation. Very rarely protein-losing nephropathies may be seen that may have quite marked hypoalbuminaemia. High albumin (>40 g/L) suggests dehydration.
- **Globulins** - raised levels (>40 g/l) generally indicate hepatopathy, parasitism or chronic inflammation although other causes are possible eg. Neoplasia and immune mediated diseases. Further assessment of the globulin fraction via serum protein electrophoresis is almost never specifically helpful and has little, if any, evidence basis.
- **Serum amyloid A** is an acute phase protein found to be highly sensitive and responsive to inflammatory reactions and offers a further valuable means of identifying inflammation/infection/neoplasia. Usually levels are close to zero and may rapidly increase to several hundred in the face of inflammation.
- **Iron** is an essential element for many microbial processes including pathogenicity. Several equine studies indicate that low serum iron is a sensitive indicator of inflammation in the horse as several mechanisms exist to sequester iron in the face of inflammatory challenge. Serum iron < 100 ug/dl (<18 umol/l) suggests ongoing inflammation. Iron deficiency is a possible, but less likely, explanation for low serum iron. Total iron binding capacity (TIBC) would be expected to be normal to high (>280 ug/dl or 50 umol/l) in cases of iron deficiency but low in cases of inflammation.

INITIAL SIMPLE BIOCHEMICAL 'SCREENING TESTS' *(requires plain serum or heparinised plasma for most biochemistry; oxalate-fluoride samples for glucose)*

- **Aspartate Transaminase (AST)** - can arise from many tissue sources but elevated plasma levels are usually of hepatic and/or muscular origin (check with CK, GGT, and GLDH). Long t½ and slow to clear and can remain elevated for at least 1-2 weeks after resolution of the inciting cause.
- **Gamma Glutamyl Transferase (GGT) -** the most sensitive indicator of chronic hepatopathy (ie unusual to see a genuine liver disease case with a normal GGT) but raised levels don't rule out other problems as other diseases may be concurrent (eg. multisystemic eosinophilic disease or lipaemic infiltration of the liver in anorexic ponies). Also Cushing's disease cases and pressure from distended intestine often causes slightly high levels. The pancreas contains higher concentrations of GGT than the liver but rare pancreatic adenocarcinomas probably only show high GGT if there

is concurrent liver involvement. The kidney is also rich in GGT but this tends to be lost into urine rather than serum (see later).

- **Alkaline Phosphatase (AP)** - potentially very useful. Arises from many sources but high levels in adult horses are usually from hepatopathy (biliary) and enteropathy cases. Nearly all hepatopathies show raised levels and more than half of enteropathies. NB. young, growing horses have normally high levels derived from bone sources. IAP isoenzyme may have dubious reliability.
- **Creatinine & urea** - insensitive indicators of renal disease but are highly likely to be raised if renal disease is severe enough to be causing weight loss. Weight loss is commonly the only clinical sign in equine cases of chronic renal failure (CRF) and polydipsia/polyuria are not very common. Urea is not uncommonly up to 9 or 10 mmol/l in normal horses and can be raised a little further (eg 11-12 mmol/l) by wasting, dehydration (check urine SG) or high protein diets. Urea may be low (<3 mmol/l) in hepatic failure. A further potential source for confusion is high urea and creatinine as a result of acute renal failure (ARF) secondary to another underlying primary source of weight loss. Both severe dehydration and hyperlipaemia may result from other disease processes and may trigger secondary ARF.
- **Glucose** – this may be used as a simple screening test for Cushing's disease. Most Cushing's disease cases have normal serum glucose but a persistent fasted hyperglycaemia is highly suggestive of Cushing's disease. Alternative considerations of the cause of hyperglycaemia include acute stress/pain/anxiety, alpha$_2$ agonist sedatives or a cereal based feed in the previous 3-4 hours. Glucose is usually normal in enteropathies and hepatopathies but occasionally may be slightly low in the latter.

INITIAL FAECAL EXAMINATION

- **Parasite eggs/larvae** - an adult parasite burden is greatly overestimated as a cause of weight loss in adult horses but emergence of larval cyathostomes is a common cause of acute weight loss (esp *young* horses in *winter* that have been *recently dewormed*) usually but not necessarily with diarrhoea.
- **Sand** - Chronic weight loss may result from abrasion and space occupying within colon. A large sand deposit in a faecal sample is supportive of the diagnosis but abdominal radiography is the diagnostic modality of choice.
- **Blood** - faecal occult blood tests are not often helpful. A positive may indicate GI bleeding (NB may be intermittent) – NSAIDs, gastric ulcers, neoplasia or just prior rectal examination. Also high numbers of leucocytes in stained smears may be significant
- **Culture** - Not very helpful and hard to recommend (*Campylobacter sp.* or *Salmonella sp* ? relevant)

**FURTHER CLINICAL PATHOLOGY** (following consideration of above results)

FURTHER SERUM BIOCHEMISTRY *(requires plain serum or heparinised samples)*

- **Bile acids** – a useful test of liver function when liver enzymes are found to be increased to help determine severity of the underlying hepatopathy. After excretion in bile, BAs are reabsorbed into the circulation in the ileum and should then be removed from the portal circulation by the liver for recycling. The test is very specific

for hepatic insufficiency but can sometimes be increased up to 10 or 20 μmol/l from anorexia without liver disease (also often high in foals).

- **Bilirubin** - total bilirubin (T-Bil) is usually increased in hepatic failure and also in haemolysis and anorexia (and malabsorption?). The major fraction (usually>95%) of T-Bil is indirect (unconjugated) bilirubin that has not undergone hepatic processing; with a lesser fraction (usually<5%) of direct (conjugated) bilirubin that has undergone hepatic processing. Very high levels of TBil (>100 μmol/l and sometimes >500) usually indicate haemolysis or biliary obstruction and can be differentiated by calculating the direct vs indirect fractions (haemolysis ≈ 5% direct vs biliary obstruction often up to 25-50% direct). Lower levels of TBil (30-150) are harder to interpret and could indicate mild haemolysis, hepatocellular disease or simply anorexia. Occasionally modest hyperbilirubinaemia is the only clinicopathological finding in a weight loss case in the absence of anorexia, liver disease or haemolysis – could this be an early indicator of malabsorption??
- **Creatine Kinase (CK)** – often mildly increased (eg 500-1000 iu/l) in weight loss cases perhaps as a result of muscle catabolism? Primary neuromuscular diseases such as polysaccharide storage myopathies or equine motor neuron disease may show mild to moderate increases in CK (and AST) and sometimes initially present as little more than weight loss cases.
- **Acid-base balance -** a hyperchloraemic metabolic acidosis in the absence of an obvious cause such as shock or diarrhoea should make you think of renal tubular acidosis which may present only as weight loss and lethargy (first reported in horses 17 years ago and suggested to be more common than we think?). Usually RTA cases are only mildly azotaemic and potassium levels are variable. Hypoproteinaemic subjects may show mild metabolic alkalosis as proteins are acidic.
- **Calcium** - may be high in some cases of neoplasia (lymphoma, squamous cell carcinoma, adenocarcinoma) as a result of secretion of parathyroid hormone related peptide (PTHrp) or other cytokines. Total calcium (usually ≈ 3 mmol/l) is often measured but can sometimes be misleading. Total calcium is often low in cases of hypoalbuminaemia due to loss of the protein bound fraction although ionised calcium may still be normal (or even high). Acid-base balance also affects protein binding (acidosis reduces protein binding and increases ionised calcium). Therefore ionised calcium measurement is always preferable (usually ≈ 1.5 mmol/L). Chronic renal failure is a further possible cause of hypercalcaemia.

URINALYSIS

- **Specific Gravity** - Simple but very useful indicator of renal function. Can be anywhere from 1.004 to 1.060 in healthy horses but if SG >1.020 then the kidneys must have significant concentrating ability and renal failure is not present. SG between 1.008 and 1.014 (same as plasma: isosthenuric) suggests that the urine is neither being concentrated nor diluted by the kidney and is consistent with renal failure (check serum urea and creatinine). SG < 1.006 indicates active water excretion by the kidney and usually indicates psychogenic polydipsia although could reflect rare cases of Diabetes insipidus /mellitus.
- **Protein -** Normally negative (or possibly a trace up to 0.3 g/l). May find significant protein loss in urine (eg >10 g/l) in rare cases of glomerulonephritis or plasma cell myelomas or urinary tract haemorrhage, neoplasia, infarction or inflammation**.**

- **GGT –** High levels of GGT exist in proximal renal tubules and is released into urine in higher quantities with tubular damage – very sensitive (almost too sensitive) and may be raised by subclinical renal insult. Normally urine GGT is similar to plasma range ie. up to 30-50 iu/l and unlikely to be significant unless in the 100s. Should be interpreted in light of urine SG – ie. slight elevation in concentrated urine is probably not significant. For further precision the GGT: creatinine ratio can be used (divide urine GGT [iu/l] by the urine creatinine [in mmol/l]; normal <5 iu/mmol).
- **Cells** - Increased numbers of blood cells and/or casts is associated with urinary tract infection/infarction/inflammation/neoplasia (NB dipsticks don't differentiate between blood, Hb and Mb).
- **Glucose** - Glycosuria in some cases of Cushing's disease, acute stress or detomidine (threshold about 10-13 mmol/l in plasma)

PERITONEAL FLUID ANALYSIS

Relevantly, but fairly non-specifically, it is common to find horses with inflammatory bowel disease and other causes of hypoalbuminaemia that produce profuse quantities of peritoneal fluid that runs freely following the peritoneal tap procedure and tends to be quite dilute in terms of low cell counts and protein (a subclinical ascites).

- **Cells -** Usually has a WBC count of 1 or 2 x $10^9$/L - mostly PMNs (about 60-70%). Peritonitis has fairly consistently results in high WBCs (eg. 100+ - up to 500 occasionally), abdominal abscesses and neoplasms have variable effect. Borderline total nucleated cell counts around 5-10 x $10^9$/l represent a modified transudate and are more difficult to interpret but clearly do infer intra-abdominal disease. Intra-abdominal neoplasia in horses is rarely specifically identifiable by a peritoneal tap and exfoliated neoplastic cells. However, mild to moderate increases in total nucleated cell counts and protein concentrations are often found but this is easily confused with low-grade septic peritonitis. May detect intrabdominal haemorrhage eg. splenic/hepatic neoplasia. Although the procedure of paracentesis itself has no effect on cell counts and proteins even when repeated several times, it certainly will with accidental gut tap whereupon cell counts rapidly rise (often >100).
- **Protein** - Normal total usually under 15 g/l and rises with inflammatory (esp. septic) reactions eg. often 40-70 g/l in septic peritonitis but abdominal abscesses and neoplasms have variable effect. Clots if >30g/l. Very common to see very dilute PF samples in weight loss cases (eg. Protein 2 g/l) - ? why
- **Glucose** - Should be at least similar to and usually slightly higher than blood value eg 5-7 mmol/l. In septic and inflammatory conditions glucose falls often to trace levels but at least 2 mmol/l less than blood glucose value.
- **Culture** - difficult - often negative growth

ORAL GLUCOSE TOLERANCE TEST

It is perhaps a sad reflection that this crude test is still a major diagnostic tool in the investigation of equine malabsorption syndromes. It has no relevance to large intestinal diseases. Flat curves are almost always significant so well worth doing NB there are some instances of flat curves (<20% rise) recovering. Intermediate curves (20-67% rise) often indicate small intestinal pathology and should be repeated in a few weeks. Normal curves (>67%) are reasonably reassuring. Severely hypoalbuminaemic cases may have depressed peaks (?bowel oedema) in the absence of SI pathology. Often normal horses peak between 90-150 minutes and peak may only be 60-70%.

- 12 hour fast (allow water)
- Take 'baseline' OxF blood
- Give 1g/kg glucose as warm 20% solution by stomach tube (ie. 0.5kg in 2½ litres for 500kg)
- Take blood hourly for 5-6 hours (or just once at 2 hours?)

TISSUE BIOPSY

Tissue biopsy enables a very accurate diagnosis as long as representative area is biopsied. Biopsies can be submitted for histopathology and culture.

**Liver biopsy**

It is possible to miss diseased tissue in localised hepatopathic disease but in reality the vast majority of hepatopathies are diffuse. Liver biopsy is an extremely safe procedure when performed ultrasound guided. Haemostasis is not usually a practical problem even if clotting times are prolonged. Liver biopsy is the gold-standard technique to help determine cause, prognosis and guide specific therapy of liver disease cases.

Prognosis can be offered based on scoring the biopsy:

| | ***absent*** | ***mild*** | ***moderate*** | ***severe*** |
|---|---|---|---|---|
| ***Fibrosis*** | ***0*** | ***0*** | ***2*** | ***4*** |
| ***Irreversible cytopathology*** | ***0*** | ***1*** | ***2*** | ***2*** |
| ***Inflammatory infiltrate*** | ***0*** | ***0*** | ***1*** | ***2*** |
| ***Haemosiderin*** | ***0*** | ***0*** | ***0*** | ***2*** |
| ***Biliary hyperplasia*** | ***0*** | ***0*** | ***2*** | ***4*** |

Horses with score 0-1 tend to do very well. Scores of 2-7 have a guarded prognosis and merit reasonably aggressive therapy. Scores of 8 or more are associated with a poor prognosis.

The cellular pattern found in the biopsy also indicates various therapeutic approaches. eg neutrophils – antimicrobials; lymphocytes/plasma cells – glucocortcoids.

**Rectal biopsy**

Simple and easy test to perform. Use specialised forceps (or possibly a bottle top!). This is a test only for optimists – certainly worth doing *if the horse has (or has had) diarrhoea* but false negatives are very common. Vast majority come back as normal or non-specific. Only around 1 in 4 cases of colonic disease is the diagnosis made *ante mortem* by rectal biopsy. False positives also sometimes arise – esp. with respect to eosinophils (eg. lots of eos found in biopsy but horse turns out to have lymphoma or liver disease – interpret with caution).

**Bone marrow aspirate or biopsy**

Worth doing in all cases of anaemia or persistently abnormal leucocyte changes. May help differentiate causes of anaemia – eg. chronic inflammation/neoplasia, chronic haemorrhage, iron depletion from chronic bleeding, myelophthisis, leukaemias etc..

Bone marrow biopsies/aspirates can be taken from the ventral sternum level with points of elbow or from the tuber coxae.

Technique for aspiration:

- Clip, scrub and local.
- Insert 18g needle with stylet (spinal) until hit bone
- Steady needle and push through into sternum
- Attach 20ml syringe washed with EDTA
- Pull back plunger to 10ml then release. Repeat if necessary
- Make immediate smear on glass slides and air dry

Marrow sample should look blood-like but you should see may look fatty or gritty elements when smeared.

## Endocrinopathic Laminitis

It has long been realised that most cases of laminitis tend to be seen in certain recognisable individuals. Occasional cases will be seen related to other factors such as feeding accidents, toxaemic diseases (colitis, metritis) or chronically excessive load bearing but the fact remains that most laminitis cases could have been predicted based on key signalment and clinicopathologic data. Recent published reports confirm the common presence of endocrinopathy in the vast majority of laminitis cases and, specifically, equine metabolic syndrome (EMS) and pituitary pars intermedia dysfunction (PPID) have risen to high prominence in our thoughts about causation of everyday laminitis cases seen in practice. A further addition to the family of endocrinopathic causes of laminitis is the rare but significant finding of iatrogenic laminitis following glucocorticoid therapy.
Each and every laminitis case encountered in practice deserves considered screening for evidence of known risk factors (usually endocrinopathic disease) as, clearly, failure to control pre-existing risk factors inevitably predicts further recurrence of laminitis. This probably represents the most important practical consequence of recent interest in endocrinopathic laminitis whereby our focus is drawn towards proactive prevention of disease by identification and control of risk factors, in preference to a reactive clinical approach to attempt to modify the clinical course of disease after it has occurred.

Before further consideration of the pathophysiology, diagnosis and treatment of these conditions, it is worth further defining their origins.

### What is Equine metabolic syndrome?

Metabolic syndrome is one of the greatest human health threats in the developed world associated with freely available, high calorie food and drink high in sugars and a more sedentary lifestyle. More recently there has been recognition of an analogous equine health threat associated with more generous feeding and management practices, especially in a sedentary population of horses, ponies and donkeys. Both human and equine metabolic syndrome are primarily created and maintained by chronically excessive caloric intake and relative physical inactivity particularly in certain predisposed genetically related groups. Perhaps the primary fundamental difference between the human and equine conditions is that affected humans are susceptible to cardiovascular disease whereas laminitis appear to be the main disease consequence in affected horses. The roots of understanding of what we now know as EMS actually began in the 1980's (Coffman and Colles 1983) although the relevance and importance of the condition was not widely realised before Philip Johnson's description in 2002.

Equine Metabolic Syndrome might be regarded as ***"a collection of coexisting risk factors, associated with metabolic and endocrine dysregulation, that signal an increased susceptibility to laminitis"***. Such individuals tend to be from certain breed types, are often obese, and demonstrate dysregulation of insulin-glucose dynamics ("dysinsulinaemia") as well as disordered lipid metabolism.

Both human and equine subjects with metabolic syndrome are generally recognised to fail to normally regulate the fine and dynamic balance between serum glucose and insulin concentrations, a status referred to as dysinsulinaemia or insulin dysregulation (Frank and Tadros 2014). Fundamentally this may be an acquired state associated with obesity and/or

may have genetic determinants in certain breeds. Intuitively it makes sense that natural selection may have supported evolution of dysinsulinaemia in nutritionally harsh environments. An insulin resistant phenotype tends to preserve scarce glucose supplies for use in vital non-insulin dependent tissues such as the central nervous system, renal tissue and cardiac muscle; and, furthermore, facilitates gluconeogenesis and the mobilisation of glycogen and fat stores when required at times of limited food supply, offering a clear survival advantage.

As insulin also plays a key role in lipid metabolism, it is not surprising that dyslipidaemia is also seen in association with increased laminitis risk. Obesity and IR in combination promote lipolysis leading to increased plasma concentrations of non-esterified fatty acids released from adipose depots and also, subsequently, increased plasma triglyceride as hepatic VLDL synthesis and export is increased.

**What is Pituitary Pars Intermedia Dysfunction?**

The secretory capacity of the *pars intermedia* in a normal horse is autonomous and is controlled by tonic inhibition by dopaminergic neurons from the hypothalamus. The primary pathophysiologic event in PPID is suggested to be oxidative damage to these tonic inhibitory dopaminergic neurons leading to hypersecretion and growth of the uninhibited *pars intermedia* (McFarlane et al 2005). Various pathologic stages are recognised from hypertrophy and hyperplasia to micro- and macro-adenoma formation (Miller et al 2008). The dysfunctional pars intermedia tends to synthesise and secrete excessive peptide products beginning with the parent peptide proopiolipomelanocortin (POMC) which is sequentially cleaved to lead to increased concentrations of the presumed primary end products of alpha- and beta-melanocyte stimulating hormone, corticotropin-like intermediate lobe peptide (CLIP) and beta-endorphin as well as intermediate peptides such as lipotropins and adrenocorticotropin (ACTH) (Figure 1, Wilson et al 1982). However, despite the fact that ACTH concentrations tend to be increased in PPID cases, PPID is not synonymous with hyperadrenocorticism. This paradox is probably explained by the finding that the immunoreactive measurable ACTH found in PPID cases appears to have impaired bioactivity compared to that from normal horses.

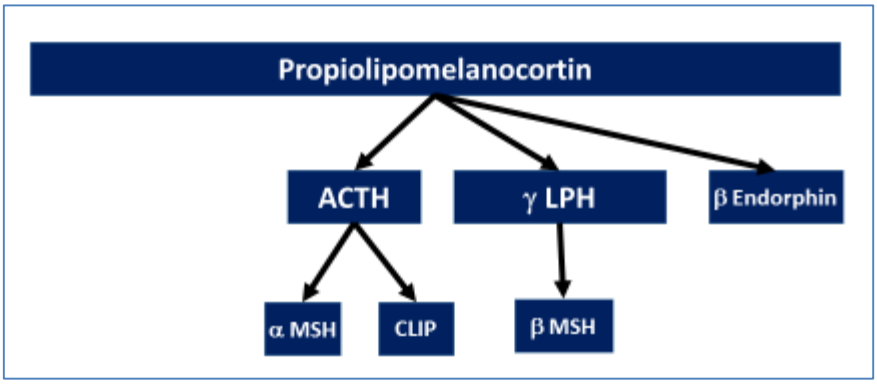



*Figure 2. Simplified cascade of peptide secretion from the pars intermedia*

PPID cases are at increased risk of laminitis although the mechanism by which this comes about is not yet understood (McGowan et al 2013a). It is relevant to note that PPID cases tend to be hyperinsulinaemic and insulin resistant and that this is associated with their risk of laminitis (Walsh et al 2009). However, the exact origins of IR or hyperinsulinaemia are not

well understood. Indeed few if any of the clinical signs of PPID are well explained. Laminitis does appear to be the most important consequence of PPID in terms of mortality and serious morbidity (McGowan et al 2004) although additional clinical signs that may be observed in PPID cases include excessive hair growth (hypertrichosis) and/or delayed to absent seasonal shedding, lethargy, mild to moderate muscle wastage ("top-line"), increased sweating (hyperhidrosis), polydipsia and polyuria and increased susceptibility to infections (including parasites). However, a coexisting spectrum of prominent clinical signs represents end-stage disease and is not typical of most cases. There is undoubtedly a significant population of subclinical PPID cases, presumably in the early stages of pathologic development, and also clinically subtle cases showing, for example, only mild laminitis with no other signs suggestive off PPID. Unpublished data from Liphook Equine Hospital and the Boehringer Ingelheim "Talk about Laminitis" scheme indicates approximately half of PPID cases with laminitis have no additional clinical signs suggestive of PPID.

PPID is clearly an age-related disease with increased prevalence in older horses. One study estimated >20% of horses >15 years old to be affected (McGowan et al 2013a) although it is clear that younger horses may also be affected with several well described cases between 5 and 10 years of age (e.g. Heinrichs et al 1990).

**Pathophysiology of endocrinopathic laminitis**

Increased risk of laminitis has been associated with EMS, PPID and exogenous glucocorticoid administration although the exact causal pathways are not yet understood. However the commonality of dysinsulinaemia with all 3 endocrinopathies and also with laminitis is noteworthy (Frank and Tadros 2014). Dysinsulinaemia potentially comprises up to 3 related but distinct components: insulin resistance, hyperinsulinaemia and hyperglycaemia (or glucose intolerance). These are inter-related as described in figure 2 but it is important to realise that they are not synonymous and that each can exist with or without the others. Several studies have investigated the relative pathophysiologic (and diagnostic) importance of these 3 components. It is immediately notable that intolerance of exogenous glucose challenge and resting hyperglycaemia are not common in endocrinopathic cases. Thus any direct pathophysiologic relevance of hyperglycaemia or glucose toxicity resulting from glucose intolerance seems doubtful (in contrast to humans). Other studies have indicated that experimentally induced hyperinsulinaemia, in the absence of hyperglycaemia or IR, will consistently lead to the development of acute laminitis in horses and ponies (Asplin et al 2007, de Laat et al 2010). Thus, current evidence emphasises the primary pathogenic (and perhaps diagnostic) relevance of hyperinsulinaemia *per se* in the finding of increased risk of laminitis in endocrinopathies. That is not to say that hyperglycaemia or IR are irrelevant, but that any effect that they might have is probably by indirectly promoting hyperinsulinaemia. The precise means by which hyperinsulinaemia leads to laminitis is not clear although this does not appear to be associated with normal binding with the insulin receptor as laminar epithelial cells appear to be devoid of such receptors. It is postulated that especially high plasma levels of insulin will stimulate insulin-like growth factor (IGF) receptors with consequent dysregulation of laminar growth, proliferation and development, which may well be key to laminitis onset (de Laat et al 2013).

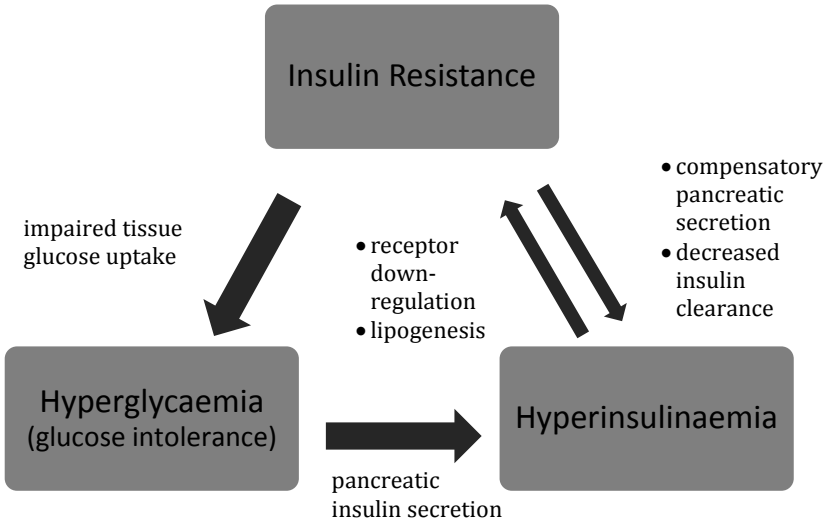



*Figure 2. Flow diagram illustrating the interrelated components of dysinsulinaemia*.

**<u>Diagnosis of endocrinopathic laminitis</u>**

Chronicity and recurrence are frequent features of endocrinopathic laminitis. This is probably for the logical reason that if the endogenous and exogenous risk factors associated with the previous laminitis episode (e.g. IR, obesity, PPID, excessive grazing) are still present. Indeed, a common question from the owner of a *de novo* laminitic animal is "*Will this mean that my pony will always continue to suffer from laminitis*?". This question can be answered by the famous quotation from Henry Ford: *"If you always do what you've always done, you'll always get what you've always got!"* It is obvious that recurrence should be expected in those cases where the fundamental causal factors are not subsequently identified and controlled effectively. It is therefore vital that laminitis cases encountered in practice are not simply treated and managed for laminitis in an isolated fashion, but that epidemiology is considered thoroughly so that identification and control of significant risk factors can be instigated. This comprises investigation of historical, clinical and clinicopathologic factors. It is reasonable to assume endocrinopathy is likely to be present unless preceded by obvious toxaemic disease or chronically excessive weight bearing. Thus investigation of endocrinopathic disease is indicated for both diagnosis, treatment and management choices and for ongoing monitoring of the case. In this respect it is helpful to specifically relate the tests performed to the underlying pathophysiologic considerations above resulting in three separate test categories below.

1. <u>Tests for hyperinsulinaemia</u>

Although insulin can be measured under a variety of circumstances (fasting, resting, post-oral sugar challenge, post-intravenous glucose challenge) it is most biologically plausible and relevant to consider endogenous insulin response to oral sugars as this appears to have some analogy with response to grazing lush pasture.

Investigation of clinical cases of endocrinopathic laminitis indicates that the minority of cases show a resting or fasting hyperinsulinaemia. However, the majority of cases show an abnormally excessive insulin response to dietary non-structural carbohydrates (NSCs; sugars, fructans, starches) which appears to reflect a biologically plausible mechanism whereby pasture (or cereals) trigger laminitis only in certain individuals (e.g. a fat native pony and not a lean Thoroughbred). As hyperinsulinaemia appears to have direct causality in laminitis cases then establishing the insulinaemic status of an individual is important in giving some indication of laminitis risk.

In the USA, the "oral sugar test" (OST) has proved popular (Schuver et al 2014), whereas in the United Kingdom the "in-feed glucose test" has been more commonly used (tables 2 and 3). However, more recently a higher dose OST (see table 2) has become more used in the UK. These two similar tests challenge the horse with corn syrup and glucose respectively and compare the insulinaemic response of the tested individual to that expected in a normal animal. It is assumed that those individuals responding excessively in terms of insulinaemia would likely respond in a similar fashion when consuming NSC-rich grass, placing them at increased risk of laminitis.

| **Oral Sugar Test** |
| --- |
| • Fast overnight (allow 1 flake of hay)<br>• Dose with 45 mL Karo Light corn syrup per 100 kg BWT<br>• Measure serum insulin at 60-90 minutes post dosing<br>• Normal response < 40 mU/L insulin |

*Table 2. Outline procedure of the oral sugar test.*

| **In-feed Glucose Test** |
| --- |
| • Overnight fast<br>• Give 1.0 g/kg BWT glucose or dextrose powder in a non-glycaemic feed (e.g. chaff)<br>• Measure serum insulin and plasma glucose after 2 hours<br>• Normal response: 2 hour insulin < 87 mU/L |

*Table 3. Outline procedure of the in-feed glucose test (unpublished, Liphook Equine Hospital)*

2. Tests for factors associated with hyperinsulinaemia

There are 2 major factors that augment insulinaemic responses; hyperglycaemia and IR. Hyperglycaemia is rarely seen in endocrinopathic laminitis cases except when as a result of catecholamine release in very painful and/or stressed cases. In contrast, the finding of IR in laminitis cases is common and probably has indirect causality via promotion of hyperinsulinaemia. This may be as a result of compensatory insulin secretion in the face of insulin ineffectiveness and/or as a result of prolonged circulation of insulin in the presence of IR.

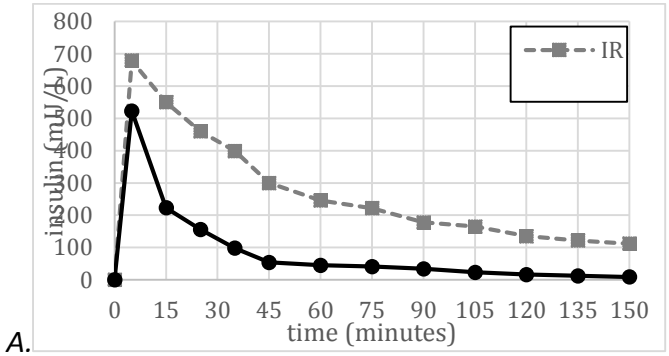
Tests for IR must clearly examine the physiologic effectiveness of insulin and necessitate intravenous challenge testing. The widely accepted gold standard methods comprise the

hyperinsulinaemic euglycaemic clamp and the frequently sampled intravenous glucose tolerance test but neither is practical for routine clinical use. Thus pragmatic methodological compromises must be made and 2 further simpler tests are more widely advocated for practice situations:

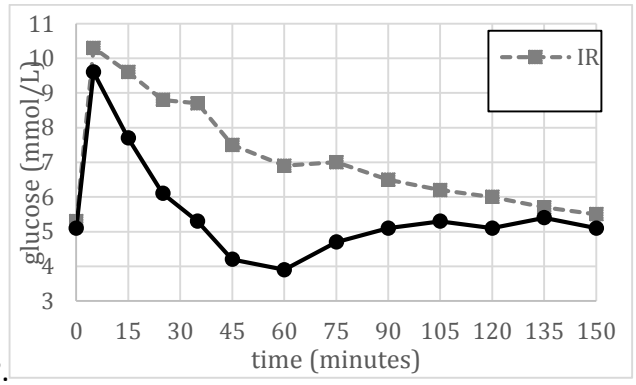
The combined glucose insulin test (CGIT, Eiler et al 2005) (table 4) has the basis that, following intravenous administration of exogenous glucose and insulin, IR individuals demonstrate poorer correction of induced hyperinsulinaemia and hyperglycaemia (Figure 3).

- glucose is administered as 150 mg/kg 50% dextrose iv,
- followed by insulin (0.1 U/kg) iv
- blood samples collected @ 1, 5, 15, 25, 35, 45, 60, 75, 90, 105, 120, 135, and 150 mins

*Table 4. Protocol for combined glucose insulin test*




*A.*




*B.*

*Figure 3. A. Insulin, and B. Glucose responses during the CGIT in normal (black circles) and IR (grey squares dashed line) horses*

In order to make the CGIT more acceptable in practice, a shortened test has been advocated comprising measurement of plasma glucose and insulin at 0 and 45 minutes. A normal response is regarded as return of glucose to baseline by 45 minutes and insulin concentration < 100 mU/L at this time (Frank 2011). Repeated measurement of these

responses following management changes can be used to assess the impact on moderating IR.

The insulin response test (IRT, Bertin 2005) is a more recently described and slightly simpler test for IR, comprising intravenous insulin challenge only and dispensing with the need for exogenous glucose in the CGIT (Table 5, figure 4).

| |
|---|
| • 0.1 U/kg insulin iv<br>• blood samples collected @<br>0, 20, 40, 60, 90, 120,<br><br>180, and 240 min |

*Table 5. Protocol for the insulin response test*

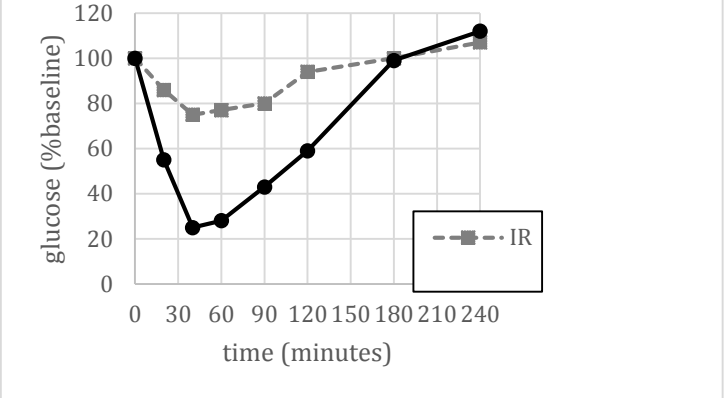



*Figure 4. Glucose responses during the IRT in normal (black circles) and IR (grey squares dashed line) horses*

Again the IRT has a curtailed "2-step" format comprising testing at baseline and 30 minutes only. A normal response is expected to indicate a >50% decrease in baseline glucose at 30 minutes, whereas individuals with IR show less marked glucose decreases. There is a rare but potential danger of hypoglycaemia (especially 30-90 minutes post insulin) with this test (and also to a lesser degree with CGIT) and so horses should be closely monitored for signs of weakness, tremors, etc… and treated with intravenous glucose if required.

3. <u>Tests for factors associated with insulin resistance</u>

Any factor that is associated with IR, causally or otherwise, is also inevitably indirectly associated with hyperinsulinaemia. Several considerations exist within this category including obesity and several clinicopathologic markers of disordered adipose metabolism including hypertriglyceridaemia, increased concentrations of non-esterified fatty acids (NEFAs), hyperleptinaemia and hypoadiponectinaemia

Obesity clearly represents a risk factor for laminitis and although the precise links are not fully understood, a causal association with IR seems likely. The term obesity implies that a

degree of adiposity is present to the extent that health becomes compromised. Thus obesity is really a functional rather than a morphometric term. In spite of this, for convenience, obesity is generally defined by measures of size (e.g. body mass index, neck circumference, girth:height ratio, etc..) but it should be no surprise that cases are seen where the morphometric assessment does not appear to correspond to health status. Consequently individuals are encountered in both human and equine populations that appear morphologically obese but metabolically normal, and those that might be described as physically lean but appear metabolically more typical of functionally obese individuals. Laminitis-prone individuals are often overtly and unequivocally morphologically obese with an absence of palpable ribs, large fatty deposits behind the shoulders and tail-head and a large firm crest. However, others may have palpable or even visible ribs leading some to describe them as "lean", although retaining a large cresty neck or perhaps other hidden fat deposits. The point at which an individual's health becomes compromised by the presence of adipose deposits (i.e. when obesity develops) is variable and dependent on the amount, the site and the metabolic activity of adipose tissue in that individual, emphasising the importance of "regional obesity".

Body condition scoring (BCS) is perhaps the most frequently used semi-objective index of obesity (Henneke et al 1983). Lack of clarity and user-friendliness is not aided by confusing and poorly defined descriptive terminology that is hard to apply, requiring the user to distinguish fat deposits that feel "*spongy", "soft",* "*very soft", "patchy" or "bulging"*. Nevertheless BCS has been shown to correlate well with markers of IR and laminitis susceptibility. The "cresty-neck score" (CNS) is a semi-objective means of describing regional obesity with respect to the apparently particular associations between crest fat, IR and laminitis *(Carter et al 2009a).* Practical and objective morphometric measures of both abdominal/trunk fat (girth:height ratio, waist:height ratio) and crest fat (crest height, neck circumference, neck circumference:height ratio) have been described by several studies although these objective morphometric measures are generally less strongly correlated with body fat percentage and serum biochemical indices of IR than are the semi-objective BCS and CNS. Fat depth measured ultrasonographically in specific areas such as shoulder, intercostal space, rump and retroperitoneal layer, might have potential to be used as a further objective measure of adiposity.

Horses and ponies with EMS and PPID are often characterised by abnormal circulating lipids and lipid metabolites presumably as a result of IR and, possibly in the case of EMS, obesity. Release of NEFAs along with glycerol from adipose stores is strongly inhibited by the effects of insulin and, conversely is promoted in IR states. NEFAs and glycerol, once released from adipose tissue, are taken up by hepatocytes for re-esterification into triglyceride and inclusion within very low density lipoprotein particles (VLDLs) that are released into plasma to transport the triglyceride to peripheral tissues for oxidation or for storage. VLDL production and secretion are also highly opposed by insulin with IR states consequently promoting VLDL secretion which is reflected by higher measured plasma triglyceride concentrations. Obese, insulin resistant and laminitis-prone horses have been shown to have higher than normal plasma triglyceride concentrations, NEFAs, VLDL and HDL-cholesterol (Frank et al 2006).

Recent interest is growing in the pathophysiologic relevance and diagnostic usefulness of adipokines in obese horses (Radin et al 2009). Adipokines are a large and diverse family of proteins important in the pathophysiology of conditions associated with obesity and are

synthesised and secreted by adipocytes, macrophages and other cells present in adipose tissue. Several adipokines have been identified and studied in other species including leptin, adiponectin, resistin, visfatin, apelin, chimerin, retinol binding protein 4 as well as inflammatory cytokines released both by adipocytes and inflammatory cells within the fat such as TNF-alpha, IL-6, MCP1 (CCP-2) and IL-1. Leptin is the best characterised adipokine and acts to suppress appetite centrally and improve insulin sensitivity peripherally. Obesity is paradoxically associated with hyperleptinaemia as a result of leptin resistance. Adiponectin is a further adipokine peptide found as a trimer, hexamer, or high molecular weight multimer, with the latter being most biologically active. Adiponectin has beneficial metabolic, vascular, insulin-sensitising and anti-inflammatory effects and it is decreased in both obesity and IR in horses.

4. Tests for PPID

The precise causal mechanisms by which PPID predisposes to laminitis are not known and therefore this is included here as a separate category. However, in reality, PPID may be a factor promoting hyperinsulinaemia (fitting into category 2 above) and/or as a factor promoting IR (fitting into category 3 above).

Many theoretical diagnostic choices exist in suspected PPID cases although only a few tests have gained good support from evidence-based studies and are also widely available, namely basal plasma ACTH concentration, overnight dexamethasone suppression test and the TRH stimulation test. These are further described below (Durham et al 2014).

*Plasma ACTH concentration*

It is clear that ACTH is more stable in vitro than once thought, but nevertheless certain care has to be taken with sample processing:

- Collect sample in an **EDTA tube**
- Sample should be **chilled** as soon as possible following collection *(within 3 hours)*
- Plasma should be separated (by gravity or centrifugation) prior to dispatch to the laboratory *(as haemolysis affects the result).* However, if separated by gravity then it is important that the sample does not freeze and it must therefore not come into direct contact with any frozen components in the temperature-controlled packaging. The receiving laboratory can then centrifuge the sample on arrival.
- Sample should **remain chilled** *en route* to the testing laboratory *(freezing is unnecessary)*

Plasma ACTH is increased in the presence of pituitary *pars intermedia* and/or *pars distalis* hyperactivity. Increased *pars intermedia* secretion occurs in PPID but is also known to occur in normal horses and ponies in the autumn (Copas and Durham 2012). Longer days following the spring equinox appear to trigger gradually increasing pars intermedia secretion, peaking in late September/early October and then rapidly declining toward basal levels from the aurumn equinox to late November/early December (AE Durham, unpublished data, figure 5). Thus basal ACTH can only be interpreted validly when properly derived seasonally adjusted reference ranges are used. Evidence suggests that the sensitivity and specificity of basal ACTH for PPID diagnosis are greater in the autumnal months than at the rest of the year (as long as seasonally appropriate reference intervals are used) (McGowan et al 2013b).

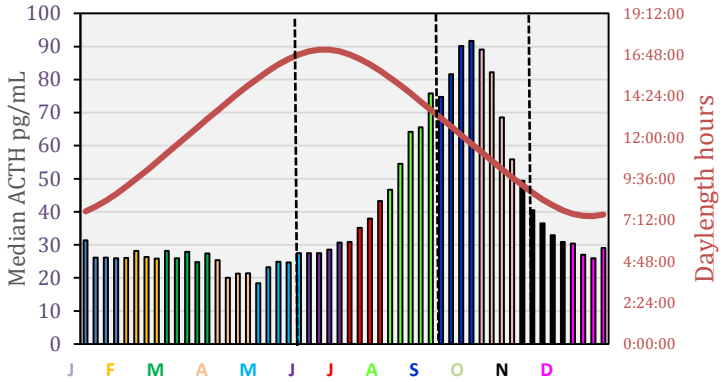



*Figure 5. Plasma ACTH variability through the year in a combination of >35,000 horses (with and without PPID) (AE Durham unpublished data). Dshed lines indicate times of initial increase in ACTH, peak and return to baseline.*

The possible effects of stress and/or pain (e.g. concurrent laminitis) leading to increased *pars-distalis* secretion of ACTH has not yet been fully evaluated under all circumstances but does not appear to be significant unless fairly marked pain/discomfort/stress is present (e.g. Towns et al 2010). However, it remains clearly preferable to measure basal plasma ACTH when these additional factors are not present as it may prove difficult to interpret tests returning mild to moderate increases in ACTH in the presence of pain/distress etc…

*Overnight dexamethasone suppression test (ODST)*

- Collect a serum sample for baseline cortisol at approximately 5.00 pm
- Following this, administer im or iv dose of 40µg/kg dexamethasone *(10 mL of 2mg/mL solution per 500 kg)*
- Collect a 2nd serum sample approximately nineteen hours later (11.00 am the following day) for analysis of the post-dexamethasone cortisol concentration *(the exact timing of this is not critical; 16 to 24 hours will probably suffice).*

There are no special storage/postage requirements. A normal horse is expected to have almost complete suppression of endogenous cortisol in the 2$^{nd}$ sample and a cutoff of < 27nmol/L is generally applied. PPID is considered to be confirmed if the 19-hour sample contains a cortisol concentration greater than 27 nmol/L (Dybdal et al 1994).

The ODST response tends to be exaggerated in the autumn with many normal horses failing to demonstrate cortisol suppression following dexamethasone injection. Unfortunately it is not currently possible to reliably interpret results of this test between July and November.

*TRH stimulation test*

Several studies have indicated that increased endogenous ACTH secretion occurs immediately following injection of exogenous Thyrotropin Releasing Hormone (McFarlane et al 2006). The secretory response is greater in PPID cases than in normal horses and tends to show a profile with a peak ACTH concentration around 5 minutes post-TRH followed by a decrease back towards baseline. It is common for horses to show mild and innocuous

reactions following TRH injection such as the occasional tremor, cough, yawn or flehmen reaction, but no serious adverse effects are noted.

This test appears to have greater sensitivity than basal ACTH concentrations although is by no means as reliable as initial publications appeared to indicate. Nevertheless it is still probably the most accurate diagnostic test for PPID outside of the autumn months. However, it is clear that response to TRH is magnified in the autumn requiring further validation of this test at that time of year, which hasn't thus far been performed. Therefore currently this test should be avoided between July and November inclusive. However, it is noteworthy that this period for avoidance of TRH stimulation happens to coincide with the period when basal ACTH has maximal diagnostic sensitivity and specificity.

- Collect a baseline EDTA plasma sample for ACTH
- Inject 1mg TRH iv
- Collect a further EDTA plasma sample 10 minutes later for assessment of post stimulation ACTH

PPID is indicated by either a baseline plasma ACTH value greater than the seasonally adjusted reference range (typically >29 pg/mL) and/or a post stimulation plasma ACTH at 10 minutes of > 200 pg/mL.

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## Nutrition of the Elderly Horse

Nutritional advice is frequently sought by owners of horses and ponies when discussing various medical complaints and, indeed, proper evidence based nutritional strategies are important in the management of many medical disorders such as colic, diarrhoea, respiratory disease, weight loss, liver disease, obesity, laminitis, myopathies, developmental orthopaedic diseases etc… Advice obtained from nutritionists in the employment of feed manufacturers may not always be impartial and it is helpful if the veterinary surgeon is in a position to offer advice and is able to comment knowledgeably on advice offered from other quarters. Elderly horses may present certain nutritional problems primarily relating to weight loss, malabsorption, poor dentition, and insulin-resistance (e.g. PPID). There are various theoretic nutritional strategies to deal with these problems effectively but they are all underpinned by similar basic principles.

Although it is by no means unusual for elderly horses to be overweight, poor condition and problems maintaining reasonable condition are probably more common. Thus perhaps the most important dietary problem to solve in the context of clinical nutrition of the elderly horse is ***how to achieve greater caloric intake without creating additional medical problems***. When faced with trying to increase caloric intake of horses, the traditional approach of "*reach for the cereals*" is likely to create further morbidities, especially in older horses. Cereal starch may well be calorie-dense (e.g. oats digestible energy (DE) approximately 13-15 MJ/kg, high energy mixes and cubes typically 10-14 MJ/kg) but the high starch content (oats typically 40-50%, high energy mixes/cubes typically 20-30%) does create potential problems with proven links with colic, gastric ulceration, diarrhoea and laminitis for example. Starch is simply not a normal dietary constituent for horses. The equine GI tract evolved anatomically and physiologically in the absence of significant starch intake and it is clear that, as a species, horses are very poor at digesting starch compared with most other monogastric species. Thus ideally we are trying to provide an increased caloric intake in the form of low sugar and starch feeds which are well tolerated by the equine GI tract and do not simulate excessive hyperinsulinaemia placing them at risk of laminitis.

We are rather spoiled for choice when it comes to equine feeds. This is both a blessing and a curse! On the one hand it creates a confusing market for owners and plenty of scope for inappropriate choices based on poor knowledge and advice. On the other hand it creates the opportunity for well-informed owners to source great feed sources that can be beautifully customised to their horses' particular needs. This article will outline some of the basic nutritional targets we might try to achieve with examples of feed types appropriate to achieve these targets. The discussion will concentrate on nutritional and dietary principles to enable advice to be offered in such cases.

A simplified approach to dietary formulation requires consideration the points listed below.

1. <u>How many kilograms of dry matter (DM) will the horse eat?</u>

As a general rule, voluntary feed intake of horses will approximate 2 to 3% of their bodyweight as dry matter (DM) each day. If highly palatable feeds are offered (e.g. grazing) and/or if the individual is a greedy eater then this may be in excess of 5%. If the diet is 100% preserved forage then it is unlikely to be much greater than 2 to 3%.

2. What are the horse's energy requirements?

Dietary energy requirements in horses are generally expressed as apparent digestible energy (DE) (=ration energy minus faecal energy). This should be expressed in kJ or MJ although US publications will use kcal and Mcal (conversion of J→cal x 0.239; cal→J x 4.186). Daily maintenance requirements of non-pregnant adult horses living in a field without additional exercise are considered to typically lie between **127 – 152 kJ/kg bodyweight**. Clearly if weight loss is a concern then the upper end of this range is likely to be the target. The average daily maintenance DE requirements for horses (in MJ/day) can be roughly estimated by dividing bodyweight (kg) by 7 (e.g. 500 kg bodyweight/7 = 71 MJ/day) although an additional 10% might be added to this approximation if weight gain is needed (e.g. 78 MJ/day for 500 kg bodyweight). Light exercise should be encouraged where possible to maintain musculoskeletal strength and perhaps general well-being. However even light exercise may increase DE requirements by at least 20% (e.g. a further 15 MJ/day for 500 kg bodyweight).

3. What are the horse's protein requirements?

Daily crude protein (CP) requirements for field maintenance typically lie between *1.0 - 1.5 g/kg bodyweight*. This typically corresponds to a CP concentration of around 6 to 8% in the overall ration. There appears little harm in increasing protein concentration modestly and therefore overall CP of perhaps 8-10% seems appropriate in geriatric horses, especially where forage is the primary protein source and might lack certain essential aminoacids. High protein feed balancers are a very useful component of geriatric diets as a means of ensuring good protein intake by adding a small amount of concentrated protein (and minerals/vitamins) to the ration. Remember to examine the nutritional declaration though as some so-called balancers appear to have quite low CP content (eg. <10%) and are probably inappropriate for this purpose.

4. Can the horse's requirements be met by forage alone?

The GI tract of horses is designed to ferment forage and grass and this is generally the best diet for maintenance of GI health. However, forage nutritional quality is highly variable and frequently unknown to the owner which is a fundamental concern when this is generally the major nutrient source provided. Forage analysis is readily available and inexpensive via several feed suppliers and is a useful adjunct to dietary planning. Hays might typically contain between 6 and 10 MJ/kg DE and 4-12% CP as dry matter (DM). Furthermore it is not unusual to find that water soluble carbohydrate content (WSC=sugars and fructans) can be remarkably high in some cases (eg >20%) and can be a significant insulin stimulus. For maintenance requirements most forages will almost invariably represent adequate, and frequently excessive, DE intake in healthy individuals but older horses in poor condition and perhaps with dental and absorptive problems may struggle to keep weight on with even free access to good quality forage, especially if protein is low.

Clearly masticatory ability is crucial to forage consumption and digestibility. Where necessary consideration should be given to using commercially available chopped and processed forage which may be generally above average nutritional quality and also the chopped nature suits horses better with dental problems – e.g. alfalfa, grass cubes, chaffs (figure 2). These diets can become a partial or total hay substitute where appropriate. If access to good quality hay or haylage is available then purchase of a garden shredder can enable manufacture of home-made chaff that can be fed to horses with masticatory problems.

5. If not, can energy requirements be met with supplementary high fibre feeds?

When forage alone does not supply adequate calorific intake then further high-fibre feeds should be offered in preference to cereal-based mixes. Non-molassed sugar beet pulp is one of the highest energy fibre feeds and provides an excellent source of low starch and sugar (<5%) calories in horses that have problems maintaining weight or those that cannot chew well. Digestible energy content similar to competition cubes is typical of beet pulp (10-13 MJ/kg) and there is reasonable protein content also (around 8-10% CP). Further high energy, low sugar/starch, high fibre feeds include "Coolstance", a coconut-based feed with <11% sugar and starch but very high energy (15 MJ/kg DE) and protein (20% CP) and also chopped alfalfa products (often around 10-12 MJ/kg DE and 12-16% CP). Some "complete" pelleted feeds are also available for horses but it is important to establish that sugar/starch content is low (ideally <10%) and that fibre content is high (preferably >25% crude fibre). Where possible at least some chopped hay or chaff should be fed alongside these "complete" diets.

6. If not, will additional dietary oil meet energy requirements?

Vegetable oils typically provide approximately 40 kJ/mL (4 MJ per 100 mL). They can be fed relatively safely to horses although they may decrease fibre digestibility in the colon at high levels. Typically a gradual increase from 0.1 mL/kg BWT up to a 1.0 mL/kg BWT over about 2 weeks will be acceptable to most horses should they require the extra energy. Palatability can be an issue although for increased calories any edible oil is fine – eg maize, sunflower, granola, vegetable, coconut etc….. Linseed and soya oil tend to be expensive. Margarine can be given if preferred by the horse. When fed at 1 mL/kg BWT daily, vegetable oil will provide around a quarter of normal dietary energy requirements and tends to produce a very attractive shine on the horse's coat.

7. If not, add cereal-based mixes/cubes (maintain at least 1½% BWT forage supply)

A small amount of cereal based mix might be useful as an energy and protein supplement and is easily consumed when dentition is poor and requirements are not being met by fibre-and-oil diets. Such mixes and cubes are typically between 10 and 30% starch and 9-13 MJ DE per kg but should never be offered at a rate of more than 1 g/kg starch per meal (about 1-2 kg feed per 500 kg). In insulin resistant subjects (e.g. PPID cases) then these cereal-based starchy feeds should generally be avoided as they are particularly hyperinsulinaemic and may increase the risk of laminitis.

8. Check vitamin, mineral, protein requirements are being met.

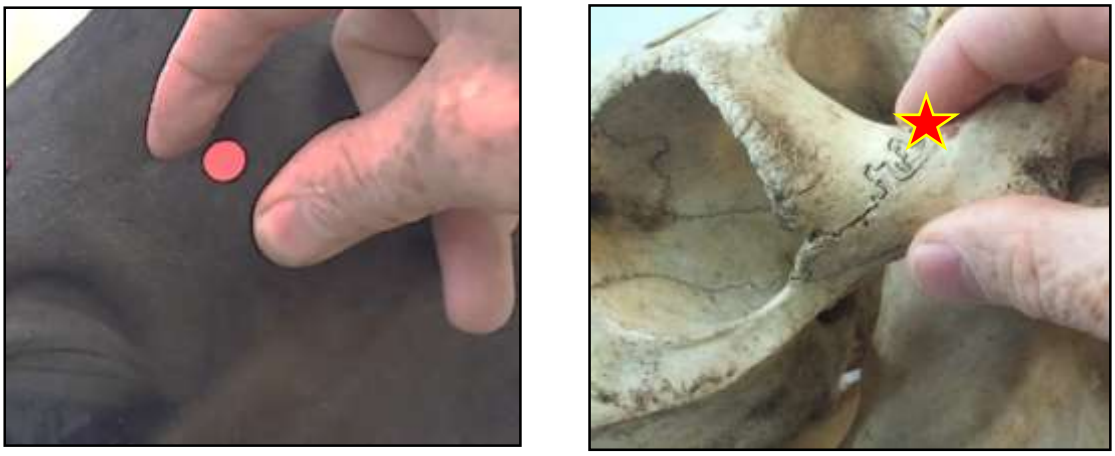
Commercially available "ration-balancers" are widely available for provision under such circumstances. Typically a small quantity of pellets are given which contain a concentrated mix of proteins (e.g. 15-25%) and minerals and vitamins. Starch may appear high in these balancers (eg 20-25%) but is generally not much of an issue given the small amount fed. Particular consideration might be given to antioxidant vitamins C and E especially where high oil levels are being fed. Addition of 1-2 IU vitamin E per kg bodyweight is reasonable.

With the nutritional resources widely available to horse owners in the UK, there is much that can be done to maintain condition in elderly horses without creating additional diet-related health risks. The main combined aims of offering high-energy, adequate protein, high-fibre, low-sugar and starch feeds are readily achievable given a multitude of possible feed constituents. Clearly close monitoring of key age- and nutrition-related health concerns including dentition and endocrinopathies should also parallel involvement in the dietary planning.

## Non-healing corneal ulcers in horses

Corneal ulceration is a common problem in equine practice. Horses are inquisitive animals and have prominent eyes: a combination making them predisposed to traumatic injury of the cornea. The majority of cases are simple and respond well to empirical treatment but unfortunately many cases are also encountered that stubbornly refuse to heal. This article intends to outline a diagnostic and treatment approach to such cases.

Examination of painful equine eyes is an almost impossible procedure unless the horse is sedated well and an auriculopalpebral nerve block is performed. Important findings such as foreign bodies and conjunctival nodules are easily missed, as are ulcers themselves unless proper control of the horse and its eyelid is achieved. The auriculopalpebral branch of the facial nerve (CrN VII) controls the muscle of the upper eyelid and is blocked where it can usually be palpated subcutaneously running over the zygomatic arch just caudal to the ventral depression of the arch, caudal to the orbit (Figure 1). Between 2-5 mL local anaesthetic are used via a 25 gauge needle.



*Figures 1 a and b. Position for auriculopalpebral nerve block to paralyse the upper eyelid to facilitate examination of a painful eye.*

The eye should then be carefully and closely examined with direct illumination looking closely for irregularities in the corneal surface, grey corneal oedema, vascularisation and any evidence of secondary uveitis (especially a constricted pupil). If any ulcers are found then the overlying conjunctiva should be carefully checked for irregularities or foreign bodies. Fluorescein dye can be used to better demonstrate ulcerated epithelium but should be diluted rather than applying a fluorescein strip directly to the eye which tends to introduce far too much dye. This author prefers to place a fluorescein strip into a plain vacutainer containing 5 mL sterile water and then using this diluted fluorescein in the eye itself via a 2 mL syringe and needle hub after breaking off the needle. Corneal stromal staining is massively enhanced by shining a blue light onto the eye in a darkened stable.

A general simple assessment of the nature and depth of the ulcer is important prognostically (Figure 2). A simple superficial corneal deficit is encouraging although does not mean it will inevitably heal quickly! A deeper ulcer continuing into the corneal stroma will inevitably take longer to heal. Evidence of necrosis with mucoid, mushy cornea is certainly alarming and indicates a more aggressive, urgent and possibly surgical approach is required.

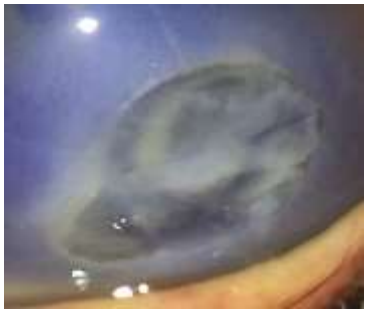
a)  b)  c) 

*Figure 2. Images of a simple epithelial defect (a); an ulcer involving the deeper corneal stroma (b); and an ulcer demonstrating evidence of acute necrosis ("melting").*

Sampling from the ulcer is important especially if there are concerning features such as marked uveitis, stromal involvement or a failure to respond well to initial medication. A smear collected from the ulcerated area can give crucial clinical information within minutes. It is better to collect this using the blunt edge of a scalpel blade (or a cytology brush) rather than a swab as the possible detection of fungal hyphae in the smear cannot then be confused with filaments from the swab (fig 3).

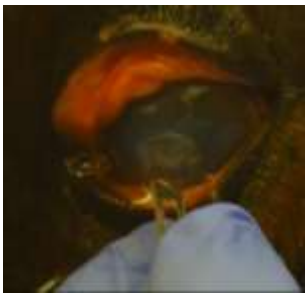
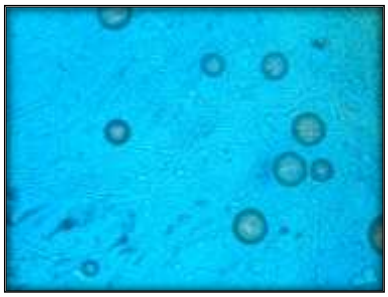
a)  b) 

*Figure 3. a) Collection of a corneal scrape from an ulcerated eye using the blunt edge of a scalpel blade, and b) Filamentous fungal hyphae detected in scraping (not cotton bud filaments*

Early diagnosis and specific treatment of fungal keratitis is very important and not uncommon especially in the warmer months. Additionally, especially problematic pathogens such as Streptococci can be immediately identified in the stained smear as chains of cocci. A swab can then be collected following the smear for further culture (bacterial and fungal) although this will inevitably take a few more days. Bacterial infection of the ulcer warrants topical antimicrobial therapy although it is important not to be too led by the reported antimicrobial sensitivity patterns reported by the laboratory. Predicted sensitivity/resistance and also MIC values are designed with reference to predicted *systemic* drug levels and have little relevance to the far higher concentrations achieved in tear film with topical ophthalmic preparations. For example, Enterobacteriacea or Pseudomonas with an MIC of 16 ug/mL would be reported as resistant based on expected maximum plasma drug concentrations following intravenous gentamicin of perhaps 40 ug/mL (i.e. less than 8 x MIC). However, a good clinical response to topical gentamicin drops is very likely as it is known that just 3 drops 0.5% gentamicin drops can achieve >350 ug/mL in tear film, high enough to kill even apparent highly resistant bacteria. Voriconazole is generally the preferred topical antifungal agent although is expensive and often not readily available. Where not available topical enilconazole (Imaverol diluted 1 in 50) can be used or alternatively Clotrimazole ointment.

Where ulcers are showing slow or absent healing then consideration should be given to blocking the effect of matrix metalloproteinases which impede healing. Ulcerated corneas contain at least 3 times normal MMP concentrations in the tear film and, interestingly, the contralateral normal eye also tends to have higher MMP levels than normal suggesting a partially systemic effect on corneal MMP expression. Many choices of antiproteinase exist including autologous plasma, serum, 20% acetyl cysteine and calcium chelators such as 0.2% EDTA solution and tetracycline ointment. All have been shown to be effective although some are more active against specific MMP isotypes meaning that at least two different agents may be indicated. Studies have indicated that serum and doxycycline have better activity versus MMP-2 whereas EDTA and acetylcysteine have better activity against MMP-9. It is this author's general practice to alternate antiproteinase treatments with autologous serum (or plasma) and 0.2% EDTA solution with the intention of broad spectrum antiproteinase effects.

The timing and duration of antiproteinase treatment is perhaps the most crucial element of treatment of non-healing corneal ulcers and, in this author's view, probably the primary reason for treatment failure. As mentioned above, MMP concentrations are increased in tear film of ulcerated eyes and intuitively will constantly resist healing and/or promote deterioration. It should be considered that any agent instilled into the eye is unlikely to remain present for longer than 10 or 15 minutes before being washed away by the tear fluid. Thus, even given an example of application of antiproteinase every 4 hours (which would require hospitalisation or a very committed client!), then the MMPs are very unlikely to be inhibited for longer than 6% of the time (i.e. 6 x 15 minutes per 24 hours), leaving them uninhibited and attacking the cornea still for the other 94% of the time! Even hourly instillation would only provide 25% MMP inhibition over time(24 x 15 mins per 24 hours). Thus serious thought should be given to continuous infusion of antiproteinases via a subpalpebral catheter making use of a balloon reservoir or infusion pump device. Unfortunately this generally means that hospitalisation is required although the increased chances of achieving reasonably prompt healing will often make this a cost effective option.

Indeed subpalpebral lavage catheter placement is pretty much mandatory for any horse (however good natured) receiving intraocular medications more than 3 or 4 times daily. Catheters are easily placed under sedation with the lower lid towards the medial canthus being the preferred site for avoidance of complications. Lower eyelid subpalpebral lavage catheters are extremely well tolerated with complications being exceedingly rare (figure 4).

*Figure 4. Subpalpebral lavage catheters greatly facilitate ocular medication and are easy to place.*

Additional relatively simply tactics that can be used alongside medications discussed above include grid keratotomy, diamond burr debridement and tarrsorhaphy. Grid keratotomy can be performed under sedation and topical analgesia of the cornea. Although the equine cornea is less than 1 mm thick, it is a pretty tough structure and light application of the edge of a 19 gauge needle, a scalpel blade or a specific depth-limited keratotomy knife, is a very low risk procedure in sedated horses. Published studies indicate good resolution rates of non-healing ulcers post-keratotomy (e.g. 70% healed within 2 weeks) although this author's experiences have not been quite so dramatic! Similarly diamond burr debridement (figure 5) can be applied to corneas after sedation and topical analgesia and this carries an even more impressive published healing rate of >90% at 2 weeks. Again however, although a probably useful technique, this author's experiences have been frequently disappointing following this procedure. As long as the non-healing ulcer appears stable at least with no obvious threat of deeper extension, abscessation or uveitis, then tarrsorhaphy should also be considered. This author has frequently found chronic non-healing ulcers to heal well during a week of enforced eyelid closure (perhaps due to absence of frictional forces on the delicate early healing ulcerated epithelium during blinking?). This can be achieved with one or two sutures carefully and gently placed from the upper to lower eyelids. Ultrasound can be used to offer reassurance of globe integrity, corneal thickness, pupil size, aqueous clarity, etc… during the period of tarrsorhaphy although, as mentioned above this technique is only really indicated in ulcerated corneas that appear stable and uncomplicated, albeit non-healing.

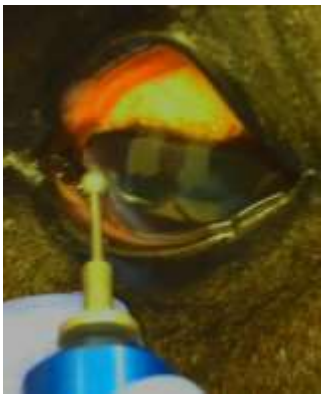


*Figure 5. Debridement of a non-healing ulcer with a diamond burr.*

Finally surgical options should be considered either when conservative medical approaches have failed after several weeks of treatment, when further threat to the eye is seen such as progressive deepening or necrosis of the ulcer, or as a means of attempting to expedite a slowly healing corneal ulcer. Conjunctival pedicle flaps may be placed under general anaesthesia and offer both structural stability and vascularisation of the ulcer bed. Provided dehiscence does not occur then good strength and healing is expected within about 2 weeks of surgery. Permanent scarring of the ulcerated area is to be expected which could cause significant visual deficit if large. Application of amnion grafts tend to encourage corneal healing with much less, if any, residual scarring but are offered by relatively few equine hospitals in the UK.

## CARDIAC CONDITIONS

The prevalence of cardiac murmurs is high in horses but associated clinical problems are rare. Problems may be detected as an adventitious sound (murmur) and/or as a rhythm irregularity (arrhythmia).

**Murmurs**

When a murmur is detected there are at least 3 key questions to be answered:

1. Is the murmur associated with any cardiac disease or abnormality?
2. If so, is this causing the horse any problems currently?
3. If not, is it likely to cause the horse any problems in the future?

With experience, clinicians should be able to answer Item 1 with reasonable certainty by history, clinical examination and simple auscultation and also have an impression of the likelihood of item 2.

**General Clinical Examination**

- Mucous membranes
- Arterial pulse
- Jugular distension/pulse
- Oedema
- Respiratory sounds

**Cardiac examination/auscultation**

- Palpation of apex beat
- Heart rate
- Heart sounds
- Cardiac rhythm

Echocardiography will answer item 2 with more certainty but item 3 is extremely difficult to answer with absolute reliability using any method. Thus echocardiography is recommended for any horse that has, or is suspected to have, a murmur associated with cardiac disease or abnormality.

Interpretation of auscultatory findings in horses is aided by a few general observations:

a. Valvular disease in horses tends to produce murmurs of insufficiency (ie regurgitation) and not stenosis.
b. By far the commonest valvular abnormalities of potential significance in equine practice are ***aortic insufficiency*** and ***mitral insufficiency***
c. Occasional cases of tricuspid insufficiency and ventricular septal defect are also seen

d. Tricuspid valve insuffiency is rarely if ever clinically significant
e. Pulmonic valve disease and other pathologic causes of murmurs are very rare

These generalisations allow the follow simplification to be applied to most cases:

There are essentially 3 pairs of common murmurs that should be differentiated on the basis of auscultation:

**1. <u>Left sided systolic murmurs – aortic ejection & mitral insufficiency</u>**

These are probably the most commonly encountered murmurs in horses.

a. Many horses will have a murmur as the large volume of blood ejected from the left ventricle enters the aorta (***aortic ejection*** murmur). This is not associated with any cardiac disease process. Some horses will have this under normal circumstances and others will have it under conditions of catecholamine release – eg stress, excitement or colic. This murmur should be shorter than the duration of systole – usually early systolic – with a perceptible quiet "gap" between the murmur and the 2nd heart sound. They are usually low grade and do not radiate. They will be heard high up towards the shoulder level and cranially under the triceps muscle over the aortic area.
b. ***Mitral (left AV) valve insufficiency*** is far less common than aortic ejection murmurs but is an important differential of it. The key auscultated difference is that mitral insufficiency produces a pan or holo-systolic murmur and there is no quiet gap between the 1st and 2nd heart sounds. Additionally mitral insufficiency murmurs tend to be best heard low down towards the apex beat and are often louder. Mitral murmurs are potentially serious and should always be subject to echocardiographic assessment. Nevertheless many successful competition horses cope well with these murmurs as long as the degree of leakage and volume overload is mild (and stays mild).

2. **<u>Left sided diastolic murmurs – diastolic squeak & aortic insufficiency.</u>**

    a. ***"Diastolic squeaks"*** are short musical diastolic sounds frequently heard on the left side but can be on the right occasionally. They were reputed to be heard only in young horses ("2 yo squeaks") but are often heard in older horses too. They are probably associated with the rush of blood down into the empty ventricle at the beginning of diastole and are therefore usually best hear low down towards the apex beat. They are of no consequence.

    b. ***Aortic insufficiency*** is a fairly common murmur usually heard in mature to elderly horses. This is an easy murmur to identify as it is a very long – sometimes harsh and sometimes quite musical – murmur lasting throughout diastole (pan/holodiastolic). Point of maximal intensity is invariably high up under the triceps over the aortic area. Most horses cope well with aortic regurgition and can be ridden normally (albeit they are usually older horses and don't do so much work) but some are found echocardiographically to be suffering from marked volume overload and should then not be ridden. A bounding, hyperkinetic pulse is a poor prognostic sign as are frequent associated premature beats.

3. **<u>Right sided systolic murmurs – tricuspid regurgitation and ventricular septal defect.</u>**

    a. ***Tricuspid (right AV) valve insufficiency*** is common in fit athletic horses probably as a result of training effects on cardiac dimensions. It is rarely if ever problematic to the horse or cardiac function. The murmur is pan or holosystolic and tends to be best heard high up under the triceps towards the shoulder.

    b. ***Ventricular septal defects*** are occasionally encountered (especially Welsh ponies) as pan/holosystolic right sided murmurs. They sound very similar to tricuspid regurgitation but are usually far lower down towards the sternum. There may occasionally be an associated left sided systolic murmur also ("relative pulmonic stenosis"). When VSDs are often first encountered in adult horses with no porior suspicions of cardiac disease or poor performance. VSDs less than about 2cm diameter appear to cause little or no cardiac compromise.

Congestive heart failure is uncommon in horses but may present as acute respiratory distress (left sided failure) and/or peripheral oedema (right sided failure). Treatment is rarely effective for long but may be attempted with frusemide (1 mg/kg q 12 h), digoxin (0.01 mg/kg orally q 12h) and/or benazepril (0.25-0.5 mg/kg q24h.

**Arrhythmias**

Abnormalities of rhythm essentially require diagnosis via ECG. Atrial fibrillation is undoubtedly the commonest arrhythmia that causes poor performance as it reduces ventricular filling at high heart rates. Other arrhythmias associated with poor performance less frequently include ventricular and atrial premature complexes. It is not so easy to see

why these should cause poor performance as often the heart rate (per minute) is normal, albeit irregular and it maybe they simply reflect myocardial disease/dysfunction.

Atrial fibrillation may be treated by electrocardioversion where available, although most cases are still treated with oral quinidine sulphate. Quinidine blocks sodium channels prolonging the action potential, depressing myocardial function and slowing conduction. Additionally it has blocks both cholinergic and α-adrenergic receptors promoting tachycardia, vasodilation and hypotension.

Geriatric horses are usually treated with quinidine sulphate at a dose of 22 mg/kg q 2 hours via an indwelling stomach tube. They should be left quietly in the stable throughout treatment due to inevitable hypotension. Toxic effects are more likely when plasma levels are > 0.005 mg/mL plasma and after about 4-6 doses. Where plasma drug concentration is not possible then frequency of doses should be extended to every 6 hours after 4 to 6 doses if restoration of sinus rhythm has not occurred.

It is important for the owner to be aware that quinidine is a potentially dangerous treatment with a very narrow therapeutic range. ECG should be monitored throughout treatment and prolongation of the QRS complex by >25% indicates toxicity. Treated horses commonly become depressed/sedated and muzzle oedema often develops. Anorexia, flatulence, colic and diarrhoea are also common and result from gastrointestinal irritation. Neurologic signs, laminitis and urticaria are seen occasionally. Weakness and collapse can also occur due to hypotension. Perhaps the most concerning toxic effect of quinidine is additional arrhythmias such as supraventricular tachycardia, ventricular tachycardia or torsades de pointes. Sodium bicarbonate (0.5–1.0 mEq/kg IV) should be given to increase protein binding of quinidine where toxicity is suspected. Digoxin (0.002 mg/kg iv or 0.01 mg/kg orally) may be used to counteract supraventricular tachycardia whereas ventricular tachycardia and torsades de pointes are best treated with intravenous magnesium sulphate (50 mg/kg diluted in saline and given over 30 minutes).

| | **Auscultation** | **ECG** | **Clinical significance** |
|---|---|---|---|
| **2º AV Block** | Normal resting heart rate (or low)<br>Regular rhythm and occasional pauses<br>Isolated 4th heart sound during pause | Occasional P-wave not followed by QRS-T complex | - May occur as often as one beat in three.<br>- Generally dropped singly but two beats may be dropped in succession<br>- No clinical significance<br>PHYSIOLOGICAL ARRHYTHMIA |
| **Atrial fibrillation** | Normal or raised H.R.<br>Irregularly irregular rhythm<br>Heart sounds of variable intensity | "F" fibrillation waves<br>Absence of "P" waves<br>Irregular R-R interval | - Clinical signs depend on athletic use of horse and presence or absence of underlying heart disease<br>- Poor prognosis if:- HR > 60, G. 3-6 or louder murmurs > 4 months duration |

| | | | |
|---|---|---|---|
| **Atrial (supra-ventricular) Premature Complexes** | Premature beat and compensatory pause | Premature P wave. | Unlikely to affect performance unless multiple during exercise.<br><br>Isolated APC's generally okay. |
| **Ventricular Premature Complexes** | Premature beat and compensatory pause | Premature QRS-T not preceded by a P wave.<br><br>VPC differs from other QRS complexes. | If isolated - insignificant. Detected post-exercise as HR slows. |

## Weakness, Ataxia and Collapse

Although neurologic disease in horses is not as common in UK as some other countries, cases will be encountered in equine practice and these will mostly present as ataxia and/or weakness. Ataxia refers to proprioceptive deficits whereby the individual is unaware of limb position, whereas weakness refers to motor deficits whereby initiation of motor function is impaired. Commonly both coexist although some neurologic conditions might demonstrate one and not the other. Clinical differentiation of the 2 may not always be straightforward although evidence of frequent "mistakes" in foot placement, treading on the contralateral foot, tripping when going up and down steps, circumduction when circling etc… all suggest ataxia. Weakness may be indicated by a low foot flight and responses to pushing and pulling at rest and during walking.

When presented with a horse showing signs of weakness/ataxia it is useful to apply a grade to the affected limbs. Forelimbs will commonly not be affected to the same extent as hindlimbs. Although symmetric ataxia/weakness is common, some cases are seen with obvious right-left differences also.

The first question when presented with a case of ataxia/weakness is to establish whether or not the case is truly neurologic in origin or has an alternative explanation. This again is not always straightforward but is aided by consideration of some of the commoner non-neurologic diseases that might mimic neurologic ataxia/weakness and require ruing out. These include:

- **colic** - some cases may stagger and go down although this is generally easily distinguished from neurologic disease
- **laminitis** - especially hindlimb laminitis which can present with a quite bizarre gait. It is worth palpating digital arteries each side of the fetlock to see if they are bounding and therefore suggestive of laminitis. Abaxial sesamoid nerve blocks could also be placed for greater security to see of the gait changes
- **hepatic encephalopathy** – can present with a great variety of clinical signs although weakness and ataxia are common. Most cases will be a bit depressed also but this is not always the case. If in doubt then check liver enzymes such as GGT, or even better ammonia if you can get to a lab within an hour.
- **acute myopathy** – exertional rhabdomyolysis is generally very painful and arises during exercise and will usually not be easy to confuse with neurologic disease. Seasonal pasture myopathy (atypical myopathy) is an increasingly recognised condition of grazing horses, especially young horses and especially in the autumn. An array of clinical presnetations can occur from being found dead – to severe pain and depression – to apparently pain free recumbency – to stiffness and unusual gait. Most case are fairly marked and severe. This is an easy diagnosis to miss unless you have it in mind. The easiest immediate way to make the diagnosis is from examining a urine sample which will generally be very dark red-brown as a result of myoglobinuria.
- **orthopaedic disease/injury** – recumbent horses will be encountered that have suffered spontaneous limb fractures and might not always be obvious. Although distal limb fractures can be easily seen/felt, fractures of proximal bones such as humerus, femur and pelvis may be tricky to establish. Often a marked pain response

is not present even when the limb is manipulated but time taken to palpate, compare and even auscultate the affected limb is well spent. Additionally, elderly horses are not infrequently encountered which have become recumbent and struggle to rise as a result of severe osteoarthritis. Often analgesics, anti-inflammatories and some human assistance succeed in getting the horse up but it is firth worth establishing that no limb fractures are suspected.

If neurologic disease is truly suspected then though should be given to localising the site(s) of injury/disease. Many cases can be explained in terms of a single site but where the neurologic signs are incompatible with this then thought should be given to multi-site injury, or more likely diffuse disease such as viral myeloencephalitis or hepatic encephalopathy.

Grading of ataxia/weakness is important and can be done as follows:

0. normal
1. minimal deficits noted with normal gaits and requires manipulative tests (crossing legs, tail sways, tight circles, walking up and down hills, blind folding, backing)
2. mild abnormal gaits seen at a walk (walks like has been sedated) and more obvious response to the manipulative tests.
3. Easy to see at a walk, look like a drunken camel at a trot, very obvious at a canter but they do not fall.
4. Very ataxic – will fall especially in tight circles or backing. Usually will refuse to go any faster than a walk.
5. Recumbent – may not even be able to become sternal even with encouragement

The main causes of ataxia/weakness seen in horses in UK include:

- Cervical spinal compressive injury
- Acute vestibular disease
- EHV1 myeloencephalopathy

Other occasional to rare cases will be seen involving non-cervical spinal damage; so-called “grass staggers” (tremorigenic mycotoxins) and; possibly other viral myeloencephalitides such as West Nile Virus.

**Spinal Injury**

Spinal injury is typified by ataxia and weakness in the absence of any cranial signs such as depression, altered behaviour or cranial nerve signs.

***Cervical***

Most commonly the cervical spine is affected with consequent disturbance of neurologic function of both fore and hind-limbs. However, due to the more superficial position of hind-limbs nerve tracts, the hindlimbs are typically 1 clinical grade worse than the forelimbs. Thus a grade 3 hindlimb score would be expected to show obvious deficits (Grade 2) in front, whereas a grade 1 hindlimb score would probably appear normal in front. Classically cervical

lesions are referred to as Wobbler syndrome and are best recognised in young growing large breed horses. In mature horses, facet arthropathy is probably more common than stenosis and malalignment although all of these can occur. Assessment of facet arthropathy is difficult and many mature horses will be seen with radiographic changes in their facets without any problems. Inevitably equine cervical radiography is severely limited by the inability to acquire dorsoventral views so often diagnoses are made on the tentative basis of a combination of clinical and suggestive radiographic changes. Even myelography may not be definitive!

Cervical spinal ataxia is a concerning clinical signs although horse will often improve or even recover using a combination of rest, systemic anti-inflammatories or ultrasound guided injection of affected facet joints.

***Cauda equina spinal lesions***

Additionally, when hindlimb ataxia is encountered where forelimbs appear unaffected, careful examination for signs of disease of the *cauda equina* (caudal to the junction of the S3-S4 spinal cord segments which approximates skeletally to the lumbosacral junction) is important.

Suggestive clinical signs of disease of the *cauda equina*:

- Reduced tail tone/sensation
- Reduced anal tone/sensation
- Altered skin sensation of the perineal/pelvic region
- Penile prolapse/impotence
- Urinary retention/incontinence
- Faecal retention/incontinence
- Pelvic limb ataxia/weakness/paraplegia/muscle wastage

A spectrum of clinical signs is possible depending on the site and extent of nerve involvement. When only coccygeal nerves are affected (Co 1-5) then reduced/absent tail tone and/or altered tail skin sensation are noted. Further cranially, affected sacral segments (S1-S5) results in altered sensation and conscious control of the perineum, anus, pelvic area and penis (pudendal n, caudal rectal n) and/or autonomic control of the penis, bladder and rectum (pelvic n). Lumbo-sacral (L5-S2) spinal nerve disease affects sciatic function (strictly only S1-S2 nerve roots are part of *cauda equina*) that may result in absence/depression of the hindlimb withdrawal reflex in response to stimulation of the coronary band and perhaps weakness and muscle wastage of the gluteals and caudal thigh muscles.

Mid to caudal lumbar segments (L3-L6) (not part of the *cauda equina*) supply the femoral nerves that control craniomedial thigh muscles and wastage/weakness may occur when these muscle are denervated. Cranial lumbar (L1-L4) spinal nerves (not part of the *cauda equina*) supply sensation to the caudal abdomen, prepuce and udder.

Note that spinal lesions cranial to L3 may be associated with some hindlimb weakness/ataxia and even bladder paralysis but there will be normal tail/anal tone and no neurogenic atrophy of hindlimb muscles. Additionally hindlimb reflexes, muscle tone and limb spasticity are likely to be exaggerated with lesions cranial to L3 due to uninhibited reflex arcs.
The most common causes of ataxia with cauda equina disease in horses comprise trauma (eg. Sacral #) and EHV1 myeloencephalitis with rare cases of Polyneuritis equi. With the

potential contagious implications of neurologic EHV1 (see later), this is clearly an important sign to recognise.

## Acute vestibular disease

Sudden onset ataxia is occasionally encountered in horses showing additional signs relating to brain injury/disease and therefore spinal injury can be ruled out as a sole cause. Commonly these cases demonstrate head tilt and markedly assymetric ataxia suggestive of vestibular disease (cranial nerve VIII). Nystagmus and strabismus might also be seen and occasionally other cranial nerve signs, most commonly facial paralysis given the close anatomic positioning of the VII and VIII cranial nerve nuclei. Other brain signs such as depression/stupor and additional cranial nerve signs such as dysphagia (IX-X) might also be seen.

Many such cases present with grade 3-4 ataxia. Strictly weakness is not present with vestibular disease although this is not always easy to establish. Severely ataxic horses clearly represent a danger to themselves and to attendants and so serious consideration must be given to safety. A good proportion of these cases will improve significantly so don't rush to euthanase, especially if not recumbent. There are 2 main causes of acute vestibular disease in horses: temporohyoid osteoarthropathy (THO) and basisphenoid fracture.

***Temporohyoid osteoarthropathy*** (THO)

The hyoid apparatus links the larynx, tongue and base of the skull via articulations with the ventral aspect of the petrous temporal bone on left and right sides. These articulations can be easily visualised in the roof of the guttural pouches and can be seen to move when the horse swallows or vocalises. The temporohyoid joints (between the stylohyoid bone and the petrous temporal bone) may be prone to osteoarthritic changes for unknown reasons. During this process signs might be noted relating to head shaking or discomfort whilst eating or vocalising (or no premonitory signs). Severe neurologic problems may arise following natural progression of osteoarthritis to fusion of the temporohyoid joints. Once this has occurred, if severe stresses are placed thought the hyoid apparatus by swallowing, tongue movement or vocalisation, then the weakest part may fracture – which tends to be the petrous temporal bone. As this site of fracture is invariably adjacent to the nucleus of the CrN VIII (vesibulocochlear nucleus) the acute onset vestibular disease ensues. Facial paralysis is also common due to the close proximity of CrN VII and the horses might be depressed from haemorrhage or even infection spreading via CSF.

Confirmation of diagnosis is best achieved via guttural pouch endoscopy where an enlarged and deformed dorsal stylohyoid bone is seen and failure of the stylohyoid bone to articulate when water is squirted into the horse's mouth.

Cases should be treated with anti-inflammatories, antimicrobials and also boluses of 7.2% (hypertonic) saline to reduce brainstem oedema. If the horse can be maintained safely then commonly improvement is seen within 24 hours. Further surgical treatment to decouple the hyoid apparatus (ceratohyoidectomy) is recommended to prevent recurrence.

***Basisphenoid fracture***

This disease closely mimics THO and is hard to distinguish from it. Classically horses with basisphenoid fracture will have a history of head trauma from rearing a striking the poll – but this is not always observed by attendants. Young and flighty horses are clearly greater suspects. Sudden traumatic impact to the back of the poll results in rapid poll extension which leads to a sudden pull of the rectus capitis muscles which attach to the underside of the cranium on the basisphenoid bones. Fracture usually occurs at the site of the original symphysis but might often not be obvious on radiographs due to non-displacement or obliquity. Again guttural pouch endoscopy is a useful adjunct to diagnosis as the ruptured rectus capitis muscles run between the guttural pouches and associated haemaorrhage is seen under the guttural pouch mucosa in the medial septum. Treatment is aimed at reducing inflammation and preventing infection and is largely the same as for THO. Outcome is variable although, again, there is much scope for improvement which may continue to occur over several weeks so don't be too hasty to give up.

**Equine Herpesvirus 1 myeloencephalopathy**

EHV1 undoubtedly has the greatest clinical importance of the equine herpesviruses. EHV4 is a common cause of relatively mild respiratory disease and also a rare cause of abortion in mares. EHV4 is endemic worldwide and antibodies can be detected in almost 100% of horses (perhaps 25% of horses have EHV1 antibodies). The main clinical differences between EHV1 and EHV4 are the milder EHV4 respiratory disease and the sporadic and relatively rare nature of EHV4 associated abortion. Neurologic disease associated with EHV4, if it exists, is apparently very rare indeed.

EHV-1 infection is widespread and it should be expected that all horses will be at risk of infection resulting in subclinical infection or respiratory disease, and less frequently abortion, neonatal mortality and myeloencephalopathy. Most horses are inevitably exposed to EHV1 early in life and long-term latent infection is then established in the lymphoreticular system and trigeminal ganglion with the possibility of recrudescence and shedding at times of stress (e.g. foaling, sales, mixing, training, transport...). The prevalence of latent EHV1 infection in horse populations has been estimated at between 60 and 90% but may well be higher as more sensitive detection techniques are applied.

**Mechanisms and pathways in EHV1 infection**

Infection with EHV1 is initially via the respiratory epithelium. Infection and replication within epithelial cells leads to respiratory disease, secondary bacterial infection and shedding of further virions for 7-14 days. Virus is transported to local lymph nodes from where develops a leucocyte-associated viraemia.

Following viraemia, endothelia of the spinal cord and the late-pregnant (8-11 m) uterus appear especially predisposed to EHV1 infection although the brainstem is occasionally infected also. Endothelial infection leads to local inflammation (vasculitis), thrombosis and haemorrhage leading to ischaemic necrosis. In cases of uterine infection, the foetus is also usually infected although endometrium-positive, foetus-negative cases of abortion are reported. During outbreaks of EHV1 myeloencephalopathy (EHM) only around 10% of exposed horses develop neurologic signs although variable but often higher levels (eg 30-50%) of morbidity are seen in EHV1 abortion outbreaks.

The determinants of whether infection results in simple respiratory disease, or more serious disseminated necrosis of the CNS or uterus, are not entirely clear. Expression of adhesion molecules has been demonstrated on the surface of endothelial cells in the late-pregnant uterus that facilitate transfer of EHV1 from infected leucocytes although similar mechanisms have not yet been demonstrated in the CNS.

Variability in virus strains appears to be important in determining the outcome of infection. A single nucleotide polymorphism in the DNA polymerase ($DNA_{pol}$) gene of EHV1 leads to a single aminoacid change in viral DNA polymerase. This has been identified as an important determinant of pathogenicity of different strains. The $DNA_{pol}$ $N_{752}$ strain is the commonest circulating strain and is responsible for >95% of EHV1 abortions and 15-25% of cases of neurologic disease. $DNA_{pol}$ $D_{752}$ strains (e.g. Ab4 virus) are the commonest cause of neurologic disease and can, experimentally, reliably induce abortions. Latent carriers may be infected with either or both strains.

It appears at present that the prime factor determining the risk of neurologic EHV1 infection is the higher magnitude and duration of viraemia associated with $D_{752}$ strains. However, other factors almost certainly exist. Although reports exist of EHM in weanlings, cases are largely restricted to horses > 3 to 5 years old. Interestingly this is the age group in which it becomes unusual to observe EHV1 respiratory disease suggesting that immune status influences outcome of infection. One study suggested that previous EHV1 vaccination increased the risk of EHM although further examination of that data suggest this effect may have been related to age rather than vaccination status (i.e. vaccinated horses were older). Horses (vs ponies and small breeds) and females have also been found to have increased susceptibility in some studies. The majority of EHM outbreaks occur in late autumn, winter, and spring. Repeat respiratory disease is well recognised in young horses as natural immune resistance appears to be short lived (<3-6 m). In contrast, horses suffering repeat attacks of EHM are not reported although the rarity of the disease might bias this finding. Repeat EHV1 abortions are reported but rarely in consecutive pregnancies.

Evidence suggests that several years following experimental EHV infection, latency tends to persist in association with the same strain used for infection. This might create concerns of further risk from horses that have been involved in, and have recovered from, an outbreak of EHV myeloencephaolpathy as they are more likely to be carrying neurotrophic strains (probably $D_{752}$). Introduction of new horses is a commonly reported feature preceding EHM outbreaks. However, given that $D_{752}$ can be found in 5–20% of latently infected horses, the extra risks associated with horses exposed to neuropathogenic strains during outbreaks of EHM are likely unlikely to be significant.

## Clinical signs

Following infection, signs generally arise within 3 days (up to 10 days). Three clinical syndromes arise from EHV1 infection: respiratory disease, abortion/neonatal death and EHM.

Respiratory disease is the most common presentation. This is generally mild and typified by nasal discharge, lymphadenopathy and pyrexia. Coughing is not typical.

Abortion outbreaks (storms) are recognised following EHV1 infection of mares in late pregnancy. EHV1-associated pregnancy is rare in the first half of pregnancy and is generally

seen in the last 3 months. Solitary cases may occur or the outbreak might comprise more than half of at-risk animals. Weak and gradually succumbing foals may represent a very late gestational EHV1 infection. Prior to death lymphopaenia and icterus may be suggestive signs of EHV1 infection.

The main neurologic sign associated with EHM is hindlimb ataxia. This may progress to marked paresis leading to recumbency in some cases. Other cauda equina signs such as urinary incontinence, lack of anal tone, faecal retention and tail weakness may also be seen. Less frequently cranial nerve signs or cerebral signs including abnormal mentation and head pressing might be seen. Pyrexia is a common premonitory sign of impending EHM during outbreaks. Some outbreaks have been preceded by cases of EHV abortion or respiratory disease but this has not been consistent. Morbidity is variable and dependent on many factors but might be from 10% to 90% of individuals. Mortality is variable in different outbreaks and may be from 5% to 30% of horses showing neurologic signs. Horses becoming recumbent for >24hrs appear to have a poor prognosis.

## Diagnosis

### Virus isolation

This is the gold standard test for diagnosis of EHV-1 although takes time (3-7 days) for a result. It is performed on nasal/ nasopharyngeal swabs or buffy coat samples in heparinised blood. Gauze swabs and viral transport media are required. Positive virus isolation strongly supports a diagnosis of EHV1-related disease. It is advisable during an outbreak that in-contacts are also sampled (especially with signs of pyrexia) to increase the diagnostic rate.

### PCR

This allows for rapid identification of the presence of EHV1 infection. It is also performed on nasal/nasopharyngeal swabs or buffy coat samples in heparinised or EDTA blood (check with lab). Nasal swabs are associated with higher diagnostic rates than nasopharyngeal. Gauze swabs and viral transport media are required. If viral transport medium is not available, then a dry

swab in a sterile tube can be submitted for PCR. Higher sensitivity and specificity than virus isolation may result in positive PCR results when virus isolation is negative due to insufficient virus. Real-time PCR can be used to distinguish $D_{752}$ and $N_{752}$ strains although the usefulness of this finding is limited as EHM can be caused by either strain.

### Serology

A ≥ 4-fold increase in antibody titre, by serum neutralisation (SN), complement fixation (CF) or ELISA, in samples collected 10–20 days apart provides reasonable evidence of EHV-1 infection although is clearly retrospective. Serologic tests don't generally distinguish between antibodies to EHV1 and EHV4 although an ELISA targeting the C-terminal portion of glycoprotein G of both viruses is available for distinguishing serologic response to each virus. Both the CF and ELISA tests only reliably detect recent infections (<2-3 months previously).

### Cerebrospinal fluid

Analysis of CSF often shows yellow discolouration (xanthochromia), increased protein concentration (1-5 g/L) and possibly a monocytic pleocytosis (>5/microlitre) in horses with

EHM although these changes are inconsistent. Antibody titres in CSF are not helpful due to leakage of serum from damaged blood vessels into the CSF. PCR is also rarely helpful due to such a low viral content of CSF.

**Histopathology**

Post mortem examination of brain and spinal cord helps confirm EHM. Vasculitis and thrombosis of small blood vessels and virus detection via immunohistochemistry, in situ hybridization and PCR can also be performed.

Examination of endometrial biopsies and placenta may demonstrate typical pathology and viral antigen more consistently than examination of aborted foetuses following EHV1 infection of pregnant mares although the latter should always be submitted for examination. Unexplained neonatal deaths warrant post mortem examination for signs of EHV1 infection including necrotising bronchopneumonia and detection of viral antigen.

## Vaccination

There is no evidence that current vaccines can prevent EHM. However, reduction of cell-associated viraemia is likely to reduce the risk of EHV1 abortion and EHM. High serum antibody titres stimulated by vaccination appears unable to affect the cell-associated viraemia of EHV1 or to reduce abortion following experimental challenge. In contrast, stimulation of mucosal antibodies and cytotoxic T lymphocytes by vaccination is likely to help prevent infection of the respiratory tract and limit virus replication, shedding and further spread of infection.

In the UK there are 2 EHV vaccines both containing inactivated EHV1 and EHV4: "*Duvaxyn EHV1,4"* (Fort Dodge) uses Carbopol 934P adjuvant and "*Equilis Resequin"* (Intervet) uses aluminium hydroxide and Immunostim™ adjuvant (the latter also contains inactivated influenza viruses). Duvaxyn EHV 1,4 claims to "reduce clinical signs due to infection with Equine Herpesvirus 1 and 4 and to reduce abortion caused by EHV-1 infection" whereas Equilis Resequin claims only to reduce EHV-associated respiratory disease. Nevertheless, the widespread use of inactivated vaccines has been associated with reduced incidence of EHV-1-related abortions in the USA although other factors may well have contributed to this observation.

Vaccination in the face of an EHV-1 outbreak is a little controversial primarily because of previous suspicions of vaccination increasing the risk of EHM. However, this association is not proven and there are no reports of vaccination in the face of infection precipitating or exacerbating EHM. EHV-1 vaccination (especially boosters given to previously vaccinated horses) can contribute to reducing the spread of infectious virus.

## Disease control and prevention.

Guidelines for the prevention of EHV1 disease are published as Codes of Practice byThe Horserace Betting Levy Board

As stated in the recent ACVIM consensus statement on EHV1, the priorities for management of an EHV-1 outbreak are:

1. Early diagnosis.
2. Prevention of further spread.

3. Management of clinical cases.

The 3 key principles for control of spread of EHV-1 are:

1. Subdivide horses into small, isolated, closed groups.
2. Minimize risks of introduction of EHV-1
    a. exogenous - isolate new horses for ≥3weeks
    b. endogenous – reduce stress induced viral reactivation
3. Maximize herd immunity through vaccination.

Horses with EHM , and possibly EHV1 abortion, can shed infectious virus for at least 21 days after initial infection. Therefore affected horses must remain in isolation during this period. EHV may be transmitted by aerosol, infected horses and fomites.

A period of 28 days since any new cases of EHV-1 infection is currently recommended before isolation restrictions are lifted.

A reduced quarantine period of 14 days might be implemented if the absence of pyrexia (temperatures measured twice daily) followed by negative PCR for 2 to 4 consecutive days can be determined.

Virus in the environment is very unlikely to survive longer than 21 days. Further disinfection may be accomplished using thorough cleaning followed by application of a number of disinfectants (such as quaternary ammonium

compounds, accelerated peroxide and peroxygen compounds or iodophor disinfectants), although phenolic disinfectants are the best choice in the presence of organic materials.

**Treatment.**

The treatment of horses with EHM involves general supportive care including attention to fluid therapy and nutrition, and frequent bladder and rectal emptying. NSAIDs and antimicrobials are also frequently administered.

Glucocorticoids have often been used with the aim of reducing the vasculitis although no evidence basis exists to support this.

Antiviral drugs have received more pharmacologic attention recently.

Acyclovir is a thymidine kinase inhibitor that selectively inhibits replication of herpesviruses. Bioavailability appears to be variable and low in horses which limits is practical application. In contrast valacyclovir, although expensive, shows reasonable bioavailability and has been recommended at 30 mg/kg per os q8h for the 1st 48 hours, then 20 mg/kg per os q12h.

**Epilepsy & "Narcolepsy/cataplexy"**

Repeated seizure activity (***epilepsy***) is occasionally seen in adult horses but is uncommon due to their relatively high seizure threshold. Hereditary juvenile types exist in some breeds (eg Arabians) but far more idiopathic cases are seen in practice. Motor activity predominates and most cases show generalized seizures with recumbency and loss of consciousness. Post-ictal signs such as unilateral blindness, facial paralysis, wandering etc.. may help define the primary focus of seizure activity. Occasionally partial seizures occur with localized motor

signs only – eg unilateral facial twitching. Most cases appear to be non-progressive but reduced seizure frequency often results from phenobarbitone medication (5-10 mg/kg po bid) or phenytoin (1-2 mg/kg bid-tid).

So called "***narcoleptic/cataplectic***" cases are seen relatively frequently in equine practice. Subjects appear to suddenly fall asleep – occasionally collapsing to the ground but more frequently waking up and recovering mid-fall. No overt motor activity or more than momentary unconsciousness occurs unlike in epileptic cases. Other than appearing sleepy, no neurologic deficits are detectable. The attacks frequently follow tacking up and grooming but may occur at other times too. True brain disease is probably a very rare cause of these sleep attacks in horses and it is almost invariably the case that there is evidence of sleep deprivation in affected individuals. ***(NB. provocative testing for narcolepsy using physostigmine in horses carries a significant mortality rate!).***

The key question to ask in history taking is *"Do you ever see the horse lying down to sleep?"*. The answer is almost always negative. A full, restful sleep cycle cannot take place without lateral recumbency in the horse and failure to do this results in chronic sleep deprivation and a tendency to fall asleep. Most cases appear related to orthopaedic disease (eg acute injury or chronic osteoarthritis) and may respond well to specific therapy or simply NSAIDs. Sometimes temporary signs associated with various other illnesses are also seen. Occasional cases fail to lie down is as a result of psychologic insecurity and a more stable herd environment may help this problem.

## Urinary Disorders

Horses may present for investigation of their reno-urinary system where the owner or carer reports abnormalities manifestly related to urination and/or water intake. Additionally there are clinical circumstances where reno-urinary disease is not necessarily obvious although the clinician should recognise the requirement for monitoring and investigation of possible reno-urinary dysfunction. These reasons are outlined in table 1.

| **Common owner-reported reno-urinary concerns** | **Reasons for veterinary-advised monitoring/investigation of reno-urinary tract** |
|---|---|
| • Increased urine production<br>• Increased drinking<br>• Discolouration of urine<br>• Blood in urine<br>• Increased frequency of urination<br>• Discomfort during urination<br>• Incontinence | • Critical care/suspected hypovolaemia (e.g. peri-operative colic cases, colitis etc..)<br>• Reduced urine production<br>• Weight loss, colic and/or subdued behaviour in the absence of localising signs<br>• Electrolyte disturbances |

*Table 1. Reasons for investigation of reno-urinary tract*

**Glossary**

***Anuria*** – absence of urine production. A cardinal sign of acute renal failure and generally indicating acute renal injury.

***Oliguria*** – decreased urine production. Also a sign of acute renal failure

***Haematuria*** – presence of blood in urine (easily confused with other causes of pigmenturia)

***Pigmenturia*** – discoloured urine. Generally representing whole blood (haematuria), haemoglobin (haemoglobinuria) or myoglobin (myoglobinuria) although other causes include bilirubinuria or simply from high urinary concentration as a normal response to dehydration.

***Hyposthenuria*** (typically <1.008) – urine is more dilute than plasma indicating that the kidneys are actively excreting water. Typical of excess water intake (e.g. Primary [psychogenic] polydipsia) or failure of urinary concentrating mechanisms (e.g. diabetes insipidus).

***Isosthenuria*** (typically 1.008-1.014) – urine is of similar concentration to normal plasma indicating that the kidneys are neither concentrating the urine nor excreting water. This could be an indicator of renal failure or might just reflect a normal water balance at the time of sampling.

***Hypersthenuria*** (typically >1.015) – this is a normal situation where urine is more concentrated than normal plasma indicating that the kidneys are actively reabsorbing water and excreting metabolic by-products.

***Pollakiuria*** – frequent passage of small amounts of urine. Frequent voluntary voiding of small amounts of urine should be differentiated from simple overflow from a paralysed bladder.

***Dysuria*** – difficulty passing urine

***Stranguria*** – straining to pass urine

## OWNER-REPORTED PROBLEM 1: Increased drinking and urine production

Polyuria and/or polydipsia (PU/PD) are probably the most common owner-reported clinical signs of reno-urinary dysfunction. Intuitively water intake must be equally balanced by water losses otherwise progressive over hydration or dehydration will occur. Water intake is primarily by drinking although grazing will contribute a significant proportion of water intake in grazing horses (fresh grass typically >80% water). Metabolic production of water also contributes a small fraction. Water losses in normal horses are primarily by faecal output that typically accounts for 50-75% of water losses. Urinary losses comprise less than half of water losses with a further minor contribution from sweat and respiratory evaporation.

PU/PD is probably under-recognised in grazing horses, but is usually immediately obvious when horses are stabled for significant parts of the day as bedding is excessively wet and water buckets are emptied. ***Typical water intake for adult horses is between 4-6% BWT/day (40-60 mL/kg; 20-30 L per 500 kg)*** although could be as low as 1-1½% BWT in normal grazing horses or as high as 8-9% BWT in lactating mares, horses in hard work and in hot environmental conditions. Polydipsia in adult horses can be defined by water consumption >10% BWT daily (>100 ml/kg; 50 L per 500 kg) although lesser intakes (>7.5% BWT daily) might sometimes be judged excessive depending on the managemental, dietary and physiologic conditions.

Although harder to quantify than water intake, ***normal urine production is typically between 1½ - 3% BWT daily (15-30 mL/kg; 7½-15 L per 500 kg)*** and polyuria is usually defined as urine production >5% BWT daily (>50 mL/kg; 25 L per 500 kg). Urine can be collected and quantified in male horses by tying a plastic container underneath the prepuce (e.g. an inverted 2 litre plastic milk container with the bottom removed), which is then emptied periodically to collect the accumulated urine.

When investigating suspected PU/PD you should first consider possible normal physiologic responses as listed in table 2. Pathologic causes (table 3) should then be considered and investigated in a logical fashion as detailed below.

| Polydipsia | Polydipsia and Polyuria | Polyuria |
|---|---|---|
| • Lactation<br>• Heavy exercise<br>• Hot weather | • High protein diet<br>• High salt diet | • Alpha-2-agonist sedatives |

*Table 2. Physiologic considerations to explain polydipsia and polyuria*

**Common causes**

- Primary (psychogenic) polydipsia
- Pituitary pars intermedia dysfunction (PPID)

**Uncommon and rare causes**

- Chronic renal failure
- Liver failure
- *Diabetes mellitus*
  - *type I*
  - *type II*
- *Diabetes insipidus*
  - neurogenic (central)
  - nephrogenic (renal)

*Table 3. Pathologic causes of PUPD in adult horses*

The vast majority of adult horses with polydipsia and polyuria will be found to be affected by primary (psychogenic) polydipsia or pituitary *pars intermedia* dysfunction (PPID) or. The latter is more common in older horses whereas the former is seen more frequently in younger horses. Primary polydipsia has been attributed to boredom in stabled horses although in many cases no apparent cause is identified.

***Chronic renal failure*** (CRF) is rarely encountered in equine practice and, even when it is diagnosed, many affected horses do not suffer from noticeable PU/PD (weight loss is often the only clinical sign) (Schott et al 1999). ***Hepatic insufficiency*** may sometimes be associated with PU/PD. The cause is unknown but has been proposed to be as a result of failure of hepatic degradation of aldosterone leading to sodium retention and consequent stimulation of thirst to correct hyperosmolality (Durham et al 2003). ***Diabetes mellitus*** (DM) is defined as persistently increased plasma glucose concentrations (typically 7-18 mmol/L). The renal threshold for glucose in horses is probably between 9-12 mmol/L with PU/PD and glycosuria occurring when plasma levels exceed this range. Very rare equine cases of type 1 DM are reported in association with primary pancreatic disease. Most cases of diabetes mellitus (DM) in horses are type 2 and result from chronic insulin resistance generally associated with PPID (N.B. Not all PPID cases with PUPD have diabetes mellitus) (Durham et al 2009). ***Diabetes insipidus*** (DI) is very rare in horses but is reported either as a neurogenic (central) form associated with inadequate vasopressin (ADH) secretion or as a nephrogenic (renal) form associated with failure of the nephron to respond to vasopressin (Schott 2011). Central DI may be a result of PPID or other central neurologic disease (e.g. trauma or encephalomyelitis) and idiopathic cases are also reported. Nephrogenic DI may also be seen with PPID, hypercalcaemia (e.g. paraneoplastic disease), renal tubular damage (e.g. aminoglycosides, tetracyclines, NSAIDs etc.) and as a congenital hereditary problem in males.

The limited list of common differential diagnoses makes PU/PD an attractive problem to investigate in horses if a logical approach is followed (see below and figure 1).

**STEP 1. Quantify and confirm the presence of polydipsia (and polyuria?)**

It is both easier and diagnostically acceptable to verify and quantify water intake only. Quantification of urine production can be achieved but is less practical (see above). It is usual to quantify water intake in horses during a 24 hour period of being fully stabled.

- If water intake during 24 hours is >10% BWT (>100 mL/kg) then PD is confirmed and PU is almost inevitable.
- If water intake is 7-10% BWT (70-100 mL/kg) then PD may be suspected if there are no apparent physiologic causes (see table 2).

**STEP 2. Initial simple blood and urine tests**

The simple panel of blood tests in table 4 can be used to rule in or rule out several differential diagnoses. ***Polycythaemia*** may indicate dehydration and failure to control urine output (e.g. diabetes insipidus) whereas ***anaemia*** might result from chronic renal failure for example. Increased serum ***urea*** and ***creatinine*** are highly sensitive indicators of chronic renal failure and ***gamma-glutamyltransferase*** is highly sensitive for liver disease. Serum ***calcium*** (preferably ionised fraction) is increased in many cases of chronic renal failure and plasma ***glucose*** will be increased in diabetes mellitus. Basal plasma ***ACTH*** (or ACTH response to TRH) are the currently recommended tests for PPID.

- Haematology
- Urea
- Creatinine
- GGT
- Calcium (ionised)
- Glucose
- ACTH

*Table 4. Initial simple blood tests*

Urinalysis is also important as part of the initial assessment. When catheterised urine samples are obtained, consideration of the effects of sedation is important. $\alpha_2$ agonist sedatives (detomidine, xylazine, romifidine) have acute diuretic, hyperglycaemic and glycosuric effects. The diuretic effect is unlikely to alter the concentration of the subsequently collected urine sample as a few millilitres of most recently produced dilute urine should not significantly affect the concentration of a litre or so of accumulated urine already in the bladder. However, even a small amount of glycosuria might confuse diagnostic interpretation. Hence acepromazine (5-10 mg/100 kg iv) perhaps supplemented by a nose twitch or a small dose of detomidine (0.5 mg/100 kg iv) should be used as necessary in geldings, taking care not to over-interpret mild glycosuria. In mares the use of stocks or a stable door may avoid the need for sedation.

***Urine Specific gravity*** (USG) should be measured by refractometer rather than on dipsticks. Most normal horses will have USG between 1.020 and 1.040. It is useful to compare the USG

to the expected SG of filtered plasma entering the glomerulus (which is between 1.008-1.014).

- ***SG <1.008 (hyposthenuria)*** suggests that the kidney is actively excreting water and is typical of primary (psychogenic) PD and diabetes insipidus.
- ***SG between 1.008-1.014 (isosthenuria)*** suggests that the kidney is neither actively concentrating nor diluting the filtrate and is consistent with (but not diagnostic for) chronic renal failure. Other causes of PU/PD might coincidentally happen to fall in the isosthenuric range. Therefore, when isosthenuric samples are obtained, serum urea and creatinine should be checked to rule in or rule out possible chronic renal failure.
- ***SG ≥1.015 (hypersthenuria)*** indicates that the kidney is actively concentrating urine although ***SG ≥1.020*** is usually regarded as more convincing of good renal concentrating ability and therefore ruling out diabetes insipidus or chronic renal failure.

***Glycosuria*** indicates diabetes mellitus, and usually PPID, although other causes of *diabetes mellitus* are rare possibilities (N.B. acute stress or $\alpha_2$ agonist sedatives also cause hyperglycaemia and glycosuria).

**STEP 3. Partial Water Deprivation Test**

On the basis of the simple tests in STEP 2 it should be possible to confirm/rule out most differential diagnoses in table 3 including chronic renal failure, *diabetes mellitus*, PPID and liver disease. This commonly leaves 2 further differential diagnoses: ***primary (psychogenic) polydipsia*** (common) and ***diabetes insipidus*** (rare). These 2 conditions can be differentiated by investigating the ability of the horse to produce concentrated urine when water access is limited. Renal concentrating ability is lost with diabetes insipidus. Horses with primary polydipsia have kidneys that are capable of concentrating urine although it is not uncommon that this capability is temporarily lost due to washout of medullary electrolytes which help maintain an osmotic concentration gradient. This ability is generally regained within a day or two of preventing washout by restricting water intake. Although response to total water deprivation can be assessed, it is usually safer and more informative to conduct a partial water deprivation test which allows restoration of renal concentrating ability in cases of primary polydipsia. ***Thus, the simple object of the partial water deprivation test is to establish whether or not the horse can produce concentrated urine: psychogenic polydipsia cases can; diabetes insipidus cases cannot.***

Important prerequisites for this test are firstly, that other differential diagnoses are ruled out (uncommon and rare causes, table 3), especially chronic renal failure (must have normal serum urea and creatinine concentrations); and secondly, that urine must be hyposthenuric (<1.008) (otherwise unlikely to be primary polydipsia or diabetes insipidus).

The test procedure is as follows:

1. Weigh horse accurately (if possible)
2. Take baseline urine sample and measure USG (should be <1.008 in suitable cases)
3. Keep the horse stabled and allow 1.0-1.2% BWT aliquots of water (e.g. 5-6 L per 500 kg) every 6 hours for up to 2-3 days.

4. Examine for clinical signs of dehydration and check serum urea and creatinine and USG at least every 6 hours (and reweigh if possible).

The test should be stopped and the horse allowed to drink if any evidence of dehydration/hypovolaemia is detected such as concerning clinical signs (sunken eyes, tacky membranes, dark membranes, long capillary refill, increased skin tenting); serum lactate, urea and/or creatinine increase above laboratory reference limits; or there is a ≥5% reduction in bodyweight.

If no concerning evidence of dehydration develops then the test continues until USG increases above 1.020, confirming renal concentrating ability, and therefore primary polydipsia as a concluding diagnosis. If the test has to be curtailed, leading to suspicion of diabetes insipidus, then the further tests in STEP 4 are indicated.

**STEP 4. Further investigation of suspected diabetes insipidus**

Diabetes insipidus can arise from failure to secrete vasopressin (central) or failure of the nephron to respond to vasopressin (renal). In response to water deprivation above, a modest increase in serum vasopressin to typically between 4-8 pmol/L is expected (normal serum vasopressin in euhydration: 1-2 pg/mL or 1-2 pmol/L [pg/mL → pmol/L x 0.926]), but can be much higher (eg >20 pmol/L). Low resting vasopressin concentrations and failure of an increase in response to water deprivation imply **central *diabetes insipidus*** with secretory failure. Normal horses and those with primary (psychogenic) polydipsia or nephrogenic *diabetes insipidus* cases would be expected to have normal resting vasopressin concentration and increased concentrations in response to water deprivation.

The vasopressin (vasopressin) response test is used to differentiate central from renal (nephrogenic) forms of diabetes insipidus. The test involves intravenous administration of 20 micrograms desmopressin (equivalent to 80 IU vasopressin) followed by monitoring USG over the subsequent 8 hours. The aim of the test is to confirm suspected ***nephrogenic diabetes insipidus*** and can only be interpreted usefully when preceded by partial water deprivation testing with the dual findings of failure to concentrate urine (implying diabetes insipidus) *and* increased serum vasopressin after water deprivation (ruling out central diabetes insipidus). Horses with nephrogenic *diabetes insipidus* show little to no response to vasopressin administration whereas central diabetes insipidus cases will respond with increasing USG during the test (as would normal horses or those with primary polydipsia).

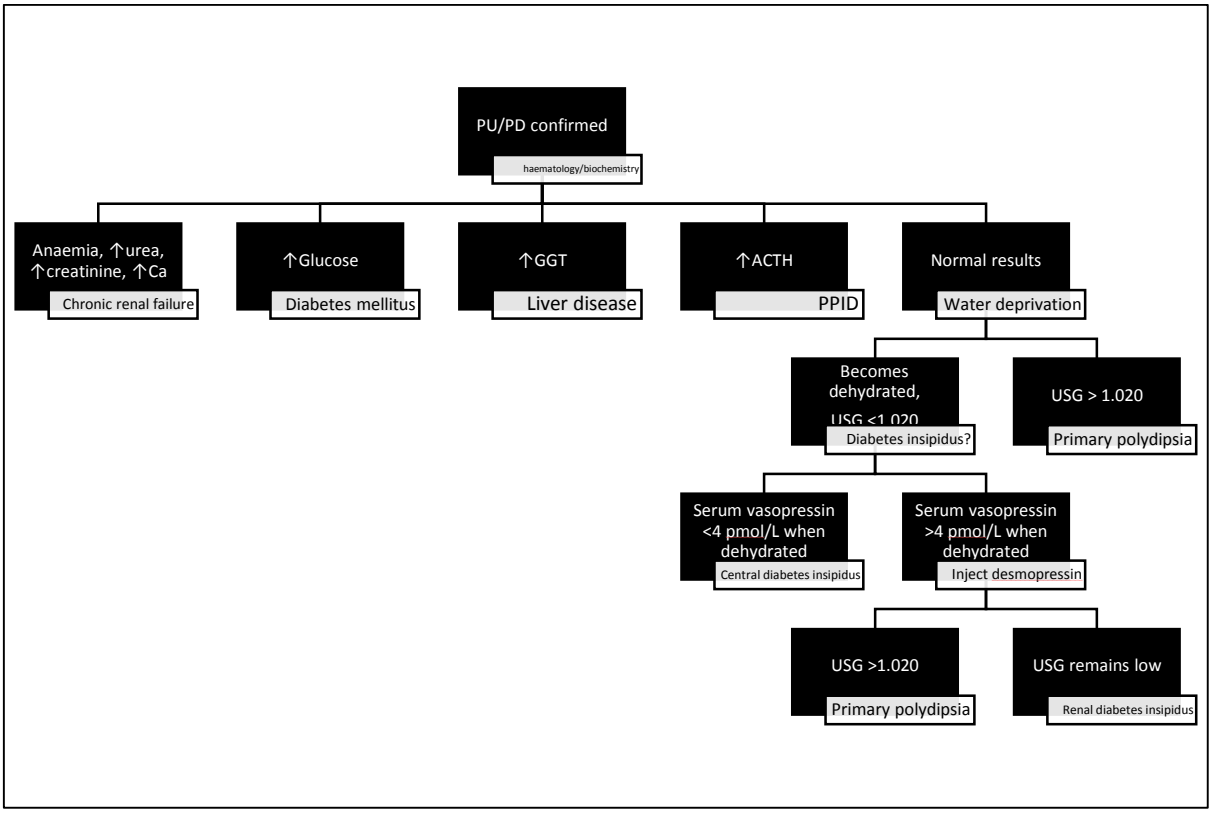



*Figure 1. Flow chart outlining logical protocol for investigating polydipsia and polyuria (see text for further details).*

## OWNER-REPORTED PROBLEM 2: Discoloured urine (pigmenturia/haematuria)

Investigation of discoloured (typically red-brown) urine should begin with logical consideration of the primary differential categories, comprising haematuria, haemoglobinuria, myoglobinuria and excessively concentrated urine. It should be remembered that the "blood" indicator square on urinary dipsticks will return a positive result for blood, haemoglobin or myoglobin. Myoglobinuria is expected to be seen in association with clinical signs consistent with acute myopathy as well as increased serum concentrations of AST, LDH and CK. Haemoglobinuria occurs with acute haemolysis with associated anaemia and perhaps hyperbilirubinaemia. Highly concentrated urine (>1.050) will not cause a positive "blood" reaction on urinary dipsticks but will probably show a protein positive result. When haematuric urine samples are centrifuged, the supernatant should clear whereas haemoglobinuria or myoglobinuria should not. Urinary sediment should then be checked with microscopy to see if whole blood cells are present. Differential diagnoses for the three categories should then be considered and explored further (table 5).

| HAEMATURIA | HAEMOGLOBINURIA | MYOGLOBINURIA |
|---|---|---|
| • Urolithiasis (usually bladder)<br>• Cystitis<br>• Pyelonephritis<br>• Reno-urinary neoplasia<br>• Urethral tear (stallions)<br>• Idiopathic renal haemorrhage | • Immune mediated haemolysis<br>  • idiopathic<br>  • penicillin induced<br>  • paraneoplastic<br>  • neonatal isoerythrolysis<br>• Toxins/drugs<br>• Liver failure<br>• DIC<br>• Infectious<br>  • *Babesia/Theileria*<br>  • Equine Infectious Anaemia<br>  • *Anaplasma*<br>  • *Leptospira* | • Acute myopathy<br>  • Exercise-associated<br>  • RER<br>  • PSM<br>  • Non-exertional<br>  • Seasonal pasture-associated myopathy<br>  • White muscle disease |

*Table 5. Main differential diagnoses for pigmenturia*

Further investigation of haematuria is aided by cystoscopy. This is a simple procedure that can be conducted under sedation (e.g. acepromazine plus alpha-2-agonist) using an endoscope at least 1.1 m long (in stallions and geldings). Rare reports exist of collapse and possible death during the procedure due to air embolism following inflation of the bladder to aid visualisation. The true risk of this serious complication has not been quantified although the problem may be avoided by using water, saline or carbon dioxide to inflate the bladder rather than simple air, especially if mucosal compromise is expected. Cystoscopy offers an excellent view of the bladder and ureteral openings. Noting uni- or bilateral ureteral pigmenturia is useful as haemoglobinuria an myoglobinuria will be bilateral whereas renal haemorrhage will most likely be unilateral. The urethra is harder to examine due to contractions around the endoscope although slow withdrawal should allow an adequate examination.

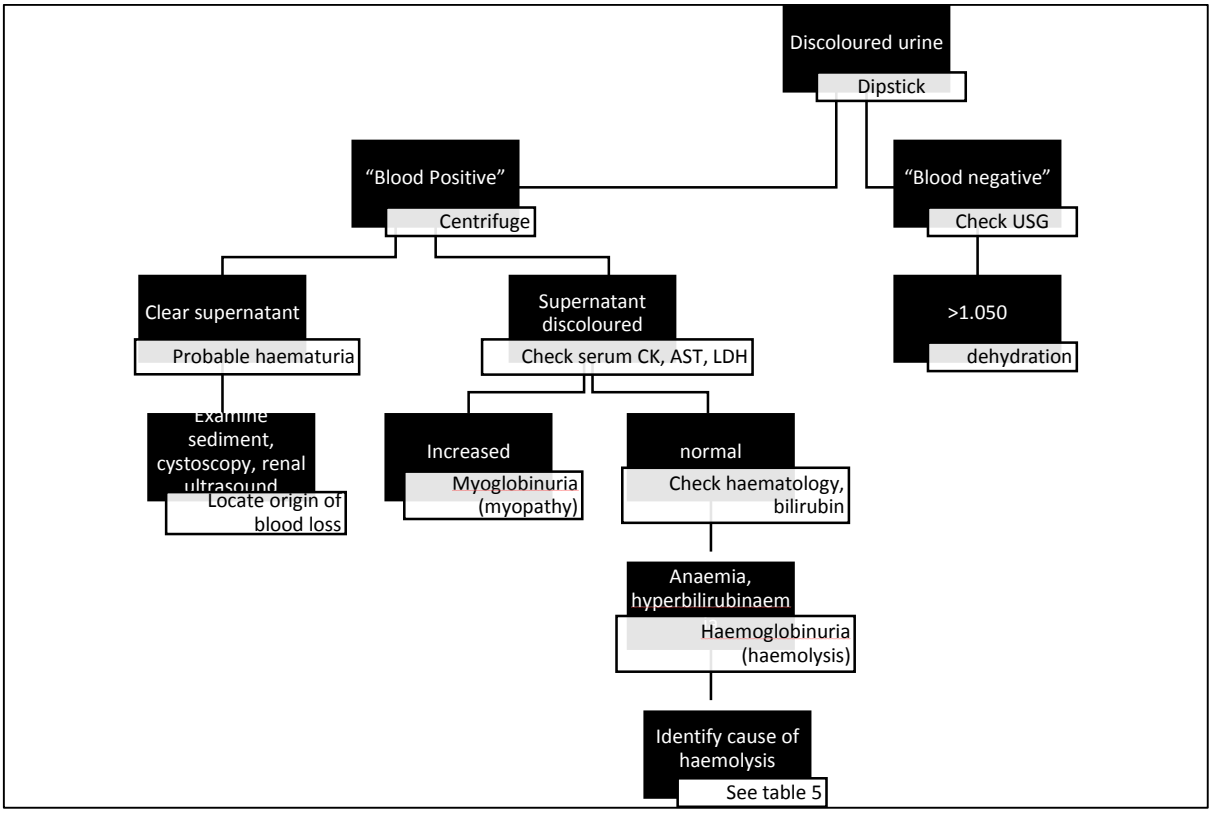



*Figure 2. Flow chart outlining logical protocol for investigating discoloured urine (see text for further details).*

**OWNER-REPORTED PROBLEM 3: Discomfort associated with urination (dysuria/stranguria, pollakiuria)**

This is uncommonly encountered in adult horses although can indicate problems such as urolithiasis, cystitis, bladder/urethral neoplasia or local inflammation (urethra, vagina). Local visual (speculum), ultrasonographic and endoscopic examination should be diagnostic. Cystitis is uncommon in horses but when it occurs it tends to be in females. Urinary examination and culture should reveal numerous neutrophils as well as bacteria. In contrast, urolithiasis tends to occur in the bladder of mature geldings and stallions (Duesterdieck-Zellmer 2007). Due to the spiculated surface of bladder calculi in horses (invariably calcium carbonate), gross or microscopic haematuria tends to be present, especially after exercise.

**OWNER-REPORTED PROBLEM 4: Urinary Incontinence**

Somatic, sympathetic and parasympathetic systems are all important in supplying motor innervation to the bladder.

- **Somatic motor** innervation providing conscious control of the urethral sphincter is provided via the pudendal nerve (S2-S4).
- **Sympathetic** innervation derives from spinal cord segments L1 to L4 with preganglionic fibres synapsing at the caudal mesenteric ganglion, joining the paired hypogastric nerves and passing via the pelvic plexus to supply inhibitory innervation

to the detrusor muscle ($\beta_2$-receptors) and stimulatory innervation to the proximal urethra ($\alpha_1$- and $\alpha_2$-receptors).

- **Parasympathetic** preganglionic neurons derive from the sacral spinal cord (S1-S3), combining to form the pelvic nerve, and synapse either within the pelvic plexus or within the bladder wall to supply stimulatory innervation to the detrusor muscle. Sensory neurons in the bladder wall that respond to stretch or pressure have axons within the pelvic nerve and sacral spinal nerves and enter the sacral cord to communicate with motor neurons in response to bladder fill.

Lower motor neuron lesions either result in a bladder that is atonic and distended (bladder paralysis due to damage to parasympathetic neurons) or result in reduced contractility of the proximal urethra (damage to the pudendal nerve, or sympathetic neurons). Typically overflow incontinence follows with continual dribbling of urine and a bladder that empties easily on application of manual pressure *per rectum.* Should somatic or α-adrenergic sympathetic innervation remain intact then the bladder may become distended and atonic without emptying easily; however, this scenario appears uncommon. Following motor paralysis reflex micturition may still occur whilst the detrusor muscle remains healthy although emptying will never be complete and sabulous material may accumulate eventually leading to stretching and damage to the detrusor muscle and a common end-stage combination of neuromyopathy.

**Differential diagnoses for incontinence**

The most common causes of urinary incontinence are listed in table 6. Most of these problems are neurogenic preventing bladder emptying and leading to overflow incontinence with a full bladder. Such cases may or may not present with more diffuse signs of cauda equina neuropathy such as reduced tail/anal/perineal tone/sensation, rectal paralysis/faecal retention, penile paralysis, hind limb ataxia/paresis and gluteal muscle atrophy. In addition to neurogenic incontinence, consideration should also be given to urethral/bladder irritation/obstruction due to inflammation or masses that might contribute to incontinence in the absence of bladder paralysis.

- Sacro-coccygeal trauma/fracture
- Idiopathic bladder paralysis ("sabulous cystitis")
- Urolithiasis
- Cystitis/urethritis
- EHV1 myeloencephalitis
- *Polyneuritis equi*
- Equine Protozoal Myeloencephalitis (imported horses)
- Sacral spinal neoplasia (e.g. melanoma, squamous cell carcinoma)
- Sacral spinal abscessation (e.g. *Rhodococcus equi, Streptococcus equi*)
- Ectopic ureters

*Table 6. Main diagnostic considerations of urinary incontinence in horses*

Rearing, falling and getting stuck under gates/partitions/horse-walkers are common causes of sacral injury, luxation and fracture in horses. Depending on the fracture site, different cauda equine neuropathy signs may be shown including bladder paralysis. Diagnosis is via a combination of history, neurologic examination, rectal palpation, radiography, scintigraphy

and ultrasound. Lumbosacral tap may indicate haemorrhage. Surgical fixation is reported although most cases tend to be managed conservatively and can sometimes result in significant improvement in neurologic deficits over 1-3 months post injury.

Idiopathic bladder paralysis is frequently referred to as sabulous cystitis due to the clay-like (really a misnomer as sabulous means sand-like) sludge invariably present in a distended and paralysed bladder. The condition is assumed to represent the end-stage of a range of conditions that result in incomplete emptying of the urinary bladder such as neurological disease or musculoskeletal disease (e.g. back pain) that inhibits normal posturing for urination. Crystalloid material, mostly calcium carbonate, is a normal constituent of equine urine and will form an ever-progressing sediment if the bladder fails to empty completely during urination. Cystitis often accompanies accumulation of sludge and is assumed to result from constant irritation of the mucosa by the crystalloid material and/or ammoniagenesis by urease-producing bacteria protected within the static deposit. Stretching and inflammation of the bladder wall may have a deleterious effect on the detrusor muscle leading to a spiral of decreasing bladder function, crystalloid accumulation and a combined neuro-myopathy. Urinary incontinence and sabulous cystitis have been associated with a grave prognosis especially as they are often accompanied by urethral sphincter and detrusor dysfunction by the time diagnosis is made. However, horses with urinary incontinence and sabulous cystitis can be managed successfully.

Treatment options for end-stage neuro/myogenic bladder dysfunction are similar regardless of cause; the aim being to encourage bladder emptying whilst hoping for spontaneous recovery, or at least an improvement, as reflex neurological activity develops (Rendle et al 2008). The primary method of treatment is endoscopically guided removal of sediment by saline lavage facilitated by the use of a suction pump. Removal of sediment frequently appears to improve bladder function possibly due to a reduction in resistance to detrusor contraction and/or removal of inflammatory stimuli. Bethanechol chloride is a parasympathomimetic drug that acts predominantly on the smooth muscle of the bladder and gastrointestinal tract when administered at low doses. Dose rates of 0.025-0.075 mg/kg subcutaneously q 8h or 0.25-0.75 mg/kg per os q 6-12h have been recommended. The occurrence of significant detrusor myopathy secondary to chronic stretching is thought to prevent the drug from having any beneficial effects and response tends to be poor to non-existent in most cases. Alpha-adrenergic blocking agents such as phenoxybenzamine and skeletal muscle relaxants such as diazepam and dantrolene have been suggested to relax the urethral sphincter encouraging bladder emptying. While these treatments may be effective in upper motor neurone paralysis there is little indication for their use in the apparently more common lower motor neurone paralysis or end-stage disorders with detrusor dysfunction.

Particular strains of EHV1 associated with an especially high magnitude of viraemia, and therefore a greater likelihood of spread to the brain and spinal cord, are associated with neurologic disease (Lunn et al 2009). This may occur either as an outbreak or may affect only one individual on a premises. Pregnant and lactating mares appear to be especially susceptible and foals and young horses appear less susceptible than older adult horses. Non-specific signs typical of many viral infections – lethargy, pyrexia, nasal discharge, cough, leg

oedema – are often seen in affected and/or in contact horses prior to neurologic signs but this is not always the case. Additionally other signs attributable to EHV1 infection such as abortion and neonatal death may precede an outbreak. Hindlimb ataxia and weakness are the commonest signs progressing to recumbency in some cases. Generally neurologic signs do not progress beyond 24-48 hours after onset. Other *cauda equina* signs such as loss of tail tone, anal tone, faecal and urinary retention/incontinence are common. Most commonly horses with EHV1 myeloencephalitis show signs of *cauda equina* disease but multifocal distribution of neurologic deficits is possible including forelimb gait deficits, cranial nerve signs, vestibular signs and cerebral signs such as blindness and depression.

Firm diagnosis of EHV1 myeloencephalopathy is often difficult. Clinically, severe ataxia and weakness along with other signs of *cauda equina* disease (especially as an outbreak) is suggestive of EHV1 myeloencephalitis as the major differential diagnoses of sacral trauma and polyneuritis equi tend not to have marked limb signs. Xanthochromia is usually seen in CSF but this is not specific and could reflect spinal trauma for example. Demonstration of a 4 fold increase in serum antibodies over 10-14 days is considered diagnostic but is a) retrospective, and b) not found in all cases. A negative/low titre in the acute phase of disease is unusual but does not rule out the condition. Virus isolation in nasopharyngeal swabs or heparinised blood samples (affected horse and/or in contacts) is also recommended but may fail to detect virus in some cases.

Polyneuritis equi is a rare condition considered to be caused by a combination of inflammatory and immune mediated reactions resulting in granulomatous neuritis. The *cauda equina* is most commonly affected although many cases show distant nerve involvement including cranial, and rarely peripheral, nerves. Often an initial caudal and perineal hyperaesthesia and self trauma is seen and often interpreted as tail pruritus (sweet itch). The affected area gradually becomes less sensitive and eventually insensitive along with development of tail weakness, loss of anal tone, penile prolapse, faecal retention and urinary incontinence. Hind limb gait deficits and perhaps muscle wastage may be seen but are rarely very prominent. Occasionally other neuropathies are seen such as asymmetric deficits of cranial nerves including trigeminal (V), facial (VII) and vestibulocochlear (VIII). Other cranial nerves might also rarely be affected (eg II, III, VII, IX, X, XII) and occasionally also forelimb gait deficits are seen. Diagnosis is primarily a clinical one including ruling out the main differential diagnoses above (i.e. sacral trauma and EHV). Anti P2 antibodies have been of interest in the past but increased titres are not specific for PNE and are not easily available.

Problems 1 to 4 above represent the most common reasons why owners/carers present their horses for investigation of suspected reno-urinary disease. However, there is an additional set of circumstances where reno-urinary disease may not be manifestly obvious but nevertheless warrants specific monitoring and investigation and it behoves the attentive veterinary surgeon to identify such circumstances as outlined below.

**VETERINARY ALERT 1: Acute hypovolaemia and/or reduced urine output**

Horses with severe illness associated with problems such as colic, endotoxaemia and colitis are often typified by the presence or threat of hypovolaemia. Thus monitoring of the critical

care case frequently focuses on assessment of effective intravascular circulation. Many clinical markers such as heart rate, mucus membrane colour, capillary refill time, blood pressure and temperature of extremities are central to such monitoring although adjunctive clinicopathologic analytes are also important. Measurement of plasma lactate concentration probably represents the most popular means of assessment of hypovolaemia although as the kidneys receive a relatively high blood flow and represent the main mechanism for plasma water regulation, markers of renal perfusion and function are also very helpful in assessing the critical care case as well as being important to monitor to avoid secondary acute renal injury.

The most easily assessed and useful reno-urinary analytes indicating hypovolaemia and acute renal injury are USG and serum creatinine concentration and both tend to increase with hypovolaemia. Total urinary output would also be useful to monitor but is less easy to measure. Plasma creatinine concentration is inversely proportional to renal blood flow and glomerular filtration and values within reference limits are reassuring indicating that the kidneys are adequately perfused. Increased serum creatinine concentration is an indicator for urgent plasma expansion in the critical care case. However, although high USG (e.g. >1.040) is an indicator of hypovolaemia which should decrease in response to fluid therapy, lower USG values (e.g. isosthenuria) cannot always be taken as reassuring as they could indicate intrinsic renal failure to concentrate urine (in which case plasma creatinine will be increased).

Acute renal failure is typified by anuria or oliguria and it is important to remember that it is potentially reversible with urgent therapy (Geor 2007). Acute renal injury may arise most commonly from hypovolaemia and poor renal perfusion (pre-renal injury) and/or from direct insult to the kidney itself (table 7). Failure to excrete urine due to post renal disease is most common in neonates where bladder rupture is a well-known congenital complication of the parturition process. In contrast, bladder ruptures or urinary tract obstructions are rarely seen in adult horses.

| Pre-renal | Intrinsic renal | Post renal |
|---|---|---|
| • Hypovolaemia<br>  • colitis<br>  • colic surgery<br>  • endotoxaemia | • Drugs<br>  • NSAIDs<br>  • Aminoglycosides<br>• Myoglobin<br>• Haemoglobin<br>• Pyelonephritis | • Bladder rupture (foals)<br>• Urethral obstruction (rare) |

*Table 7. Examples of acute renal injury in horses (N.B. often multiple factors may coexist)*

In addition to increased serum creatinine, another useful marker of acute renal injury is enzymuria. Of several enzymes normally contained within renal tubular epithelial cells, gamma-glutamyl transferase (GGT) is generally favoured as an indicator of acute tubular injury. Urinary GGT concentration is usually similar to plasma concentration (e.g. 20-40 IU/L) although this analyte is best assessed after correcting for urine concentration by dividing urine GGT concentration (IU/L) by urine creatinine concentration (mmol/L).

*For example, normal equine urine might contain 25 IU/L GGT and 10,000 micromol/L creatinine.*

*GGT:creatinine ratio = 25/10 = 2.5 IU/mmol (typical reference limits up to 5.0 IU/mmol)*

*In a horse with acute tubular insult (e.g. a dehydrated acute myositis case with myoglobinuria having been treated with NSAIDs), the urine might contain 105 IU/L GGT and 15,000 micromol/L creatinine.*

*GGT:creatinine ratio = 105/15 = 7.0 IU/mmol*

Electrolyte abnormalities are not uncommon in the face of acute renal injury. Hyperkalaemia, hyponatraemia and hypochloraemia are frequently seen.

Post-renal failure cases (typically bladder rupture in foals) should be treated by establishing urinary drainage and correcting electrolyte abnormalities and are discussed in greater detail elsewhere.

The most important response to acute pre-renal or intrinsic renal injury is to rapidly ensure good renal blood flow, using aggressive fluid therapy with isotonic electrolytes, and to re-establish normal urine production. Intravenous sodium chloride 0.9% is generally the fluid of choice; although if only Hartmann's or lactated Ringers is available then this will be satisfactory as the potassium content of such fluids is no higher than normal plasma concentrations (4 mmol/L) and will not potentiate hyperkalaemia if present. Colloid therapy with plasma would be acceptable (especially if hypoproteinaemic) although concerns regarding the potential for renal injury with hetastarch means that such fluids are probably best avoided. If urinary output is not observed within 2 hours of aggressive fluid therapy (e.g. 20 mL/kg BWT/hour; or 10 L/hour for 500 kg) then frusemide should be administered as boluses (2-4 mg/kg iv) or constant rate infusion (0.12 mg/kg loading dose followed by 0.03-0.24 mg/kg/hour; 60 mg bolus, then 15-120 mg per hour per 500 kg). Failure to produce urine for 12-24 hours represents a poor prognosis.

**VETERINARY ALERT 2: Weight loss, subdued behaviour, mild colic**

There are many potential causes for the clinical signs listed above. However, it is important to remember that chronic renal diseases may present in such a fashion in horses and that polydipsia and polyuria, which typify chronic renal failure in several other species, do not always occur (or are not noticed) in horses (Schott et al 1999). Chronic renal failure is not a problem that is commonly diagnosed in equine practice. When cases arise they may follow-on from known acute renal insults such as those discussed above, although more commonly an "end-stage" kidney is encountered without knowledge of inciting causes. Glomerulonephritis (immune-mediated), pyelonephritis and hydronephrosis (secondary to renal calculi) are all encountered occasionally. Renal neoplasia is rare in horses and when seen does not tend to cause renal failure due to unilaterality with a normally functioning contralateral kidney.

Increased serum concentrations of creatinine and urea are invariably present in chronic renal failure and most cases are also hypercalcaemic, anaemic and hypoproteinaemic. Urine is typically isosthenuric and may contain excessive concentrations of protein (>5 g/L). Other abnormalities such as traces of blood or leucocytes might also be seen in the urine as well as enzymuria. Ultrasound might indicate hyperechoic and/or small kidneys and, not infrequently, secondary renal calculi.

Renal biopsy might be considered for a more specific diagnosis and grading of disease. However, this is a highly specialised and potentially dangerous technique and a careful risk-benefit assessment should be performed and discussed with the owner. Colic (usually mild) and haematuria are common post biopsy. As chronic renal failure invariably affects both kidneys, the right kidney is usually selected for biopsy due to its more superficial position. A 10-15 cm, 14 gauge biopsy needle is used under real-time ultrasound guidance to minimise risks.

In the absence of biopsy then urinary examination can be used to guide therapy – e.g. many leucocytes in the urine might indicate infection and antimicrobial therapy and high urinary protein might indicate glucocorticoid therapy in case of glomerulonephritis. Fluid therapy is generally indicated in the early stages of treatment in order to help reduce azotaemia. Long term prognosis is guarded although many horses will stabilise with a mild to moderate azotaemia remaining. Careful attention to water intake is important and dietary provision that will not potentiate hypercalcaemia but nevertheless provides adequate protein to limit catabolism.

**VETERINARY ALERT 3: Electrolyte Disturbances**

As the main regulator of serum electrolyte concentrations, renal disease should always be considered when abnormal electrolyte concentrations are encountered. As previously mentioned hyperkalaemia, hyponatraemia and hypochloraemia are frequently seen in acute renal injury and hypercalcaemia is common in chronic renal failure.

***Renal tubular acidosis*** (RTA) is a rarely diagnosed problem where renal acid-base regulation becomes dysfunctional (Aleman et al 2001). Clinical signs are frequently vague including lethargy, inappetance and perhaps even mild colic. There are several forms of RTA which may have different electrolyte abnormalities although ***hyperchloraemia*** causing a metabolic acidosis is a consistent finding. Azotaemia is generally present but may be very mild.

***Urinary fractional electrolyte excretion rates ("Creatinine clearance ratios")*** are occasionally useful for investigation of renal function and/or electrolyte disturbances although are not terribly well validated and can produce inconsistent results. They are generally performed on simultaneously collected serum and urine samples. It is vital that serum is separated from the cellular fraction promptly as leakage of potassium and phosphate from dying cells will significantly alter serum electrolyte concentrations. For this test it is assumed (slightly incorrectly!) that the sole route of serum creatinine loss is the urine and that it is neither secreted nor absorbed by the kidney. Thus each electrolyte is compared with creatinine (nominally neither secreted nor absorbed) to give an impression of the renal handling of each electrolyte.

Assuming that creatinine is neither secreted nor absorbed by the kidney and that the sole route of loss of creatinine is via urine, then filtered creatinine should be equal to urinary creatinine:

***Glomerular filtration rate (GFR) x serum creatinine concentration ($S_{CR}$)*** *(=filtered creatinine)*

should be equal to:

***Urinary output x urine creatinine concentration ($U_{CR}$)*** *(=urinary creatinine)*

*or,* ***GFR x $S_{CR}$ = urine output x $U_{CR}$***

Rearranging this formula leads to:

***GFR = urine output x $U_{CR}/S_{CR}$***

(NB. this formula can be used to estimate GFR based on calculating the volume of a 24 hour urine collection, $U_{CR}$ of the collected urine and a mean $S_{CR}$ from several blood samples during the test: normal 1.5-4 ml/kg BWT/min and reduced in chronic renal failure cases)

If the same were true of an electrolyte "*E":* i.e. it was neither secreted nor absorbed by the kidney and that the sole route of loss was via urine, then:

***GFR = urine output x $U_{CR}/S_{CR}$ = urine output x $U_E/S_E$***

Solving this formula leads to:

***$U_{CR}/S_{CR} = U_E/S_E$***

or:

***($U_E$ x $S_{CR}$) / ( $S_E$ x $U_{CR}$) = 1 (or 100%) = urinary fractional excretion rate of "E"***

Thus values <1 (or <100%) signify active retention (ie reabsorption) of the electrolyte whereas values >1 (or >100%) signify active excretion. Typical normal values comprise:

| | | |
|---|---|---|
| *Na* | *0.03 – 0.5%* | *(ie 99.5 - 99.97% filtered Na is reabsorbed)* |
| *K* | *15 - 70%* | *(ie 30 - 65% filtered K is reabsorbed)* |
| *Cl* | *0.2 – 1.7%* | *(ie 99.8 - 98.3% filtered Cl is reabsorbed)* |
| *Ca* | *< 7%* | *(ie >93% filtered Ca is reabsorbed)* |
| *$PO_4$* | *<0.5%* | *(ie >99.5% filtered $PO_4$ is reabsorbed)* |
| *Mg* | *< 15%* | *(ie >85% filtered Mg is reabsorbed)* |

High values (signifying decreased reabsorption) are consistent with renal tubular failure (esp Na and Cl) although excessive electrolyte consumption should also be considered. Dietary electrolyte deficiency may be detected via certain patterns of clearance ratios, such as calcium deficiency triggering increased renal calcium resorption (increased clearance ratio) and phosphate excretion (low clearance ratio) due to the effect of parathyroid hormone.

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# Medical Problems in Geriatric Horses

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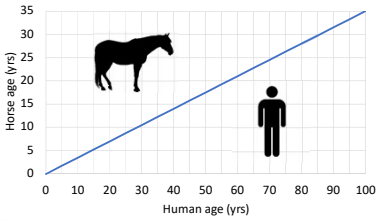
## What is a Geriatric Horse?

2.85 human years ≈ 1 horse year?

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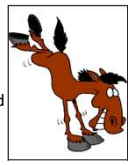
## National Animal Health Monitoring and Surveillance (NAHMS)

- 1998 NAHMS report
  - 1 in 13 horses >20 yrs old
- 2015 report
  - 1 in 9 horses > 20 yrs old


- of all horses that are over 20 yrs, 1 in 8 are over 30 yrs
- geriatric horses presenting to veterinary hospitals have increased by 55% in recent years
- > 50% of horses over 20 years are still actively exercised



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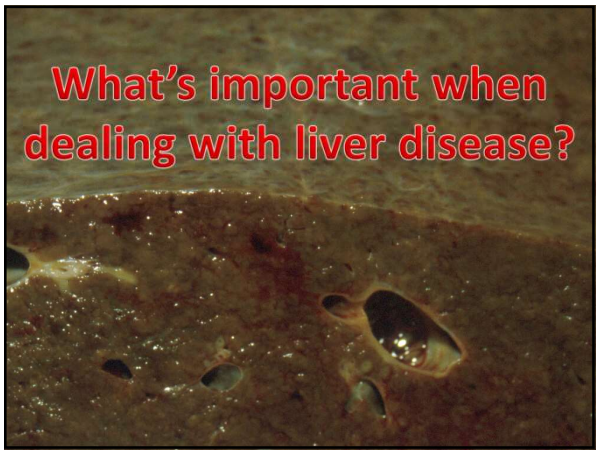


## Logical investigation of liver disease

| | |
|---|---|
| ***STEP 1*** | Liver disease is diagnosed from high serum enzyme concentrations (GGT, AST,GLDH) |
| ***STEP 2*** | Is there hepatic insufficiency? (bile acids, globulins, albumin) |
| ***STEP 3*** | Take blood samples to determine if a single horse/multiple horses are affected (usually multiple) |
| ***STEP 4*** | Take biopsy to determine severity/prognosis and confirm/excludesome specific causes (pyrrolizidine alkaloids, haemosiderosis, septic cholangitis, neoplasia….) |
| ***STEP 5*** | If cause is unclear from biopsy then consider forage mycotoxins and viral hepatitis |
| ***STEP 6*** | Change forage and administer medications according to histopathology findings |

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## How do you treat a lame horse?

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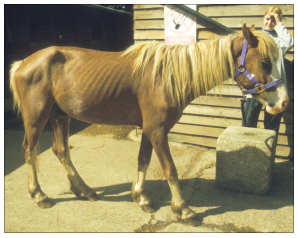
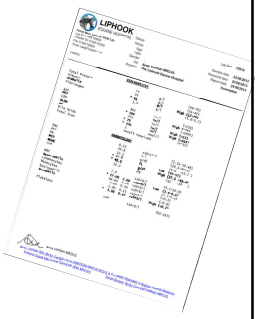
## How do you treat a horse with liver disease?

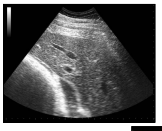




## How do you treat a horse with liver disease?

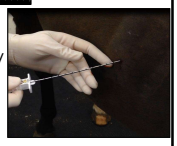
You need to know:

1. What exactly is wrong with the liver?
2. Is the damage reversible?
3. Are other horses affected too?



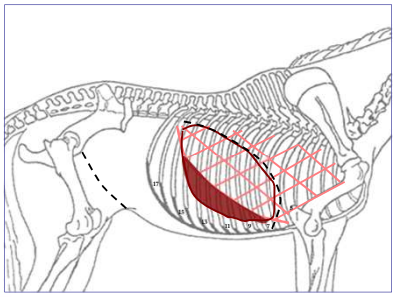
scan

biopsy

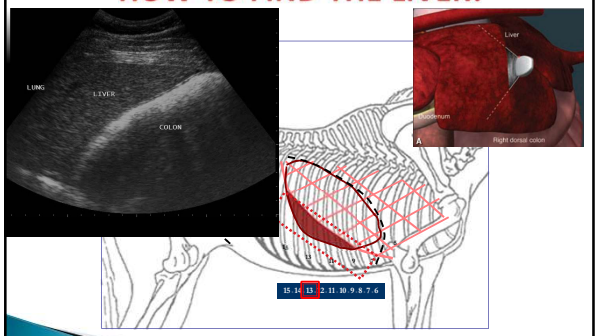


blood test herdmates

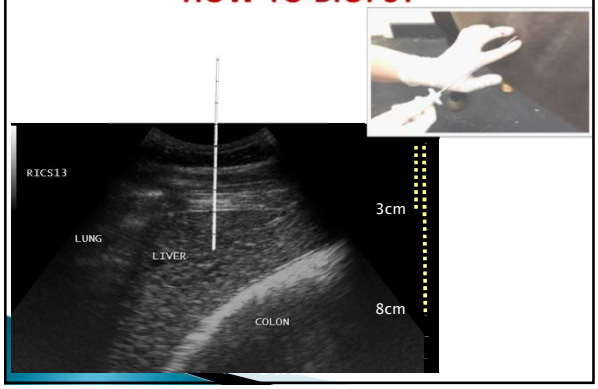
## HOW TO FIND THE LIVER!



## HOW TO FIND THE LIVER!




## HOW TO BIOPSY




## Adverse Effects of Biopsy?

**Evidence**

- Johns *et al* 2008
  - 33 liver biopsies
    - 19 (58%) had clotting abnormality
    - 3 showed decrease in PCV post biopsy
    - 1 showed diaphragmatic haematoma
  - No association with presence of clotting abnormality
  - No clinical adverse effects

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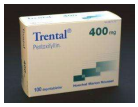
## Therapies – fibrosis

- prednisolone *1 mg/kg q24*
- azathioprine *3 mg/kg q24*
- pentoxyfylline *10 mg/kg q12*
- flavonolignans (sylimarin)?
- S-adenosyl-L-methionine?
- vitamin E *2-4 IU/kg q24*
- benazepril *0.25-0.5 mg/kg q 24*
- colchicine *0.03 mg/kg q 24*

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## Therapies – antiinflammatory

- prednisolone *1 mg/kg q24*
- azathioprine *3 mg/kg q24*
- pentoxyfylline *10 mg/kg q12*
- flavonolignans (sylimarin)?
- S-adenosyl-L-methionine?
- vitamin E *2-4 IU/kg q24*
- antimicrobials *(x 4-8 wk)*
- triclabendazole *15 mg/kg*



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## Therapies – iron removal

- Phlebotomy
  - 1.5% BWT q 2 weeks
- Desferoxamine??

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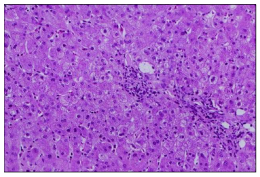
## So what are the common pathology of equine liver disease?

- occasional specific findings:
  - Septic cholangitis
  - Neoplasia
  - Haemosiderosis
  - Pyrrolizidine alkaloids



- ……but mostly not specific for the cause

e.g.
- *moderate non-septic periportal inflammation,*
- *mild biliary hyperplasia*
- *early portal fibrosis*
- *multifocal individual necrotic hepatocytes with neutrophilic infiltrates*

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## Hepatopathy Outbreaks

- Possible causes:
  - Toxicity
    - Pyrrolizidine alkaloids
    - Iron
    - Mycotoxins
      - (aflatoxins)
      - fumonisin B1
  - Infectious disease
    - *Fasciola hepatica*
    - Viral hepatitis
      - Non Primate Hepacivirus
      - Equine Pegivirus
      - Theiler's Disease Associated Virus


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## Key parts of a Hepatopathy Investigation

- Blood test herdmates
- Scan and Biopsy liver
- Consider causation - treatment doesn't work when the cause is still present!

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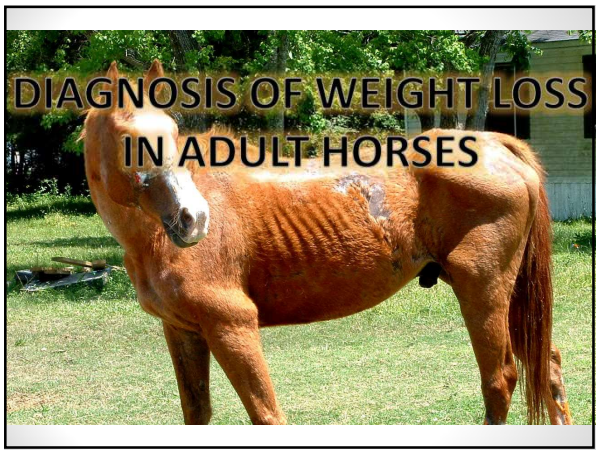
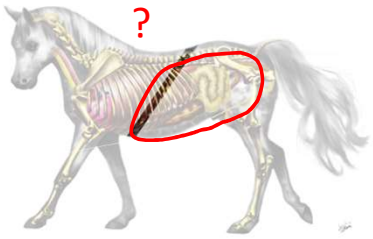



## Main differential diagnoses of non-specific weight loss




## Main differential diagnoses of non-specific weight loss

**Common**

- Protein-losing enteropathies
  - Parasitism
  - NSAID toxicity
  - Sand enteropathy
  - "Inflammatory Bowel Disease"
  - Infiltrative neoplasia
  - *Lawsonia intracellularis* (weanlings)
- Liver disease
- Chronic inflammation
  - Infections
  - Parasitism
  - Neoplasia

**Less common**

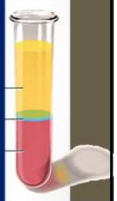
- Chronic renal failure
- Motor neuron disease
- Diabetes mellitus (PPID)

## Initial Chemistry Panel

| | |
|---|---|
| ▪ proteins | ⇨**protein loss, inflammation, liver** |
| ▪ AST | ⇨**liver, muscle** |
| ▪ γGT | ⇨**liver**, *(pancreatic), (intestinal?)* |
| ▪ AP | ⇨**liver, intestinal**, *(bone)* |
| ▪ CK | ⇨**muscle** *(myopathy, catabolism, recumbency)* |
| ▪ creatinine | ⇨**renal** *(dehydration or renal insufficiency)* |
| ▪ glucose | ⇨**stress, PPID, *diabetes mellitus*, $\alpha_2$ sedatives** |
| ▪ calcium | ⇨**renal failure, neoplasia** *(PTHrp)* |

## Serum Proteins

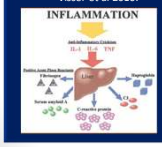
- Albumin *(29-40 g/L)*
  - ⇧ dehydration
  - ⇩ protein losses
    - nearly always gastroenteric
      - parasites, NSAIDs, sand, IBD, lymphoma,….
    - lost into effusion?
    - renal?
    - chronic inflammation?
    - rarely hepatic
- Globulins *(26-42 g/L)*
  - ⇧ inflammatory and/or hepatic

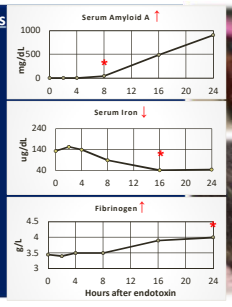


## Acute Phase Proteins

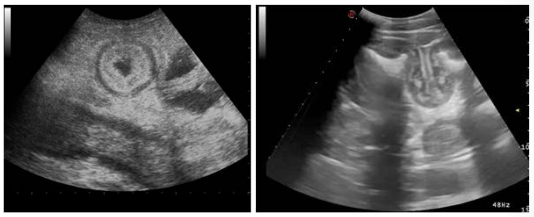
**Acute phase proteins**

- Serum Amyloid A
  - 1st choice?
- Iron *better than* fibrinogen
  - Borges *et al* 2007
  - Corradini *et al* 2014
  - Visser et al 2016:




## Ultrasound

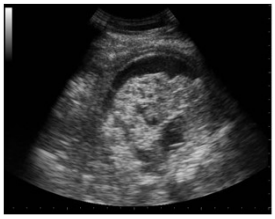


Thick jejunum

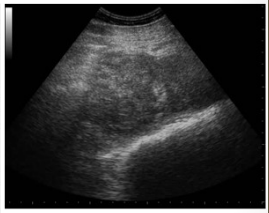


Thick colon

## Ultrasound



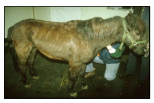
Colon adenocarcinoma

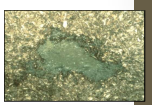


Hepatic carcinoma

## NSAIDs and the Colon

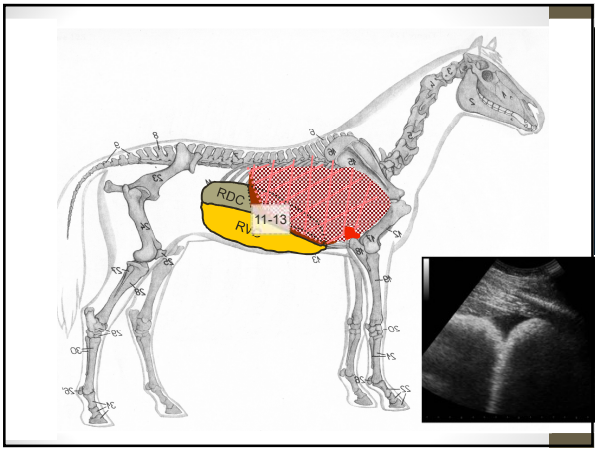
- right dorsal colon is the prime target for NSAID toxicity
- clinical signs
  - weight loss
  - oedema
  - depression
  - anorexia
  - colic
  - diarrhoea
  - oral ulcers





## NSAIDs and the Colon

- right dorsal colitis - diagnosis
  - "large intestinal protein losing enteropathy"
    - albumin ↓
    - globulins ↓ ↑
    - SAA ↑
    - iron ↓
    - alkaline phosphatase ↑

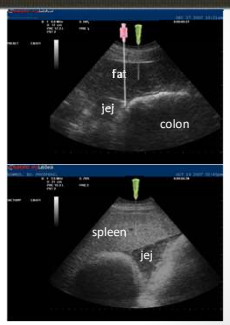



## Paracentesis

- Lowest point of midline abdomen?
- Choose site with ultrasound?
- Use:
  - 1½-2" 19g needle
  - 9cm spinal needle
  - 9 cm teat canula (local, #15 scalpel)
- Clip, scrub, (local anaesthetic?)

## Reasons for failure

- not deep enough (retroperitoneal fat)
- splenic penetration
- colonic penetration (enterocentesis)
- bad luck / very little fluid present

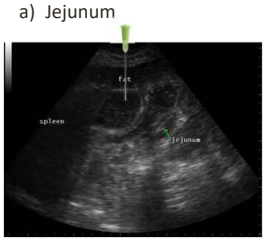




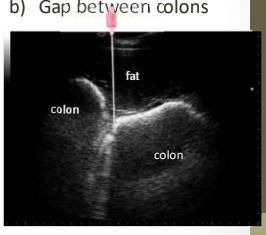



## Aim for:

a) Jejunum

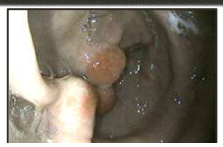



b) Gap between colons



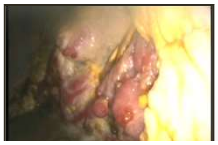

## Gastroscopy

*Severe squamous ulcers*



Pyloric nodules and inflammation

Gasterophilus larvae

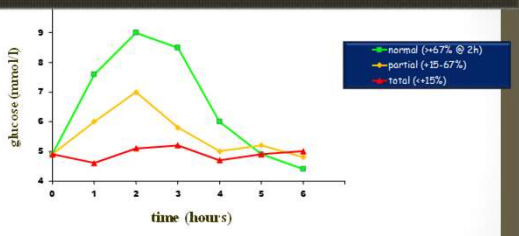


Gastric squamous cell carcinoma

## Oral Glucose Absorption

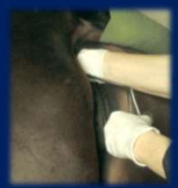
1. 12 hour fast (allow water)
2. Take 'baseline' OxF blood
3. Give 1g/kg glucose as warm 20% solution by stomach tube (ie. 0.5kg in 2½ litres for 500kg)
4. Take blood q30-60mins for at least 5 hours

## Oral Glucose Absorption



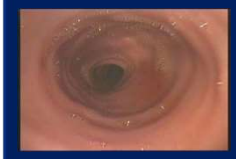

## Intestinal biopsy

- rectal mucosal biopsy
  - abnormal findings in 50% intestinal disease cases (Lindberg et al 1996)
  - NB mostly non-specific
  - NB. 30-35% cases had diarrhoea
  - requires very distal disease



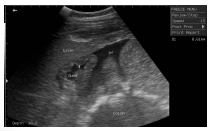
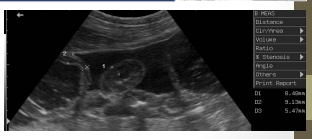
## Intestinal biopsy

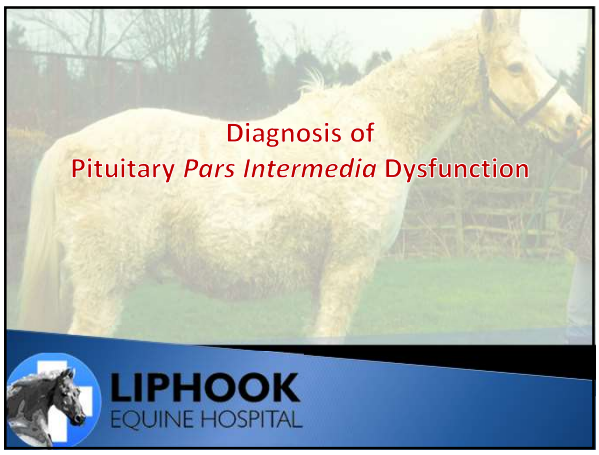
- duodenal mucosal biopsy
  - very small biopsies
  - crushed biopsies
  - requires very proximal disease
  - helpful only in a few cases (Brazil 2009, Recknagel 2010)



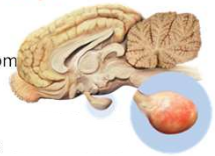

## Non-specific weight loss investigation

1. Mainly abdominal disease
2. Enteropathies commonest
3. Abdominal ultrasound very useful part of investigation



## What is pituitary pars intermedia dysfunction (PPID)?



- the *pars intermedia* is controlled by tonic inhibition from dopaminergic neurones from the hypothalamus
- in PPID there is decreased inhibitory dopaminergic input to the *pars intermedia*
- the consequence of loss of inhibition is:
  - hypertrophy→hyperplasia→adenoma
  - hypersecretion

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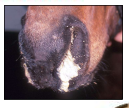
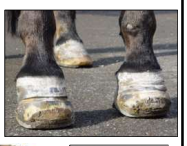
## Why is PPID a problem?

- Subclinical
- Excessive hair growth
- Susceptibility to laminitis
- Polydipsia/polyuria
- Lethargy
- Excessive sweating
- Susceptibility to infections
- Fat redistribution





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## Why is PPID a problem?

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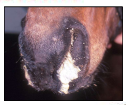

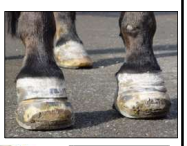

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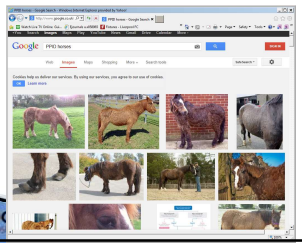
## Clinical signs and PPID

- do not expect all PPID cases to be old, hairy and drinking a lot
  - recognised from 6yo (mostly >10yo)
  - often the first (and only) signs are laminitis



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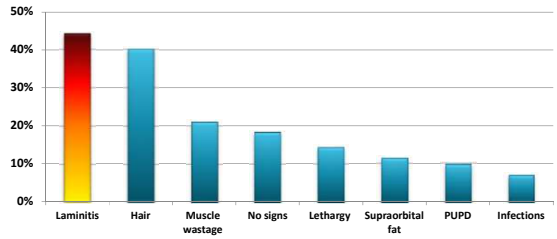
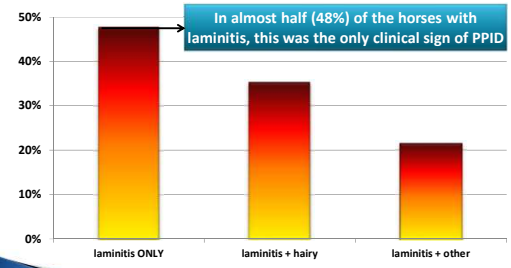
## Clinical signs of PPID

- 4623 PPID+ cases :




## Clinical signs of PPID

- 2045 PPID+ cases with laminitis:



## Basal plasma ACTH concentration

1. *Collect into EDTA tube*
2. *Chill sample within 3 hours of collection*
3. *Centrifuge as soon as possible*
4. *Keep chilled during shipping to laboratory*

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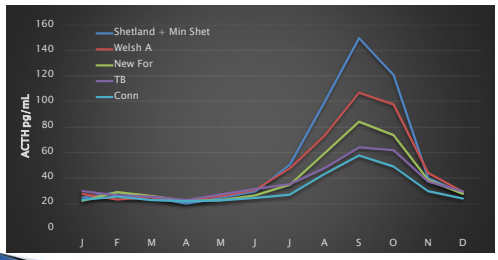
## Breed and ACTH

- Shetland/Miniature Shetland ponies > all other breeds July to October (P<0.01)
- Welsh section A ponies > TBs and Connemaras August to October (P<0.05)
- New forest ponies > Connemaras August to October (P<0.001)

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## Borderline or unexpected results

- with any slowly progressive disease it is inevitable that some results will be in the "grey-zone"
- how can you increase the accuracy of PPID testing?
- stimulation testing
  - Autumn (bio-stimulation test!)

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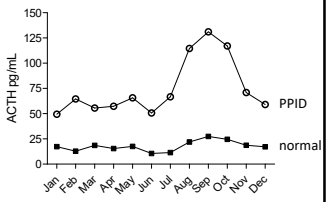
## Seasonality and ACTH

The autumnal rise in ACTH secretion:

- also occurs in horses with PPID
- is more marked in PPID cases than in normal horses

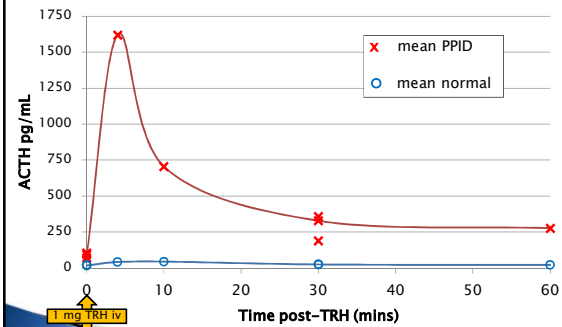



Copas & Durham 2012

## Borderline or unexpected results

- with any slowly progressive disease it is inevitable that some results will be in the "grey-zone"
- how can you increase the reliability of the test?
- stimulation testing
  - Autumn (bio-stimulation test!)
  - TRH stimulation test

## TRH stimulation test *(of ACTH)*




Data from: McFarlane et al 2005, Beech et al 2007,2011

EQUINE ENDOCRINOLOGY GROUP

http://sites.tufts.edu/equineendogroup/

Recommendation for interpretation of basal ACTH and TRH stimulation test

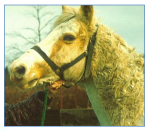
| Non-fall months: mid-November to mid-July | | | |
|---|---|---|---|
| | Negative | Equivocal | Positive |
| resting ACTH or time 0 | <30 pg/mL | 30-50 pg/mL* | >50 pg/mL |
| 10 min after TRH | <110 pg/mL | 110-200 pg/mL | >200 pg/mL** |

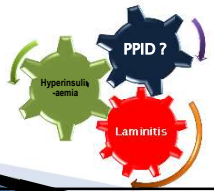
| Fall months: mid-July to mid-November*** | | | |
|---|---|---|---|
| | Negative | Equivocal | Positive |
| resting ACTH | <50 pg/mL | 50-100 pg/mL | >100 pg/mL |

using Immulite method

# Laminitis, insulin and PPID?

- PPID cases with insulin > 188 mU/L less likely to survive (McGowan *et al* 2004)
- Insulin concentration correlated with grade of laminitis (Walsh *et al* 2009)
- Change in insulin correlated with change in laminitis grade (Walsh *et al* 2009)



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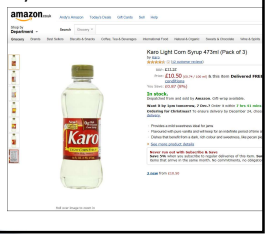
# Testing for Hyperinsulinaemia

- **PPID cases as well as EMS cases may be prone to laminitis because of an excessive insulin response to carbohydrate ingestion**
- ***Oral*** sugar challenge tests may directly mimic this effect
  - **Glucose/dextrose** (1 g/kg in chaff)
    - measure insulin and glucose 2 hr later
    - normal response < 81 mU/L
  - **Karo light corn syrup** (45 mL/100 kg)
    - measure insulin 60-90 mins later
    - normal response < 40 mU/L

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## Summary - PPID

- **Clinical**
  - not all cases show "end-stage" clinical signs
  - laminitis is a prominent problem
- **Diagnostics**
  - basal ACTH or TRH stimulation are preferred tests
  - don't forget insulin (may reflect laminitis risk)
- **Treatment** *(pergolide)*
  - recheck 30-60 days after starting treatment/increasing dose
  - when controlled, recheck every 3-6 months (including one check Aug-Oct)
  - if treatment response is poor, try adding cyproheptadine or just keep going!

## NUTRITION OF THE GERIATRIC HORSE

## CLINICAL NUTRITION OF THE GERIATRIC

**Major problems**

1. Poor mastication
2. Weight loss
3. PPID

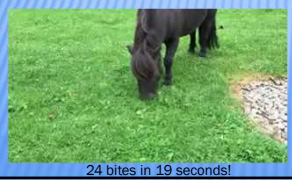
## CLINICAL NUTRITION OF THE GERIATRIC

| Major problems | Solutions / pitfalls |
|---|---|
| 1. Poor mastication | • diet that requires less chewing<br>• high starch/sugar diets cause GI problems |
| 2. Weight loss | • diet with higher energy density<br>• high starch/sugar diets cause GI problems |
| 3. PPID | • non-glycaemic diet<br>• non-glycaemic diets may have low energy |

↑energy - ↑fibre - ↓starch

## HOW MUCH DO HORSES EAT ?

- well, that depends……
- typically 2-3% BWT daily as DM (10-15 kg DM/500 kg)
- grazing ≈5%
- forage only ≈2%
- poor dentition 1-2%?



24 bites in 19 seconds!

## ENERGY REQUIREMENTS

| | daily DE (kJ/kg) | approx. MJ |
|---|---|---|
| **Adult maintenance BWT/7** | **127-152** | |
| **Adult light work** | **(M+20%)** | **BWT/6** |
| Adult heavy work | (M+100%) | |
| Early pregnancy | M | |
| Late pregnancy | (M+30%) | |
| Early lactation | (M+90%) | |

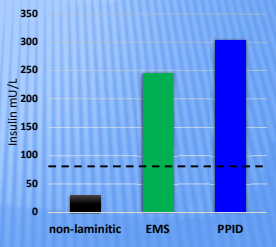
## PROTEIN REQUIREMENTS

| | daily CP (g/kg) |
|---|---|
| **Adult maintenance** | **1.25** |
| **Adult light work** | **1.5** |
| Adult heavy work | 2.0 |
| Early pregnancy | 1.25 |
| Late pregnancy | 1.8 |
| Lactation | 3.0 |


## PROBLEM 1: SUGAR, INSULIN AND LAMINITIS


**Remember:**

- ✖ an excessive insulin response to glucose is also a characteristic of PPID (Cushing's disease)

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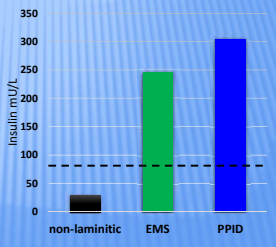
## PROBLEM 1: SUGAR, INSULIN AND LAMINITIS


**Remember:**

- ✖ Limit starch/sugar to <10% of dietary energy

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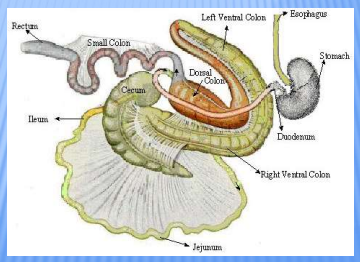
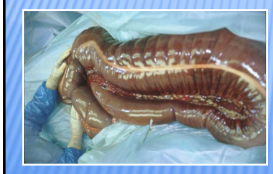
## PROBLEM 2: STARCHES AND COLIC

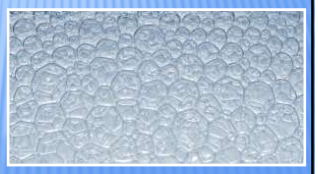
- the equine small intestine has a very limited capacity to digest starch *(because horses were never intended to eat starch!)*




## PROBLEM 2: STARCHES AND COLIC

- undigested starch arrives in the large bowel
  → rapid fermentation, gas, froth, acid, bacterial death
  →Colic/diarrhoea





## PROBLEM 2: STARCHES AND COLIC


*(Tinker et al 1997;Hudson et al 2001)*

## CEREAL – HOW MUCH IS OK?

- Gastrointestinal concerns
  - < 1 g starch per kg BWT per meal
  - = 500 g starch/500 kg BWT = <2.5 kg low energy concentrates
- Endocrine laminitis concerns
  - <0.1 g starch per kg BWT per meal?
  - = 50 g starch/500 kg BWT = <0.5 kg low energy concentrates


## FAT – HOW MUCH IS SAFE TO FEED ?

- fat is no more a natural feed than starch for horses
- nevertheless it is well tolerated
- type of fat unimportant: all ≈ 40kJ/mL
- begin feeding at 0.1 mL/kg BWT
- maximum rate of 1.0 mL/kg BWT
- 500 mL oil = 20 MJ = 1.5 - 2 kg concentrate feed

*(most concentrates = 1-1.2 kg/scoop)*

## WHICH 2 FEEDS HAVE THE *HIGHEST* ENERGY CONTENT?

A. Readigrass (chopped grass)
B. Alfa-A-Oil
C. Racehorse cubes
D. Kwikbeet (beet pulp)
E. Competition mix

## ENERGY CONTENT OF FEEDS?

| Digestible Energy (MJ/kg) | | | | |
|---|---|---|---|---|
| 13.2 | 12.5 | 12.5 | 12.2 | 11.0 |
|  |  |  |  |  |
| **Starch + Sugar (%)** | | | | |
| 5.0 | 6.5 | 11.0 | 28.0 | 28.0 |

**Horses have evolved to extract energy from low starch and sugar, high fibre feeds**

## FEEDING HORSES WITH LIVER PROBLEMS

- special diets are only required if the liver is *failing*
  - Liver *disease* (in the absence of failure) does not require special dietary management
- the liver controls nutrient storage/supply
  - feeding "little and often" seems sensible
- high dietary protein can exacerbate hepatic encephalopathy *(neurologic signs relating to high blood ammonia)*
  - however protein restriction causes muscle breakdown
  - advice to humans is to eat vegetarian protein!
- no need for B vitamins (if eating OK) and iron is hepatotoxic!
- supplementation with vits A,D,E,K may be helpful

## SUMMARY

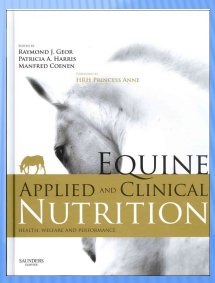
- Be aware of basic dietary facts and figures
  - DM intake
  - DE requirements
  - CP requirements
- Encourage fibre and oil feeding
- You don't need cereal starch for energy
- Cereals and starch promote:
  - GI disease in all horses
  - Laminitis in horses with endocrinopathies

**EQUINE APPLIED AND CLINICAL NUTRITION**

**Health, Welfare and Performance**

Editors : **Ray Geor, Pat Harris & Manfred Coenen**

Saunders

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# Medical Problems in Geriatric Horses

Professor Andy Durham
*BSc.BVSc.CertEP.DEIM.DipECEIM.MRCVS,*
*RCVS & European Specialist in Equine Internal Medicine*
The Liphook Equine Hospital
Hampshire

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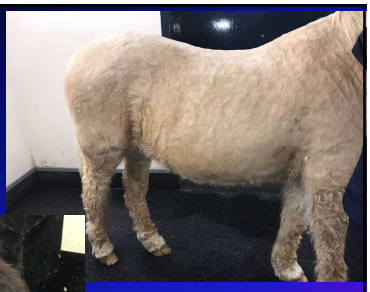
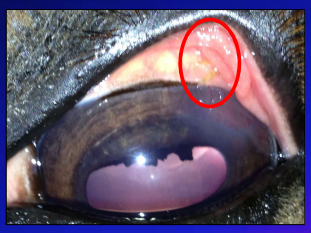
- PPID may be associated with poor ulcer healing
- total serum cortisol is normal
- but tear cortisol often increased



## Auriculopalpebral block

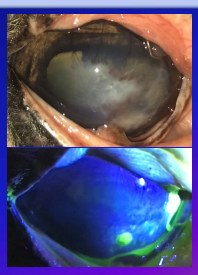
- ★ Auriculopalpebral - Motor nerve (facial VII)
- sedation

## FOREIGN BODIES



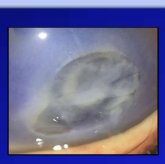
## ASSESSMENT

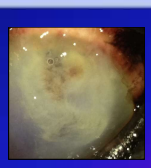
- use a ***small*** amount of fluorescein
- use a blue light
- size of ulcer may actually be very different (bigger or smaller) than it looks without fluorescein



## CORNEAL STROMAL COMPROMISE?


Epithelial defect


Epithelial and stromal defect

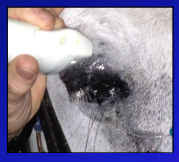

Stromal necrosis

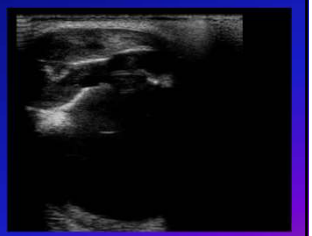
## CORNEAL STROMAL COMPROMISE?


Iris prolapse

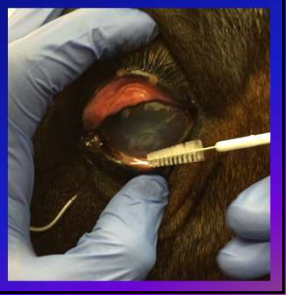
## CORNEAL STROMAL COMPROMISE?

- 7.5MHz+ linear transducer
- sedation
- gel on eyelid

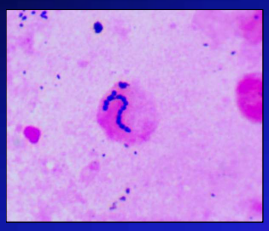


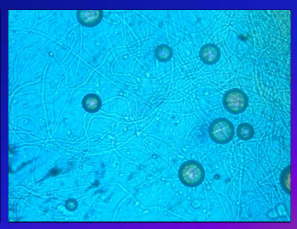


## Microscopy and Culture



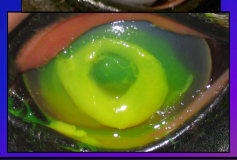
## Microscopy





## Particularly nasty pathogens

1. β haemolytic Streptococci
2. Aspergillus
3. Pseudomonas

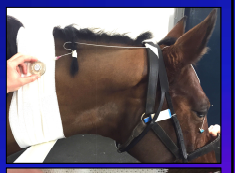


## Treatment of non-healing Corneal Ulcers

- Drugs
  - Antibacterial *(gentamicin, chloramph., ciproflox.)*
  - Antifungal *(enilconazole, voriconazole)*
  - Antiprotease *(EDTA solution, serum)*
  - Atropine?
- Painful eyes = hard to treat!
- Subpalpebral lavage catheter is essential

## Treatment of non-healing Corneal Ulcers

- presence of ocular medications is very short-lived (15mins?)
- non-healing ulcers have very high matrix metalloprotease concentrations (MMP 2,9)
- inhibition of MMPs is required ***constantly***
- q 4h = 6x15mins = 1.5h/24h = treated for 6% of the time!
- need applications ≤ q 1 hour or constant infusion
- ("Infudisk")

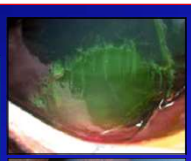


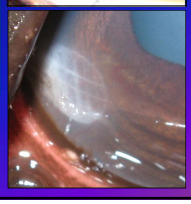
## Grid keratotomy as a treatment for superficial nonhealing corneal ulcers in 10 horses

*Veterinary Ophthalmology* (2007) **10**, 3, 162–167

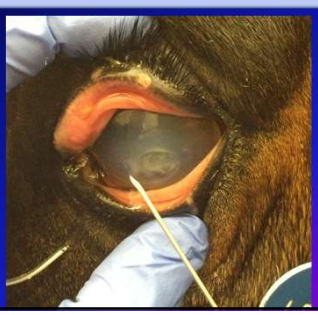
A. Brünott,* M. H. Boevé† and M. A. Velden*
*Departments of Equine Sciences and †Clinical Sciences of Companion Animals, Utrecht University, Yalelaan 8, 3584 CM, Utrecht, the Netherlands

- 10 horses with chronic non-healing ulcers
- mean duration 9 w (range: 2w–5m)
- 7/10 healed in a mean 8 days (range 3-15)
- Grid pattern remained for up to 6 wks





## GRID KERATOTOMY

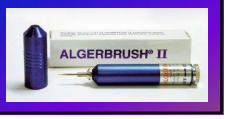


*Veterinary Ophthalmology* (2014) 17, Supplement 1, 76-81 DOI:10.1111/vop.12148

**Treatment of nonhealing corneal ulcers in 60 horses with diamond burr debridement (2010–2013)**

Mary Lassaline-Utter,* Tim J. Cutler,† Tammy M. Michau‡ and Catherine M. Nunnery§

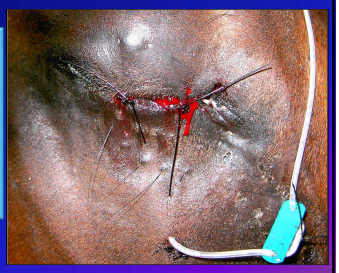
- 60 horses with chronic non-healing ulcers
- mean duration 29 d (range: 1w-6m)
- 60 treated with diamond burr
- All healed with mean 15.5 days
- Failed in 5 cases




## DIAMOND BURR DEBRIDEMENT

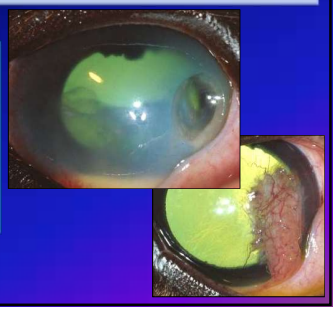
## OTHER TREATMENTS

- tarrsorhaphy



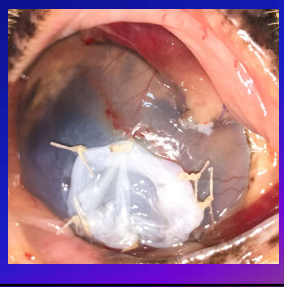
## OTHER TREATMENTS

- tarrsorhaphy
- conjunctival pedicle flap



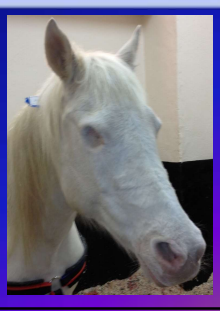
## OTHER TREATMENTS

- tarrsorhaphy
- conjunctival pedicle flap
- amnion graft (standing)



## Assessment & Treatment of Corneal Ulcers

- Proper examination requires
  - Sedation
  - Auriculopalpebral block
- Many cases are simple and heal quickly
- Those that don't require:
  - subpalpebral lavage
  - frequent/constant medication
  - tarrsorhaphy
  - grid keratotomy
  - diamond burr debridement
  - surgery



## Cardiac disease in the Elderly Horse

*Joint ACVIM/ECEIM Consensus Statement*

*J Vet Intern Med* 2014;28:749–761

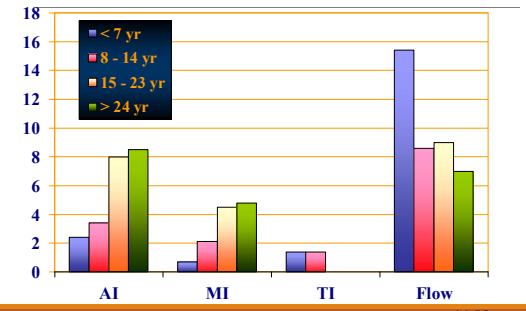
**Recommendations for Management of Equine Athletes with Cardiovascular Abnormalities**

V.B. Reef, J. Bonagura, R. Buhl, M.K.J. McGurrin, C.C. Schwarzwald, G. van Loon, and L.E. Young

# Cardiac disease

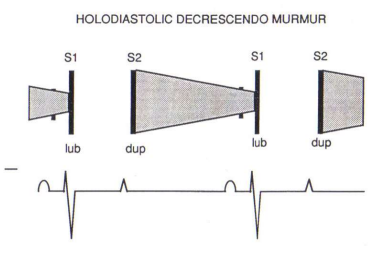
| | | |
|---|---|---|
| 1. | aortic regurgitation | common |
| 2. | mitral regurgitation | occasional |
| 3. | atrial fibrillation | occasional |
| 4. | congestive heart failure | rare |

## Age association with cardiac murmurs




n=1153

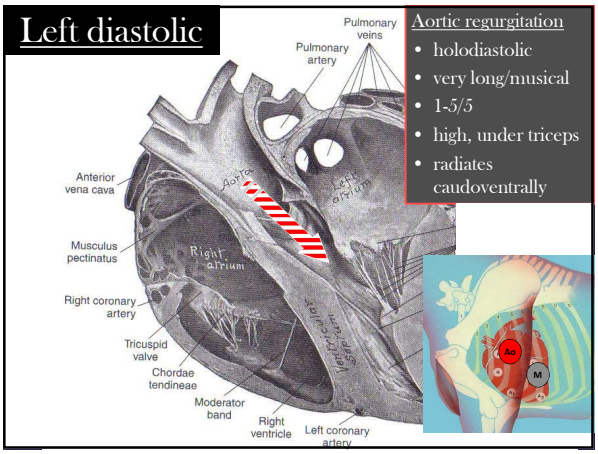
## Left diastolic




Aortic regurgitation

- holodiastolic
- very long/musical
- 1-5/5
- high, under triceps
- radiates caudoventrally

## Left diastolic

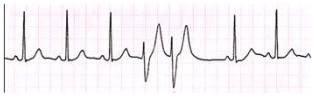



Aortic regurgitation
- holodiastolic
- very long/musical
- 1-5/5
- high, under triceps
- radiates caudoventrally

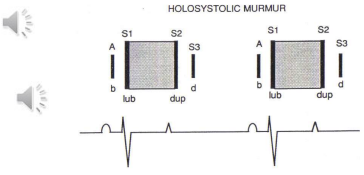
## Aortic regurgitation – clinical significance

- usually clinically insignificant
- usually self limiting via increased contractility
- bounding pulses reflect severe regurgitation
- volume overload may lead to mitral regurgitation

**Prognosis poorer if:**
- **Multiple murmurs**
- **VPCs**
- **Murmur grade > 4**
- **Hyperkinetic pulses**
- **Pulse pressure > 60 mmHg**

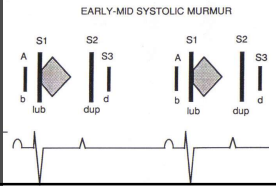


## Left systolic

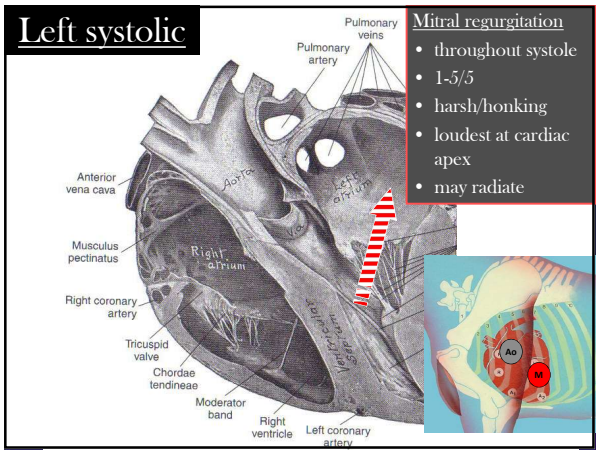



Mitral regurgitation
- throughout systole
- 1-5/5
- harsh/honking
- loudest at cardiac apex
- may radiate

Ejection/flow murmur
- usually early
- 1-3/5
- high, under triceps
- localised



## Left systolic

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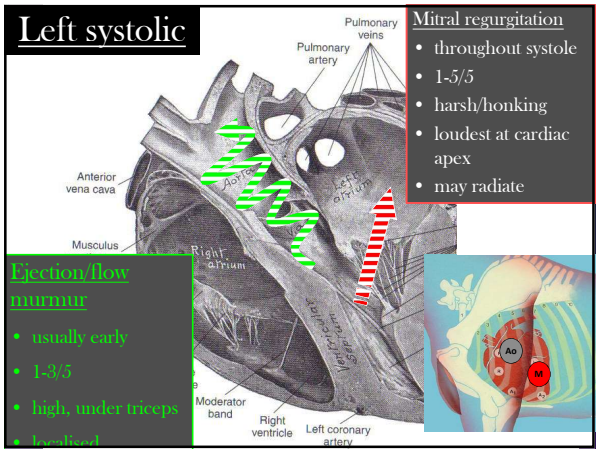
## Left systolic




Mitral regurgitation
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- harsh/honking
- loudest at cardiac apex
- may radiate

Ejection/flow murmur
- usually early
- 1-3/5
- high, under triceps
- localised

## Mitral regurgitation – clinical significance

Unpredictable:
- Often remain stable
- May (or may not):
  - progress to left and right sided congestive heart failure?
  - develop atrial fibrillation?
  - cause respiratory signs?
  - cause collapse – pulmonary artery rupture?

## Atrial fibrillation – characteristics

- commonest pathologic arrhythmia
- random rhythm
- 'f' waves
- normal rate (if not secondary to congestive heart failure)
- no 'a' sound heard *(unlike 2nd degree AV block)*

AF

AV block

## Atrial fibrillation – significance

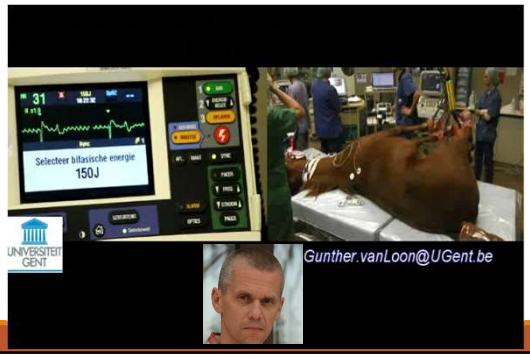
- loss of atrial systole only important during exertion (high heart rate)
- therefore often unimportant in geriatrics
- if present >4 months less likely to convert
- if detected incidentally may be longstanding?
- may be secondary to cardiac hypertrophy in congestive heart failure

## Atrial fibrillation – medical treatment

is it worth it?

1. monitor ECG continuously
2. do not move the horse
3. leave stomach tube in place
4. quinidine sulphate 22 mg/kg q 2h for up to 5 or 6 doses
5. watch ECG for widening of QRS by >25%
6. after 5-6 doses give q 6h?

## Atrial Fibrillation – transvenous electrocardioversion (TVEC)

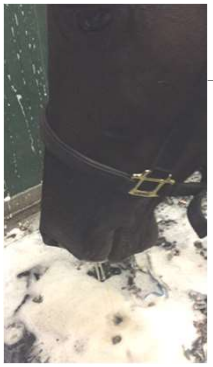



## Congestive heart failure -clinical signs

LEFT (mitral/aortic) ⇨ RIGHT

- tachycardia
- murmur
- cough
- tachypnoea
- exercise intolerance
- foamy nasal discharge

- tachycardia
- murmur
- venous distension
- oedema
- jugular pulse
- weight loss
- (ascites, pleural effusion)



## Congestive heart failure - treatment

digoxin 10-15 ug/kg q 12h *per os (5 -7.5 mg per 500kg)*

- *vagolytic - reduces HR*
- *increases contractility*

frusemide 1-2 mg/kg q 12h (or more often)

- *reduces volume overload*

benazepril 0.5 mg/kg q 24h *per os (250 mg per 500kg)*

- *ACE inhibition*

## Summary

**Potentially serious** *(echocardiography recommended)* **when:**

1. A murmur has become louder on re-examination
2. Grade 3-6/6 left pan/holo-systolic (mitral?)
3. Grade 3-6/6 left pan/holo-diastolic (aortic?)
4. Grade 4-6/6 right pan/holo-systolic (tricuspid or VSD?)
5. Continuous or multiple murmurs
6. Other
   - important arrhythmias (whether or not there is a murmur)
   - suspected myocardial damage
   - suspected congestive heart failure

## Neurologic disease in the elderly horse

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## Clinical Approach

1. **History** (sudden onset?, trauma?, in contact disease?, age?)
2. **General examination** (pyrexia, respiratory disease etc..)
3. **Neurologic examination**
   a) **is it obviously neurologic?**
   - consider colic, myopathy, laminitis, other orthopaedic disease/injury

   b) **if so, are there localising signs?**
   - ataxia/weak only → **spinal**
   - forelimbs + hindlimbs → **cervical** (hind>fore)
   - tail/anal tone, bladder, hindlimbs only → **cauda equina**
   - vestibular signs (head tilt, nystagmus, strabismus) → **brain stem**
   - other cranial nerves (eg. facial VII) → **brain stem**
   - depression, seizures, blindness, circling.. → **cerebral**
4. **Further diagnostics** (radiography, bloods, swabs etc…)

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## Important differentials of ataxia/weakness

- Laminitis – esp hindlimb laminitis
- Musculoskeletal disease (trauma, osteoarthitis, myopathy)
- Hepatic encephalopathy
- **Spinal compression (usually cervical)**
- **Acute vestibular disease**
  - **temporohyoid arthropathy**
  - **basisphenoid #**
- **Viral myeloencephalopathy – EHV1, WNV**

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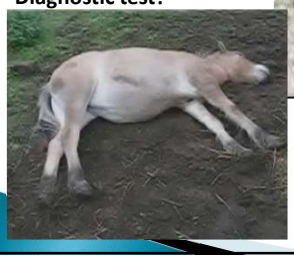
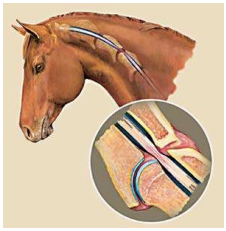
## Neurologic or not?

**Diagnostic test?**



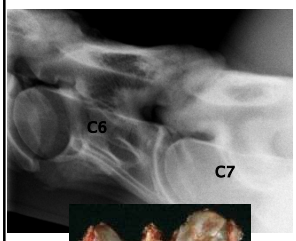
EHV1 myeloencephalitis

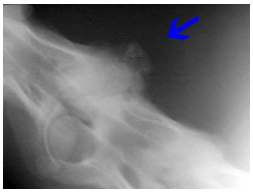
## Cervical spinal compression

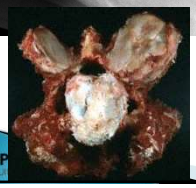


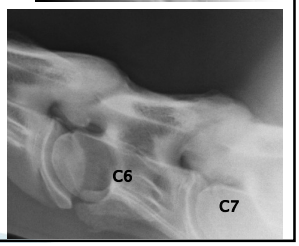
- Common
- Young or old (DOD vs DJD)
- Usually acute onset
- Hindlimbs worse than forelimbs (usually by 1 grade)
- May be asymmetric
- May improve with anti-inflammatories/rest

## Facet arthropathy



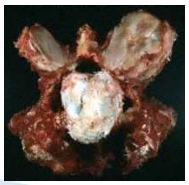







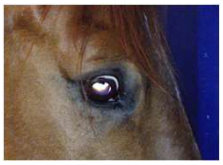

## Facet arthropathy

- Usually older horses
- History of trauma??
- More likely to be assymetric?



## Acute vestibular disease

- not uncommon
- generally caused by:
  - temporohyoid osteoarthropathy or
  - basisphenoid fracture
- acute onset usually severe ataxia (grade 3-5)
- not weak (but hard to tell!)
- usually bright but may be depressed
- usually have head tilt
- may have facial paralysis also
- nystagmus variable and may disappear



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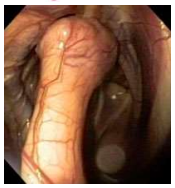
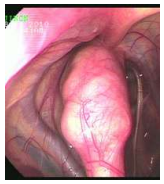
## Temporohyoid Osteoarthropathy

- May (or may not) have history of headshaking or difficulty eating
- Acute presentation
- Fusion (arthrodesis) of temporohyoid joint
- Mechanical stress → fracture of petrous temporal bone → vestibular damage
- often improve over 24-48 hours
- diagnose with guttural pouch endoscopy or CT





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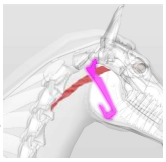
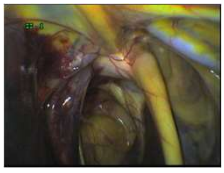
## Basisphenoid fracture

- History (may not be known) of rearing/falling over
- Often younger horses
- Impact to occiput → rapid poll extension → longus capitis muscles pull on basisphenoid → basiphenoid # ± longus capitis rupture
- radiographs but might miss the fracture (e.g. oblique/non-displaced)
- Guttural pouch endoscopy
  - good mobility of stylohyoid articulation (no arthrodesis)
  - haemorrhage in medial wall
- Computed tomography





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## EHV 1 myeloencephalopathy

- EHV1 neurologic disease rare < 3-5 years old
- EHV1 respiratory disease rare > 3-5 years old

either/or ??

- disease manifestation related to immune status?
- EHV1 vaccination predisposes to neurologic disease?
  - 1984 California outbreak vaccinates 9-14x more likely to get neurologic signs
  - N.B. vaccinates were older
- females and horses (vs ponies) predisposed?
- autumn/winter/spring ?

## EHV 1 myeloencephalopathy

**Clinical signs**

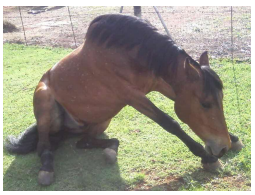
? premonitory pyrexia/respiratory signs/abortion ?

- morbidity
  - variable: from single cases to 90% morbidity
  - reports are frequently of single cases
- mortality
  - 5-30% neurologic cases
  - >95% cases recumbent for 24 hrs

## EHV 1 myeloencephalopathy

**Clinical signs**

- develop over 24-48 hours then stabilise/improve
- *cauda equina* syndrome (usually)
  - hindlimb ataxia/weakness
  - urinary overflow incontinence
  - tail paralysis
  - faecal retention
- usually remain bright and eating
- possibly cranial nerve signs
- possibly cerebral signs



## EHV 1 myeloencephalopathy

**DIAGNOSIS**

Seroconversion

- 4x⇧ CF test (or high titre if not-vaccinated)
  - 2 serum samples 2-3 weeks apart

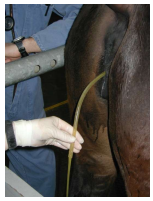
PCR/virus isolation/immunohistochemistry:

- leucocytes (heparinised blood)
- nasal/nasopharyngeal swab (in contacts?)
- *post mortem* (CNS)

## EHV 1 myeloencephalopathy

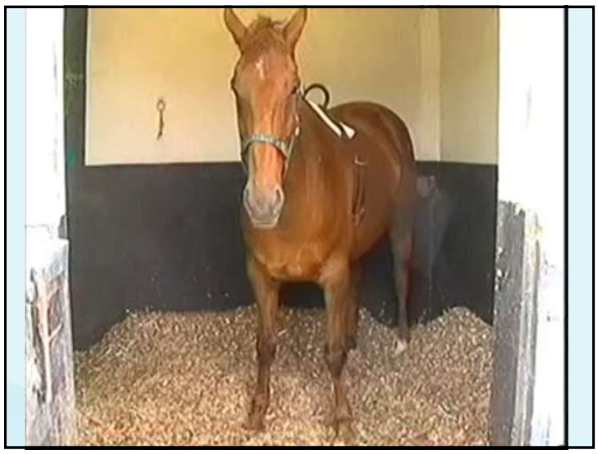
**TREATMENT**

- supportive
  - fluids
  - catherisation
  - empty rectum
- glucocorticoids
- antivirals
  - valacyclovir



40 mg/kg per os q8h for the 1st 48 hours, then 20 mg/kg per os q12h.

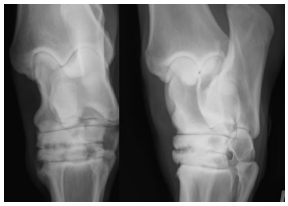
- 19 yo hunter gelding
- collapse in stable and when tied up
- otherwise bright, alert, working well



- Narcolepsy
  - a neurologic disorder characterised by sudden, recurrent compulsion to sleep
- Sleep deprivation
  - a medical/orthopaedic disorder associated with chronic discomfort
  - psychological insecurity

## Sleep deprivation

- not seen lying down for several weeks
- out in day, in at night
- trots sound but positive hindlimb flexion tests
- hock radiographs – moderate osteoarthritis
- hocks medicated, course of PBZ
- within 7 days – seen lying down
- no further collapses



## Seizures

- uncommon in adult horses
  - trauma
  - PPID
  - procaine toxicity
  - parasitism
  - abscess
  - mouldy corn
  - hepatic encephalopathy?
- may be general or partial
- rarely last > 1minute
- may be short lived or recurrent (epilepsy)
- possible post-ictal signs (eg depression, blindness) may persist for minutes to days

## Treatment of seizures

- Anti-oedema
  - Glucocorticoids? *0.05-0.20 mg/kg dex iv*
  - **Hypertonic saline 7.2%** ***2-4 ml/kg iv***
  - Mannitol 20% *2-5 ml/kg iv*
  - Frusemide *1 mg/kg iv*
- Anticonvulsants
  - **Detomidine** ***10-30 µg/kg iv***
  - **Midazolam** ***0.05-0.10 mg/kg iv, then 0.1-1.0 mg/kg/hour***
  - Diazepam *0.05-0.20 mg/kg iv*
  - Pentobarbitone *5-10 mg/kg slow iv*
  - **Phenobarbitone** ***2-10 mg/kg bid po***
  - Phenytoin *1-2 mg/kg tid po*

## Treatment of Hepatic Encephalopathy – reduce cerebral oedema

- Astrocytes detoxify Ammonia → glutamate
- Glutamate → osmotic draw of water → oedema (gross or microscopical)
- 2-3 litre bolus of 7.2% NaCl
  - can have a dramatic acute effect on hepatic encephalopathy signs

## Treatment of Hepatic Encephalopathy – reduce $NH_3$

- Lactulose 0.3 ml/kg sid-qid
- Antibiotics: metronidazole 15 mg/kg *per os qid*
  neomycin 15 mg/kg *per os qid*

## Summary

- Is it neurologic disease?
- Where is the lesion? *(cerebral vs brain stem vs spinal)*
- Vestibular signs
  - temporohyoid arthropathy
  - basisphenoid #
- Check liver
- Consider infectious causes
  - EHV – cauda equina signs
  - WNV – tremoring??

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## Urinary Tract Disorders

Andy E Durham
Liphook Equine Hospital

## Urinary Tract Problems

- Polydipsia/polyuria
- Pigmenturia
- Incontinence
- Frequent/painful/difficult urination
- Acute/Chronic renal failure

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## Polydipsia & Polyuria - definitions

**Polydipsia**

- normal water intake ≈ **4–6 % BWT** *(20-30 L/500kg)*
- *suspicious if* ***>7% BWT*** *(>35 L/500kg)*
- definite if **>10 % BWT** *(>50 L/500kg)*

**Polyuria**

- normal urine production ≈ **1½–3 % BWT** *(7½–15 L/500kg)*
- suspicious if **>3% BWT** *(>15 L/500kg)*
- definite if **>5 % BWT** *(>25 L/500kg)*

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## Polydipsia & Polyuria – initial blood tests

**Common causes**

1. Primary (psychogenic) polydipsia
2. **PPID (Cushing's disease)**

**Uncommon causes**

3. Liver failure
4. Chronic renal failure
5. *Diabetes mellitus*
6. *Diabetes insipidus*
   - neurogenic (central)
   - nephrogenic (renal)

| Blood | Urine |
|---|---|
| **ACTH** | SG |
| GGT, bile acid | GGT:creatinine |
| Urea | Glucose |
| Creatinine | |
| Calcium | |
| Glucose | |

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## Polydipsia & Polyuria – initial blood tests

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| Blood | Urine |
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| ACTH | SG |
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   - nephrogenic (renal)

| Blood | Urine |
|---|---|
| ACTH | SG < 1.008 |
| GGT, bile acid | GGT:creatinine |
| Urea | Glucose |
| Creatinine | |
| Calcium | |
| Glucose | |

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## Tests to differentiate Psychogenic polydipsia from Diabetes insipidus

### Partial water deprivation test

**Only perform the test if:**

- normal serum urea and creatinine
- urine SG < 1.008
- no signs of dehydration

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## Tests to differentiate Psychogenic polydipsia from Diabetes insipidus

### Partial water deprivation test

**Protocol:**

- allow restricted water access
  - 1% BWT q 6 hours (=4% BWT/day) (4 x 5 L per 500 kg)
- check urine SG q 6 hours
- monitor for signs of dehydration (clinical and plasma lactate or creatinine)

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## Tests to differentiate Psychogenic polydipsia from Diabetes insipidus

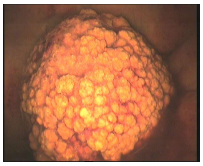
### Partial water deprivation test

**Interpretation:**

- Urine SG increases to >1.020 = able to concentrate urine = **psychogenic polydipsia**
- Becomes dehydrated and urine <1.014 = cannot concentrate urine = ***diabetes insipidus***

## Bladder stones

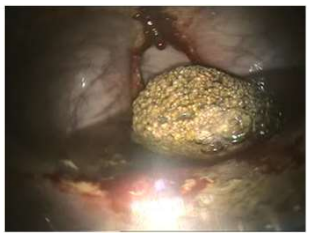
- haematuria (post-exercise) is often the only sign
- mature to elderly horses
- much more common in males
- calcium carbonate
- very spiky!



## Bladder stones

**Diagnosis**

- Rectal palpation
- Rectal ultrasound
- Endoscopy



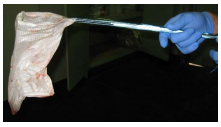
## Bladder stones

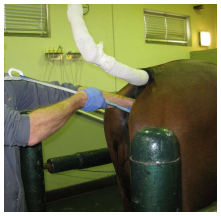
**Diagnosis**

- Rectal palpation
- Rectal ultrasound
- Endoscopy

**Treatment**

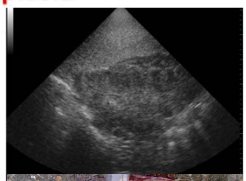
- Geldings – surgery
- Mares – removal via urethra

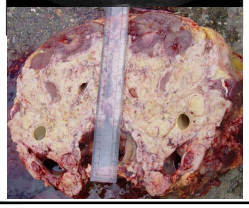




## Renal Neoplasia

- Uncommon
- Weight loss, haematuria
- Urea and creatinine are normal
- Blood samples may be inflammatory
- Diagnosed with ultrasound
- Hopeless prognosis



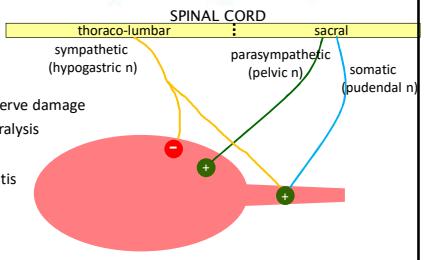


## Incontinence (dribbling urine)

**Causes**

Usually sacral (p-symp) nerve damage

- Idiopathic bladder paralysis
- Sacral trauma
- EHV1 myeloencephalitis

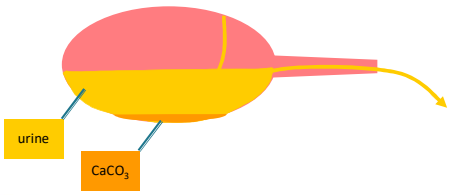


## Idiopathic Bladder Paralysis

- *= "sabulous cystitis"*
- males
- any age
- urinary incontinence
- large atonic, easily expressed bladder
- may feel a "dinner plate" in bladder = settled sediment

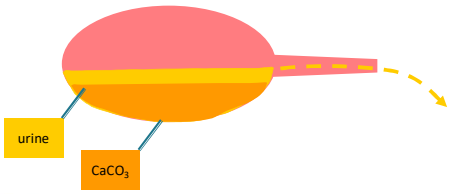
## Idiopathic Bladder Paralysis

Normal urination



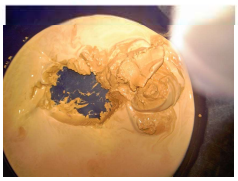

## Idiopathic Bladder Paralysis

- *= "sabulous cystitis"*
- Clay-like material accumulates = calcium carbonate sludge
  → stretches bladder → irreversible bladder muscle damage



## Idiopathic Bladder Paralysis

- the condition cannot be *cured*
- but they can be *managed*
- flush out sabulous material
- treat bacterial/irritant cystitis ?
- repeat as necessary (q 6months?)
- bethanechol (Myotonine) ?



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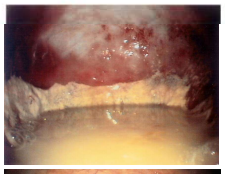
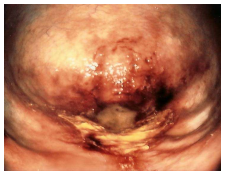
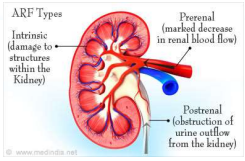


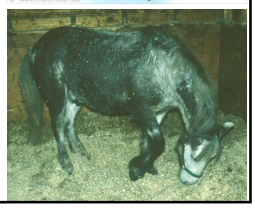


## Renal Failure

**Acute** (reversible?)

- may develop in critical care cases *(colic, colitis etc…)*
- usually due to:
  - dehydration
  - or drugs *(gentamicin, NSAIDs, bisphosphonates)*
- may resolve with aggressive fluid therapy/frusemide



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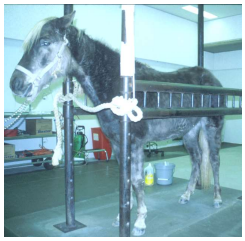
## Renal Failure

**Chronic** (irreversible?)

- cause usually unknown
- Clinical signs
  - usually just dull and weight loss
  - polydipsia/polyuria are variable
- Blood
  - urea and creatinine ↑↑
  - usually calcium ↑
- Urine
  - isosthenuria (urine SG 1.008-1.014)
  - protein?
  - blood?



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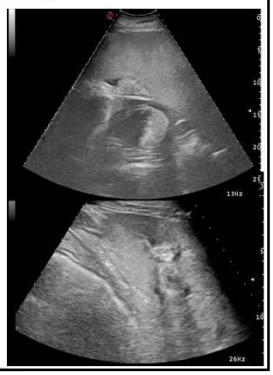
## Renal Failure

**Chronic** (irreversible?)

Ultrasound

- kidneys may be small and hyperechoic
- may have calculi?
- may have hydronephrosis?



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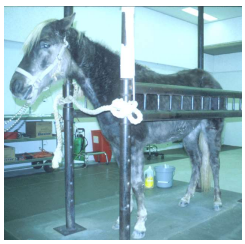
## Renal Failure

**Chronic** (irreversible?)

- Treatment:
  - Intravenous Fluid Therapy
    - >3 litres/hour

    → decrease creatinine by about 50-100 µmol/L per day
  - but usually increases again!
  - can often do well if creatinine stabilises < 300 µmol/L *(normal <175 µmol/L)*



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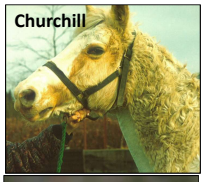
## Therefore managing the older sports horse is important.....

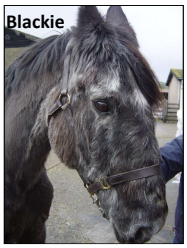
- 26% of all >15yo still competing
  - eventing, dressage, show-jumping and driving
- 62% Hacking /pleasure riding
- Years of training needed to reach the top
- Winner of Dressage and Eventing at Rio 2016 Olympics both aged 14 yrs
- Many elite horses are older than 15yo

Valegro

La Biosthetique Sam










**14-32 YEARS OLD**