Another Skinny Horse with a Normal Physical Exam: Now What (Part 2)?
Hal Schott, DVM, PhD, DACVIM
Department of Large Animal Clinical Sciences, Michigan State University, East Lansing, MI, USA
Weight loss or ill thrift is a common presenting complaint for many medical problems of horses. Although gastrointestinal diseases are a more common cause of weight loss, liver disease and chronic kidney disease can also cause weight loss as a primary complaint.

HEPATIC DISEASES OF HORSES
Although relatively uncommon, a number of liver diseases occur in horses. Causes include intoxication (most commonly from ingestion of toxic plants), altered metabolic function (hypertriglyceridemia and hepatic lipidosis), and ascending infection (cholangiohepatitis with or without cholelithiasis). Although recognized for over a century, serum hepatitis (Theiler’s disease) has recently been found to be associated with a viral infection. Presenting complaints for liver disease are non-specific and include lethargy, decreased appetite, and weight loss / ill thrift. Detection of icterus can provide an important clue although it is important to remember that anorectic horses and those grazing pasture may also have moderate yellowing to mucosal membranes. Additional signs may vary from photosensitization in areas of non-pigmented skin to bizarre neurological deficits characteristic of hepatic encephalopathy. Serum biochemical abnormalities, ultrasonographic imaging, and hepatic biopsy are useful in further determining the cause of liver disease. Unfortunately, due to the large functional reserve of hepatic tissue, nearly 80% of liver function must be lost before clinical disease becomes apparent. Consequently, the prognosis for recovery from may be guarded to poor.

CLINICAL SYNDROMES OF HEPATIC DISEASE
Hepatotoxicity and Photosensitization
Photosensitization syndromes are termed primary when exogenous photodynamic agents are either ingested or administered to horses. The classic example is ingestion of Hypericum perforatum (St. John’s wort) that contains hypericin. Use of medications (e.g., phenothiazines, thiazides, potentiated sulfonamides, tetracyclines, and others) can also cause primary photosensitization but these reactions are uncommon and appear to be idiosyncratic in nature. Secondary photosensitization is the more commonly recognized syndrome in horses that develops when phylloerythrin, a photodynamic metabolite of chlorophyll, accumulates with liver disease. Although secondary photosensitization can be a sign of any type of liver diseases, it is more commonly recognized with ingestion of hepatotoxic plants. Detection of icterus during physical examination coupled with finding elevated hepatic enzyme activities, particularly increased \( \gamma \)-glutamyl transferase activity, on a serum chemistry profile allows diagnosis of hepatic disease as the primary problem. A simple yet important clue that ingestion of a hepatotoxic plant by horses at pasture is the cause of liver disease is detection of photosensitization and elevated hepatic enzyme activities in several horses within a group. Treatment of photosensitization is supportive and typically consists of topical wound care. Occasionally, systemic anti-inflammatory medications and antimicrobial agents may be required. Prevention of further skin injury is accomplished by limiting exposure to ultraviolet light by stabling horses during the day (turn out at night) or applying sun block to non-pigmented skin.

Grazing pasture containing alsike and red clover is probably the most common cause of secondary photosensitization of horses in North America. Pyrrolizidine alkaloid-induced hepatotoxicity by ingestion of tansy ragwort is likely the second most important cause. There is no breed, sex, or age predilection for the problem and, curiously, these plants were imported to the United States from Europe in the 1800s. Despite these similarities, progression of liver disease and outcome is quite different for these two intoxication syndromes. Alsike (Trifolium hybridum) and red (Trifolium pratense) clover were imported as forage crops and can often be found in grass seed marketed as a pasture mix. Most cases of photosensitization from ingesting clover are reported from April through November in years when there has been a particularly wet spring or heavy late summer rains allowing abundant clover growth.
Poisonings in horses may occur as a result of exposure to alsike or red clover both at pasture or when fed as hay. As little as 20% of alsike clover in the diet, either at pasture or in hay, has been associated with signs of poisoning. Depending on the percentage of clover in the diet, clinical signs of illness can be seen as early as 2–4 weeks after initial exposure. The toxic agent that causes hepatic failure remains unknown: it is unclear as to whether the entire alsike or red clover plant, some component of the plants, a toxic metabolite produced by the plants, or a fungal toxin is responsible for the disease. The presence and consumption of the flower appears to be most associated with the development of signs. Cymodothea trifolii, a fastidious fungus that causes “black blotch” or “sooty blotch” disease of clover and alfalfa, has also been linked to development of liver disease in horses. Finally, although both types of clover are considered toxic, most reports of clinical disease have implicated alsike clover as the more important plant causing liver disease.

Tansy or common ragwort, Senecio jacobaea, is a weed of the sunflower family. In North America, ragwort has become a problem weed in pastures, rangelands, and clear-cuts on both the east and west coasts, particularly in Oregon. Ragwort competes with valuable forage species, but it derives its greatest economic importance from the losses it causes to livestock, particularly cattle. Ragwort can be lethal when animals ingest 3–7% of their body weight in ragwort over one to two days. However, acute poisonings seldom occur because the low palatability of the plant usually results in only small quantities being consumed per day. Chronic ingestion leads to progressive loss of hepatic function manifested by weight loss and secondary photosensitization.

A history of exposure to either clover or ragwort is clearly important to determine in the evaluation of horses presented with chronic weight loss, icterus, and photosensitization. However, it is not uncommon for owners to be unaware of exposure to these plants and the pasture may need to be examined by an extension agent or hay samples may need to be examined for contamination with these plants. Although abnormalities detected on physical examination and laboratory analysis of blood samples may not differ markedly with these two intoxications, further examination of the liver typically shows substantial differences. Specifically, with clover toxicity the liver may be normal in size to enlarged with rounded margins on ultrasonographic examination while the liver is more often small with ragwort intoxication. This difference likely reflects a more prolonged and insidious course of liver damage with ragwort in comparison to a more acute insult with clover. Next, histopathological examination of hepatic biopsy samples reveals bile duct proliferation and perilobular, centrilobular, and periportal fibrosis. Mild hepatocellular swelling and vacuolization along with areas of mild mononuclear inflammation may also be observed but megalocytosis is uncommon. The extent of fibrosis is of clinical importance because proliferating fibrous tissue gradually constricts the functional parenchyma. If fibrosis is limited to centrilobular regions and “bridging” fibrosis, extending from the centrilobular to periportal regions, is absent, the prognosis is usually favorable and horses can fully recover from clover toxicity. In contrast, with ragwort toxicity fibrosis is typically much more extensive and megalocytosis is a characteristic histopathological finding. Thus, it should not be surprising that the prognosis for chronic ragwort toxicity is guarded to poor with humane euthanasia required for most affected horses.

Hypertriglyceridemia, Hyperlipemia, and Hepatic Lipidosis
Hypertriglyceridemia, hyperlipemia, and hepatic lipidosis develop consequent to mobilization of fat reserves to provide energy during periods of negative energy balance. Although a secondary problem, these metabolic alterations must be addressed because they represent a serious complication that can significantly worsen the prognosis of the underlying primary disease. Certain equine breeds, notably donkeys, burros, and miniature horses, and overweight and pregnant horses are more predisposed than lean animals. In addition to specific treatment of the primary disease process, appropriate nutritional support (a carbohydrate substrate) is required to enhance metabolism of triglycerides.

Equids develop fat reserves when energy intake is above that required to maintain body condition. This is a natural process, especially prior to onset of winter or during gestation, in order to prepare the animal for periods during which energy demand will be increased. However, when energy (feed) intake decreases suddenly and completely, mobilization of fatty acids from fat reserves can lead to rapid increases in serum triglyceride concentrations (TG) that exceed the capacity of the liver to process these energy substrates. Hypertriglyceridemia is defined as an elevation of TG above the upper end of the
reference range and minor increases in TG are common with many diseases that result in a decreased appetite. The term hyperlipemia is used when plasma becomes grossly discolored a milky white, usually when TG exceed 1,000 mg/dL (11.3 mmol/L). Equids with hyperlipemia often have a dull attitude and likely experience nausea that further contributes to a poor appetite. Further, their livers can be markedly increased in size and liver rupture and fatal hemorrhage into the abdominal cavity may occur. Treatment requires provision of carbohydrate substrate, in the form of an intravenous dextrose solution and/or forced enteral feedings via a nasogastric tube, as carbohydrates are needed for the liver to process triglycerides. In conjunction with appropriate treatment of the underlying primary disease, additional treatments that may be used to counteract hypertriglyceridemia include heparin and insulin administration. Severe hypertriglyceridemia and hyperlipemia can also develop in horses with endocrinopathies including insulin resistance and pituitary pars intermedia dysfunction. Of interest, equids with this complication of the endocrinopathy do not appear to have the severe clinical signs observed in equids with other systemic disease, possibly due to an alteration in metabolism in equids with endocrinopathies, rather than overwhelming hepatic lipidosis.

**Cholangiohepatitis and Cholelithiasis**

Horses with cholangiohepatitis can have weight loss / ill thrift as the presenting complaint. In addition, recurrent colic, fever, and secondary photosensitization may also be recognized. Physical exam of horses with cholangiohepatitis often reveals a dull attitude but occasionally hepatic encephalopathy can also develop. Detection of icterus is variable. Clinicopathological assessment reveals elevated hepatic enzyme and transabdominal ultrasonography is useful to assess liver size and presence of choleliths in horses with liver disease. Obstructive disease (cholangiohepatitis with or without associated choleliths) typically leads to an enlarged liver with a rounded edge that extends beyond the costochondral junctions on the right side. A liver biopsy is relatively easy to collect and provides useful information for prognosis (extent of hepatic fibrosis).

Treatment of cholangiohepatitis requires long-term antimicrobial treatment, usually with a potentiated sulfonamide, until liver enzyme activities have returned to normal. This may require months of antimicrobial treatment and GGT activity is the one enzyme to monitor. Periodically, colic episodes or exacerbation of liver disease resulting in anorexia may need to be addressed with further supportive care (e.g., fluid therapy, NSAIDs, etc.).

**Serum Hepatitis (Theiler’s Disease)**

Sir Arnold Theiler first described serum hepatitis, a highly fatal form of acute hepatitis, nearly a century ago after horses were vaccinated against African horse sickness in South Africa. Vaccination involved simultaneous administration of infectious virus and convalescent equine antiserum and hundreds of horses succumbed to the fatal hepatopathy. The first cases of Theiler’s disease were recognized in the United States during the 1930 pandemic of western equine encephalomyelitis (WEE) that began in California and then spread throughout the western states. After the initial outbreak of WEE, a second wave of disease occurred 2 to 3 months later in horses that had been immunized using anti-WEE antiserum alone or in combination with live WEE virus. These subsequent cases also presented with an encephalopathy that actually had a higher mortality rate than the initial WEE outbreak and pathologic examination revealed centriflobular or massive hepatic necrosis similar to that described by Theiler. Since these early reports, development of Theiler’s disease after use of equine serum or plasma products has been recognized worldwide. Curiously, “spontaneous” outbreaks of serum hepatitis have also been recognized in which no equine serum or plasma products had been administered. As had been well recognized in other species, these spontaneous outbreaks created the suspicion that a viral agent may be the cause of the hepatopathy. Recently, an outbreak of serum hepatitis in horses was associated with infection with a previously unrecognized flavivirus similar to human hepatitis C virus. The virus was detected by high throughput pyrosequencing and was called Theiler’s disease-associated virus (TDAV). This new technique, direct metagenomic analysis that allows scanning of the genome for novel nucleic acid sequences has now identified three new blood-borne flaviviruses in horses: TDAV, non-primate Hepacivirus (NPHV), and equine Pegivirus (EPgV).

TDAV was discovered during investigation of a 2011 outbreak of serum hepatitis following administration of botulinum antiserum to 22 horses on a farm experiencing botulism. Two lots of
botulinum antiserum were used and 8 of 17 horses treated with one lot of botulinum antitoxin developed serum hepatitis within 7 to 9 weeks after treatment. Hepatitis was not observed in the 5 horses that were treated with a separate lot of botulinum antitoxin or in 53 other horses on the farm that had not received antitoxin. A novel virus belonging to the family Flaviviridae was identified in the serum of two clinical cases of Theiler’s disease as well as in the botulinum antitoxin the two horses had received. The nucleic acid sequences of the viruses in the two hepatitis cases and in the botulinum antitoxin were very similar. Serum of the other horses was tested by quantitative reverse transcriptase-polymerase chain reaction for TDAV and all 17 horses that received the one lot of botulinum antitoxin tested positive for the new virus. Further, one of the 3 horses from which the botulinum antitoxin was produced also tested positive for TDAV. The 17 TDAV-positive horses were retested after one year and persistent TDAV viremia was detected in 4 horses. The level of viremia was unchanged over time in these chronically infected horses. Horses from the index farm were also retested following the outbreak and no additional horses became positive, suggesting direct horse-to-horse transmission or transmission by insect vectors is unlikely to occur. At present, the association of TDAV with Theiler’s disease remains incompletely understood and further cases will be necessary to fully determine any association between TDAV infection and Theiler’s disease.

Non-primate Hepacivirus was actually the first of the three new blood-borne flaviviruses to be found in horses. It was found in serum of clinically normal horses and, to date, there is no association between detection of this virus and clinical or subclinical hepatic disease. Equine Pegivirus is the most recently described equine hepatitis virus. Similar to NPHV, no clinical disease has been associated with this infection, although some horses that test positive for the virus may have subclinical increases in serum hepatic enzyme activities.

**Chronic Kidney Disease**
Recently, the term chronic kidney disease (CKD) has been introduced in human and small animal medicine for patients with chronic renal disease. Rather than describing patients as have chronic renal failure (CRF, often an end stage problem) use of CKD shifts attention to detection of earlier stages of chronic renal disease. Although CKD is by nature a progressive disorder, early detection and interventions may slow the rate of progression thereby prolonging life and, for people, delaying the potential need for renal replacement therapy.

CKD in the horse may be divided by clinical and pathologic findings into two broad categories: glomerular disease (glomerulonephritis) and tubulointerstitial disease (chronic interstitial nephritis). However, pathology in one portion of the nephron usually leads to altered function and eventual pathology in the entire nephron such that CKD is an irreversible disease process characterized by a progressive decline in GFR. However, the rate of decline in GFR is variable making the short-term (months to a couple of years) prognosis guarded to favorable while the long-term prognosis remains poor. Unfortunately, because renal disease is often advanced when horses are first presented for clinical evaluation, the inciting cause leading to CKD may be difficult to ascertain, and end stage kidney disease (ESKD) may be the pathologic diagnosis.

**Clinical Signs and Laboratory Findings**
The most common clinical sign observed in horses with CKD is weight loss. A small plaque of ventral edema, between the forelimbs, is another frequent finding. Moderate polyuria and polydipsia (PU/PD) are also usually present. Often, urine produced by horses with CKD is light yellow in color and transparent as it is relatively devoid of normal crystals and mucus. Accumulation of dental tartar, especially on the incisors and canine teeth, gingivitis, and oral ulcers are other findings that may be detected in horses with CKD. Decreased performance may be an early complaint in competitive horses while growth may be stunted in young horses with renal hypoplasia or dysplasia.

Laboratory findings in horses with CRF vary depending on diet and the cause and extent of renal damage. Most horses with clinical signs of CRF have moderate to severe azotemia (Cr usually 5 mg/dl or greater). The BUN to Cr ratio may vary, depending on protein intake, muscle mass, hydration and degree of azotemia but is usually > 10. Mild hyponatremia and hypochloremia may accompany CKD but serum concentrations of these electrolytes can often remain within reference ranges. Hypercalcemia, with serum concentrations sometimes approaching 20 mg/dl, appears to be a laboratory finding that is unique to
horses with CKD. Hypercalcemia is not a consequence of hyperparathyroidism as parathormone concentrations are not elevated in horses with this finding. The magnitude of hypercalcemia is dependent on diet and high values can return to the reference range within a few days of changing from alfalfa to grass hay. Acid-base balance usually remains normal until CKD becomes advanced but metabolic acidosis may be found in horses with end stage disease. Many horses with CKD are moderately anemic (packed cell volume 25–30%) likely due to decreased erythropoietin production. Horses with glomerulonephritis may have hypoalbuminemia and hypoproteinemia while horses with advanced CKD of any cause may also have mild hypoproteinemia due to intestinal ulceration.

Urinalysis findings may vary depending on the cause of CKD. As mentioned, urine is relatively devoid of normal mucus and crystals making samples transparent. Further, a hallmark of CKD is urine specific gravity in the isosthenuric range (1.008 to 1.014), although heavy proteinuria in an occasional horse with glomerulonephritis may produce values up to 1.020. Quantification of urine protein concentration is required to accurately assess proteinuria. Urine protein concentration in normal horses is usually less than 100 mg/dl and the urine protein to Cr ratio should be less than 0.5:1. With significant proteinuria, urine protein to Cr ratio is usually greater than 1:1. Horses with chronic interstitial nephritis usually do not have significant proteinuria.

**Diagnosis of Chronic Kidney Disease**

A diagnosis of CKD is most commonly made in horses with azotemia and isosthenuria that present with a complaint of weight loss and/or decreased performance. Detection of hypercalcemia also strongly supports CKD. Rectal examination may be helpful. Horses with ureteral calculi, often have enlarged ureters that can be palpated as they course through the retroperitoneal space. Although kidneys of horses with CKD are typically small with an irregular surface, these changes are not always apparent on palpation of the left kidney. Ultrasonographic imaging is useful for evaluating kidney size and echogenicity and may reveal fluid distention (hydronephrosis, pyelonephritis, or polycystic disease) and/or presence of nephroliths. Horses with significant renal parenchymal damage and fibrosis often have increased echogenicity of renal tissue that may be similar or even greater than that of the spleen.

**Treatment of Chronic Kidney Disease**

Treatment of horses with CKD is most likely to produce improved renal function if there is an acute, reversible component exacerbating CKD (acute on chronic syndrome). If an acute component is detected, it should be corrected rapidly (as described for AKI/ARF) with the goal of minimizing further loss of functional nephrons. Further, surgical removal or fragmentation of stones via lithotripsy may be indicated in horses with calculi that are thought to be causing obstruction of urine flow. Treatment of horses with stable CKD consists of supportive care: providing sufficient water, electrolytes, and nutritional support. In addition to Cr, serum electrolyte concentrations and acid-base balance should be measured regularly. Although no adverse effects of hypercalcemia in horses with CKD have been documented, decreasing calcium intake (replacing alfalfa or other legume hays with grass hay) may result in a return of serum calcium concentration to the normal range. NSAIDs are best avoided in horses with CKD.

Nutritional management aimed at maintaining body condition is the most important aspect of supportive care of horses with CKD. Access to good quality pasture, increasing carbohydrate (grain) intake, and adding fat to the diet are recommendations to increase caloric intake. Over the past couple of decades restricting dietary protein intake by human and veterinary patients with CKD was thought to have beneficial effects; however, the current recommendation is to provide adequate amounts of dietary protein and energy to meet or slightly exceed predicted requirements while maintaining a neutral nitrogen balance. Adequacy of dietary protein intake can be assessed by the BUN to Cr ratio: values > 15 suggest excessive protein intake while values < 10 may indicate protein-calorie malnutrition.

Progressive loss of nephron function with CKD precludes successful long-term treatment. However, horses with early CKD may be able to continue in performance or live as pets for quite some time (months to a few years). In general, as long as Cr remains < 5 mg/dL and the BUN:Cr ratio is < 15, horses seem to maintain a fair attitude, appetite, and body condition. However, once Cr exceeds 5 mg/dL, the rate of progression of CKD appears to accelerate and signs of uremia (anorexia, poor hair coat, and loss of body condition) become more apparent.
Due to the variable nature of progression, each case should be handled on an individual basis with the emphasis on maintenance of body condition until humane euthanasia becomes necessary.

REFERENCES

Hepatotoxicity

Hypertriglyceridemia and Hepatic Lipidosis

Cholangiohepatitis

Theiler’s Disease

Chronic Kidney Disease