*** CLICK HERE ***

Current Articles & Research

Reproduction
Foal Disorders
Lameness

Check back often for new additions

The Equine Liver in Health and Disease

The liver might not get as much airtime as, say, the horse's lungs or intestines, but it is an essential organ for life. It accounts for at least 1.6% of an adult horse's body weight and performs many vital functions: processing nutrients from food; making proteins and bile; storing glucose, vitamins, and minerals; maintaining immune function; and removing toxins from the blood.

At the 2015 American Association of Equine Practitioners Convention, held Dec. 5-9 in Las Vegas, Thomas Divers, DVM, Dipl. ACVIM, ACVECC, Professor of Veterinary Medicine at Cornell University's College of Veterinary Medicine, described the liver in great detail during the Frank J. Milne State-of-the-Art Lecture.

Liver Function
The equine liver is unique is many ways, one of which is how blood flows through it. Normally, oxygen-rich arterial blood circulates to an organ, and then oxygen-depleted venous blood returns back to the heart and through the lungs to pick up more oxygen to send back through the circulation. But with the liver, the relatively deoxygenated hepatic portal vein provides the organ with a large proportion of oxygen. Ten percent of a horse's total blood volume of the body resides in the liver, so any disease can have significant consequences.

Divers explained the liver's multiple functions: "It is a vascular organ, a metabolic organ, and a secretory and excretory organ." It is responsible for:

- Bile production and secretion (bile is important for helping metabolize fats);
- Detoxification processes;
- Blood storage and filtration;
- Metabolism of carbohydrates, fats, proteins, free fatty acids, volatile fatty acids, sugars, and glycogen;
- Protein synthesis of acute phase proteins, albumin, fibrinogen, and clotting factors; and
- Endocrine activity. Hepcidin, for example, is a liver-produced hormone that regulates iron distribution in the body. "Hepcidin decreases absorption of iron from the intestine and sequesters circulating iron in phagocytes (white blood cells that engulf bacteria, other cells, and particles)," said Divers. "Because iron is important for bacterial growth, when there is an infection, the liver and hepcidin try to hide it from the bacteria."

Divers then described the relative importance of the liver's three zones. The innermost Zone 1 (closest to the portal circulation) is the most metabolically active and has the most oxygen, nutrients, and toxin exposure. Zone 3 is the least oxygenated and the most affected by low oxygen levels caused by disease, such as hemolytic anemia. Zone 3 is also important for enzyme activity for drug metabolism and some metabolism of certain plants into their toxic components (e.g. pyrrolizidine alkaloids).

Liver Function Tests
Divers noted that liver failure in horses is relatively rare, in part because at least 70% of the organ must be affected before functional biochemical changes and signs of liver disease occur. Conversely, liver disease is common and often associated with filtering and detoxification of the portal circulation.

"While enzymatic tests are useful for detection of disease, they don't reliably attest to function," he said. Specific enzymes (GGT, ALP) point toward problems with the biliary tract (ducts that make and transport bile) while others (GLDH, SDH, AST) track injury to the liver cells (hepatocytes), referred to as hepatocellular injury. Bilirubin concentrations are another measure of liver health. Blood testing that demonstrates more than 25% of bilirubin in the conjugated form (converted in the liver by an acid so that it is soluble in water, and generally excreted through the bile into the small intestine) points to biliary obstruction as part of the disease process. In addition, a horse with cholangiohepatitis (inflammation of the biliary tract) is likely to have a greenish-orange color to its urine, as conjugated bilirubin passes from blood to the urine.

Veterinarians can also test bile acids to determine liver function; these values are excellent prognostic indicators of chronic disease, said Divers. Because horses don't have a gall bladder, they secrete bile continuously through the biliary tract. Normally, most bile acid recycles back through the liver, with 1-2% going through the intestines. Other useful measures for liver disease are globulins and iron: High globulin levels are often indicative of the body's response to inflammation, and high iron levels are unique to a horse with hepatic disease.

With liver failure, it is not uncommon to see neurologic signs along with marked icterus (jaundice, yellowing of the mucous membranes). Often the horse develops blindness and is ataxic (uncoordinated). Other clinical signs range from edema (fluid swelling) along the ventral midline, weight loss, and dermatitis to colic, stomach impaction, and laryngeal paralysis.

Divers suggested taking a biopsy of the liver to pin down a diagnosis if the veterinarian is unsure of the inciting cause of disease and/or needs to pursue bacterial culture of the liver. The biopsy helps define acute versus chronic disease, to localize the zone most severely affected, identify the type of disease process, and determine whether the predominant problem is within the biliary tract or the liver tissue. The practitioner usually uses ultrasound to guide the biopsy, which also yields information about liver health.

Causes of Liver Failure
Cholangiohepatitis A common cause of liver disease in the horse is cholangiohepatitis, which typically begins as obstruction of the bile ducts with concurrent inflammation of the liver cells. It might begin as an ascending bacterial infection from the small intestine that, when chronic, forms sludge within the bile ducts that eventually turns into bile "stones." An affected horse usually has fever and abdominal pain. Other signs include icterus, photosensitivity (skin sensitivity to sunlight), weight loss, and, rarely, central nervous signs. Because this syndrome does not directly affect the hepatocytes (liver cells) as severely as it does the bile ducts, the horse maintains normal clotting factors and ammonia levels.

When the sludge turns into brown pigment stones, or cholelithiasis, these calcium bilirubinate stones won't always be visible on an ultrasound exam. Ideally, said Divers, you'd want to treat the horse early before stones form. Long-term (typically weeks to months) antibiotic therapy is important for eliminating the bacteria, along with fluid therapy to lessen the thickness of the sludge, and anti-inflammatory medications to help with a horse's comfort. The drug ursodiol (used in humans to dissolve gallstones) might help decrease inflammation and make the bile more liquid and easier to excrete. The veterinarian might need to clear the obstruction surgically if medical treatment does not resolve the sludge or stones.

"Horses with colon displacements to the right may sometimes have similar clinical signs and laboratory findings as with cholangiohepatitis," Divers added. "Right-sided colon displacements may stretch the hepatoduodenal ligament (which is located between the liver and the duodenum, which is a portion of the small intestine), causing obstruction of bile flow. With both disorders, the horse may have colic signs, marked jaundice, increased GGT and conjugated bilirubin levels, but fever and high white blood cell count would only be expected with cholangiohepatitis."

Theiler's Disease Divers discussed an important, although sporadic, cause of liver failure in the adult horse, which occurs when administration of tetanus antitoxin, plasma, or serum products causes serum-associated hepatitis. This syndrome can occur with a rapid onset of hepatocellular necrosis (liver cell death) and neurologic signs (due to hepatoencephalopathy, or abnormalities in brain function that occurs when the liver is unable to remove toxins from the blood) four to 10 weeks after administration of an equine-origin blood product. The liver decreases in size and has a firm consistency with sharp, flat edges. Disease duration can be six hours to three days.

Clinical signs include marked jaundice, sweating, discolored urine, and distinct neurologic signs such as head pressing into a solid object and/or repetitive yawning. The horse might also experience gastric impaction due to impaired intestinal motility.

An identical pathologic (causing tissue damage) and clinical disease (visible signs of illness) can occur without any history of administration of equine-origin blood products. This form of non-biologic Theiler's develops only in adult horses, sometimes as small outbreaks and usually in the fall of the year. "The reason for neurologic signs subsequent to liver failure is primarily because of ammonia-induced toxicity," said Divers. Nerve cells called astrocytes process ammonia into a substance called glutamine; excess ammonia and, therefore, glutamine causes fluid increases in the astrocytes, resulting in cerebral edema and brain dysfunction.

Aggressive treatment is important. "If treatment can keep the horse alive for four days, it may have complete recovery, as the liver can regenerate quickly," said Divers.

He listed crystalloid intravenous fluids, glucose, pH balancing, antibiotics, and nutritional supplementation as important supportive measures for managing hepatoencephalopathy, along with strategies to prevent injury from abnormal neurologic behaviors. He suggested using lactulose and oral antibiotics to decrease intestinal ammonia production. It's also important to keep the bowel active with quality forage and easily digestible feed to prevent constipation, as a sluggish intestine increases ammonia production in the gut. Supplement the horse with potassium, because potassium deficits increase ammonia production in the kidney. He warned against using a nasogastric tube to provide oral fluids and/or laxatives in the event that the horse suffers a nosebleed and swallows blood into the bowel, causing marked increases in intestinal ammonia production.

Liver Viruses Researchers suspect that there is a viral component to the serum-related and non-serum-associated Theiler's disease cases, due to incubation times (the duration from infection to appearance of clinical signs) and pathology similarities to human viral hepatitis. In fact, scientists have discovered four new equine hepatitis viruses in horses since 2012:

- Nonprimate hepatitis virus (NPHV), also called hepacivirus, which is a hepatocellular virus and the closest known relative to human hepatitis C.
- Equine pegivirus (EPgV), which does not have an effect on the liver and so far has not been associated with disease.
- Theiler's disease-associated virus (TDAV), which is similar to the pegivirus but has been associated with liver disease.
- A fourth virus that has been associated with numerous recent cases of Theiler's disease; more information is forthcoming in research publications.

Lastly, Divers mentioned Kirkovirus, which veterinarians found in the liver and spleen of a single horse dying from acute hepatic necrosis.

The NPHV virus was first identified incidentally in screening tests for equine infectious anemia (EIA) from healthy horses. More than 2% of adult horses have the virus present in their blood and may be chronically infected. Up to 44% have positive antibodies in their serum, indicating widespread exposure. This virus does not affect donkeys or mules, but it is found all over the world in horses. At this time it is not known how NPHV is transmitted, but the high seroprevalence (presence of antibodies in blood within a population) suggests that other avenues of infection occur besides blood products. Once a horse is infected, the virus replicates in the liver and causes transient disease but rarely, if ever, liver failure.

Veterinarians first identified equine Pegivirus in 12 of 74 adult horses in Alabama. It does not seem to have any correlation with clinical disease.

Theiler's disease-associated virus is similar to the hepatitis C virus in humans. In one outbreak, eight of 17 horses that had received an equine biologic product developed biochemical liver changes; four showed clinical signs and had abnormal laboratory findings that are associated with hepatic failure. The incubation period was 47-63 days. All infected horses recovered, but four remained viremic (had virus circulating in their blood) for up to 12 months. There does not appear to be horizontal (i.e., horse-to-horse) transmission. Divers reported that TDAV is not the cause of fulminant (acute and severe) Theiler's disease, and after deep sequencing of samples of tetanus antitoxin-associated Theiler's disease in 2014, researchers found another virus that Divers and other researchers are currently focusing on to help unravel the century-old mystery of "what causes Theiler's disease." This newly discovered and yet-to-be-reported virus is hepatotropic and was consistently associated with Theiler's cases in 2014 and 2015 but can also be found in a small percentage of normal horses, requiring further research to prove its association with Theiler's disease.

Hyperammonemia Without Liver Disease
Divers noted that horses can develop excess ammonia in the blood (hyperammonemia) without being affected by liver disease. "This is more common in horses than in other species, and it occurs mostly in adults with no breed predilection," he said. "Most are out on pasture. It is possibly related to changes in the intestinal microbiome (combination of microbial communities present), resulting in an increase in urease-producing bacteria. Or there may be both an increase of intestinal ammonia production along with increased intestinal permeability of ammonia, which overwhelm the liver's ability to metabolize ammonia."

A horse often has mild intestinal disease just prior to the onset of hyperammonemia and fulminant clinical signs within one to two days. Divers reports a 50% mortality rate in affected horses. He said horses with excess ammonia in the bloodstream quickly develop Alzheimer type 2 cells in the brain. This development was reported many years ago in foals given a paste iron product prior to receiving colostrum, causing a highly fatal, iron-induced liver failure.

Liver Disease Induced by Toxic Plants
The most commonly encountered liver-toxic plants that horses consume are those that contain pyrrolizidine alkaloids (PA). Divers said the flowers and seeds are usually the most toxic components, then the leaves, stems, and finally the roots. The plants are most toxic when growing and heading toward bloom. "A horse needs to eat approximately 2% of its body weight of the toxic plant in order to develop liver failure," he said. "Normally, PA-containing plants tend to be bitter, and horses will avoid them. Horses may not be able to avoid them when they are incidentally baled in hay or chopped up in cubes." Examples of PA-containing plants include fiddleneck, groundsel, ragwort, hounds tongue, and rattlebox.

When PA-containing plants are consumed, the liver metabolizes the pyrrolizidine alkaloids to their toxin, which kills liver cells and/or exerts anti-mitotic (cell dividing) effects on them, eventually causing widespread fibrosis (scarring) of the liver. The toxin is cumulative, causing ongoing hepatic damage until eventually the horse exhibits acute onset neurologic signs. Initially, the horse might show signs of weight loss, reduced appetite, jaundice, and photosensitization. Once you identify a horse with clinical signs, however, it might be too late to investigate the hay or forage source for noxious plants. If the source of the toxin is forage fed to all horses in a herd, multiple horses might be affected.

Elevated GGT enzyme levels are suggestive of exposure to plant toxins, including PA, but liver function tests and biopsy might better determine the cause and severity of the disease. In chronic cases, the liver can become small, nodular, and cirrhotic (late-stage fibrosis) with a thickened fibrous capsule.

The PA toxin is associated with a high mortality rate in clinically affected horses. "Attempts at treatment include the same supportive care for many other causes of fulminant liver failure," stressed Divers. For a horse with chronic liver disease not yet showing neurologic signs, Divers recommended feeding a moderate protein diet to avoid catabolism (tissue breakdown) of muscle mass that could lead to increased blood ammonia. He suggested offering branch-chain amino acid (leucine, isoleucine, and valine found in legumes) sources of protein along with antioxidants such as vitamins E and B, glutathione inducers (n-acetylcysteine, SAMe, or silybin), and supplementing with zinc.

Alsike clover causes "big liver disease," with the liver weighing as much as 5% of a horse's body weight due to extensive bile duct proliferation.

Photo: Aiwok/Wikimedia Commons

Other Plant Toxins Alsike clover poisoning occurs mostly in Canada and the Northeastern United States. This knee-high clover causes "big liver disease," with the liver weighing as much as 5% of a horse's body weight due to extensive bile duct proliferation—that would be 60 pounds in the 1,200-pound horse, when it would normally be around 20 pounds. Researchers suspect that mycotoxin growing on the clover is the inciting cause. Incidence increases during wet seasons.

Veterinarians identified another toxic plant, *Panicum dichotomiflorum*, in equine cases in Maryland and Virginia. Affected horses were stabled, not pastured. But once they were no longer offered the *Panicum*-contaminated hay, most recovered within 34 days. The toxin in this case might be due to a saponin (foaming compound in certain plants) that causes oxidative injury to the hepatocytes. In Texas and Nebraska, other *Panicum* spp have caused liver failure in horses.

Prevention is the best strategy in all plant toxicity cases. "Avoid putting horses out on denuded pastures if there is an increased risk of the presence of these toxic plants," said Divers. "High-protein diets may be somewhat protective."

Take-Home Message
The liver is an extremely complex organ, tasked with so many of the vital functions that maintain and sustain health and life. Liver disease in the horse can develop as an acute form or persist in a more chronic form. The potential problems that can occur with the liver are many and varied. Timely recognition of mild clinical signs, followed by biochemical tests, ultrasound, and biopsy, can all help the veterinarian determine the nature of the problem and begin therapy.