Liver Failure

The liver is a large organ located in the cranial abdomen just below the diaphragm. It has many important functions including:

- Pivotal roles in protein, carbohydrate, and fat metabolism
- Synthesis of most plasma proteins (albumin, globulin)
- Production of most coagulation factors necessary for clotting
- Detoxification and excretion of toxins and drugs
- Removal and destruction of worn-out red and white blood cells
- Formation and elimination of bile

The liver has an enormous reserve capacity and is able to regenerate up to 75% of its functional capacity in only a few weeks if a disease process can be stopped and therapy initiated with supportive care.

Liver failure occurs when there is injury to liver cells, also known as hepatocytes, which leads to cellular dysfunction and cell death. This injury can be caused by:

- An infectious agent (viral, bacterial, fungal, protozoal, rickettsial, leptospirosis, feline infectious peritonitis)
- A drug (acetaminophen, non-steroidal anti-inflammatories, phenobarbital, etc.)
- A chemical agent or toxin ( aflatoxin)
- Metabolic disease (pancreatitis, septicemia, hepatic lipidosis or “fatty” liver)
- Infiltrative disease (cancer, copper)
- Inflammatory disease (hepatitis, cholangiohepatitis)
- Trauma or hypoxic injury

History and Clinical Signs

Because of the great functional reserve of the liver, a large portion of reserve capacity must be lost before signs or symptoms appear in a pet. Most clinical signs observed in dogs and cats in liver failure are nonspecific but can include decreased appetite, vomiting, diarrhea, weight loss, dehydration, and yellow discoloration of the eyes, skin and gums. Increased thirst and urination may be observed as well.

As mentioned above, the liver plays a very important role in the production and activation of many clotting factors. This is why pets with severe liver dysfunction have a tendency to develop bleeding disorders. Bruising may be noted on the body as well as excessive bleeding from blood draw sites. Pets in liver failure are predisposed to forming stomach ulcers, therefore bloody vomit and dark tar like stools may be observed.
Pets in liver failure may develop a visible yellow tone to the skin, mucous membranes, and sclera (whites of the eyes). This is known as icterus or jaundice and is caused by the accumulation of bilirubin in the tissues. Bilirubin is a product of red blood cell destruction and is the major pigment in bile. During liver failure, the hepatocytes are unable to process bilirubin leading to the yellow discoloration.

Ascites is the accumulation of fluid in the abdomen. It is often observed in dogs with chronic liver failure but is uncommon in cats. Ascites is most commonly caused by portal hypertension (increased pressure in the vessels leading to the liver) and sodium retention. Portal hypertension occurs when something impedes the flow of blood through the liver. This leads to free fluid building up in the abdomen. Fluid accumulation may also be due to the decreased production of albumin. Albumin is a plasma protein made by the liver which is necessary to help keep fluid in the blood vessels. As albumin production diminishes, fluid begins to leak from vessels causing ascites and edema. Edema can been seen as swollen legs, paws, or face, and as increased breathing rate and effort.

Hypoglycemia (low blood glucose) is a complication of end stage liver failure due to the liver's central role in carbohydrate metabolism. Normal blood glucose levels are maintained by the healthy liver during normal fasting states.

In more severe cases, metabolic abnormalities can lead to an abnormal function of the central nervous system known as hepatic encephalopathy. Clinical signs of hepatic encephalopathy can range from minimal changes in behavior, to complete deterioration of mental function, coma, and seizure activity. As liver failure progresses, ammonia and other toxic substances begin to accumulate in the blood. The healthy liver normally detoxifies these substances and prevents them from reaching the systemic circulation. When liver function deteriorates higher than normal concentrations of these toxic substances reach the central nervous system resulting in hepatic encephalopathy. If hepatic encephalopathy progresses, it can lead to brain swelling.

**Diagnostic Testing**

A chemistry panel and a complete blood count are primary screening tests for liver disease. Elevated liver enzymes can reflect damage, inflammation, or irritation of the liver, but they tell us nothing about the functioning capacity of the liver. Liver enzymes measured on a chemistry panel are:

- Alanine Transferase (ALT)
- Aspartate Transferase (AST)
- Alkaline Phosphatase (ALKP)
- Gamma-Glutamyl Transpeptidase (GGT)
- Iditol Dehydrogenase (ID or SDH)

Chemistry panel values that are indicative of liver function are:

- Bilirubin
- Blood Glucose (BG)
- Cholesterol
- Albumin
- Blood Urea Nitrogen (BUN)

Serum bile acids and ammonia tests are also specific tests to evaluate liver function. A coagulation profile is often warranted in patients with liver disease to help predict their
risk of developing a bleeding problem. Other diagnostics such as radiographs and ultrasound may also be helpful in diagnosing liver disease. Finally, cytologic or histologic evaluation may be necessary to determine the underlying cause of liver disease. Cytology refers to the microscopic evaluation of a group of cells. Cells can be obtained from the liver by a procedure called fine needle aspiration. A needle is inserted into an area of interest and cells are then aspirated (pulled into) into the needle. Histology refers to the microscopic evaluation of a sample of tissue obtained through biopsy. A liver biopsy is obtained via ultrasound guided Tru-cut biopsy, or by a surgeon. This method is preferred over fine needle aspiration as it gives significantly more information.

Treatment

It is important to find the underlying cause of liver disease in order to better treat your pet. The more quickly a cause can be identified and eliminated, the better the chance of recovery. Treatment may include strategies to reduce and prevent inflammation, oxidative damage, fibrosis, and copper accumulation when applicable. Some commonly used medications are:

- **Ursodiol (Ursodeoxycholic Acid)**
  - A “good” bile acid used to increase bile flow, prevent hepatic cell death, reduce immune-mediated inflammation, and prevent oxidative damage
  - Must be given with food
  - Well tolerated in dogs and cats

- **Vitamin E**
  - An antioxidant that scavenges free-radicals which are responsible for causing oxidative damage to cells
  - Should be given with food

- **Denamarin** - A combination of **SAMe** and **Silymarin**
  - Liver protectants
  - No significant side effects
  - Must be given on an empty stomach at least one hour before a meal; do not cut or crush tablets; do not remove from foil package until ready to give to pet

- **SAMe** (S-Adenosyl-L-methionine)
  - A natural metabolite of the liver used to prevent oxidative damage

- **Silymarin** (milk thistle)
  - A free radical scavenger used to prevent oxidative damage

- **Sucralfate**
  - A gastroprotectant used to treat stomach ulcers
  - Can be given as a slurry dissolved in 5-10 mL of water
  - Give on an empty stomach at least 2 hours before or after food or another medication
  - Can cause constipation

- **Pepcid (famotidine)**
  - Used to reduce stomach acid production for the prevention and treatment of stomach ulcers with no significant side effects
- **Vitamin K**
  - May need to be supplemented due to deficiency in diseased liver states
  - Necessary for the activation of some clotting factors
  - Should be given with food
  - No significant side effects

- **Metronidazole**
  - An antibiotic used to treat bacterial infections in the liver from the gastrointestinal tract
  - Can cause nausea and vomiting, lethargy and weakness
  - Is metabolized by the liver, so decreased dose is given to patients with liver disease
  - Can be toxic to the nervous system. Signs of intoxication include vomiting, depression, dilated pupils, dizziness, stumbling, head-tilt, disorientation, tremors, and seizures. If you observe any of these signs in your pet, discontinue the medication and inform your doctor immediately.

- **Amoxicillin**
  - An antibiotic used to treat bacterial infections
  - Can cause inappetence, vomiting and diarrhea
  - Give with food to decrease stomach upset

- **Lactulose**
  - Used to reduce ammonia levels
  - Appropriate dose is achieved when 2-3 pudding-like soft stools are observed per day
  - Diarrhea may develop

- **Prednisone / Prednisolone**
  - A glucocorticoid used to treat hepatitis because of its anti-inflammatory and immunosuppressive properties
  - A life threatening crisis can develop if this medication is suddenly stopped. Do not chance the dose of this medication unless directed to by your doctor
  - Do not give aspirin or any non-steroidal drug (Rimadyl, Metacam, Deramaxx, etc.) with this medication. Doing so could cause stomach ulcers
  - Side effects include:
    - Increased thirst and urination; water must always be available
    - Increased hunger and weight gain; do not feed more
    - Stomach ulcers; alert your doctor if bloody vomit or black tar-like stools or coffee ground-like stools are observed
    - Vomiting and Diarrhea
    - Muscle wasting
    - Elevated liver enzymes
    - Panting
    - Increased risk of forming blood clots
- **D-penicillamine**
  - A copper chelator used to treat copper toxicosis
  - Adverse effects include nausea, vomiting, and depression

Routine supportive care should be implemented and consist of fluid therapy and nutritional support. Fluid therapy will help maintain hydration and provide support to the cardiovascular system. Nutritional support is essential in helping the liver to regenerate. A feeding tube may need to be placed in patients that will not eat on their own, or in patients who don’t consume adequate amounts of food. In most severe cases, total parental nutrition may need to be provided where the patient receives all of its nutrients through an intravenous catheter.