

# Chronic Liver Disease

The liver is the largest gland in the body. It is located in the abdominal cavity and lies just in front of the stomach next to the diaphragm. The liver is the body's "detoxifier." All of the blood circulates through the liver to be filtered and cleaned before returning to the heart. Liver disease can present itself very quickly or can occur very slowly over many months.

**CAUSES** of liver disease include infections, consumption or exposure to poisons, abnormal blood flow (usually a birth defect), hereditary disorders, autoimmune disease, cancer, etc. Cats can also develop liver disease from just not eating for a few days, regardless of the cause of the poor appetite. Untreated liver disease can result in inflammation of the liver, bile stones, and cirrhosis.

## **SIGNS of Liver Disease:**

- Loss of appetite
- Depression
- Vomiting
- Jaundice (yellowish discoloration of the lips or eyes)
- Increased thirst
- Discoloration of the urine or stool
- Bloating of the abdomen due to fluid build-up
- Bruises on the gums or belly due to poor blood clotting ability
- Inflamed, scaly skin that does not respond to the usual treatments for skin infection

**DIAGNOSIS** of the specific type of liver disease is confirmed by physical examination, blood tests, ultrasound testing, radiographs (x-rays), and sometimes biopsy.

**TREATMENT** of chronic liver disease:

## **Milk Thistle – Marin®, DenaMarin®**

Milk thistle (silymarin) is an herbal antioxidant which has recently been embraced by conventional veterinary internal medicine specialists. It is often used in management of liver disease in people and some benefit has been shown in medical journal articles. A study in dogs fed mushrooms toxic to the liver showed a protective effect against toxicity when high doses of milk thistle were given at 5 and 12 hours post exposure. Veterinarians have used milk thistle for dogs with chronic liver disease and to protect against liver toxicity due to anti-seizure drugs.

## **SAMe (S-adenosyl-L-methionine) – Denosyl®, DenaMarin®**

This product is an antioxidant and anti-inflammatory food supplement. SAMe has particular importance in liver cells. SAMe can influence inflammation, promotes healing (cell replication and protein synthesis), protects the liver cells, and is important in promoting important liver function. It is a building block of essential chemical in the cells.

The liver, which can be likened to a large lymph node situated in the center of the body, undergoes great exposure to toxins. Therefore liver has an enormous responsibility to protect the rest of the body from free radicals, and oxidation. In the normal state, the liver is an important source of SAMe for itself and for the body. However, reduced liver size, impaired function, or nutritional deficiencies may directly impair production of SAMe. The effects of this may include methionine intolerance and increased production and accumulation of oxidants derived from primary systemic or liver/gall bladder disease, thereby leading to worsening liver damage.

SAMe deficiency appears to be an enabling factor in liver disease pathogenesis. The accumulation of certain harmful bile acids perpetuates liver damage. In SAMe deficiency, certain chemical reactions in the liver may

become impaired, which enhances bile acid toxicity. Studies have shown that addition of SAME to cell cultures reduced toxicity of harmful bile salts. Clinical benefit has been demonstrated in humans with different forms of bile stasis. Recent work has also shown that SAME provides therapeutic benefit effect when used with Actigall® (ursodiol).

SAME helps restore liver cell function by stimulating cell repair, fighting free radicals, suppressing inflammation, and improving chemical reactions in the liver, and eliminating toxins, among many other things. No significant side effects are noted, other than occasional stomach upset. If this happens, give SAME with food.

## **Antibiotics**

Antibiotic therapy is indicated for treatment of various kinds of inflammatory and infectious liver disease or failure. One of the normal functions of the liver is that it "cleans up" the blood from the gut, removing toxins, bacteria and other infectious organisms, before that blood is sent to the rest of the body. There are many organisms that live in the normal gut which could potentially infect the liver or the rest of the body, if not dealt with. A sick liver sometimes needs antibiotics to help achieve this goal. Some liver patients need antibiotics only as needed, and others need to take an antibiotic such as amoxicillin, metronidazole, or neomycin every day.

Antibiotics that should be avoided in treatment of liver disease include chloramphenicol, lincomycin, sulfonamides, erythromycin, and tetracycline. These drugs are either inactivated by the liver, require hepatic metabolism, or are capable of producing hepatic damage. Tetracyclines can also potentially be toxic to the liver. Cultures of the liver or gall bladder, if they can be safely done, can help guide therapy for chronic infections.

Another role of the liver is to remove chemicals from the blood stream that can be toxic to the brain, and cause poor coordination, stupor or even seizures. When enough of these toxins build up in the blood, a condition called "hepatic encephalopathy" or HE can occur. Some of these toxins are produced by certain bacteria in the colon, and chronic antibiotic administration can help manage this problem.

One of the liver's many important functions is to act as a very large lymph node, removing pathogens from the blood that is collected from the abdominal organs and taken to the liver prior to going to the rest of the body. Dogs and cats with chronic liver disease may have decreased lymph node function of the liver, resulting in tendency to get infections when other dogs would not. Bacterial exposure should be treated more aggressively in pets with liver disease than usual (dental care, minor cuts and surgeries, etc.). Failure to do so could result in overwhelming infection, pneumonia, etc.

## **Actigall® (ursodiol)**

Ursodeoxycholic acid (Ursodiol; Actigall®) has been used in the management of chronic hepatic disease in humans, including chronic active hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and gallbladder disease. Significant improvement in symptoms and laboratory tests has been reported in many patients undergoing treatment for these diseases. Ursodiol is a naturally occurring bile acid. The exact mechanisms of its beneficial effects in inflammatory hepatic diseases remain controversial. It is believed that there is a favorable change in the bile acid pool, rendering the naturally occurring bile acids less toxic.

Ursodiol is usually well tolerated, and in some cases the response can be dramatic. It may be the only effective drug in animals where corticosteroid therapy or other immunosuppressive drug therapy is either too risky or ineffective. Ursodiol also is effective at thinning the bile, and can be used to treat sludged bile and gall stones.

Actigall® is available as a 300 mg capsule preparation, and also as a generic 250mg tablet, the generic being much more affordable. Cats are usually given 1/4 tablet once daily, either given by mouth or mixed in a small amount of food.

## **Diet**

Special diet for liver disease usually becomes necessary only when liver disease is advanced. The easiest way to accomplish the nutritional goals below is to feed Hill's Prescription diet L/D.

Protein restriction (17-22% of calories) is indicated for advanced liver disease, because HE can result if the body takes in more protein than the liver can detoxify. Too much protein restriction can also cause problems, as the liver needs some protein to produce the many proteins necessary for the body to function (albumin, clotting factors, etc.). Highly digestible (high biologic value) proteins will minimize protein byproducts that might contribute to HE. Consider cottage cheese, eggs, tofu, chicken, etc.

Amino acid carnitine should be increased. Aromatic amino acids such as tyrosine, phenylalanine, and tryptophan should be minimized, as they can increase risk of HE. Branched chain amino acids should be increased.

Fermentable and bulk fiber should be increased, as it will help control HE, by trapping and binding toxins, and keeping toxic things moving out of the body. Fiber can help slow the digestive tract and maintain blood sugar levels in those dogs with liver disease that tend to have low blood sugar. Calories in the form of grains (30-50%) can minimize HE by replacing the calories lost by restricted protein. Metamucil can be added to the diet for increased fiber.

Fats usually need to be increased, to maintain body weight in the face of protein restriction.

Excess sodium should be avoided if there is fluid accumulation in the abdomen, or if albumin is low in bloodwork. If potassium levels fall, it will need to be supplemented. Excess copper should be avoided in Bedlington Terriers, Labrador Retrievers and other breeds predisposed to Copper Storage Disease. Liver, shellfish, organ meats and cereals are all high in copper content, and should be avoided. Zinc has anti-scarring and liver protection properties, and is often supplemented in patients with liver disease. Zinc deficiency is well documented in people with liver disease, but has not been evaluated in dogs and cats with liver disease. Over supplementation of iron should be avoided.

Vitamin K is required for clotting and levels can drop in dogs and cats with chronic liver disease, especially if there is bile obstruction and/or chronic diarrhea. It should be supplemented if clotting times are abnormal, or if surgical procedures are done. B vitamins are often not properly stored in a sick liver, and often need to be supplemented, especially if the patient takes diuretic therapy for fluid accumulation in the abdomen, or drinks a great deal of water.

Multiple small meals rather than fewer large meals can help, especially so if there are blood sugar abnormalities or HE. Multiple small meals can help prevent nutritional overload of the liver, resulting in toxins spilling over into the bloodstream.

## **Probiotics**

Probiotics are beneficial bacteria that live in the colon. Supplementing probiotics may help reduce harmful bacteria in the colon that contribute to HE. Recommended brands are Culturelle® which can be purchased at your local pharmacy, or veterinary products such as Purina Fortiflora® and Nutramax ProViable®. There are many probiotics on the market which are not effective. We have a separate handout on this information – please request it if you are using probiotics or are interested in the information.

## **Lactulose**

Lactulose (Cephulac®, Enulose®) is a sugar solution used in long-term management of HE. Lactulose, which is not digested or absorbed in the small intestine, is broken down by bacteria in the colon to reduce the pH there. This traps ammonia in the colon, and keeps it from getting into the bloodstream to harm the brain. The fermentation products of lactulose also act as a laxative, which helps decrease the numbers of harmful bacteria in the colon.

The dosage can be increased as necessary until the desired effect of 2-3 soft stools per day is reached. Side effects include diarrhea and flatulence. Lactulose can be given to patients in hepatic encephalopathy crisis (manifested as stupor or coma) via stomach tube or enema, by your veterinarian.

Intestinal antibiotics such as neomycin with or without metronidazole, may act along with lactulose to markedly decrease colonic bacterial numbers. Long-term lactulose therapy should be instituted if dietary protein restriction does not control clinical signs of HE.

## **Corticosteroids**

Cortisone therapy is used for some types of inflammatory and autoimmune liver disease, including chronic inflammatory hepatitis, cholangiohepatitis, and immune-mediated liver disease. They are not usually used unless these conditions are proven by liver biopsy of some sort. Corticosteroids have several therapeutic benefits in liver disease. They reduce the inflammatory component of liver disease and arrest destruction of liver cells in chronic inflammatory and immune-mediated liver disease. They may also be of value in reducing mild degrees of scarring. Corticosteroid use may lead to an increase in serum albumin levels and bile flow, which can be helpful in some cases. Corticosteroids are more often used in cats with liver disease, as compared to dogs.

The preferred corticosteroids are prednisone or prednisolone. Because corticosteroids are normally metabolized by the liver before excretion by the kidneys, the dosage must be carefully calculated to avoid signs of corticosteroid excess. Long-term therapy is usually necessary for chronic inflammatory hepatitis. The course of therapy for cholangiohepatitis is variable (3-4 months to several years). Affected animals should be monitored by periodic recheck of blood chemistry profiles and bile acid assays and repeat liver biopsies where possible.

The down side of using corticosteroids is that at high doses, they can suppress the immune system and allow infection to develop, which is a significant risk in liver disease patients.

## **Azathioprine**

Azathioprine (Imuran®) is an immunosuppressive agent that has been beneficial in treatment of many autoimmune disorders, as well as in treatment of chronic inflammatory hepatitis in people. It is most often used in combination with prednisone therapy. Azathioprine should be considered when a patient cannot tolerate corticosteroids at high dosages or when prednisone therapy alone is inadequate in controlling inflammatory liver disease. The prednisone dose often can be halved when used with azathioprine without lessening the desired immunosuppressive effect of therapy. The dosage should be decreased by 50% after a few weeks, and alternate day therapy is used when the disease is in remission. Early signs of azathioprine toxicity include low blood cell counts, gastrointestinal upset, skin reactions, and liver toxicity. These effects are not common in dogs and usually resolve with reduced dosage or discontinuation.

## **Colchicine**

Colchicine has been used in treatment of hepatic fibrosis (scarring), a common sequel to liver damage, which can result in cirrhosis. Early scarring often resolves after the initiating cause is removed. A moderate amount of scarring resolves with corticosteroid therapy but more advanced scarring requires more specific therapy. Colchicine may be capable of inhibiting production of the proteins that cause scarring (collagen) and promoting collagen breakdown in certain situations.

Side effects of long-term colchicine use include vomiting, increased movement in the gut, diarrhea, and poor absorption of nutrients. Although improvement may be noted in patients with hepatic fibrosis, there is no proven increase in survival time in patients on colchicine therapy as compared to untreated controls. For this reason, colchicine is rarely used for liver failure.

## Copper Reduction Therapy

Copper reduction therapy is indicated if there is an elevated level of copper in the liver, called Wilson's Disease – biopsy is required to determine this. Copper reduction therapy is indicated if the copper level is greater than 750 ug/g dry weight liver. Treatment strategies include dietary copper restriction, therapy to limit copper absorption (dietary zinc), and copper chelator therapy (d-penicillamine, trientine).

Zinc given as either the acetate, sulfate, or gluconate salt has proven effective in preventing hepatic copper accumulation in humans with Wilson's disease. Oral zinc therapy has also been shown to be beneficial in some Bedlington terriers with copper toxicity of the liver. Dietary zinc works by inducing enzymes bind copper in the gut. Vomiting is a potential side effect. Zinc gluconate administered in a time release capsule may be less likely to cause vomiting.

Copper chelators include penicillamine (Cuprimine® or Depen®) and trientine (Syprine®). Chelators bind with copper either in the blood or the tissues and then promote its removal through the kidneys. Side effects include nausea and vomiting. If side effects occur they can be decreased by giving the medication with a small amount of food (e.g., cheese, bread). Often side effects will resolve after the first several weeks of therapy. Trientine may be a more effective copper chelator. A significant advantage of this drug is that there are no associated GI side effects. Unfortunately this drug is very difficult to obtain (recently taken off the market by the manufacturer in the US).

Copper reduction therapy is a long process. It many take months to years to effect a substantial reduction in hepatic copper.

## Anti-Nausea Medications

Patients with liver disease sometimes need medications for nausea, to keep them feeling good and eating well. These medications might include maropitant (Cerenia®), ondansetron (Zofran®) or others. Maropitant is the most effective, but it also is the most expensive.

## Ulcer Medications, Antacids

For many reasons, dogs with liver disease are prone to ulcers and bleeding into the GI tract. Antacids (Prilosec®, Zantac®, Pepcid®) and coating agents (sucralfate) are used as needed to control this problem. Cimetidine (Tagamet®) should be avoided in liver disease because it is metabolized by the liver and is an enzyme suppressor altering hepatic metabolism of other drugs. Proton pump blocker antacids such as omeprazole (Prilosec®), esomeprazole (Nexium®), pantoprazole (Protonix®) and lansoprazole (Prevacid®) should be used only for a short time – weeks at most, then patients that need chronic antacids should be transitioned to H2 blockers such as famotidine (Pepcid®, ranitidine (Zantac®) or nizatidine (Axid®) for long term use.

## Diuretics

Diuretics such as furosemide (Lasix, Salix, Disal) are sometime used to control accumulation of fluid in the abdomen, when the fluid becomes uncomfortable for the patient. If the patient fails to respond to furosemide, another diuretic called spironolactone can be tried, which works a little differently. Fluid is reduced just enough to allow the patient to be comfortable, as removing a large amount of abdominal fluid too fast can cause problems for a liver disease patient.

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### References:

Wendy Blount, DVM, PracticalVetMed  
HomeCare Client Handouts