

MANAGEMENT OF CHRONIC LIVER DISEASE IN DOGS

Todd R. Tams, DVM, Diplomate, ACVIM
VCA West Los Angeles Animal Hospital
Los Angeles, California, USA

Antibiotics

Antibiotic therapy is indicated for treatment of suppurative hepatitis, cholangiohepatitis and hepatic encephalopathy, and prevention of septicemia. The bactericidal function of the hepatic reticuloendothelial (RE) system may be compromised in hepatic disease, especially if hepatic blood flow or oxygen tension is altered, resulting in septicemia. In hepatic bacterial encephalopathy, antibiotics are used to help reduce colonic bacterial numbers in an effort to decrease ammonia formation. Cholangitis has several causes, including bacterial invasion, which warrants antibiotic therapy. The regimen may be modified in accordance with specific information obtained from cultures of bile, hepatic tissue or blood. In cases of compromised hepatic RE function (e.g. hepatitis from any cause, septicemia) the antibiotics selected generally are directed against intestinal organisms.

Antibiotics routinely used in treatment of patients with liver disease include penicillins (ampicillin 10 mg/lb TID, amoxicillin 10 mg/lb BID), cephalexin (Keflex, Dista) 10 mg/lb TID, enrofloxacin (Baytril) 1.2 - 2.3 mg/lb BID, and metronidazole (Flagyl, Searle) 5-10 mg/lb BID. Chloramphenicol and tetracycline are alternative choices that are effectively excreted in the bile, however, tetracycline is potentially hepatotoxic. Although high hepatic tissue levels are reached with chloramphenicol, the plasma half-life can be prolonged and toxicity may occur in patients with liver disease.

Metronidazole is highly active against Bacteroides and other anaerobes that exist in high numbers in the colon. Bacteriologic studies have suggested that gram-negative anaerobes are major generators of ammonia from peptides. Metronidazole's effectiveness against these bacteria could help reduce production of endogenous ammonia, thus benefiting patients with hepatic encephalopathy. It may also be useful in treatment of any liver disorder complicated by inability of the hepatic RE system to clear bacteria absorbed through the portal circulation. The combination of metronidazole and an aminoglycoside may be superior for this purpose. Metronidazole may also be useful in treatment of some chronic inflammatory conditions because it helps reduce cell-mediated immune responses. I sometimes use metronidazole for 2-6 months or longer, in conjunction with maintenance levels of corticosteroids, for liver disease patients that may have both a bacterial and inflammatory component, or that are unable to tolerate required dosage levels of corticosteroids used alone to control the disease. Metronidazole is my routine drug of choice for chronic administration in hepatic encephalopathy patients. It can be used safely in combination with other antibiotics.

Antibiotics that should be avoided in treatment of liver disease include chloramphenicol, lincomycin, sulfonamides, erythromycin, and hetacillin. These drugs are either inactivated by the liver, require hepatic metabolism, or are capable of producing hepatic damage.

If septicemia or peritonitis occurs in conjunction with liver disease gentamicin 1 mg/lb TID IM or SC is administered for 5-7 days (while monitoring renal function carefully) in conjunction with cephalothin (Keflin, Lilly) at 10 mg/lb TID IV or cefoxitin (Mefoxin) at 10 mg/lb TID to QID IV for broad-spectrum coverage while awaiting culture and sensitivity results. If an anaerobic organism is identified on culture the antibiotics most likely to be effective include penicillin G 10,000 u/lb every 4-6 hours IV, metronidazole, or clindamycin 2.5-5 mg/lb BID PO.

Corticosteroids

Corticosteroid therapy is indicated in treatment of chronic active hepatitis, cholangiohepatitis, and immune-mediated hepatopathies. Corticosteroids have several therapeutic benefits in liver disease. They reduce the inflammatory component of liver disease and arrest destruction of hepatocytes in chronic active hepatitis and immune-mediated hepatopathies by reducing tissue lymphocyte and plasma cell numbers. They may also be of value in reducing mild degrees of fibrosis. Corticosteroid use may lead to an increase in serum albumin levels and bile flow and may decrease serum transaminase levels.

The preferred corticosteroids are prednisone or prednisolone. Because corticosteroids are normally metabolized by the liver before renal excretion, the dosage must be carefully calculated to avoid signs of corticosteroid excess. In general, the starting dosage of prednisone for inflammatory liver disease in dogs is 0.5 mg/lb divided BID for 2-4 weeks, followed by a decrease in dosage by one-half at each of several ensuing 2-6 week intervals, until an alternate day remission dosage of 0.1 - 0.2 mg/lb is reached.

Long-term therapy is usually necessary for chronic active hepatitis. Reinstitution of therapy after a relapse is not often as successful in controlling the disease as the initial therapy. 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.

Azathioprine

Azathioprine (Imuran), a thiopurine compound, is an immunosuppressive agent that has been beneficial in treatment of many immune-mediated disorders, as well as in treatment of chronic active 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 the disease. The prednisone dose often can be halved when used with azathioprine without lessening the desired immunosuppressive effect of therapy. The initial canine dosage of azathioprine is 1 mg/lb given PO once daily. The dosage should be decreased by 50% after several months and alternate day therapy is used when the disease is in remission. Early signs of azathioprine toxicity include leukopenia, thrombocytopenia, gastrointestinal upset, dermatologic reactions, and hepatotoxicity. 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, a common sequel to hepatic inflammation and necrosis. It is characterized by abnormal deposition of collagen in the liver without a loss of normal architecture. Early fibrosis often resolves after the initiating cause is removed. A moderate amount of fibrosis resolves with corticosteroid therapy but more advanced fibrosis requires more specific therapy. Colchicine may be capable of inhibiting hepatic collagen synthesis and promoting collagen breakdown in certain situations.

Side effects of long-term colchicine use include vomiting, hyperperistalsis, diarrhea, and malabsorption, and are attributed to its direct effect on the intestinal mucosa. Although clinical and histologic 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. The dose of colchicine is 0.07 mg/lb SID. Patients should be observed for possible adverse effects during the required long-term therapy.

Lactulose

Lactulose (Cephulac; Schiapparelli Searle) is a disaccharide used in long-term management of hepatic encephalopathy. Lactulose, which is not digested or absorbed in the small intestine, is hydrolyzed by colonic bacteria. The resultant colonic acidification increases conversion of ammonia to ammonium, which is less diffusible, thus decreasing systemic ammonia levels. The fermentation products of lactulose also act as an osmotic laxative, which helps decrease the numbers of colonic bacteria.

For maintenance therapy, lactulose is given at 5 ml (3.3 g) /2.5 lb/day divided TID; 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 at 20-60 ml (13-40 g) every 4-6 hours. Alternatively, lactulose may be given in this situation as intermittent enemas diluted with water to total 200-300 ml (300-450 g). Intestinal antibiotics, such as neomycin with or without metronidazole, may act synergistically 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 encephalopathy.

Actigall

Ursodeoxycholic acid (Ursodiol; Actigall) has been used in the management of chronic hepatic disease in humans, including chronic active hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. Significant improvement in symptoms and laboratory parameters have been reported in many patients undergoing treatment for these diseases.

Ursodeoxycholic acid is a naturally occurring dihydroxylated bile acid. One of its uses is for dissolution of radiolucent gallstones. 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 retained endogenous bile acids less toxic.

I have used ursodeoxycholic acid in animals with various cholestatic diseases including dogs with chronic active hepatitis, fibrosis, and cirrhosis and in cats with cholangiohepatitis, either alone or in combination with other drugs. The drug is very well tolerated, and in some cases the response can be dramatic. Use of ursodeoxycholic acid should be considered as either primary or adjunctive (in combination with immunosuppressive or antiinflammatory drugs) treatment in animals with chronic liver disease. It may be the only effective drug in animals where glucocorticoid therapy or other immunosuppressive drug therapy is either contraindicated or ineffective. Ursodeoxycholic acid is also a powerful choleretic agent that can be used to treat sludged bile and cholelithiasis. The recommended dose is 5 to 7 mg/lb per day, administered either once daily or divided BID.

Actigall is available as a 300 mg capsule preparation. Fractions of a capsule can easily be prepared for use in cats and small dogs. Cats are usually given 1/6 capsule once daily, mixed in a small amount of food. Many cats will actually still eat their food even if Actigall is sprinkled on the top. The medication is expensive (\$2.50 to \$3.15 per capsule at pharmacies in Los Angeles).

SAMe (S-adenosyl-L-methionine)

This product is an antioxidant and antiinflammatory nutraceutical. Derived from the amino acid methionine and ATP, SAMe initiates three major biochemical pathways: *transmethylation*, *transsulfuration*, and *aminopropylation*. It has particular importance in hepatocytes that conduct or influence the bulk of intermediary metabolism. SAMe has modulating influence on inflammation, promotes cell replication and protein synthesis, has cytoprotective effects, and is important in promoting sulfation and methylation. It is a precursor of essential intracellular oxidants.

The liver, which can be likened to a large lymph node situated in the center of the body, undergoes great exposure to injurious products including free radicals, oxidants, and endotoxins. The liver has enormous cytoprotective capabilities, conjugation pathways, and antioxidants. Membrane damage by free radicals and oxidation is a basic mechanism of cell pathology in nearly all liver and biliary tree diseases. In the normal state, the liver is an important source of SAMe for itself and for the body. However, reduced hepatic mass, 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 hepatobiliary disease, thereby leading to worsening liver damage.

SAMe deficiency appears to be an enabling factor in liver disease pathogenesis.

The accumulation of membranocytolytic bile acids perpetuates liver damage. Sulfation of membranocytolytic bile acids reduces their toxicity, which allows them to be eliminated. Taurine conjugation also reduces bile acid toxicity. In SAMe deficiency, both sulfation and taurine conjugation may become impaired, which enhances bile acid toxicity. Studies have shown that *in vitro* addition of SAMe to cell cultures reduced toxicity to hydrophobic bile salts. Clinical benefit has been demonstrated in humans with different forms of cholestasis. Recent work has also shown that SAMe provides an adjunctive therapeutic effect when used with ursodeoxycholic acid.

SAMe helps restore hepatocyte function by simultaneously stimulating cell repair, attenuating free radical production and accumulation, suppressing inflammation, and improving conjugation, membrane function, and toxin neutralization and elimination. SAMe may improve hepatocellular handling of organic ions (e.g., bile acids), attenuate alkaline phosphatase induction, and beneficially alter glutathione stores and metabolism in dogs given chronic high dose glucocorticoid therapy.

Oral administration on an empty stomach optimizes bioavailability. The recommended dose is 10 mg/lb/day (see dosage table below). Conditions for which SAMe use should be considered include feline hepatic lipidosis, feline cholangitis and cholangiohepatitis, and in dogs with marked vacuolar hepatopathy from either glucocorticoid administration or idiopathic vacuolar hepatopathy, and in chronic active hepatitis. No significant side effects or changes in routine clinicopathologic parameters develop in healthy or ill humans. There are no known side effects in animals.

Several products are available over the counter but have widely varying potency. The only product recommended at this time for use in dogs and cats is Denosyl SD4 (Nutramax Laboratories, Inc., Edgewood, Maryland; www.nutramaxlabs.com). Denosyl is available in 90, 225, and 425 mg tablet sizes.

FELINE AND CANINE DENOSYL DAILY* ADMINISTRATION GUIDE					
For Cats and Small Dogs			For Larger Dogs		
Body Weight		90 mg Denosyl	Body Weight		425 mg Denosyl
Pounds	Kilograms	One tablet	Pounds	Kilograms	One tablet
Up to 12	Up to 5.5		35 to 65	16 to 29.5	
			66 to 120	30 to 54.5	Two tablets
			Over 120	Over 54.5	Three tablets
For Medium Dogs					
Body Weight		225 mg Denosyl			
Pounds	Kilograms	One tablet			
13 to 34	6 to 15.5				

*The number of tablets can be gradually reduced or increased at any time depending on the pet's needs. Many pets are maintained long-term on every-other-day or every-third-day administration.

Milk Thistle

Milk thistle (silymarin) is a bioflavonoid that has antioxidant properties. It is often used in management of liver disease in people and some benefit has been shown in refereed journal articles. A study in dogs fed hepatotoxic mushrooms showed a protective effect against clinical and pathologic changes 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 ameliorate hepatic effects of anticonvulsants. Doses vary from 50-200 mg given every 12 to 24 hours.

Silybin/silymarin has many different mechanisms of action. In vitro and in vivo studies have shown that it protects against oxidative stress, promotes hepatocyte protein synthesis, a mechanism for liver cell regeneration, inhibits leukotriene production, which can be beneficial as production of leukotrienes is a component of the inflammatory response, stimulates biliary flow and production of hepatoprotective bile salts, and increases levels of glutathione.

Many products have been available over the counter, and potency varies. However, in February 2005 Nutramax laboratories released a new veterinary product, called **MARIN**. Marin contains silybin, vitamin E, and zinc; all in a single tablet formulation. (MARIN for cats contains silybin and vitamin E only). Silybin is the most active component of silymarin, derived from the milk thistle. The silybin in Marin is in a phosphatidylcholine complex to increase bioavailability, reportedly reaching up to 10 times more than 80% standardized milk thistle formulas.

Denamarin

Denamarin is a combination of S-adenosylmethionine and silybin-phosphatidylcholine complex. Denamarin can be used in conjunction with Marin in cases where it may be desirable to provide additional levels of silybin along with vitamin E and zinc supplementation (the latter two are available in Marin but not Denamarin). If Marin is used in conjunction with Denamarin, the two products should be administered 12 hours apart for best response.

Denamarin is available in three sizes: Denamarin for cats and small dogs (90 mg of S-adenosylmethionine and 9 mg of silybin A+B), Denamarin for medium size dogs ((225 mg S-adenosylmethionine with 24 mg of silybin A+B), and Denamarin for large dogs (425 mg of S-adenosylmethionine and 35 mg of Silybin A+B).

Copper Reduction Therapy

Copper reduction therapy is indicated if there is an elevated level of copper in the liver. Copper reduction therapy is indicated if the copper level is greater than 750 ug/g dry weight liver. Therapeutic 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 hepatotoxicity. Dietary zinc works by causing an induction of the intestinal copper-binding protein metallothionein. Dietary copper binds to the metallothionein with a high affinity and when intestinal cells die and are then sloughed the metallothionein bound copper becomes excreted through the stool. The starting dose is 7.5 mg/lb BID on an empty stomach. Vomiting is a potential side effect. Zinc gluconate administered in a time release capsule may be less likely to cause vomiting. The zinc dose can be reduced to SID after 1-2 months. Serum zinc concentrations should double but ultimately should not exceed 400 ug/dl. Concentrations approaching 1000 mg/dl can result in hemolysis.

Copper chelators include penicillamine (Cuprimine 250 mg capsules or Depen 250 mg tablets) and trientine (2,2,2-tetramine, Syprine). Chelators bind with copper either in the blood or the

tissues and then promote its removal through the kidneys. Historically penicillamine has been the most commonly prescribed drug (7.5 mg/lb BID on an empty stomach). 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. Additional beneficial effects of penicillamine may include induction of metallothionein with subsequent binding and sequestration of copper in a nontoxic form; and immunosuppressive, immunomodulation, and anticollagen effects. Trientine may be a more effective copper chelator and is also used at 7.5 mg/lb BID. 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 may take months to years to effect a substantial reduction in hepatic copper.

Case Studies:

Diagnosis of Liver Disorders in Clinically Normal Dogs Based on Wellness Screening Tests

Case 1:

1.5 year SF Schnauzer. No clinical abnormalities, normal physical exam. Adult wellness panel with urinalysis ordered.

Wellness panel:

<u>CBC</u>		<u>Profile</u>	
WBC	11,100	ALT	260 (N = 12-118)
Neut	7,659	ALP	73
Lymph	1,887	BUN	9
Mono	666	Creatinine	0.8
Eos	888	T.P.	5.7
PCV	51%	Albumin	3.7
Hb	17.2	Glucose	66
MCV/MCH	WNL	K	4.3
Platelets	348,000		

HW Ag Neg

Considering a slightly increased ALT of 260, what next step would you take at your practice?

Options could include:

1. Ignore it?

2. Start a protein restricted diet right away? (not warranted or recommended at this point in time)
3. Begin hepatic supportive therapy, e.g., SAMe?
4. No treatment indicated but recommend re-check ALT in 3-4 weeks to establish a trend?
5. Perform a liver function test (e.g., bile acids assay)

Plan: Re-check ALT in 4 weeks.

Result: ALT 313.

Next step: Perform bile acids assay.

Result: Resting sample: 257 mmol/L

Post feeding sample: 113 mmol/L

Next step: Portosystemic shunt is suspected. Transcolonic portal scintigraphy study (nuclear medicine study – non-invasive study to assess for presence of an operable portosystemic shunt)

Result: Shunt present, shunt fraction 85% (N = <15%)

Next step: Shunt surgery (placement of ameroid constrictor ring)

Follow-up: Smooth recovery from surgery, bile acids nearly normal 6 weeks post op.

Summary: This is an excellent example of a case where a serious medical problem was diagnosed before the patient ever showed any clinical abnormalities. The dog was an excellent surgical candidate and the procedure and recovery went smoothly. The dog's owners expressed great appreciation to their veterinarian for establishing an early diagnosis of their pet's problem.

Case 2:

4 year NM Doberman. Presented for annual wellness exam. No clinical abnormalities, normal physical exam other than mild dental plaque.

Wellness panel:

CBC - WNL

Platelets 335,000

HW Ag Neg

Profile

ALT 940 (N = 12-118)

ALP	385
BUN	18
Creatinine	1.1
T.P.	7.6
Albumin	3.8
Glucose	90
K	4.6

Considering an increased ALT of 940, what next step would you take at your practice?

Further testing included:

1. Bile acids assay – normal
2. Abdominal radiographs – liver size normal to perhaps a little smaller than normal
3. Abdominal ultrasound – Slightly hyperechoic liver

The dog was then referred to a specialist for a liver biopsy via laparoscopy. Sufficient hepatic tissue was obtained for copper analysis (quantitation, not just special stains) and aerobic and anaerobic culture.

Results:

1. Histopath: Moderate chronic active hepatitis with biliary hyperplasia
2. Copper: 784 ppm (N = <400; toxic = >1500)
3. Anaerobic culture: Negative
4. Aerobic culture: *Pseudomonas*

Medical management was instituted:

1. Enrofloxacin 6 weeks
2. Prednisone
3. SAMe (Denosyl SD4 – Nutramax)
4. Marin (combination of silybin, Zn, and vitamin E – Nutramax)
5. Ursodiol

This is an excellent example showing the value of performing routine screening testing on a breed that is known to be at risk for chronic inflammatory liver disease. In this case, it is hoped that early diagnosis will lead to more effective disease control and less likelihood for progression to a life threatening form of the disease. It is anticipated that longterm therapy will be necessary.

References

Hoffmann G, van den Ingh TSG, Bodew P, Rothuizen J. Copper-associated chronic hepatitis in Labrador retrievers. J Vet Int Med 2006; 20:856-861.

Mehl ML, Kyles AE, Hardie EM, Kass, PH, et al. Evaluation of ameroid ring constrictors for treatment for single extrahepatic portosystemic shunts in dogs: 168 cases (1995-2001). J Am Vet Med Assoc 2005; 226:2020-2030.

Sepesy LM, Center SA, Randolph JF, et al. Vacuolar hepatopathy in dogs: 336 cases (1993-2005). J Am Vet Med Assoc 2006; 229:246-252.

