

# **A Case-based Approach to the Canine Patient with Increased Liver Enzyme Activities: Clinical Update on the Use of Nutraceuticals in the Management Liver Disease**

**Joseph Taboada, DVM, DACVIM**  
Department of Veterinary Clinical Sciences  
School of Veterinary Medicine  
Louisiana State University  
Baton Rouge, Louisiana

These lectures are interactive case-based presentations in which the audience will work through a series of cases that present for increased liver enzyme activity, with or without clinical signs. The first case is a young dog that presents for a yearly check-up, the second is an older dog that presents for gastrointestinal signs, and the third is a dog that has gotten into potentially hepatotoxic substances. The sessions will work through the diagnosis and treatment options for these cases. What would you do?

## **INTRODUCTION**

Liver disease is a problem occasionally encountered in small animal practice. In some instances the underlying problem may have been *caused* by drug therapy or exposure to hepatotoxic compounds such as xylitol or sago palm. Inflammatory, immune mediated, and neoplastic liver diseases occur more frequently as an animal ages and congenital disease such as PSS may be seen in younger animals. Bacterial infections are occasionally seen. In cats, hepatic lipidosis is common and inflammatory liver disease can occur singly or in combination with inflammation involving the gastrointestinal tract and/or the pancreas. Liver disease may be acute and resolve with proper management, or it may be a chronic, slowly-developing or waxing and waning condition. In dogs, chronic liver disease tends to progress to an eventual outcome of severe fibrosis or cirrhosis while in cats progressive disease rarely results in the same type of end stage changes. Oxidative damage is present in most forms of liver disease. Managing the underlying disease relies on good supportive measures and management of oxidative damage. There is no “magic bullet” that restores a failing or compromised liver. There are a number of compounds classified as nutraceuticals that have proven effective in supporting the diseased or damaged liver.

## **EVALUATING THE PATIENT WITH SUSPECTED LIVER DISEASE**

The clinical signs associated with liver disease are often vague, leading one to at times suspect potential liver disease for the first time only when a chemistry panel is evaluated and increased liver enzyme activities or total bilirubin are noted. Unfortunately, increased liver enzyme activity is not specific for liver disease; the liver often being affected as an innocent bystander to disease in other organ systems or liver enzyme activity being increased as an apparently incidental finding; especially in older animals. Metabolic disease such as hyperthyroidism, hyperadrenocorticism, diabetes mellitus, or hepatocutaneous syndrome and gastrointestinal diseases such as inflammatory bowel disease and pancreatitis often result in increases in liver enzyme activity. Diseases resulting in adrenal gland hyperplasia and increases in either glucocorticoids or adrenal androgens also commonly present for increased liver enzyme activities.

Clinical signs may be nondescript such as anorexia, lethargy, weakness, and weight loss. Gastrointestinal signs such as vomiting (and less often diarrhea) are common. The signs may be severe in acute disease but tend to develop more insidiously in chronic disease. As chronic liver disease becomes end stage neurologic signs, most often characterized by depressive signs and behavior changes, may be noted. Edema, most often noted as ascites, and evidence of bleeding associated with coagulopathies may be seen as liver disease becomes more chronic. In patients with cholestatic liver disease icterus may be noted.

The most common reason for a veterinarian to suspect liver disease is an increase in liver enzyme activity. Increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) activities are common findings that may be indicative of liver disease but are not predictive of

hepatocellular dysfunction. Increased transaminase activities are an indication of leakage of the hepatocellular enzymes from the hepatocytes. Increased serum activities may indicate hepatocellular membrane damage, hepatocellular necrosis, or increased hepatocellular enzyme concentration secondary to enzyme induction. Membrane damage is the most common reason for ALT and AST increases and may or may not indicate significant liver disease. It is common for animals with intestinal disease such as inflammatory bowel disease or metabolic diseases such as hyperthyroidism or diabetes mellitus to have increased transaminase activity. A complete drug history is important for patients with increased liver enzyme activities, as many drugs can damage hepatocellular membranes, induce inflammation or necrosis, or induce enzyme production. Questioning the pet owners about treatment with such drugs as NSAIDs, corticosteroids, anticonvulsants, anthelmintics, antibiotics, imidazole antifungals, antithyroid drugs, and immunosuppressive agents is especially important. Increased alkaline phosphatase (ALP) or gamma-glutamyltransferase (GGT) activity may be induced by cholestasis. The clinically significant isoenzymes of ALP are hepatic and bone derived in dogs and cats and corticosteroid-induced (C-ALP) in dogs. These isoenzymes have a half-life of approximately 72 hours in dogs but are significantly less in cats. Disease affecting the liver or biliary tree commonly increases activities of the hepatic isoenzyme of ALP. Disease increasing bone turnover increases osseous ALP activity, and the presence of exogenous or endogenous corticosteroids induces increased activities of C-ALP in dogs. Even short courses of steroids can cause significant increases in C-ALP activity that may remain increased for a month or more after the steroids are discontinued.

Increased ALP activity is a common finding on the chemistry panel of older dogs. The hepatic isoenzyme becomes increasingly more important as dogs age. When seen without concurrently increased transaminase activity liver disease is probably less likely than steroid influences such as hyperadrenocorticism, exogenous steroid administration, or increased adrenal production of adrenal androgens. Regenerative changes, such as regenerative nodules common in older dogs may result in increased ALP activity but other poorly understood derangements of adrenal steroid hormones are increasingly being recognized as causes of ALP activity increase in older dogs.

Increased liver enzyme activities alone in a dog without clinical signs or other blood work abnormalities consistent with liver disease should not automatically be considered evidence of significant hepatocellular damage. Increased liver enzyme activities in a cat are a more significant finding and should lead to earlier evaluation but may still not represent significant hepatocellular disease. When increased liver enzyme activities are noted, other parts of the chemistry panel that may become abnormal in animals with hepatocellular dysfunction should be scrutinized carefully. Increased bilirubin or decreased albumin in the patient with increased liver enzyme activities should cause the clinician to thoroughly evaluate the patient for liver disease and consider treatment. Decreased BUN or hypoglycemia may be signs of reduced hepatic function but are more commonly noted in young animals with portosystemic vascular anomalies than in older animals with acquired liver disease. If the rest of the chemistry panel is normal and the patient is otherwise healthy the panel should be repeated in 1 to 3 months. Persistent increases or other evidence of liver disease should cause the clinician to consider further evaluation and the use of antioxidants.

Increased liver enzyme activities does not necessarily indicate reduced hepatic function so a test of liver function should be considered as part of the further evaluation of the patient with suspected liver disease. Fasting and postprandial serum bile acids are the most commonly used liver function test in dogs and cats. Fasting blood ammonia or ammonia tolerance testing are liver function tests that are also sensitive and specific. Evaluating blood ammonia is the preferred test in animals with signs of hepatoencephalopathy or in icteric animals where cholestasis will have an impact on serum bile acid concentrations. Because the liver produces most of the clotting factors and other cofactors involved in coagulation it is common for patients with decreased liver function to have abnormalities of tests of coagulation such as PT, PTT, ACT, and PIVKA. Although these tests may identify loss of hepatic function, they do not correlate well with measurements of drug clearance.

Diagnosing most specific liver diseases is dependent on a tissue diagnosis; a step that can be invasive and expensive. Hepatic cytology can be used to guide the clinician but cytology can be misleading when compared to histopathology; especially in the dog. It may be useful in diffuse or infiltrative diseases such as hepatic lipidosis or neoplasia but is generally not helpful in the diagnosis of inflammatory and fibrosing conditions. Because of the higher prevalence of diffuse or infiltrative diseases in the cat, feline liver diseases lend themselves to cytologic diagnosis more than canine diseases do.

## TREATMENT CONSIDERATIONS

In addition to supportive and nutritional support, antimicrobials, antiinflammatories, and immunosuppressive therapy play a role in managing dogs and cats with liver disease. Nutraceuticals may play an important role for their antioxidative, anti-inflammatory and immunosuppressive properties. For patients with suspected loss of hepatic function, it is ideal to select drugs that rely on the kidneys for elimination rather than hepatic biotransformation.

In the case of antibiotic therapy, the  $\beta$ -lactam antibiotics (amoxicillin-clavulanate, ampicillin, cephalosporins) and fluoroquinolones are the best choice. (Hepatic reactions observed in people caused by amoxicillin-clavulanate were associated with a specific leukocyte antigen and have not been reported in animals.) The fluoroquinolones (enrofloxacin, marbofloxacin, orbifloxacin, difloxacin) have had a good safety record and increased risk of toxicity in animals with hepatic disease has not been documented. Although some of these drugs are metabolized, the clearance is low and probably not affected unless there is substantial loss of hepatic function. These drugs are also cleared by the kidneys. Fluoroquinolones have been known to cause central nervous system (CNS) problems in susceptible individuals. This is most likely caused by penetration across the blood-brain-barrier (BBB) and inhibition of the action of the GABA neurotransmitter. Problems observed have been seizures, excitement, and disorientation. Animals with seizure disorders caused by hepatoencephalopathy may be more prone to CNS problems caused by fluoroquinolones. If a complication is observed after prescribing a fluoroquinolone drug, a switch to a safer drug is appropriate. Macrolides (erythromycin, azithromycin, and similar drugs) are sometimes used for infections in animals with hepatic disease. There are no specific problems identified in patients with hepatic disease, but these antibiotics are often associated with gastrointestinal problems in animals (diarrhea and vomiting). Therefore, when prescribing these drugs, veterinarians should be careful not to mistake a drug-related problem for an underlying disease, or complication an already-existing problem. Metronidazole and related drugs (tinidazole, ronidazole) are sometimes used in patients with hepatic disease because of the anaerobic spectrum. They have been safe drugs when prescribed according to standard dose recommendations, but when doses have been exceeded, problems may arise. The most serious problem caused by metronidazole has been attributed to CNS toxicity and include seizures, ataxia, nystagmus, tremors, and rigidity. These signs have been attributed to interfering with the inhibitory neurotransmitter GABA. Because animals with hepatoencephalopathy also may be prone to CNS signs that may be similar to those seen with metronidazole toxicity, veterinarians should become familiar with the signs associated with toxicity. When using other antimicrobials, veterinarians should be aware of the common adverse effects that may occur if a drug accumulates because of a deficiency in metabolism. Drugs to avoid, if possible, include: trimethoprim-sulfonamides, tetracyclines, rifampin, nitrofurantoin, and chloramphenicol.

Immunosuppressive agents should be added to the treatment regime in cats with non-suppurative hepatic inflammation, in cats with suppurative hepatic disease that fail to respond to antibiotics alone, and dogs with inflammatory hepatopathies in which secondary fibrotic changes are occurring. Prednisolone (2-4 mg/kg/day initially then slowly tapered to 1 mg/kg QOD) is used most commonly. Other immunosuppressives that may be used in cats responding poorly to glucocorticoids include chlorambucil (1.5 to 4 mg/M<sup>2</sup> twice a week to q48 hrs; approximately 1 mg < 7 lb cat, 2 mg > 7 lb cat) [a safer alternative to azathioprine in the cat] or azathioprine (0.3 mg/kg q24-72 hrs) [Note that cats are much more sensitive to the myelosuppressive effects of azathioprine than dogs]. Azathioprine (1-2 mg/kg PO q24h to q48h) may be a more appropriate agent in dogs although a study comparing chlorambucil-prednisolone combination with an azathioprine-prednisolone combination in the treatment of dogs with chronic protein-losing enteropathy suggested that chlorambucil may be more efficacious. Cyclosporine (5-8 mg/kg PO q24h) has been used with some success in dogs with inflammatory liver disease and may be effective without concurrent prednisolone reducing steroid-induced complications and making it easier to follow liver enzyme activity as an indicator of treatment efficacy. In a recent retrospective assessment of 50 dogs with inflammatory liver disease, 76% achieved remission with normalization of liver enzyme activities within 2 months of starting cyclosporine. The median dose at the time of remission was 7.8 mg/kg/day (1.5–12.7 mg/kg/day) (Ullal, et al. ACVIM forum 2018). Ursodeoxycholic acid (Actigall®) 10-15 mg/kg PO SID is a safe treatment alternative that can be used in cats with suppurative or non-suppurative disease. The drug appears to have multiple actions including shifting the bile acid pool to a less toxic hydrophilic population, a choleric effect, reducing expression of Class 2 major

histocompatibility complex, and an antiinflammatory effect. Vitamin E (aqueous alpha tocopherol, 10-100 IU/kg/day) has been advocated for its antioxidant effects and is present in some multi-antioxidant combination nutraceuticals.

## **NUTRACEUTICALS**

Nutraceuticals such as vitamin E, milk thistle extracts, S-adenosylmethionine, and L-carnitine can play a significant role in ameliorating oxidative stress. Oxidative stress plays an important role in hepatocellular injury and injury perpetuation during liver disease; especially inflammatory liver disease and hepatocellular toxicity. Oxidative stress is defined as an imbalance between oxidant and antioxidant systems (such as an excess of reactive oxygen species [ROS] or a deficiency in antioxidants). The liver possesses a complex antioxidant network that can be divided into enzymatic and nonenzymatic pathways. Nonenzymatic defenses include glutathione (GSH), vitamin E, and ascorbate. GSH is one of the most critical parts of the liver defense against the effects of oxidative stress and is an important site of nutraceuticals activity.

### **N-acetylcysteine**

N-acetylcysteine is a stable formulation of the amino acid L-cysteine. It can be given parenterally to replenish intracellular cysteine and GSH levels. N-acetylcysteine is primarily recognized as an antidote for acetaminophen-induced red blood cell and hepatocyte toxicity. It has been evaluated and shown benefit in models of acute liver failure where positive cytoprotective effects are primarily mediated through increased GSH concentrations. Additionally N-acetylcysteine improves sinusoidal microcirculation, increases the efficiency of oxygen delivery, and decreases inflammation. High level evidence is available showing improved survival in children with acute liver failure. The recommendation in acute liver failure in dogs and cats is the same as for acetaminophen toxicity. It is to give an initial dose of 140 mg/kg followed by doses of 70 mg/kg intravenously every 6 hours for seven treatments. N-acetylcysteine should be administered through a nonpyrogenic filter (0.25 mm) using a 10% solution diluted 1:2 or more with saline. Oral administration often results in gastrointestinal irritation and vomiting. If a patient can tolerate oral medications it is better to give SAME or SAME and Silybin combinations. Indications for N-acetylcysteine use in veterinary medicine include acetaminophen toxicity, Heinz body anemia, suspected toxin-related liver injury, and acute liver failure (regardless of underlying etiology).

### **S-adenosylmethionine (SAME)**

S-adenosylmethionine (SAME) is generated from L-methionine and ATP in a two-step reaction catalyzed by methionine adenosyltransferase (MAT). The activity of this enzyme is decreased in many types of liver disease, which results in decreased concentrations of SAME in the hepatocyte. SAME is an important intermediate in the metabolism of methionine to GSH. SAME has been shown to have important cytoprotective effects that include antioxidant activity through augmentation of hepatocyte GSH levels, modification of the balance between pro- and anti-inflammatory cytokine expression, alterations in DNA/histone methylation, improvement in membrane fluidity, modulation of apoptosis, by reducing TNF-alpha induced necrosis, and decreasing malignant transformation of hepatocytes. SAME has been evaluated in a number of animal models of liver disease, experimental liver insult, and human clinical trials and has shown to be effective in treating a number of different hepatocellular toxicities (alcohol, acetaminophen, galactosamine, pyrazole, thioacetarsamide, and CCNU induced hepatotoxicity) as well as cholestatic liver disease and alcoholic cirrhosis in humans. It has been shown to significantly increase hepatic GSH concentrations in healthy dogs and cats and to reduce acetaminophen induced hepatic and red blood cell damage in cats (85 mg/kg for 3 days followed by 40 mg/kg) and dogs (40 mg/kg followed by 20 mg/kg).

SAME is available commercially as a stable tosylate salt complex (Denosyl, Nutramax Laboratories, Inc., Lancaster, South Carolina; Zentonil, Vetoquinol, Buena, New Jersey). Tablets are blister packed and enteric coated because SAME is hygroscopic and sensitive to light and heat. The tablets must not be split or crushed. Food interferes with absorption, requiring that SAME be given on an empty stomach. Denosyl is also available in a chewable form in which the SAME itself is protected by a granular barrier. While it still needs to be given on an empty stomach, a more consistent absorption is seen in dogs with the chewable formulation versus the enteric coated tablet. The recommended oral dose

is 20 mg/kg/d. SAME is well tolerated when given orally with mild GI signs being occasionally reported. While trials in dogs and cats with hepatic disease have not been conducted, work in humans and other animal models would predict that there may be value in using SAME in the management of disorders such as acute intrahepatic or extrahepatic cholestatic disorders, necroinflammatory diseases such as feline cholangitis or canine inflammatory liver disease, metabolic diseases such as feline hepatic lipidosis or hepatic copper toxicosis, and toxic or ischemic hepatopathies. SAME may have additive or synergistic effects when used with ursodeoxycholic acid.

### **Milk Thistle Extracts**

The major active ingredient of benefit in milk thistle is silymarin; a group of several closely related flavonoids, primarily silybin, isosilybin, silydianin, and silychristin. Silybin is a major active component of silymarin. Silymarin has been shown to have antioxidant, anti-inflammatory, and antifibrotic activities in the treatment of patients with liver disease. Additionally, it has choleric effects and is hepatoprotective following exposure to a number of different hepatotoxins, including acetaminophen, CCNU, ethanol, carbon tetrachloride, aflatoxin, *Amanita phalloides* toxins and others. Silybin was found to be completely protective against *A. phalloides* intoxication in Beagles at a dose of 50 mg/kg when given 5 and 24 hours after ingesting an LD50 dose of *A. phalloides*.

Silymarin's bioavailability is low due to erratic absorption from the gastrointestinal tract. It is excreted in bile as a glucuronide and sulfo-glucuronide conjugate and undergoes some enterohepatic circulation. Bile concentrations are 100 times those seen in serum. Silybin complexed with phosphatidylcholine, is three to five times more bioavailable than silymarin. Phosphatidylcholine also may have antifibrotic effects. Silybin complexed with phosphatidylcholine is the form used in the Nutramax products Marin (combined product with vitamin E and zinc), Marin *plus* (combined with vitamin E, zinc, and *Curcumin longa* extract), and Denamarin (combined with SAME). A dose of 6 mg/kg of silybin-phosphatidylcholine complex is recommended. Toxicity studies in dogs and cats as well as extensive use in humans have not shown any untoward effects. Reports of gastrointestinal signs in dogs taking the Nutramax product Marin may be associated with the Zinc in the combination and recommendations that Marin be taken with food have been made to reduce the potential for gastrointestinal signs. Silymarin may have benefit in cases of hepatotoxicity, hepatobiliary disease associated with cholestasis, and chronic necroinflammatory hepatopathies. Silymarin use is indicated in the treatment of *Amanita* mushroom toxicity, although high doses are needed to inhibit uptake of the phalloidin toxin.

The combination product that is Marin *plus* contains Curcumin in addition to Vitamin E, Zinc, and Silybin-phosphatidylcholine. Curcumin has shown to protect liver against hepatic injury and fibrogenesis by suppressing hepatic inflammation, attenuating hepatic oxidative stress, and increasing expression of the xenobiotic detoxifying enzymes. This combination product is less expensive than Denamarin and has been suggested for patients that need support for oxidative injury but cannot afford Denamarin.

### **SAME and Silybin Combined**

Nutramax markets a combined product, Denamarin™, that includes both silybin complexed with phosphatidylcholine and SAME in enteric coated and chewable tablets and is dosed according to the SAME at 20 mg/kg. The product is given on an empty stomach to maximize SAME absorption. Even small amounts of food will dramatically decrease the bioavailability. A prospective randomized controlled trial in dogs receiving CCNU with or without Denamarin™ showed decreased liver enzyme activities and potentially reduced hepatotoxicity associated with dogs in the CCNU Denamarin™ group and a higher percentage of dogs receiving Denamarin™ finishing the chemotherapy protocol. The results of this study beg the question as to whether Denamarin™ would have similar cytoprotective effects in treatment protocols with other potentially hepatotoxic drugs in dogs. A recent proprietary salt of SAME used in Denamarin *Advanced*™ has increased bioavailability allowing reduced dose to 8 mg/kg. This has decreased costs and allowed for smaller chewable tablets with increased palatability. The increased bioavailability may overcome the poor absorption that comes about when given with a small amount of food that is sometimes necessary to get the dog to eat the pill. A Denamarin *Advanced*™ for cats is also available. The smaller tablet compared to the chewable tablet for small dogs makes it easier to dose cats. It is recommended to be given on an empty stomach but crushing the tablet and giving it in a small

amount of wet food may allow for easier administration and the increased bioavailability may allow for absorption even with the small amount of food.

An ACVIM consensus statement on the diagnosis and treatment of chronic hepatitis in dogs recommended SAME be used in the treatment of chronic hepatitis based on available evidence but they could not come to a consensus on the use of silymarin (Webster et al. 2019). Based on what was said at the 2019 ACVIM forum, most members on the panel use the combination product in their practices.

## **Vitamin E**

Vitamin E is an essential nutrient made up of a family of highly lipophilic antioxidant compounds, the most bioavailable and active of which is Alpha-tocopherol. It plays a number of important protective roles, the most important of which is the protection of membrane phospholipids from oxidative damage. It suppresses activation of inflammatory cytokines and of activation of Kupffer and stellate cells. The effects of vitamin E supplementation in veterinary patients with hepatobiliary disease have not been reported except for a small pilot study of 20 dogs with chronic hepatitis fed a vitamin E-supplemented diet for 3 months. In these dogs, increases in serum and hepatic vitamin E concentrations were accompanied by an increased hepatic GSH:GSSG ratio, suggestive of an improved hepatic redox status. A dose of 10 to 15 IU/kg/d of alpha-tocopherol is recommended for dogs and cats that have necroinflammatory or cholestatic liver disorders.

## **Probiotics: Do they have a place in treating liver disease**

Much is being learned about the intestinal microbiota and the influences that changes in the microbiota (dysbiosis) can have on the gastrointestinal tract and the liver. The liver is an important first pass organ impacting toxins, nutrients, bacterial metabolites, and bacteria that translocate across the gastrointestinal mucosa. The role of microbiota in liver disease largely derives from the inflammatory pathway that is triggered from the interaction between gut bacteria, the liver, and the immune system. These changes may result in increased bacterial metabolites and cytokines such as lipopolysaccharides, peptidoglycans, toll-like receptor agonists, and bacterial DNA that can have an impact on hepatocellular health. Increased oxidative stress and hepatocellular inflammation may result in a self-perpetuating pattern of inflammation and fibrosis or in metabolic liver disease such as non-alcoholic fatty liver disease (NAFLD/NASH) in people. Manipulation of the microbiota may have an effect of reducing oxidative stress and decreasing inflammation, decreasing fibrosis, and reducing clinical signs of hepatoencephalopathy. Administration of *Lactobacillus* spp and *Bifidobacterium* spp have been shown to improve hepatic function and hepatic biomarkers in humans and rodent models of alcoholic liver disease, NAFLD/NASH as well as in cirrhosis induced hepatoencephalopathy.

There are many probiotics marketed for use in veterinary patients. Most are derived from a single strain of bacteria such as an *Enterococcus* or *Lactobacillus*. The number of CFU's vary considerably between products. Nutramax has two probiotic products, Provable DC™ and Provable Forte™ each containing multiple different strains of bacteria. Provable Forte™ contain multiple different strains of bacteria as well as prebiotics (Synbiotic). It contains at least 10 billion CFU's of seven bacterial strains including *Enterococcus*, *Streptococcus*, *Lactobacillus*, and *Bifidobacterium* spp. While studies specific to benefits of probiotics in dogs and cats have not been performed evidence in other species would suggest a potential benefit.

## **Cobalamin (vitamin B<sub>12</sub>) supplementation in liver disease**

As many as two-thirds of dogs and cats with diffuse small intestinal, pancreatic, and liver disease have been shown to be cobalamin deficient and treatment of the deficiency may be necessary to improve clinical signs. Diagnosis can be based on decreased serum vitamin B<sub>12</sub> concentrations but some patients with cobalamin deficiency on a cellular level do not have severely decreased serum cobalamin concentrations. Because of this cobalamin supplementation should be considered in all patients with liver and/or pancreatic disease, especially if they are not responding as well to treatment as one would hope. Traditionally, cyanocobalamin has been administered parenterally because of concern for ileal malabsorption of oral cobalamin. Subcutaneous injection of 250 ug in cats and 250-1500 ug in dogs depending on size should be given weekly for 6 weeks and then after another month. Serum cobalamin should be within the supranormal at that time. If clinical signs have not completely resolved and

cobalamin concentrations are within the normal range treatment should be continued monthly. However, recent studies in both dogs and cats have shown efficacy when chronic oral supplementation has been used. Nutramax markets a cobalamin product, Cobalequin™. Formulated specifically for dogs and cats as a once-daily chicken flavored chewable tablet. Oral supplementation should be continued for at least 3 months.

**Dosing schedule for oral cobalamin supplementation:**

- Cyanocobalamin orally once a day for 3 months
- 250 ug in cats or dogs up to 10 kg in body weight
- 500 ug in dogs weighing over 10 kg but less than 20 kg
- 1000 ug in dogs weighing more than 20 kg
- Re-evaluation of serum cobalamin concentration one week after stopping supplementation

**Antifibrotics**

When treating canine hepatic disease ongoing fibrosis is a concern. In dogs, unlike most cats, progression to an endstage cirrhotic liver is common with most causes of chronic hepatitis. A number of drugs have been proposed as potential antifibrotics, including colchicine, spironolactone, angiotensin II receptor blockers, statins, phosphatidylcholine, penicillamine, Silybin, SAME, and glucocorticoids. None of the drugs have proven to be very effective antifibrotics in other species. Antifibrotic drugs and nutraceuticals have not been critically evaluated in the dog. No recommendation was made by the ACVIM chronic hepatitis consensus group on this topic.

Anstee QM, Day CP. S-adenosylmethionine (SAME) therapy in liver disease: A review of current evidence and clinical utility. *J Hepatol* (2012), <http://dx.doi.org/10.1016/j.jhep.2012.04.041>. [Epub ahead of print]

Au AY, Hasenwinkel JM, Frondoza CG. Hepatoprotective effects of S-adenosylmethionine and silybin on canine hepatocytes in vitro. *J Anim Physiol Anim Nutr* 2013; 97(2):331-341.

Cesaro C, Tiso, A, Del Prete A, et al. Gut microbiota and probiotics in chronic liver diseases. *Dig Liv Dis* 2011 43:431-438.

Dandrieux JRS, Noble PJM, Scase TJ, Cripps PJ, German AJ. Comparison of a chlorambucil-prednisolone combination with an azathioprine-prednisolone combination for treatment of chronic enteropathy with concurrent protein-losing enteropathy in dogs: 27 cases (2007-2010). *J Am Vet Med Assoc* 2013; 242:1705-1714.

Filburn CR, Kettenacker R, Griffin DW. Bioavailability of a silybin-phosphatidylcholine complex in dogs. *J Vet Pharmacol Therap* 2007; 30:132-138.

Filburn CR, Kettenacker R, Griffin D. Safety and Bioavailability in Beagles of Zinc and Vitamin E Combined with Silybin and Phosphatidylcholine. *Intern J Appl Res Vet Med* 2006; 4:326-334.

Haque TR, Barritt AS. Intestinal microbiota in liver disease. *Best Pract Res Clin Gastroenterol* 2016; 30:133-142.

Skorupski KA, Hammond GM, Irish AM, Kent MS, Guerrero TA, Rodriquez CO, Griffin DW. Prospective randomized clinical trial assessing the efficacy of Denamarin for prevention of CCNU-induced hepatopathy in tumor-bearing dogs. *J Vet Intern Med* 2011; 25:838-845.

Toresson L, Steiner JM, Suchodolski JS, Spillmann T. Oral cobalamin supplementation in dogs with chronic enteropathies and hypocobalaminemia. *J Vet Intern Med.* 2016; 30:101-107.

Toresson L, Steiner JM, Suchodolski JS, et al. Oral cobalamin supplementation in cats with hypocobalaminemia. *J Vet Intern Med.* 2016; 30:417(abstract).

Ullal TV, Ambrosini Y, Rao S, et al. The evaluation of cyclosporine in the treatment of chronic hepatitis in dogs (Abstract HP03). ACVIM Forum Proceedings; 2018.

Webster CRL, Cooper J. Therapeutic use of cytoprotective agents in canine and feline hepatobiliary disease. *Vet Clin N Amer Small Anim* 2009; 39:631–652.

Webster CRL, Center SA, Cullen JM, et al. ACVIM consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. *J Vet Intern Med* 2019; 33:1173-1200.