Causes of Chronic Hepatitis in the Dog

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Chronic hepatitis is not a single disease. Many different causes (infectious, drugs, toxins, auto-immune) can provoke hepatic inflammation, necrosis, fibrosis, and cirrhosis. The severity of inflammation and duration of disease is variable, and the clinical presentation of chronic hepatitis not predictable. Some patients present with non-specific signs of weight loss and inappetence, whereas others present with a more advanced syndrome of jaundice and abdominal effusion. This talk will focus on liver diseases in dogs that have a familial predisposition.

Classification of Chronic Hepatitis in the Dog

Familial Predisposition
- Copper hepatitis in Bedlington Terriers
- Copper hepatitis in West Highland White Terriers
- Copper hepatitis in Skye Terriers
- Copper hepatitis in Doberman Pinschers (?)
- Cocker Spaniels
- Labrador Retrievers
- Standard Poodles

Infectious
- Infectious canine hepatitis virus
- Leptospira
  - grippotyphosa (serovar *grippotyphosa*)
  - australis (serovars *australis, bratsilava, muenchen)*

Drug-associated
- Anticonvulsants
- Diethylcarbamazine-oxibendazole
- NSAIDs (Carprofen?)
- Antifungals (ketoconazole, itraconazole)
- Antibiotics(trimethoprin-sulfa, tetracycline)

Idiopathic
- Lobular Dissecting Hepatitis
- Idiopathic Chronic Hepatitis

Familial Chronic Hepatitis

Chronic hepatitis occurs more frequently in certain breeds of dogs. The most well-recognized of these is the Bedlington Terrier, in which an inherited defect of copper metabolism causes pathologic accumulation of copper in the hepatocytes. Hepatic copper accumulation also occurs in other pure breeds, particularly West Highland White Terriers, Skye Terriers and Doberman Pinschers. Some dogs of these breeds have hepatic copper accumulation but do not develop clinical signs of liver disease, whereas others do. A genetic basis has yet to be identified in these breeds. Because copper is normally secreted from hepatocytes into the bile, hepatic copper accumulation can also occur secondary to cholestatic disease. Any dog with a chronic cholestatic disease can accumulate excessive hepatic copper, however concentrations are usually less compared to dogs with primary copper accumulation. American and English cocker spaniels have an increased incidence of chronic hepatitis and cirrhosis not associated with copper accumulation.

Bedlington Terriers develop chronic hepatitis as a result of an autosomal recessive metabolic defect in biliary copper excretion. In health, dietary copper is circulated to the liver where it is bound to hepatic cytosol proteins and temporarily stored. If not used, copper is sequestered in hepatic lysosomes until excreted in the bile and eliminated in the feces. The genetic defect in Bedlingtons causes copper accumulation as the dog ages, but damage usually does not occur in Bedlingtons until hepatic copper concentration exceeds 1500 - 2000 ug/gm of dry liver weight (parts per million). At this concentration, excess unbound copper causes oxidant damage to hepatocyte; chronic hepatocellular damage can slowly progress for years.

Affected dogs can be asymptomatic, or can show signs of acute hepatic failure, chronic hepatitis, or cirrhosis. Clinical signs and biochemical findings vary relative to the amount of copper accumulation. Young (< 1 yr.) to middle aged dogs are often clinically normal despite having increased hepatic copper. Increased serum ALT activity is usually the only evidence of disease in these patients. However, up to one-third of affected dogs have normal ALT activity. Acute liver failure can occur characterized by severe vomiting and depression, marked increases in serum ALT, jaundice, hepatic encephalopathy, hemolysis. Other dogs have a slow course of illness lasting months to years that eventually leads to chronic liver

failure characterized by emaciation, ascites, and jaundice.

Liver biopsy is needed for diagnosis and for staging of the disease, and should be done in all animals being considered for breeding. Pathologic changes vary from focal to diffuse hepatitis, fibrosis or cirrhosis. Specific copper stains (rubeanic acid or rhodanine) confirm excessive hepatic copper. Patients positive for copper require quantitative tissue analysis to determine therapy. Most diagnostic labs require a 1 gram sample of *non-formalin* preserved liver (approximately the size of a pea), submitted in a plastic or glass container and frozen. Normal hepatic copper concentrations should be less than 400 ug/gm on a dry weight basis. Hepatic injury in Bedlington terriers occurs when copper concentrations > 2000ug/g.

Doberman Pinschers are at an increased risk to develop chronic hepatitis and cirrhosis. The cause and pathogenesis is unknown, but the frequency of disease in this breed indicates a genetic basis. Middle-aged female Dobermans are predisposed to develop this disease; 87% of the 52 affected Dobermans reported in the literature are female. Affected dogs develop a cholestatic syndrome that progresses to cirrhosis and liver failure. Many present in advanced stages of liver failure, with anorexia, weight loss,pu/pd, coagulopathy, jaundice and/or ascites. Dogs presenting with signs of advanced liver disease often die within a few weeks of presentation. Early detection of affected dogs before depression, weight loss, and ascites occur improves prognosis; some live for years with treatment.

Non-regenerative anemia and microcytosis are often present. Increased ALT and ALP activity occurs in all affected patients, but the magnitude is variable (2-fold to > 90-fold). Mild to moderate hyperbilirubinemia occurs in most but not all affected Dobermans. In non-hyperbilrubinemic dogs, fasting bile acid concentrations are usually increased. Serum albumin is decreased in about 50% of the patients, whereas globulins are often increased. Low blood urea nitrogen, hyperammonemia and prolonged coagulation times are common; thrombocytopenia, indicates disseminated intravascular coagulation. The liver can be normal in size but is often small and irregular as a result of nodular regeneration. Portal mononuclear inflammation and fibrosis around small hepatic veins, referred to as *piecemeal necrosis,* is the typical pathologic change. Most affected dogs have excessive copper; some have excessive hepatic iron. Whether hepatic copper accumulation is the cause of or the result of disease in this breed is unknown.

West Highland White Terriers develop chronic hepatitis from hepatic copper accumulation. The trait is familial but the mode of inheritance is not known; some evidence indicates dominant mode of inheritance. Unlike Bedlingtons, hepatic copper does not increase with age. Most, WHW terriers with clinical and biopsy-confirmed liver disease have hepatic copper concentration > 2000 ug/g. However, some normal WHW have excessive copper concentrations without clinical or biopsy evidence of hepatitis. Because minimal information exists regarding the clinical course and progression of this disease, any WHW terrier with clinicopathologic evidence of liver disease of unexplained etiology (e.g. not associated with steroids, anticonvulsants, etc.) should biopsied and assessed for excessive copper. If hepatic copper 1500 ug/g, treatment to lower hepatic copper should be started.

Skye Terriers appear to have an inherited tendency to accumulate hepatic copper. The mode of inheritance and the mechanism of copper accumulation are not known. Hepatic copper concentrations in affected dogs range from 358 - 2257 ug/g, with higher concentrations correlating with severity and chronicity of disease.

American and English Cocker Spaniel dogs have an increased incidence of chronic hepatitis and cirrhosis. Young males (1.5 - 4 years of age) are most commonly affected and present after only a short course of clinical illness. Ascites is the most common presenting complaint. Weight loss, mild jaundice, melena, and signs of hepatic encephalopathy occur less frequently. Profound hypoalbuminemia is the most consistent biochemical abnormality; liver enzymes are usually increased, but are sometimes normal. Liver biopsy is characterized by periportal hepatitis with lymphocytes, plasma cells, vacuolar change, fibrosis, and nodular cirrhosis. This disease appears to be caused by accumulation of an abnormal form of alpha1-antitrypsin in hepatocytes. It is often not detected until significant hepatic damage has occurred. The prognosis is poor; most affected animals survive only a few months after diagnosis.

Labrador Retrievers have an increased incidence of chronic hepatitis of unknown etiology. Mid to older-aged females appear to be affected most frequently. Affected animals present with variable signs of chronic liver disease, although a couple dogs have presented for acute hepatitis.

Hepatic Fibrosis of unknown etiology occurs in some dogs that present with chronic liver failure and portal hypertension. Age of affected dogs ranges from 4 months to 7 years, but most are young adults. German Shepherd dogs accounted for 9 of 15 dogs reported in one study. Dogs are presented with signs of hepatic encephalopathy, jaundice, and ascites from portal hypertension. Serum ALP activity is usually extremely high, whereas increased ALT activity is a less consistent finding. The liver is usually small, firm and has an irregular surface, and multiple acquired portosystemic shunts are usually present. The primary histologic feature is hepatic fibrosis without inflammation. Some dogs have been reported to live for several years after diagnosis if given symptomatic treatment to control ascites, encephalopathy and hypoalbuminemia.

Lobular Dissecting Hepatitis refers to a specific histologic description of chronic hepatitis of unknown cause. Affected dogs are young; the mean age of 21 dogs in one report was 11 months (54% were < 7 months of age). Standard Poodles appear to be at increased risk. Clinical features are those of advanced liver disease and portal hypertension. The most common clinical finding is ascites. Increased liver enzyme activities, hypoalbuminemia and increased bile acids are typical. Inflammation, diffuse fibrosis and mild copper accumulation are typical findings. Disease is usually advanced by the time of presentation and diagnosis, treatment is entirely symptomatic, and the prognosis is poor.

Treatments for Chronic Hepatitis

Copper Hepatopathy

Regardless of the cause, accumulation of copper will cause hepatocellular damage. Any patient with chronic cholestatic liver disease in which excessive hepatic copper concentration been measured should be treated by avoiding excessive dietary copper intake, decreasing gastrointestinal copper absorption, and/or increasing hepatic excretion of copper.

Decrease Copper Absorption

Dietary restriction of copper plays a minor role in reducing hepatic copper concentration, but is valuable to prevent additional copper accumulation in dogs known to be affected with an inherited hepatic metabolic defect. Copper content in most commercial diets exceeds established minimum requirements for dogs (0.8 mg/1000 kcal ME). However, affected Bedlington terriers and other breeds that accumulate copper require diets with lower copper content to prevent accumulation of copper. Foods for dogs with suspected or confirmed copper accumulation should have less than 5 ppm copper (dry matter basis).

Organ meats (e.g. liver, heart, kidney), shellfish, legumes and cereal products are high in copper and should be avoided. Pork, poultry, fish, eggs, dairy products, vegetables, white rice, and fresh fruit are low in copper and can be used to formulate homemade diets. Prescription Diet l/d is also low in copper. Decreasing dietary copper intake will decrease accumulation of hepatic copper but will not deplete hepatic copper. This is a good supplement to copper chelation therapy in the treatment of patients with pathologically high hepatic copper.

Zinc supplementation decreases intestinal absorption of copper by inducing the synthesis of intestinal metallothionein, a metal-binding protein that regulates intestinal absorption of zinc. When dietary intake of zinc is high, metallothionein is increased and zinc absorption is blocked. Copper binds more avidly to this protein than zinc, resulting in intracellular accumulation of the copper-metallothionein complex. The copper complex is excreted in the feces when intestinal cells are shed.

Elemental zinc at a dose of 50 - 100 mg per day is recommended, given in divided doses BID and separated from feeding by 1 hour. Plasma zinc concentrations should be measured every 7 -14 days and the dose adjusted to maintain zinc concentration at 200 - 400 ug/dl (normal = 100ug/dl). Plasma

zinc concentrations >1000 ug/dl can cause hemolytic anemia. Zinc acetate is recommended. Veterinary products available include Pala Z® (Vibrac) which provides 50 mg elemental zinc/tab and Z-Bec® (Ft Dodge) which provides 20 mg elememtal zinc/tab.

Increase Hepatic Copper Excretion - Copper Chelators

Penicillamine (Cuprimine®; Depen®) chelates with many heavy metals in the blood and tissues to form stable complexes that are excreted in the urine. Penicillamine also has immune-suppressive, anti-inflammatory effects and anti-fibrotic effects. Treatment with this drug can take months to years to effectively reduce hepatic copper concentration, depending on the amount of copper initially present and on the underlying disease. In general, Dobermans and other breeds will have a more rapid response than Bedlingtons, which have been determined to have a decrease of hepatic copper of about 900 ug/g per year. Penicillamine therapy is indicated for dogs with hepatic copper concentrations approaching 2000 ug/g. Treatment of dogs with hereditary copper accumulation that are asymptomatic will prevent chronic hepatitis and progression to cirrhosis.

Penicillamine is given at a dose of 10 - 15 mg/kg BID 30 minutes prior to a meal. Side-effects occur in about a third of dogs treated with penicillamine. Vomiting and anorexia are most frequent but respond well to lowering the dose and increasing the frequency of administration from BID to TID. A small amount of food given with the drug will decrease frequency of vomiting without significantly altering absorption of the drug. Because penicillamine can chelate zinc, administration of these drugs should be staggered by an hour. In general, Bedlington terriers will require life-long treatment, whereas dogs presumed to have secondary copper accumulation (Dobermans? others?) might only need to be on chelation for 8 - 12 months. If normal hepatic copper concentration is achieved with chelation treatment, dietary copper restriction and zinc supplementation should be continued indefinitely.

Treatment with Bile Acids

Bile acids act as biologic detergents, a property that allows solubilization of lipids in bile and digestion of fat in the intestine. When bile acids accumulate during hepatic disease, these same actions can solubilize hepatocyte membranes, resulting in cell toxity. Some bile acids, particularly hydrophobic bile acids (lithocholate and conjugated lithocholates), are very hepatotoxic despite being important constituents of bile. Hydrophilic bile acids chenodeoxycholate and ursodeoxycholate are non-toxic and have therapeutic effects for certain hepatobiliary diseases.

Ursodeoxycholic acid (Actigal®) causes significant clinical and biochemical improvement in human patients with long-term cholestatic diseases. It is believed that ursodeoxycholate displaces accumulated toxic (hydrophobic) bile acids from the bile acid pool by inhibiting intestinal absorption of other bile acids. Ursodeoxycholate also increases production of the bicarbonate-rich bile, thereby increasing excretion of toxic bile acids and inducing choleresis. Ursodeoxycholate also suppresses hepatic inflammation, particularly in patients with immune-mediated hepatic disease.

I recommend use of ursodeoxycholic acid as primary or adjunctive (in combination with immunosuppressive or antiinflammatory drugs) treatment in dogs and cats with chronic cholestatic liver disease, particularly chronic active hepatitis and fibrosis in dogs and cholangiohepatitis in cats. The drug is very well tolerated in both species. Because it is an effective choleretic, it can be also be used to treat sludged bile. The recommended dose is 10 to 15 mg/kg per day, administered either once daily or divided BID. Actigal is available as 300 mg capsules which can be formulated into smaller amounts; cats require about 1/6 capsule daily. Some cats will still eat food with Actigal mixed-in.

Drugs to Decrease Fibrosis

Progressive fibrosis is a common feature of most chronic hepatobiliary diseases and can eventually result in liver failure. Early detection of liver disease and therapeutic intervention can significantly delay or prevent development fibrosis and end-stage liver failure. Identification and elimination of the cause of chronic hepatitis and decreasing chronic inflammation are the primary methods to diminish fibrosis. Anti-inflammatory therapy decreases release of cytokines and decreases migration of fibroblasts. Corticosteroids, azathioprine and colchicine are used for this purpose.

Corticosteroids have several beneficial effects in the treatment of liver disease; anti-inflammatory, choleretic, and anti-fibrotic. The dose of prednisone most commonly recommended is 1 - 2 mg/kg/day initially, gradually tapered to 0.5 mg/kg alternate-day-therapy. Evaluation of response to corticosteroids is complicated in the dog by steroid-induction of liver enzymes activities. Both ALT and ALP activities are predictably and significantly increased by corticosteroids, particularly in dogs with existing hepatic pathology. Resolution of clinical signs, resolution of hyperbilirubinemia and improvement in serum albumin are useful indicators of improved hepatic function. Although serial liver biopsies have been recommended as the standard for evaluating efficacy of steroid treatment, no convincing data exists to support this claim. I recommend using remission of clinical signs and improvement of liver function tests to determine treatment efficacy, steroid dose reduction, and eventual discontinuation of steroids.. In addition to the predictable side-effects from corticosteroids, dogs with significant hepatic dysfunction are particularly at risk for gastrointestinal ulceration and hemorrhage, hepatic encephalopathy and severe muscle wasting when tx with corticosteroids.

Azathioprine is an anti-metabolite that has immune modulating effects. It is metabolized in the liver to the active 6-mercaptopurine which competes with purines in the synthesis of nucleic acids, thereby disrupting nucleic acid synthesis. T-lymphocyte functions such as cell-mediated immunity and T-cell dependent antibody synthesis are particularly diminished. Combination therapy using azathioprine and corticosteroids is recommended especially for long-term treatment of dogs with chronic hepatitis. Initially, the dose of azathioprine is 1 mg/kg/day in combination with prednisone at 0.5 - 1.0 mg/kg/day. If possible, both drugs should be tapered to alternate day dosages (prednisone on days 1,3,5 and azathioprine on days 2,4,6 etc).The primary adverse effect of azathioprine is reversible bone marrow suppression. However, when used on an alternate day basis, this does not seem to be a common problem in the dog.

Colchicine has two therapeutic effects of potential but unproven benefit for the treatment of liver disease. Colchicine has anti-inflammatory effects mediated primarily through inhibition of neutrophil and mononuclear cell migration to the sites of inflammation. Colchicine also has anti-fibrotic effects and recently has been determined to facilitate copper excretion. Only a few case reports on the use of colchicine in dogs to treat hepatic liver disease exist. All dogs had various fibrotic hepatic disease based on biopsy, and colchicine was used in combination with other treatments. Improvement based on clinical, biochemical and histopathologic tests was reported to occur, and the dogs did not experience adverse effects attributable to the drug. The dosage (0.03 mg/kg daily) was extrapolated from the human dosage.

Antioxidant Drugs and S-Adenosyl-L-Methionine

Most if not all damage to the liver, regardless of cause, is mediated by increased production of free radicals that cause oxidative damage to cell organelles. Recent studies indicate that antioxidant therapy is beneficial in some types of chronic hepatitis. For this reason, treatment with an antioxidant drugs to scavenge free radicals might be protective against oxidant injury to hepatocytes, particularly in patients with copper accumulation.

S-Adenosyl-L-Methionine (Denosyl®) Glutathione (GSH) is a major hepatic antioxidant and is necessary for hepatic detoxification of drugs and toxins. S-adenosly-L-methionine (SAMe) is a precursor or GSH and is important in the maintaining normal hepatocyte membrane functions and hepatocyte regenerative processes. GSH concentration is decreased in patients with both acute and chronic liver diseases. Conversion of methionine to SAMe, and subsequently to GSH, is also impaired. The effects of this may include methionine intolerance and accumulation of oxidants, thereby leading to worsening of the liver damage.

Treatment of human cirrhosis patients with oral SAMe results in increased plasma concentration of GSH, cysteine and taurine; and a decrease in plasma methionine, serum bile acids and bilirubin and ALT and GGT activities. Cholestatic disease associated with oral contraceptives, alcoholic hepatitis, and drug-induced hepatotoxicity (e.g. acetaminophen, anticonvulsants) improve significantly when treated with SAMe. SAMe attenuates alkaline phosphatase induction and improves glutathione production in dogs given chronic high dose glucocorticoid therapy.

Several preparations of this neutraceutical are available over-the-counter, but potency is variable. Denosyl SD4 (Nutramax Laboratories, Inc., Edgewood, Maryland) is recommended. The recommended dose is 20 mg/kg/day given should be given on an empty stomach 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.There are no known side effects in animals.

Vitamin E (d-alpha tocopherol) has bee shown to protect the liver from copper-related oxidant damage and from oxidant damage caused by accumulation of hydrophobic bile acids that accumulate in cholestatic liver disease. Vitamin E is inexpensive and safe, and is recommended for use in dogs with any type of chronic hepatitis. The recommended dose is 50 - 400 IU/day.

Silymarin is a flavonolignan found in milk thistle which has been used as a natural remedy for hepatobiliary disease. Flavonolignans are reported to have antioxidant properties by scavenging for free-radicals that cause lipid membrane damage. Results of controlled studies in humans using milk thistle to treat patients with acute and chronic liver diseases are variable, but some evidence does indicate beneficial effects from this treatment. One study in beagles showed that dogs pre-treated with milk thistle were protected from the toxic effects of amanita mushroom poisoning, whereas placebo-treated dogs died. Limited studies and clinical experience preclude making firm recommendations regarding the use of milk thistle to treat chronic liver disease. Dosages extrapolated from human use range from 50 - 250 mg/kg/day

Many over-the-counter products are available; potency varies. Recently, Nutramax released a new veterinary product, called Marin® which contains silybin, vitamin E, and zinc in a single tablet formulation. A formulation of Marin® for cats contains silybin and vitamin E only. Silybin is the most active component of silymarin, derived from the milk thistle.

Antimicrobials

Metronidazole is used primarily for its anti-anaerobic and anti-protozoal activities. It has also been shown to have immune-suppressive activity, specifically against cell-mediated immune responses, and is frequently used in combination with steroids to treat inflammatory bowel disease in both human and veterinary patients. This combination is also used to treat chronic hepatitis. No controlled studies have been done in dogs to document therapeutic benefit of metronidazole to attenuate the inflammatory response or fibrosis that occurs with chronic liver disease; most information is anecdotal. Because metronidazole achieves good concentration in bile and hepatic tissue, it is a good drug to use to treat cholecystitis, cholangiohepatitis and hepatic abscess. This drug is also useful in the initial treatment of hepatic encephalopathy to alter the colonic anaerobic bacterial population. Because metronidazole is metabolized primarily in the liver and excreted in the feces and urine, dose reduction is recommended when treating patients with decreased hepatic function. A dose of 7.5 mg/kg PO BID to TID is recommended for dogs and cats with liver disease. The drug achieves good concentration in the bile.

Other antibiotics routinely used in treatment of patients with liver disease include penicillins (ampicillin 22 mg/kg TID, amoxicillin 22 mg/kg BID), cephalexin (Keflex, Dista) 22 mg/kg TID, and enrofloxacin (Baytril) 2.5 – 5.0 mg/kg 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.

Drugs Used in the Treatment of Chronic Liver Disease in the Dog

Generic	Product (Mfg.)	Dose	Comments
Antibacterial			
Cholangiohepatitis, Cholecystitis			
Ampicillin		22 mg/kg tid PO, SQ	Concentrated in bile
Amoxicillin		22 mg/kg bid PO	Concentrated in bile
Cephalexin		15 mg/kg tid PO, SQ, IM	Concentrated in bile
Enrofloxacin		2.5 - 5.0 mg/kg bid PO	Concentrated in bile
Metronidazole		7.5 mg/kg bid-tid PO	Anti-protozoal, Anti-anaerobic Immune modulator
Neomycin	Biosol (Upjohn)	22 mg/kg tid PO, Rectally	Short-term use for hepatic encephalopathy
Immune Suppressives			
Prednisone	Several	1 - 2 mg/kg qd - bid PO	Taper to 0.5- 1.0 mg/kg alternate day tx
Azathioprine	Imuran (Burroughs Wellcome)	1 - 2 mg/kg q 24 or 48 hrs	Use with prednisone; Monitor WBC monthly
Decrease liver Copper			
Bedlington liver disease; Doberman liver disease; any chronic hepatopathy where Copper concentrations > 2000ppm			
Chelation therapy			
D-Penicillamine	Curpimine (Merck) 125 - 250 mg caps Depen (Wallace) 250 mg caps	10 - 15 mg/kg bid PO	Give on empty stomach May cause vomiting, anorexia; do not give concurrently with other medications
Block copper absorption			
Zinc acetate or gluconate	Pala Z® (Vibrac) 50 mg Zn/tab Z-Bec® (Ft Dodge) 20 mg Zn/tab	100 mg elemental Zn bid for 3 months; then 50 mg bid for maintenance	Give on empty stomach; May cause vomiting; Hemolysis if plasma Zn > 1000 ug/dl; monitor q 3 months to maintain >200 but < 400 ug/dl
Bile Acids - Choleretic-Hepatoprotective effects			
Chronic hepatitis, cholangiphepatitis, cholecystitis			
Ursodeoxycholic Acid	Actagal 300mg caps (Ciba Geigy)	10 - 15 mg/kg/day	
Anti - Fibrotic Drugs			
Chronic hepatitis; hepatic fibrosis			
Prednisone	Several	1 - 2 mg/kg qd - bid PO	Taper to 0.5 - 1.0 mg/kg alternate day
Colchicine	Several	0.03 mg/kg qd PO	Alternate with steroids
Anti - Oxidant Drugs - Decrease toxic injury induced by drugs, toxins, inflammation			

Any inflammatory or toxic hepatopathy

Vitamin E	Several	50 - 400IU/day PO	
S-Adenosyl-L Methionine			
	Denosly-SD4	20 mg/kg qd PO	

Alter Colonic Flora / Laxative
Hepatic encephalopathy

Lactulose	Cephulac	0.5 ml/kg tid PO	Titrate dose to produce 2 - 3
	(Marion Merrell Dow)	0.3 - 0.5 ml/kg tid PO	stools per day; decrease if diarrhea occurs
		20 - 50 ml per enema	Dilute 1:2 with water
		10 ml per enema	

Diuretics
Ascites

Spironolactone	Aldactone (Searle)	1 - 2 mg/kg bid PO	Less potent than furusemide; Potassium sparing
Furosemide	Lasix (Hoechst Roussel)	1 - 2 mg/kg bid PO	May cause hypokalemia

Gastroduodenal Ulceration

Ranitidine	Zantac® (Glaxo)	2.0 mg/kg bid PO,	Interferes with hepatic
	Tabs 150 - 300mg	IV, SQ	p450 enzyme systems;
	Liquid 15 mg/ml		possible drug interactions
	Injection 25 mg/ml		
Famotidine	Pepsid® (Merck)	0.5 mg/kg qd	No hepatic interactions
	Tablet 20 - 40 mg		
	Liquid 8 mg/ml		
	Injection 10 m		
Omeprazole	Prilosec® (Merck)	0.7 mg/kg qd PO	No hepatic interactions
Sucralfate	Carafate	0.5 - 1.0 gm tid -	Do not give at same time as
	(Marion MerrelDow)	qid PO	other drugs
		0.25 gm/cat bid PO C	

Coagulopathy
Factor deficiency associated with severe cholestasis

Vitamin K1	AquaMEPHYTON (Merck & Co.)	2 mg/kg bid SQ

DIC

Heparin	Several	100 IU/kg tid SQ
Fresh plasma		10 ml/kg IV prn