INFORMATION ON CHRONIC LIVER DISEASE

Choosing Therapy for Chronic Liver Disease
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Making a Diagnosis
It is important to obtain a liver biopsy whenever possible. Specific biopsy findings that can drive therapy include: degree of fibrosis (mild, moderate, severe); predominant type of inflammatory infiltrates (neutrophils vs. lymphocytes and plasma cells); degree of necrosis (mild, moderate, severe); presence of cholestasis (mild, moderate, severe); and presence of cirrhosis (distortion of architecture by fibrosis and nodular regeneration). The location of inflammation may indicate the underlying source. For example, in portal hepatitis, inflammatory cells (esp. neutrophils) are found around portal areas without necrosis or fibrosis. This may indicate inflammation secondary to extrahepatic causes, such as septicemia, GI neoplasia, or inflammatory bowel disease. Such cases may not need aggressive primary hepatic therapy, but instead, attention to underlying abdominal disease.

When are Antimicrobials Indicated?
Antimicrobials are obviously indicated for active hepatic or biliary infection, ideally based on results of culture of bile or liver. Bile cultures can be obtained from gall bladder aspiration under ultrasound guidance, or swabs at laparotomy. If you biopsy the liver, always culture the bile, and submit both aerobic and anaerobic samples (e.g., use A.C.T. I agar tubes (Remel); good for 24 hours for both aerobic and anaerobic culture). Bile may be a more sensitive site to document hepatobiliary infection (versus liver tissue). In almost 250 cases of liver and bile cultures from dogs and cats at the University of Wisconsin, the most common isolates were *E. coli*, *Enterococcus* spp., *Clostridium* spp., and *Staphylococcus*. These bacteria can be treated with a combination of a fluoroquinolone and either amoxicillin/clavulanate, clindamycin, or metronidazole and amoxicillin. The empirical recommendation is 2 to 4 weeks of therapy, but this has never been evaluated.

When are Glucocorticoids Indicated?
The rationale for glucocorticoids (anti-inflammatory, antifibrotic, and choleretic effects) should always be weighed against potential side effects in each patient. Recommendations have been based on experience in humans with no controlled clinical trials. Common indications include predominantly lymphocytic-plasmacytic or eosinophilic inflammatory infiltrates on liver biopsy. Glucocorticoids may be used empirically if the owner refuses biopsy, progressive increases in ALT are noted, and infectious and neoplastic causes have been ruled down with ultrasound and serologies. Prednisolone is preferred in cats due to apparent poor conversion of prednisone to prednisolone. Prednisolone has a theoretic advantage in dogs with liver disease, but cytochrome P450-mediated activation of prodrugs such as prednisone is actually well conserved in liver disease unless overt failure is present. Budesonide may be less likely to induce SAP and cause other side effects in dogs. It can, however, still cause significant PU/PD and adrenal suppression in some dogs; in these patients, this relatively expensive glucocorticoid has no real advantage over prednisolone.

Precautions with Glucocorticoids
Glucocorticoids are contraindicated in patients with uncontrolled hepatic encephalopathy, ascites, active GI ulceration, hepatic lipidosis, and active hepatobiliary infection. Always
stabilize patients and treat for encephalopathy and GI ulcers before starting glucocorticoids. Add glucocorticoids as a single change (e.g., 2 weeks after other supportive care has been started) and monitor carefully for improvement or decompensation. If ascites is present, substitute dexamethasone (at 1/7 the dose) for prednisone, since dexamethasone has no mineralocorticoid activity.

**IMMUNOMODULATORY AND ANTIOXIDANT THERAPIES**

Most recommendations for these agents are extrapolated from experience in humans, and are ideally based on a patient’s individual liver biopsy findings.

**Ursodiol (Ursodeoxycholic Acid)**

This is a choleretic bile acid that also reduces hepatocellular injury and fibrosis in humans and animal models. In patients with moderate to severe cholestasis without obstruction, ursodiol is indicated as a choleretic. It is also the drug of choice for primary biliary cirrhosis in humans, which resembles feline cholangitis. Ursodiol is dosed at 10-15 mg/kg/day; 250 mg tablets or 300 mg capsules can be reformulated for cats and small dogs. Ursodiol should not be used unless bile duct obstruction has been ruled out (based on normal bilirubin or via ultrasound).

**S-Adenosyl-methionine (SAM-e; Denosyl™ SD4)**

This is a modified amino acid, important for methylation reactions in the liver and elsewhere. Methylation of membrane lipids modulates membrane fluidity and surface cell interactions. SAMe protects membranes from bile salt damage, and enhances bile excretion from hepatocytes (shown in vitro). SAMe is also an indirect precursor of glutathione; SAMe administered to dogs helps to counteract liver glutathione depletion that occurs with liver disease or with corticosteroid administration. There are no controlled clinical trials of efficacy in dogs with naturally occurring liver disease, but SAMe has been shown to prolong survival in alcoholic cirrhosis in humans. Empirical indications include chronic hepatitis or cholangitis with significant component of necrosis, or to prevent glutathione depletion in liver patients also treated with glucocorticoids. Recommended dosing is 18-20 mg/kg, on an empty stomach. Enteric-coated tablets should not be broken open.

**Milk Thistle**

*Silybum marianum* (Silymarin; also found in Marin™) is another hepatoprotective compound, which has been used for hepatic disorders since the time of the ancient Romans. It is thought to scavenge reactive oxygen species, and may have anti-inflammatory effects via inhibition of 5-lipoxygenase. Milk thistle has been shown experimentally to protect dogs against *Amanita* mushroom hepatotoxicity. There are no controlled clinical trials, but milk thistle may be used in patients with significant inflammation and necrosis on biopsy, in addition to, or instead of, SAMe (if clients prefer a 'natural' product). The empirical dosage is 4 to 8 mg/kg/day. Marin™ (if dosed by label) provides 1.5 to 4 mg/kg/day. Product formulation and potency may vary significantly from one manufacturer to another.

**Vitamin E**

Also found in Marin™, Vitamin E is a critical membrane antioxidant that protects hepatocytes against the toxic effects of bile acids in vitro. Its use has been advocated for empirical therapy for any inflammatory hepatopathy, especially hepatopathies with significant necrosis. Vitamin E may be used in addition to SAMe or silymarin, an is empirically dosed at 150-600 I.U. per dog per day. If significant cholestasis is present, use water soluble forms (Nutra-E-Sol, Liqui E). Overdoses of vitamin E can lead to a coagulopathy, and even modest doses (approximately 15 IU/kg in humans) can lead to subclinical decreases in the function of prothrombin, a vitamin K-dependent coagulation factor. Although the exact mechanism is not understood, it is hypothesized that high dose vitamin E may antagonize the effects of vitamin K. Further, vitamin E has been shown to
exacerbate the anticoagulant effect of warfarin in dogs. Until more is known, vitamin E supplementation in veterinary patients suspected of having a vitamin K-dependent coagulopathy should be based on strong rationale and should be monitored carefully. In addition, vitamin E supplementation should be avoided in patients treated with, or exposed to, warfarin or related rodenticides.

**ANTIFIBROTICS**

Three major anti-fibrotics are in common use: glucocorticoids, zinc, and colchicines.

**Glucocorticoids**

These inhibit fibroblast proliferation, and may be adequate for treatment of mild to moderate fibrosis accompanied by inflammation.

**Zinc**

Zinc inhibits collagen synthesis and decreases hepatic fibrosis in animal models. As a cofactor for superoxide dismutase (which scavenges superoxide free radicals), zinc also may have antioxidant effects. Zinc also impairs copper absorption. Zinc may therefore be useful for dogs with chronic hepatitis with moderate fibrosis, especially if mild to moderately increased copper is present. The empirical dosage is 15 mg/kg of elemental zinc per day, (or 200 mg elemental zinc per medium sized dog per day, tapered to 50 to 100 mg per dog per day based on serum zinc levels). The goal is for serum zinc levels of 200 to 500 μg/dl (2-5 μg/ml). Zinc should ideally be given on an empty stomach (1 hour before or after a meal); mix with tuna oil if nausea noted. I prefer to add zinc in as a single drug after stabilization of the patient with hepatoprotective agents and glucocorticoids (if indicated). Formulations include: Marin™: 45 mg of zinc per tablet (1 to 2 mg/kg of elemental zinc at label dose); zinc gluconate (14.3% zinc) 10 mg, 15 mg, 50 mg, 78 mg tabs; and zinc acetate (35% zinc; no commercial product; can have capsules made from reagent grade zinc acetate). GI upset is common (zinc acetate may cause less GI upset than sulfate or gluconate forms). Hemolysis can occur if serum zinc exceeds 1000 μg/dl.

**Colchicine**

This inhibits microtubule function and decreases collagen synthesis. It may be useful in dogs with chronic hepatitis and moderate to severe fibrosis, or with portal hypertension with ascites. The dosage in dogs is 0.03 mg/kg PO SID (do not use probenecid-containing formulations, which increase the risk of toxicity). Occasional GI upset usually responds to a 50% dose reduction. High dosages can cause leukopenia or peripheral neuropathy.

**D-penicillamine**

This is primarily a copper chelator, but may also inhibit fibrosis by preventing cross-linking of collagen. It is indicated for dogs with a biopsy diagnosis of copper-associated hepatopathy (Bedlingtons, some Westies, Dalmatians), with quantitative hepatic copper levels > 3000 μg /gm. The recommended dosage is 15 mg/kg twice daily, 30 minutes prior to feeding. Efficacy may take several months for decoppering of liver and improvements in ALT. Some clinicians treat with D-penicillamine for 2 months, then switch to zinc. GI upset is also common with D-penicillamine.

**ANTI-ULCER THERAPY**

Empirical anti-ulcer therapy is recommended for all acute and chronic liver disease. Liver disease is a common predisposing factor for GI ulceration, due to impaired mucosal blood flow from portal hypertension, decreased hepatic clearance of histamine and active gastrin fragments, and bile acid stimulation of gastric acid secretion. Either H₂ blockers or pump blockers can be used, although famotidine has minimal drug interactions.

**MANAGEMENT OF HEPATIC ENCEPHALOPATHY**
A check list for acute management of hepatic encephalopathy includes:

1. **Lactulose** (orally, or by enema if stupor or seizures);
2. NPO for 12 to 24 hours;
3. If no response, add **metronidazole** orally at 15 mg/kg/day;
4. If no response, add **neomycin** orally at 20 mg/kg PO three times daily.

Provide IV fluids with potassium (and dextrose for patients with portosystemic shunts or severe cirrhosis). Add anti-ulcer therapy (GI bleeding is a protein load in hepatic encephalopathy), and add vitamin K₁ if jaundiced. Withhold any glucocorticoids until encephalopathy is resolved! Give as much dietary protein as tolerated; increase the lactulose dosage if needed.

**MANAGEMENT OF ASCITES**

In patients with liver disease and ascites, avoid drugs with mineralocorticoid activity (prednisone, prednisolone, hydrocortisone, anabolic steroids). If glucocorticoids are indicated for primary liver disorder in the presence of ascites, substitute dexamethasone. **Spironolactone/hydrochlorothiazide** (Aldactazide) is an excellent diuretic for hepatic ascites. It is more potent than spironolactone alone, but causes less hypokalemia and dehydration than furosemide. The empirical dosage, based on the spironolactone component, is 0.5-1.0 mg/kg PO twice daily. Furosemide mobilizes fluid well but often leads to hypokalemia and hypovolemia. If used, use only low dosages for short periods, such as 0.5 mg/kg once or twice daily for 2-3 days. Watch for hypokalemia, hypovolemia, and weakness. Furosemide can produce metabolic alkalosis, which exacerbates hepatic encephalopathy.

**Therapeutic abdominocentesis** is indicated if significant ascites is refractory to medical management and is impairing mobility or causing respiratory compromise. Supplement with colloids during centesis (e.g., 10 mls/ kg of plasma or hydroxyethylstarch) to prevent hypovolemia and worsened hypoalbuminemia as fluid shifts back into the abdomen. Monitor body weight, hydration, and abdominal girth (measure girth at level of L2 with a measuring tape) to document improvement in ascites.

**ASSESSING RESPONSE TO THERAPY**

When using prednisone or prednisolone in dogs, you cannot rely on SAP to monitor response, since it is induced by glucocorticoids. SAP is reliable in cats. ALT may also increase with prednisone, but will usually decrease overall as inflammation subsides. Other parameters to monitor include albumin and bilirubin; body weight, body condition score, and abdominal girth; and clinical status (appetite, energy, resolution of vomiting and diarrhea, avoidance of severe PU/PD, panting.

**References**

References are available upon request.

**Speaker Information**

(click the speaker's name to view other papers and abstracts submitted by this speaker)

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