Rational Pharmacologic Therapy of Hepatobiliary Disease in Dogs and Cats

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ABSTRACT: Treatment of hepatobiliary disease in dogs and cats often involves the use of multiple drugs for their inflammatory, antifibrotic, cupruretic, hepatoprotectant, antimicrobial, diuretic, procoagulant, or antacid actions. This article reviews the indications for and optimal use of the following agents in the setting of hepatobiliary disorders of dogs and cats: glucocorticoids, azathioprine, colchicine, zinc, D-penicillamine, ursodiol, vitamin E, S-adenosyl-L-methionine, milk thistle (silymarin), carnitine and taurine, antimicrobials, lactulose, spironolactone and other diuretics, vitamin K, and gastrointestinal protectants.

Optimal therapy for hepatobiliary disease in dogs and cats involves determining and eliminating the underlying cause, such as drug exposure (e.g., phenobarbital), ingestion of toxins (e.g., moldy walnuts, garbage containing aflatoxin), or metabolic disorders (e.g., copper storage disease, portosystemic shunt). This process requires obtaining a detailed history in the context of the patient's signalment and clinical presentation. When an underlying cause cannot be determined with confidence (as is often the case), liver biopsy is essential for characterization of the nature of the changes present (e.g., suppuration, lymphoplasmacytic inflammation, necrosis, extensive fibrosis, copper accumulation, or cholestasis). Subsequent adjunctive therapy is then dictated by biopsy results.

Therapy for hepatobiliary disease in dogs and cats encompasses immunosuppressant agents, antifibrotics, cupruretics, hepatoprotectants, antimicrobials, and supportive care for encephalopathy, ascites, coagulopathies, and gastrointestinal (GI) bleeding. Unfortunately, no controlled studies exist that evaluate the efficacy or optimal dosing of these agents in animals. The rationale for using many of these drugs is often based on data from human studies, particularly those involving autoimmune hepatitis, primary biliary cirrhosis, and alcoholic cirrhosis. It is unclear whether the pathophysiology of a condition that is routinely diagnosed in veterinary patients (e.g., chronic active hepatitis, cholangiohepatitis, lipidosis) has enough in common with that of the human disease to allow reasonable extrapolations. However, human data along with anecdotal clinical veterinary experience form the basis of therapeutic regimens. This article reviews
IMMUNOSUPPRESSANTS

Glucocorticoids

Glucocorticoids act as immunosuppressants by multiple mechanisms. These agents inhibit chemotaxis of monocytes and neutrophils into sites of inflammation. They decrease phagocytosis by macrophages and impair lymphocyte blastogenesis. In addition, glucocorticoids impair antigen presentation, which results in indirect reductions in humoral antibody responses. In liver disease, these drugs are often indicated for their antiinflammatory properties. Glucocorticoids induce the transcription of a protein that inhibits phospholipase A₂, thereby decreasing the generation of potent inflammatory mediators such as prostaglandins and leukotrienes.

The antiinflammatory indications for glucocorticoid treatment ideally derive from information obtained from a liver biopsy, such as eosinophilic inflammation or lymphoplasmacytic infiltrates. Glucocorticoids can also be used when there is a systemic indication of autoimmune disease (e.g., strongly positive antinuclear antibodies) or progressive worsening of liver enzyme elevations, provided that infectious causes of liver disease have been ruled out, lymphoma has been considered, and encephalopathy and GI bleeding have been controlled. Glucocorticoids (alone or in conjunction with azathioprine) are the treatment of choice in humans with autoimmune hepatitis and induce remission in more than 80% of patients. In one retrospective study of dogs with chronic hepatitis, glucocorticoids were associated with prolonged survival times.

Side effects of glucocorticoids in dogs and cats include suppression of the pituitary–adrenal axis and iatrogenic hyperadrenocorticism (polyuria or polydipsia, polyphagia, muscle wasting, alopecia, and thin skin). Other potential complications include pancreatitis, exacerbation of GI ulceration, diabetes mellitus, and secondary infections. Because of their catabolic effects, glucocorticoids can worsen encephalopathy and hepatic lipidosis. Glucocorticoids are relatively contraindicated in the presence of active infection (leptospirosis, toxoplasmosis, bacterial cholangiohepatitis), hepatic encephalopathy, ascites (unless glucocorticoids without mineralocorticoid effects are chosen), GI ulceration, and hepatic lipidosis. Glucocorticoids may also obscure a diagnosis of lymphosarcoma and blunt a response to chemotherapy in dogs.

Prednisone and prednisolone both have an intermediate duration of action (12 to 36 hours) and are thus ideal for alternate-day dosing. Prednisone is converted by the liver to its active metabolite, prednisolone; this conversion is rapid, even with liver disease, at least in humans. Antinflammatory to immunosuppressive dosages are recommended for initial administration (Table 1), with gradual tapering based on clinical and biochemical response. Dexamethasone has no mineralocorticoid activity and is thus suitable as an antiinflammatory agent for patients that also have ascites. However, its prolonged duration of action (48 hours) leads to pituitary–adrenal axis suppression even with alternate-day therapy. The dexamethasone dose can be calculated at about one-seventh of the daily prednisone dose because of the increased potency of dexamethasone relative to prednisone.

Azathioprine

Azathioprine is a thiopurine analogue that is metabolized in the liver to 6-mercaptopurine. Metabolites of 6-mercaptopurine inhibit the proliferation of rapidly dividing cells and modify T lymphocyte functions (cell-mediated immunity and synthesis of T cell–dependent antibody).

Azathioprine may be used when severe hepatic inflammation cannot be controlled with glucocorticoids alone or when a patient does not tolerate glucocorticoids. As in other inflammatory or immune-mediated diseases, the use of azathioprine in hepatic disease may allow a decreased dosage of glucocorticoids and therefore reduce the severity of side effects. Although azathioprine is used in humans with hepatobiliary disease, no data exist on the efficiency of conversion of azathioprine to its active metabolites in hepatic insufficiency. Human studies have shown that azathioprine combined with low-dose glucocorticoids offers a satisfactory alternative for patients with intractable autoimmune hepatitis who have an incomplete response to glucocorticoids alone or who have a relapse during glucocorticoid maintenance therapy.

Side effects of azathioprine in dogs include dose-dependent bone marrow suppression (neutropenia, thrombocytopenia, anemia), pancreatitis, and idiosyncratic hepatotoxicity. Azathioprine should be avoided in cats, which are prone to develop neutropenia from azathioprine, possibly because of deficient detoxification of the agent by thiopurine methyltransferase.

For dogs, a complete blood cell count (CBC) should be obtained every 1 to 2 weeks for the first 2 months, and then every 1 to 2 months during maintenance therapy. Alanine aminotransferase (ALT) activity should also be monitored; if it increases significantly during treatment, idiosyncratic hepatotoxicity should be considered and the drug discontinued. If vomiting or anorexia occurs during azathioprine treatment, a
workup for pancreatitis is warranted. Use of azathioprine is contraindicated during pregnancy.

**ANTIFIBROTICS**

**Colchicine**

The antifibrotic agent colchicine inhibits microtubule-mediated transcellular movement of proteins and inhibits procollagen secretion into the extracellular matrix. Colchicine may also promote collagen degradation in vivo because it increases collagenase activity in vitro. In addition, colchicine suppresses the release of various mediators of fibrogenesis from macrophages. Colchicine has other potentially beneficial effects in liver disease. It may protect the liver via stabilization of hepatocyte plasma membranes, may have weak antioxidant properties, may enhance copper excretion, and may act as an antiinflammatory by inhibiting leukocyte migration and decreasing circulating cytokine levels (interleukin-2, tumor necrosis factor-α).

Colchicine treatment is suggested when there is evidence of fibroplasia or bridging fibrosis from liver biopsy results or when ascites is present. Colchicine is effective in humans with primary biliary cirrhosis, familial Mediterranean fever, and gout. Two clinical reports in dogs suggested that colchicine may be effective by improving liver function and slowing the progression of hepatic fibrosis, but no controlled studies have been performed.

Side effects of colchicine in dogs can include nausea, vomiting, and diarrhea. In humans, peripheral neuropathy, myopathy, and bone marrow suppression have also been reported. CBC and clinical status should be monitored during colchicine therapy. If GI upset occurs, lower doses, which may be better tolerated, can be tried. Use of colchicine is contraindicated during pregnancy. The probenecid-containing formulation (used for gout in humans) should be avoided because probenecid can inhibit biliary and renal excretion of many drugs.

**Elemental Zinc**

Zinc acts as an antifibrotic by inhibiting several steps
in collagen synthesis. Zinc competes with iron and chelates copper, both of which are necessary cofactors in the posttranslational modification of collagen. In rodent models of hepatic cirrhosis, oral zinc supplementation inhibited collagen deposition and reduced lipid peroxidation. In an older placebo-controlled study in humans with alcoholic cirrhosis, zinc supplementation was associated with decreased serum bilirubin and increased prothrombin levels. More recently, zinc deficiency was correlated with low albumin and high blood ammonia levels in humans with cirrhosis, and zinc supplementation was shown to lower blood ammonia concentration in these patients. Zinc may be useful in dogs and cats when mild to moderate fibrosis is documented by liver biopsy findings, and, on the basis of studies with humans and rodents, could have the additional benefit of reducing hepatic oxidant injury and encephalopathy.

In animals, side effects of zinc administration commonly include GI upset, and, less often, hemolysis (serum zinc level >1,000 µg/dl). Baseline serum zinc levels should be obtained before treatment, and serum zinc concentrations should be monitored every 2 to 3 months. The suggested goal is a serum zinc concentration of 200 to 500 µg/dl. Zinc should ideally be given when the stomach is empty to ensure adequate absorption, and its administration should be separated from ingestion of food by at least 1 hour. However, zinc can be mixed with tuna or other small pieces of meat to enhance palatability. The available formulations include zinc sulfate (23% elemental zinc) and zinc gluconate (14.3% elemental zinc) in tablets and capsules. Zinc acetate (35% elemental zinc) can be formulated from reagent-grade zinc acetate, but no commercial product is available.

**Glucocorticoids**

Glucocorticoids have significant antifibrotic effects in addition to their antiinflammatory properties. Glucocorticoids suppress the transcription of procollagen genes and inhibit the posttranslational modification of collagen via inhibition of proline hydroxylase activity. The antiinflammatory effects of glucocorticoids also contribute indirectly to inhibiting fibrosis, because inflammatory mediators such as platelet-derived growth factor and fibronectin are chemotactic for fibroblasts, and transforming growth factor–β promotes collagen synthesis.

**CUPRURETICS**

Cupruretics enhance the systemic depletion of copper, either through chelation of copper or by prevention of its absorption.

**d-Penicillamine**

D-Penicillamine reduces liver copper content by forming a chelate with plasma copper, which is then excreted in the urine. D-Penicillamine may also inhibit fibrosis by preventing cross-linking of collagen, and it may have immunosuppressive effects related to inhibition of T lymphocyte function.

Indications for penicillamine treatment include biopsy-verified diagnosis of copper-associated hepatopathy (Bedlington terriers, West Highland white terriers, Skye terriers, Dalmations, and other breeds) along with hepatic copper concentrations greater than 2000 µg/g. D-Penicillamine is used in humans primarily for its copper-chelating ability in Wilson’s disease (a familial disorder of hepatic copper excretion similar to the copper hepatopathy seen in Bedlington terriers). Results of the use of D-penicillamine as an antifibrotic agent in humans with primary biliary cirrhosis have been disappointing.

Side effects of D-penicillamine treatment in dogs include nausea, anorexia, and vomiting, which can be overcome by giving smaller doses more frequently or by mixing the drug with food (which may decrease its bioavailability). Rarer side effects in humans include fever, lymphadenopathy, skin hypersensitivity reactions, glomerulonephropathy, and neutropenia. Clinical response may take months for decoppering of the liver and improvements in ALT levels. Use of D-penicillamine should be avoided in pregnant animals.

**Elemental Zinc**

Zinc reduces hepatic copper concentrations by inducing enterocyte synthesis of metallothionein, which binds intestinal copper and prevents its absorption. Zinc may also protect the liver because it acts as a cofactor in a variety of biologic reactions, provides protection from antioxidant sulfhydryl groups, and stabilizes lysosomal membranes. Zinc may be useful when mild to moderate amounts of copper are documented by liver biopsy findings or for copper-associated hepatopathies with hepatic copper concentrations from 1,000 to 2,000 µg/g. In one report, zinc appeared to be an effective and nontoxic therapy for copper toxicosis in dogs.

**HEPATOPROTECTANTS**

Hepatoprotectants comprise a varied group of compounds that may protect hepatocytes from injury caused by free radicals, bile salts, drugs, environmental toxins, and other insults (Table 2).

**Ursodiol**

In cholestasis, the impaired biliary secretion of toxic bile acids causes their accumulation in the liver parenchyma and may contribute to subsequent hepatic...
Ursodeoxycholic acid (ursodiol) is a hydrophilic bile acid that competes with other bile acids for absorption in the ileum and shifts the bile acid profile in favor of less toxic hydrophilic forms. Ursodiol is also a choleretic in humans and in dogs; bile flow in cats in response to this drug has not been evaluated. Ursodeoxycholic acid may reduce hepatocellular injury and fibrosis, may modulate immune responses, and may act indirectly as an antioxidant by preventing bile acid–induced peroxidation.

Treatment with ursodiol has been suggested for veterinary patients with chronic active hepatitis, cholangiohepatitis, and other disorders involving cholestasis or abnormally elevated bile acid levels. This agent improves biochemical markers and liver histology in humans with primary biliary cirrhosis and improves ALT and γ-glutamyltransferase levels, but not histologic characteristics, in humans with chronic active hepatitis. No efficacy studies have been performed with dogs, although one case report suggested improvement in serum bile acid profiles with ursodeoxycholic acid treatment. In healthy cats, dosages of 10 to 15 mg/kg/day for 8 to 12 weeks were not associated with adverse effects. Humans must take the drug on a prolonged basis because interruption of therapy can induce a rebound cholestasis.

Side effects of ursodeoxycholic acid are rare in dogs and cats; GI upset has been reported in humans. Its main drawback is expense. Because this drug is a choleretic, bile duct obstruction is a contraindication to its use.

Vitamin E

Vitamin E is a potent antioxidant and protects against bile salt–induced oxidant injury in vitro. Vitamin E has also been associated with normalization of ALT levels in controlled trials involving humans with hepatitis B. Vitamin E is depleted in human patients with copper storage (Wilson’s) disease, and its levels are decreased in chronic cholestasis, although overt deficiency from cholestasis is uncommon in humans. Vitamin E supplementation has been recommended as empiric therapy for inflammatory hepatopathies in animals. Side effects of vitamin E in animals and humans are minimal unless a massive overdose is given or selenium-containing supplements are mistakenly used. Various formulations are available at health food stores and pharmacies, and water-soluble preparations are available for patients with significant cholestasis.

S-Adenosyl-L-methionine

S-Adenosyl-L-methionine (SAMe) is a metabolic intermediate that is an indirect precursor of the antioxidant glutathione. SAMe improves membrane fluidity in hepatocyte plasma membranes and can indirectly enhance bile flow by improving membrane function of the Na⁺,K⁺-ATPase pump. SAMe may also enhance bile salt conjugation to tauroine and is metabolized to polyamines such as spermidine, which are necessary for normal hepatocyte growth and repair.

SAMe is depleted in animal models of alcoholic cir-
rhosis; SAMe supplementation reverses this deficiency and ameliorates hepatic mitochondrial injury. SAMe has been reported to decrease mortality in humans with alcoholic liver cirrhosis, although a metaanalysis of eight clinical trials found no benefit. Empiric use of SAMe has been advocated for many types of chronic liver disease in veterinary patients, although controlled trials of this therapy are lacking. SAMe can increase hepatic glutathione concentrations in normal cats and has been shown to ameliorate hepatic glutathione depletion seen with long-term glucocorticoid administration in dogs. Although SAMe treatment of other forms of hepatopathy has not yet been studied, hepatic glutathione levels were reported to be abnormally low in 45% of animals with hepatobiliary disorders. In addition, SAMe may increase glutathione levels during treatment of acetaminophen toxicosis. There are no known side effects of SAMe in animals, but the drug is relatively expensive. It may interact with some tricyclic antidepressants (e.g., clomipramine), a factor that has led to neurologic side effects in humans. A loading dose may be warranted for treatment of acute acetaminophen toxicity. Available formulations include 90- and 200-mg enteric-coated tablets. Enteric-coated tablets should not be broken.

**Milk Thistle (Silybum marianum; Silymarin)**

Silymarin is an extract from the seeds of milk thistle (S. marianum), a relative of the daisy that has been used for hepatic disorders since the time of the ancient Romans. Silymarin is thought to have antioxidant effects via scavenging of reactive oxygen species and to have antiinflammatory effects via inhibition of 5-lipoxygenase. Treatment with milk thistle has been advocated for many chronic liver diseases. Results from human studies have been mixed, with some studies showing modest improvements in liver enzyme levels, liver histology, or survival and others showing no benefit. Although no studies of dogs or cats with naturally occurring liver diseases have been reported, silymarin was shown in an experimental study to protect dogs against *Amanita* mushroom hepatotoxicity. Side effects of milk thistle in humans include rare case reports of GI upset and allergic rashes. Side effects have not been well characterized in dogs and cats; as yet there are no known contraindications. Dosages in humans vary from 280 to 560 mg/day. Health food stores carry 400-mg tablets as well as other formulations. Because silymarin is marketed as a nutritional supplement, not as a pharmaceutical, product formulation and potency may vary significantly from one manufacturer to another.

**L-Carnitine**

L-Carnitine is an essential cofactor that mediates the transfer of long-chain fatty acids across the inner mitochondrial membrane for subsequent oxidation to form acetyl coenzyme A fragments. L-Carnitine is synthesized in the liver, and carnitine deficiency may lead to the accumulation of toxic acetyl coenzyme A metabolites, which impair mitochondrial function.

L-Carnitine can enhance ammonia elimination and prevent experimental ammonia-associated encephalopathy. In humans, alterations in carnitine metabolism occur in hepatobiliary disease, especially cirrhosis. Carnitine has been recommended for cats with hepatic lipidosis, although liver carnitine concentrations have not been found to be decreased in cats with this disorder. Potential indications for L-carnitine treatment include hepatic encephalopathy and hepatic lipidosis. Further studies are needed to evaluate the efficacy of prophylactic carnitine supplementation for encephalopathy in dogs and cats.

Side effects in humans and animals are minimal, but L-carnitine is expensive. D-Carnitine should be avoided because it may competitively inhibit L-carnitine uptake, with a resulting functional carnitine deficiency. Tablets, capsules, and oral solutions are available in a wide range of formulations.

**Taurine**

Taurine is an end-product of sulfur amino acid metabolism, is derived from methionine and cysteine, and is an essential nutrient in cats. Bile acids are preferentially conjugated with taurine, and bile flow can be optimized with adequate taurine pools. Taurine is not deficient in the plasma of humans with hepatobiliary disease, and this amine can protect against the effects of some experimental hepatotoxins and can prevent cholestasis in neonates. Although no studies of taurine in animals with cholestasis are available, it has been recommended for cats with lipidosis or cholestasis.

No known side effects or contraindications to taurine supplementation in animals exist except expense. Tablets and capsules are available; the formulation varies depending on the source.

**ANTIMICROBIALS**

Treatment with antimicrobial agents is indicated in hepatobiliary disease associated with parenchymal or biliary bacterial colonization, hepatic encephalopathy, and underlying infectious pathogens such as *Toxoplasma* or *Leptospira* spp (Table 3).

**For Parenchymal or Biliary Bacterial Colonization**

Antimicrobial treatment is ideally dictated by results
of culture of liver and bile obtained via needle or laparoscopic biopsy, or at laparotomy. If cultures are not available or culture results are pending, empiric antimicrobial treatment is often warranted. In humans, fever, neutrophilia, leukocytosis, and hyperbilirubinemia together have a high predictive value for positive bile culture results in patients with acute cholecystitis.

Reasonable indications for empiric use of antimicrobials in dogs and cats with hepatobiliary disease include suppurative (neutrophilic) inflammation (liver biopsy finding), leukocytosis with a shift to the left and/or toxic change accompanying marked liver enzyme level elevations, and unexplained fever with biochemical evidence of liver disease.

Common isolates from liver and bile in humans with hepatobiliary disease include gram-negative enteric bacteria such as \textit{Escherichia coli} and \textit{Klebsiella}, gram-positive aerobes such as \textit{Enterococcus}, and anaerobes.\textsuperscript{76,77} At the University of Wisconsin-Madison Veterinary Medical Teaching Hospital, liver and bile cultures obtained from dogs and cats during the past 5 years showed a similar pattern, with \textit{E. coli} (23.4\% of isolates; 32 of 137), \textit{Enterococcus} spp (13.9\%; 19 of 137), \textit{Clostridium} spp (5.1\%; 7 of 137), and coagulase-positive \textit{Staphylococcus} (4.4\%; 6 of 137) predominating. However, not all samples were submitted for anaerobic culture, and the occurrence of anaerobes such as \textit{Clostridium} was thus likely underestimated.

Antimicrobials for which \textit{E. coli} had a greater than 80\% susceptibility at the Veterinary Medical Teaching Hospital in 2001 included amoxicillin–clavulanate, fluoroquinolones, and cephalosporins (cefotetan, cefoxitin, and cefazolin). More than 95\% of isolates of coagulase-positive \textit{Staphylococcus} were susceptible to amoxicillin–clavulanate, fluoroquinolones, or cefazolin. Penicillin, ampicillin, and amoxicillin had good activity against \textit{Enterococcus} and \textit{Clostridium} spp. All these antimicrobials undergo renal elimination and are generally well tolerated.

Side effects of β-lactams and fluoroquinolones are typically GI in nature (anorexia, vomiting, diarrhea). Use of β-lactams is contraindicated in patients with known hypersensitivity to related drugs. Fluoroquinolones are contraindicated for growing dogs and
should not be used at high dosages in cats (e.g., >5 mg/kg/day for enrofloxacin) because of the possibility of acute retinal degeneration. Optimal duration of therapy for hepatobiliary bacterial infections has not been established, but the general recommendation is 2 to 4 weeks, with courses up to 3 to 6 months suggested for suppurative cholangiohepatitis. For Hepatic Encephalopathy

Metronidazole provides excellent anaerobic coverage, and its use is indicated for patients with positive anaerobic bile or liver culture results. Metronidazole is also indicated for treatment of hepatic encephalopathy because of its inhibitory effect on ammonia-generating anaerobes in the colon. However, metronidazole may not be as effective as neomycin in this setting, at least in humans. In addition, other drugs may be better tolerated, particularly by cats. At high doses or with overdose, metronidazole in dogs can cause cerebellar or vestibular ataxia and other neurologic signs that can mimic encephalopathy. Alternatives to metronidazole include clindamycin and amoxicillin–clavulanate for anaerobic infections and lactulose, with or without neomycin, for encephalopathy.

In dogs and cats, metronidazole can cause lethargy, weakness, and GI upset (particularly anorexia). Neutropenia has also been reported in humans. Metronidazole should not be used during pregnancy or lactation. When IV metronidazole is given, the dose should be infused over 30 to 60 minutes to avoid pain at the infusion site, which has been reported in humans. Metronidazole is cleared by the liver, and dosage reductions to 25% to 50% of standard dosages are suggested for humans with significant hepatic insufficiency. Tablets (250 and 500 mg), capsules (375 mg), and injectable products (500 mg/100 ml) are available.

Neomycin is an aminoglycoside antibiotic that is poorly absorbed and active locally in the colon. It decreases ammonia production by inhibiting enterocyte breakdown of glutamine to release ammonia. Use of neomycin is indicated when clinical evidence of hepatic encephalopathy or portosystemic shunting exists.

Side effects of neomycin include diarrhea and lack of compliance because of its bitter taste. Otoxicity and nephrotoxicity are reported to occur rarely with oral use; systemic administration should not be used, and neomycin should be avoided in patients with compromised intestinal mucosa. An additional contraindication is pregnancy. Aminoglycosides in general should be used with caution in patients with neuromuscular disorders (e.g., myasthenia gravis) because of their neuromuscular-blocking activity. Neomycin is available as a liquid to be taken orally (200 mg/ml).

Antimicrobials to Avoid in Chronic Liver Disease

Tetracycline leads to dose-dependent increases in hepatic lipid deposition in many species, including dogs and cats. Accumulation of triglycerides in dogs results from inhibition by tetracycline of mitochondrial β-oxidation of fats. Tetracycline should therefore usually be avoided in hepatobiliary disease. It is unclear whether doxycycline carries the same risk; there are no reported cases of steatosis with this drug.

Sulfonamides are idiosyncratic hepatotoxins in dogs. Sulfonamides generate reactive metabolites that may deplete glutathione further in patients with underlying hepatic disease and should therefore not be used in dogs with hepatic disease. Chloramphenicol should also be avoided. Hepatic insufficiency leads to decreased clearance of chloramphenicol and requires significant dosage reductions in humans to prevent side effects.

MONITORING PARAMETERS

Because controlled therapeutic trials have not been performed in dogs or cats with hepatobiliary disease, recommendations for optimal monitoring of patients during treatment with the drugs just discussed are necessarily empiric. It should be emphasized that the rational use of most of these therapies should be based on information from liver histology, whether obtained by ultrasound-guided needle biopsy, laparoscopic biopsy, or wedge biopsy at laparotomy. The best way to monitor response to therapy is through follow-up biopsy, as is done for humans. For this purpose, ultrasound-guided needle biopsy can be performed at reasonable cost and with minimal recovery time. The results of repeated biopsy, along with clinical status and biochemical data, give optimal information for adjustment of therapy.

Clinical status should be monitored with the following historical parameters: appetite, attitude, frequency of vomiting, character of stools (diarrhea, melena, constipation), degree of polydipsia, urinary accidents, mobility, and abnormal behavior. The physical examination should emphasize mucous membrane color (pallor, injection, jaundice); evidence of bruising or petechiae; hydration status (especially important for patients given diuretics); palpation of liver margins for enlargement, nodules, or pain; abdominal palpation for ascites; palpation of limbs and ventrum for evidence of peripheral edema (particularly important during fluid therapy); and rectal examination for evidence of melena. In addition, evaluation of body weight, muscle mass and body condition score, and abdominal girth measurements can determine whether weight gain or loss is due to changes in ascites or body condition.
Blood tests should include a CBC to evaluate for evidence of anemia (which, if more than mild, may suggest GI bleeding), thrombocytopenia (which may indicate GI bleeding, disseminated intravascular coagulation, or drug reaction), or leukocytosis with shift to the left or toxic change (which may indicate secondary bacterial infection). Biochemical evaluation should include assays for serum albumin, bilirubin, potassium (particularly in inappetent cats or in dogs treated with diuretics), ALT, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, and glucose (especially in patients treated with glucocorticoids). In addition, hepatic function can be followed over the long term with serum bile acid testing. Because of enzyme induction, alkaline phosphatase is an unreliable indicator of disease progression in dogs treated with glucocorticoids. However, albumin, bilirubin, and bile acid results remain helpful.

**SUPPORTIVE CARE**

**Hepatic Encephalopathy**

**Management Considerations**

Factors that worsen hepatic encephalopathy include high-protein meals, GI hemorrhage, constipation, dehydration or azotemia (diffusion of high blood urea nitrogen from the plasma to the gut leads to secondary ammonia generation), hypoglycemia, alkalosis, hypokalemia, infections, and blood transfusions (stored blood contains high concentrations of ammonia). Sources of ammonia can be regulated through IV fluid support, fasting, and control of GI bleeding. For overt neurologic signs, enemas are indicated, with warm isotonic fluid (5 to 10 ml/kg), 20% lactulose, or povidone–iodine solution (diluted 1:10). In addition, use of oral lactulose should be instituted.

Lactulose is a nonabsorbable disaccharide that is cleaved by colonic bacteria into organic acids. It acidifies the gut to cause ion trapping of ammonia as NH₄⁺, acts as an osmotic cathartic, and provides a nonnitrogen energy source for enteric bacteria. Lactulose is very effective for encephalopathy in humans; animals often tolerate lactulose better than neomycin or metronidazole.

Seizure control is often needed with acute hepatic encephalopathy (Table 4). However, benzodiazepines have the potential to worsen hepatic encephalopathy, and phenobarbital can be hepatotoxic (although this effect has not been reported with short-term dosing). In addition, both benzodiazepines and phenobarbital are metabolized by the liver and show decreased clearance in hepatic failure, at least in humans. Therefore, if these agents are used for acute management of seizures associated with hepatic insufficiency, lower dosages are indicated to avoid oversedation (for example, the use of 10% to 25% of standard dosages has been recommended in humans).

Neither phenobarbital nor benzodiazepines should be used for maintenance control of seizures in this setting. Instead, bromide, which is not protein bound, not metabolized, and not known to be hepatotoxic, is preferred. Bromide can be given as a loading dose to patients with epilepsy and phenobarbital-associated hepatopathy to allow rapid discontinuation of phenobarbital. Bromide is contraindicated in patients with significant renal impairment. Serum bromide concentrations are lowered by diets high in chloride, diuretics such as furosemide (which impair renal tubular reabsorption of bromide), and IV fluids containing chloride. Propofol is an additional option for control of intractable seizures in hepatic insufficiency. Propofol, used at subanesthetic dosages, reduced intracranial pressure in humans with fulminant hepatic failure. It also has anticonvulsant properties and has reduced the severity of seizures after portosystemic shunt ligation in dogs and cats.

In patients with encephalopathy, the clinical response and blood ammonia assay results (if available) can help monitor the initial response to lactulose, metronidazole, and neomycin. Bile acid levels are not expected to normalize initially, even with adequate control of neurologic signs, because acute therapy is directed against ammoniagenesis, not immediate resolution of underlying hepatic dysfunction.

**Ascites**

**Management Considerations**

When ascites is present, drugs with mineralocorticoid activity, such as prednisone and prednisolone, should be avoided to minimize sodium retention. If glucocorticoids are needed for the primary liver disorder in the presence of ascites, dexamethasone can be substituted, at about one-seventh of the prednisone dosage.

Along with dietary sodium restriction, diuretics such as spironolactone, furosemide, or spironolactone–hydrochlorothiazide are also warranted (Table 5). Spironolactone is an aldosterone antagonist that is less potent than furosemide but has fewer side effects (less dehydration, hypokalemia, and hypovolemia). Furosemide is a loop diuretic and can serve as an adjunct to spironolactone. Only low dosages of furosemide should be used (e.g., 0.5 to 1.0 mg/kg PO sid to bid for no more than 3 to 5 days) to avoid side effects. Patients treated with furosemide should be monitored for hypokalemia, hypomagnesemia, and azotemia as well as for clinical evidence of dehydration and weakness. Furosemide can also produce a metabolic alkalosis, which can worsen hepatic encephalopathy. Some
**Table 4. Anticonvulsants for Encephalopathic Seizures**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Use</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Loading dose: 3–15 mg/kg IV or IM for acute seizure control</td>
<td>Anticonvulsant</td>
<td>Depression, sedation, ataxia, PU/PD</td>
<td>Dosage listed is 10%–25% of standard dosage to avoid oversedation; not recommended for maintenance seizure control</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.1–0.5 mg/kg IV for acute seizure control</td>
<td>Anticonvulsant</td>
<td>Oversedation, respiratory depression</td>
<td>Dosage listed is 10%–25% of standard dosage to avoid oversedation; may exacerbate encephalopathy</td>
</tr>
<tr>
<td>Potassium bromide</td>
<td>Loading dose: 400–600 mg/kg PO (may be divided over 1–2 days); maintenance: 50–80 mg/kg/day PO</td>
<td>Anticonvulsant</td>
<td>Depression, sedation, ataxia, PU/PD, GI upset</td>
<td>Avoid with significant renal impairment; furosemide lowers bromide levels</td>
</tr>
<tr>
<td>Sodium bromide</td>
<td>42–68 mg/kg/day PO for maintenance</td>
<td>Anticonvulsant</td>
<td>Depression, sedation, ataxia, PU/PD, less GI upset than with potassium bromide</td>
<td>Maintenance dosages may be given IV; avoid with significant renal impairment; furosemide lowers bromide levels</td>
</tr>
<tr>
<td>Propofol</td>
<td>Bolus: 1.0–2.0 mg/kg IV; CRI: 0.6–0.8 mg/kg/hr IV</td>
<td>Anticonvulsant, reduces intracranial pressure</td>
<td>Apnea, hypotension, hypothermia</td>
<td>Give bolus dose slowly (over 20–60 sec) to avoid apnea; titrate CRI to effect; requires close monitoring</td>
</tr>
</tbody>
</table>

*CRI = constant-rate infusion; PU/PD = polyuria/polydipsia.

patients respond best to maintenance spironolactone combined with short pulses (for 2 to 3 days) of furosemide only when necessary. Another option is spironolactone–hydrochlorothiazide (available in combination as a human product), which is intermediate in potency between spironolactone and furosemide and is less likely than furosemide to cause hypokalemia. This combination may obviate furosemide and avoid its accompanying side effects.

With ascites, monitoring parameters include body weight, hydration, and, very important, abdominal girth. Girth can be determined with a measuring tape at the level of the second lumbar vertebra. Therapeutic abdominocentesis should be performed when the ascites is tense or refractory to medical management or when there is respiratory compromise. Only enough fluid should be removed to make the animal comfortable because excessive fluid removal can lead to hypovolemia as fluid shifts back into the abdomen. If removal of a large fluid volume is desired, concurrent administration of colloids such as plasma or hydroxyethyl starch (10 ml/kg IV over 2 to 3 hours) can help prevent rebound hypovolemia.

**Coagulopathies Management Considerations**

Significant liver disease can result in coagulopathy because of impaired production of coagulation factors and antithrombin III as well as vitamin K malabsorption secondary to cholestasis. Anorectic patients may also have decreased dietary intake of vitamin K. The prevalence of abnormal coagulation test values may be as high as 66% in dogs and 80% in cats with hepatobiliary disease.

**Indications for Vitamin K, Supplementation**

Because vitamin K malabsorption can result from prolonged cholestasis, its supplementation should be
considered in patients with cholestasis or jaundice, especially before invasive procedures such as hepatic biopsy. Vitamin K₇ should be supplemented whenever the prothrombin time or activated partial thromboplastin time is more than 30% prolonged, although PIVKA (protein induced by vitamin K absence or antagonism) testing is more sensitive and may better predict bleeding. Supplementation with vitamin K₇ may not necessarily resolve bleeding tendencies, and fresh-frozen plasma is also recommended. Vitamin K₇ should not be given intravenously because of the risk of anaphylaxis.

**Indications for Blood Component Therapy**

Fresh or fresh-frozen plasma provides coagulation factors and should be considered for any patient that has disseminated intravascular coagulation or an active hemorrhage. Plasma administration is also recommended before liver biopsy if the prothrombin time or activated partial thromboplastin time is prolonged. The platelet count should also be checked before liver biopsy because thrombocytopenia is the strongest predictor of significant hemorrhage during liver biopsy in dogs and cats. If platelet counts are less than 50,000/μL, platelet-rich plasma (6 to 10 ml/kg) or platelet concentrate (1 U/10 kg) should be administered.

Controlling coagulopathy may also help prevent GI hemorrhage, which would otherwise exacerbate hepatic encephalopathy. Fresh whole blood supplies erythrocytes in addition to coagulation factors and is more appropriate in the presence of anemia or significant hemorrhage. Stored whole blood or stored packed erythrocytes should be avoided because blood generates ammonia on storage and the ammonia load could precipitate encephalopathy.

**Gastrointestinal Ulceration Management Considerations**

Liver disease is a common predisposing factor for GI ulceration. Hypothesized mechanisms include impaired mucosal blood flow secondary to dehydration and portal hypertension, decreased hepatic clearance of histamine and active gastrin fragments, impaired mucin production, and bile acid stimulation of gastric acid secretion.

**Indications for H₂ Blockers**

Empiric indications for H₂ blockers in patients with hepatobiliary disease include nausea, inappetence, melena, and biochemical evidence of GI hemorrhage (microcytic or regenerative anemia with panhypoproteinemia, or increased blood urea nitrogen without increased creatinine level). H₂ blockers should also be employed for hepatic encephalopathy because occult GI bleeding can lead to increased blood ammonia levels. Options include famotidine or ranitidine. Cimetidine and omeprazole are not recommended because of cytochrome P450 inhibition and potential drug interactions.

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### Table 5. Procoagulants, Diuretics, and Gastrointestinal Protectants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Use</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K₇</td>
<td>1.0–1.5 mg/kg PO or SC q12h for three doses, then daily every 3–5 days</td>
<td>Repletion of vitamin K in cholestatic coagulopathy</td>
<td>Risk of anaphylaxis with IV use</td>
<td>Unlikely to completely resolve coagulopathy without plasma</td>
</tr>
<tr>
<td>Fresh-frozen plasma</td>
<td>10–20 ml/kg/day over 2–3 hr before biopsy</td>
<td>Provides clotting factors, colloid</td>
<td>Volume overload; urticaria if unit contaminated with erythrocytes</td>
<td></td>
</tr>
<tr>
<td>Spironolactone–hydrochlorothiazide</td>
<td>1 mg/kg of each component q12h</td>
<td>Diuretic for ascites</td>
<td>Dehydration; weakness</td>
<td>Less likely to cause hypokalemia than furosemide; more potent than spironolactone alone</td>
</tr>
<tr>
<td>Famotidine</td>
<td>0.5–1.0 mg/kg PO, SC, or IV q12–24h</td>
<td>H₂ blocker</td>
<td>Hypotension with rapid IV bolus</td>
<td>Give IV over 5 min; dilute 1:5 with drug diluent; no significant drug interactions</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>0.25–1.0 g PO q8h</td>
<td>GI protectant</td>
<td>Chalky taste</td>
<td>Interferes with absorption of many oral drugs</td>
</tr>
</tbody>
</table>
Indications for Sucralfate

Sucralfate may enhance healing of ulcers in patients with impaired mucosal blood flow and is warranted when there is nausea, inappetence, GI hemorrhage, or hepatic encephalopathy. Caution should be used with sucralfate in combination with other drugs, because this agent binds to and prevents absorption of many drugs, including tetracyclines, fluoroquinolones, and digoxin.105

REFERENCES


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**ARTICLE #3 CE TEST**

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. Choose the best answer to each of the following questions; then mark your answers on the postage-paid envelope inserted in *Compendium*.

1. In which of the following situations are glucocorticoids likely to be beneficial?
   a. lymphoplasmacytic hepatitis
   b. hepatic encephalopathy
   c. hepatic fibrosis
   d. a and c

2. Which of the following is not a reported side effect of colchicine?
   a. bone marrow suppression
   b. peripheral neuropathy
   c. glomerulonephropathy
   d. vomiting

3. In which of the following situations might zinc supplementation be useful?
   a. neutrophilic hepatic inflammation
   b. biopsy diagnosis of fibrosis
   c. as an adjunct to other cupruretics, such as d-penicillamine
   d. b and c

4. Which of the following statements about ursodiol is true?
   a. Treatment with ursodiol may help relieve bile duct obstruction.
   b. It is relatively inexpensive, and side effects are rare.
c. Efficacy studies in dogs have not been performed. 
d. Its use is contraindicated in cats due to adverse effects in this species.

5. Which of the following statements about SAMe is true?  
a. It is an indirect precursor of glutathione. 
b. Controlled efficacy trials are lacking in veterinary patients for most hepatopathies. 
c. It may interact with some tricyclic antidepressants. 
d. all of the above

6. What is a potential indication for using L-carnitine? 
a. hepatic encephalopathy 
b. hepatic lipidosis 
c. any liver disease because it is relatively inexpensive 
d. a and b

7. Which of the following antibiotics is relatively contraindicated in patients with hepatobiliary disease?  
a. amoxicillin 
b. sulfonamides 
c. metronidazole 
d. neomycin

8. Which of the following factors can worsen hepatic encephalopathy?  
a. dehydration 
b. GI hemorrhage 
c. hypokalemia 
d. all of the above

9. In the treatment of ascites, which of the following diuretics is associated with the most side effects?  
a. hydrochlorothiazide 
b. furosemide 
c. spironolactone 
d. a and c

10. Which of the following is an empiric indication for H₂ blockers in animals with hepatobiliary disease?  
a. melena 
b. hepatic encephalopathy 
c. inappetance 
d. all of the above