

Supportive and Symptomatic Care for Dogs and Cats with Hepatic Failure

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HEPATIC THERAPY

General objectives for therapy of hepatic failure revolve around attempts to eliminate causative agents, if known, to suppress or eliminate mechanisms that potentiate the illness, to provide optimal conditions for hepatocellular regeneration, and to control manifestations of complications that develop. Clinical manifestations of hepatic failure are often similar in acute or chronic hepatic failure, differing primarily in the severity and number of complications that develop. Little controlled work has been done on therapy of spontaneous hepatic diseases in the dog or cat. Most therapeutic recommendations are based on conclusions obtained from trials in experimental animals or humans.

Specific Therapy for Hepatic Failure

Therapy for hepatic diseases may be either specific (directed at a causative agent) or supportive and symptomatic (directed at the signs of failure regardless of the cause). At present, there is little in the way of specific therapy available for the majority of known hepatic diseases. This is because the cause for many is not identified or known. If the cause is known, it has no specific treatment (viruses), or it is no longer present when the disease is diagnosed (cirrhosis). Clinicians are compelled to treat the manifestations of hepatic failure symptomatically in an attempt to prolong the patient's life until sufficient repair and regeneration occurs to sustain life. Even if complete recovery is not possible, as is often the case, by utilizing appropriate therapeutic manipulations, many animals can remain asymptomatic for months or years. Where specific therapy is available, it should obviously be utilized.

Supportive And Symptomatic Therapy

Regardless of the cause for hepatic failure in dogs and cats, most cases will receive supportive and symptomatic therapy in addition to any specific drugs that may be indicated. Such care is designed to reduce or eliminate the severity of clinical signs while providing optimal conditions for hepatic regeneration. Even if cures are not possible, improvement in the patient's quality and quantity of life can be attained in many instances. In addition to rest and dietary modifications, a number of drugs may be given to patients in hepatic failure to reduce major complications that develop.

Dietary Modifications

Dietary therapy is the single most important means of modifying the clinical course of most spontaneous liver diseases in dogs and cats. Dietary modifications are going to be most effective in animals with subacute or chronic diseases because these patients will often be willing to voluntarily consume sufficient quantities of nutrients and calories to meet their body's maintenance needs as well as those necessary for hepatic repair and regeneration. Animals with acute severe liver disease usually are unwilling to consume any food at all and must be force-fed or given parenteral hyperalimentation to meet their caloric needs.

Dietary therapy involves adjusting the diet so that optimal quantities and types of nutrients are provided to the animal. The intake of the animal must be balanced with its ability to metabolize these foodstuffs with a failing liver. Protein restriction and modification is of major importance. The goal is to minimize the alterations in nitrogen metabolism induced by hepatic

failure. Appropriate adjustments in the type and quantity of protein ingested by the patient will lead to a reduction in blood ammonia and a return of circulating branched-chain to aromatic amino acid ratios towards normal. The type and quantity of protein, as well as the frequency of feeding, are all important in reducing clinical signs of hepatic failure.

Cottage cheese is a high quality protein source for animals in hepatic failure. Dogs usually find this food more palatable than cats. Cottage cheese contains no additives, is easily and completely digested and has a good ratio of branched-chain to aromatic amino acids. The beneficial effects of cottage cheese are related to the fact that it undergoes less putrefaction and ammonia production by intestinal bacteria during digestion, and that there is a reduction in urease positive bacteria within the colon when it is fed. Cottage cheese is superior to intravenous casein hydrolysates in terms of both nitrogen retention and stabilization of plasma amino acid ratios. The lack of food additives in cottage cheese is important as many commercial pet foods contain additives that are metabolized by intestinal bacteria to potent hepatotoxins. The efficient digestion of cottage cheese within the small bowel results in little residues being available for colonic bacteria to metabolize. Decreasing intestinal residues reduces both the numbers of colonic bacteria and the toxic waste products of their metabolism. Low residue diets also decrease intestinal ammonia production by reducing desquamation of intestinal epithelium. Reduced intestinal cell turnover also results in less protein loss through intestinal lymphatics. Food should be provided to patients with hepatic failure three to four times per day. Hepatic failure patients have reduced ability to handle normal quantities of dietary substrate. By dividing the total daily nutrient intake into several smaller meals, these patients will maintain their appetite and intake which will speed their recovery.

Dogs with hepatic failure should receive approximately 1 gm/lb/day (2 gm/kg/day) of high biologic value protein. This amount should be adequate for maintenance needs as well as that needed for repair and regeneration of the liver, without leading to signs of encephalopathy. Cats have a significantly higher protein need and should receive sufficient good quality protein to provide 30 per cent of their caloric needs as protein. In estimating the protein requirements of patients it is important to know the serum albumin concentration. Severe protein restriction in hypoalbuminemic patients may further deplete serum albumin concentrations and lead to ascites or edema. If clinical signs improve on reduced protein diets but serum albumin concentrations do not, the protein content of the diet should be supplemented. The author recommends increasing the protein available by 0.25 gm/lb/day (0.5 gm/kg/day) at weekly intervals until either protein anabolism is evident or signs of encephalopathy develop. It is not necessary to increase the protein beyond 2.5 gm/lb/day (5 gm/kg/day). A commercially available reduced protein diet which works well in many dogs and cats with hepatic failure is canine or feline k/d. If animals will eat enough to meet their caloric needs, this diet will provide sufficient protein for their metabolic demands. In some animals, even this reduced protein diet cannot be tolerated and an ultra-low protein prescription diet, u/d, for dogs, or s/d for cats, must be utilized. Although this diet may not totally meet the protein needs of the liver failure patient, it may allow them to survive longer and more comfortably than with other available diets.

An easily digested carbohydrate source should form the basis for the bulk of the required daily calories for animals with hepatic failure. The carbohydrate source chosen should be easily digested so that minimal residues remain in the colon where intestinal flora may convert them to volatile fatty acids. An inexpensive and useful carbohydrate source that meets these needs is boiled white rice. A high carbohydrate diet provides an easily assimilated source of nonprotein calories, which spares body tissues from catabolizing muscle protein for energy, and reduces the catabolism of dietary nitrogen for energy.

Fats should be given so that they comprise 6 per cent of the dietary calories on a dry weight basis. This will be accomplished by supplying 0.51 gm/lb/day (1.32 gm/kg/day) of fat in the diet. Fats are necessary to supply essential fatty acids, fat soluble vitamins (A, D, E, K), and improve palatability. Excessive fat supplementation may worsen signs of encephalopathy if the fat source contains large quantities of short chain fatty acids, e.g., coconut oil. However, short chain fatty acids are primarily derived from dietary carbohydrates and to some extent amino acids, not ingested fats. In general, milk fat, and seed oils are not sources of short chain fatty acids. Another reason for moderate fat restriction is that patients with hepatic failure may have reduced intestinal bile salts which are important for normal fat assimilation. If excessive fats are fed the animal may develop fat malassimilation and steatorrhea.

Vitamin and mineral supplementation can be important, especially when diets are formulated at home. Hypovitaminosis is common in liver failure and is caused by multiple factors. Decreased intake associated with anorexia is of major importance. In addition, increased physiologic demands, accelerated intestinal losses, malutilization and impaired storage capacity all combine to increase dietary needs for vitamins. Vitamins most often deficient in humans with hepatic failure include folic acid, B₆, B₁₂, thiamin, A, E, riboflavin, nicotinic acid, and pantothenic acid. In addition, the minerals zinc and cobalt are often deficient. Vitamins B₆ and B₁₂ are particularly important for normal cell regeneration. Cats normally have 2 to 8 times the needs of dogs for B-complex vitamins. It is recommended that daily B-complex vitamin requirements for dogs and cats be doubled. Vitamin C has recently been shown to be reduced in the blood of dogs with experimental hepatic insufficiency and it should be supplemented at 12 mg/lb/day (25 mg/kg/day).

Zinc acetate has been supplemented in cirrhotic humans with chronic hepatic encephalopathy, and in short term studies, patients receiving zinc supplementation had significantly improved neurologic status. Blood urea nitrogen concentrations returned to normal following zinc supplementation, implying that zinc deficiency impaired the efficiency of the urea cycle. The recommended dosage for zinc in dogs and cats is 2.2 mg/lb/day (5.0 mg/kg/day). Vitamin and mineral supplements that contain copper should be avoided. This is particularly important for dogs that have copper storage defects or in animals with chronic cholestasis. Of the fat soluble vitamins, K and D are the most important. If hemorrhagic tendencies develop in association with prolonged cholestasis, parenteral vitamin K₁ 0.5 to 1.5 mg/lb/day (1 to 3 mg/kg/day,) IM may help to return clotting parameters to normal in a few days. If coagulopathies are a result of chronic hepatocellular failure, parenteral vitamins will not be utilized by the failing liver. Fresh whole blood is necessary to stabilize clotting abnormalities in this situation.

The routine use of lipotropic agents containing methionine in dogs and cats in hepatic failure should not continue. Metabolites of oral methionine can induce signs of hepatic encephalopathy quite easily in experimental dogs. It also acts synergistically with short chain fatty acids and ammonia to induce coma. Recently, it has been shown that methionine can also induce a severe Heinz body hemolytic anemia in cats at dosages of 0.25 to 0.5 mg/lb/day (0.5 to 1 gm/kg/day). Lipotropic drugs are of proven value only in cases in which confirmed deficiencies exist. Animals receiving a nutritious diet with adequate quantities of protein have no need for methionine supplementation which may actually worsen signs of disease.

For animals that are totally anorectic, nutritional support may be supplied by force feeding one of several nutritionally complete liquid diets formulated for use in humans. They can be force-fed by syringe or administered through a nasoesophageal catheter or pharyngostomy

tube. Isocal has been used as the sole source of nutrition in experimental dogs that had portal caval shunts surgically constructed (Eck fistula dogs). The dogs maintained normal weight, and serum albumin concentrations and had no central nervous signs, while those eating standard dog chow continued to deteriorate. Although the liver of Isocal-treated dogs continued to atrophy, the dogs appeared clinically normal. This diet has a relatively high ratio of carbohydrate per gram of protein, which has a protein sparing effect on the body. The author has experience with similar diets, Ensure-HN and Impact, which are used commonly in anorectic cats with idiopathic lipidosis. These formulations provide one calorie per milliliter of diet and are an efficient and useful method of providing oral alimentation to patients in liver failure that will not eat on their own. For cats, taurine will need to be supplemented at 50 mg/day to these human enteral diets.

Several benzodiazepine derivatives may be tried as appetite stimulants for anorectic cats. These drugs are not as effective in dogs. Benzodiazepine compounds stimulate the hunger center in the brain and can cause voracious feeding in normal cats. Of the available compounds, oxazepam is the most potent, followed by lorazepam, which is more potent than diazepam. Dosages as low as 0.05 mg/lb (0.1 mg/kg) increased food intake by 50 per cent, while 0.12 mg/lb (0.3 mg/kg) caused a 72 percent increase in food intake in normal cats. This effect occurred even when the drug was given 12 hours prior to feeding. Dosages of 4.5 mg/lb (10 mg/kg) resulted in sleepiness and ataxia. Diazepam was not as effective, but dosages of 0.12 mg/lb (0.3 mg/kg) caused a 39 per cent increase in food intake and 0.45 mg/lb (1.0 mg/kg) caused an 82 per cent increase in feeding. In the author's experience, diazepam stimulates a very transient interest in eating in cats with hepatic failure, and usually makes them sleepy even at 1.5 to 3 mg total dose. Oxazepam deserves more clinical evaluation in anorectic cats with liver failure to see if it will shorten the time necessary for forced feeding.

Drugs in Hepatic Failure

The liver is quantitatively the most important organ involved with drug metabolism, although the kidney, brain and other organs make significant contributions. For many drugs metabolized in the liver, their duration and intensity of action may be increased in the presence of liver disease. However, not all enzyme systems are equally affected by hepatic failure. A number of therapeutic agents cause nonspecific induction of hepatic drug metabolizing enzymes, and their metabolism may actually be increased, even in the presence of liver failure. There is no test of liver function that can be run to determine if a given drug will be metabolized normally in a patient with liver failure. As a general rule, most commonly used drugs are well tolerated by patients with hepatic failure and can be prescribed, as long as animals are monitored for signs of toxicity.

Antibiotics

Adequate hepatic function does not seem to be a critical factor in the handling of most antibiotics by patients with liver failure. They are generally given at standard recommended dosages and dosage intervals. Antibiotics are indicated as specific treatment for primary bacterial hepatitis, hepatic abscesses, bacterial cholangitis, or cholecystitis, and are of great value in the suppression of intestinal bacteria that are responsible for many of the signs of hepatic encephalopathy (see Complications of Hepatic Failure).

The selection of antibiotics to be used for the treatment of nonhepatic infections should be made with caution. It is best to avoid drugs that require hepatic inactivation or excretion since they may reach toxic levels if the failing liver is unable to effectively remove them from the circulation. Conversely, for treating specific infections of the liver, drugs that are metabolized and eliminated by the liver are ideal since very high tissue concentrations will develop.

All tetracyclines are concentrated in the liver and excreted in bile. Biliary concentration may reach 5 to 32 times the serum concentration. Parenteral preparations are known to be toxic in high dosages in humans. A reversible lipidosis occurs in dogs given chlortetracycline, which is the most hepatotoxic of the group. Tetracyclines also suppress hepatic protein syntheses and thus impair albumin synthesis and enzyme activity in the liver. Prolonged use of these drugs have been associated with decreased vitamin K absorption in man. Because they generally cause anorexia in dogs and cats and have toxic side effects, they are poor choices for animals with hepatic failure.

Penicillins, and their newer derivatives, ampicillin and amoxicillin, reach high tissue concentrations in the liver. They are primarily renally excreted, and are quite safe to use in animals in hepatic failure. Hetacillin requires conversion to ampicillin by the liver, so this would not be a good choice for animals in liver failure. Cephalosporins also do not require hepatic metabolism for biologic activity and are useful for treating systemic infections in patients with liver failure.

Chloramphenicol is conjugated by the liver and then excreted by the kidney. Concentrated hepatic tissue and biliary levels are attained. Disadvantages to chloramphenicol outweigh the potential benefits. The drug is a potent inhibitor of hepatic microsomal enzyme systems and thus inhibits the clearance of many other drugs and waste products produced endogenously. Its half-life is often prolonged in chronic liver disease and may augment its toxic potential. It also produces anorexia and reversible erythroid hypoplasia both in dogs and cats and thus cannot be recommended for use.

Lincomycin, clindamycin, and erythromycin estolate are all cleared by the liver or known to be hepatotoxic and should be avoided in patients with liver disease because it may potentiate their toxicity.

Sedatives, Anticonvulsants, Anesthetics and Analgesics

Sedatives should be avoided in hepatic failure, since their use is commonly associated with the development of hepatic coma. Phenobarbital is primarily excreted by the kidney and is the safest hypnotic. Convulsive states are best controlled using short acting compounds like diazepam (Valium) or chlordiazepoxide (Librium) at reduced dosages. There is potential for hepatotoxicity associated with the use of both phenytoin and primidone. They should not be used to control seizures in animals with evidence of preexisting liver disease.

Avoid analgesics, anesthetics and barbiturates in patients with hepatic failure. If analgesia is required, meperidine, codeine, butorphenol, oxymorphone, or combinations of diazepam and ketamine are better tolerated than morphine. Start with smaller dosages that you would normally use and give more if necessary, rather than give a relative overdose to start with. Of all the inhalent anesthetics, halothane has been frequently incriminated in cases of fulminant hepatic failure in humans following repeated exposures. Similar experiences in dogs or cats are extremely rare. Halothane in combination with hypoxia and metabolic acidosis may be hepatotoxic. Because of its relative safety compared to other anesthetics, the author has no concern about using halothane for anesthetizing metabolically fragile patients in hepatic failure.

Anabolic Androgenic Steroids

Several reports have attributed beneficial effects to the use of androgenic anabolic steroids in the treatment of chronic liver disease in humans. Drugs evaluated include testosterone propionate, methandrostenolone, testosterone, methenolone enanthate, and norethandrolone. Administration of these drugs generally was continued for many months. The bulk of clinical studies indicates a trend in favor of a positive effect for anabolic steroids in the course and prognosis of patients with cirrhosis and possibly other liver diseases. Anabolic steroids appear to stimulate both hepatic RNA synthesis and protein synthesis in the regenerating liver, and protect against the induction of fatty liver. One interesting report concerns the use of norethandrolone at 120 mg once daily for severe alcoholic fatty liver in humans. The lipidosis was dramatically reversed in 2 weeks of this treatment. This effect was not observed when 25 mg of daily testosterone was used. These compounds warrant clinical evaluations in cirrhosis and idiopathic lipidosis. Regardless of the drug used, for anabolic steroids to be effective, sufficient non-protein calories must be taken in to meet metabolic demands or no anabolic effects will be seen. Methyltestosterone has been shown to have a mild toxic effect on the dog liver and should be avoided.

Glucocorticoids

The use of glucocorticoids in hepatic failure remains a controversial subject. They have proven efficacy only in human chronic active hepatitis and primary biliary cirrhosis. Their potential for use in canine chronic active hepatitis and feline cholangitis/cholangiohepatitis is common but confirmed evidence for benefit is lacking. The potential benefits to steroid use include increased appetite, reductions in serum bilirubin concentrations, reductions in transaminases, lessened BSP retention, and increased serum albumin concentrations. Glucocorticoids also have a mild choleric effect, and might be useful in diseases associated with cholestasis. In spite of these many potential benefits, they are also known to have many disadvantages. Glucocorticoids fail to prevent the progression of most acute liver diseases to chronic phases; they may increase the chance of intercurrent infections developing; they generally do not increase life expectancy; they fail to alter the histology of most liver diseases; and they can aggravate the management of ascites by promoting sodium retention. Previously stable cirrhotic dogs may deteriorate rapidly following the administration of steroids. Recent information indicates they also increase the incidence of peptic ulceration in cirrhotic men. In general, patients in which steroids may have a beneficial effect are those with prolonged anorexia and weight loss in which increased food intake would be beneficial and those with suspected immune mediated hepatobiliary diseases.

The dosage and type of glucocorticoid used may be more important in patients with hepatic failure than with other steroid responsive diseases. Short-acting steroids should be chosen; prednisone or prednisolone are the drugs of choice. Prednisone must be converted to its active form, prednisolone, by the liver. This should make prednisolone the best choice for animals in liver failure, but most pharmacologic studies of this problem have concluded the benefits of one drug over the other are minimal. Another important factor to consider in the use of steroids is that their half-life is often prolonged in animals with liver failure. Unless the dosage is reduced or the dosage interval is increased from those usually considered, signs of

iatrogenic hyperadrenocorticism may develop. Maintenance dosages in dogs may be as low as 0.2 mg/kg/day.

Ursodeoxycholic acid (Actigall)

This naturally occurring bile acid appears to have unique hepatoprotective effects against other more toxic bile acids. It is known that some bile acids have the potential to be hepatotoxic in high concentrations as would occur in cholestasis of any kind. The hydrophobic, lipophilic bile acids, chenodeoxycholic acid and deoxycholic acid have the greatest potential to cause injury. They are known to increase in the circulation in chronic liver diseases. Conversely, the hydrophilic, lipophobic bile acid, ursodeoxycholic acid, has just the opposite effects. When used chronically by the oral route, ursodiol results in decreased concentrations of hepatotoxic serum bile acids and may modify the rate of progression of chronic cholestatic liver diseases. Ursodiol is proposed to exert this hepatoprotective effect via three mechanisms; 1) hypercholeresis, 2) a direct protective effect or by displacement of hydrophobic bile acids from the circulation, and 3) immunomodulation. Only anecdotal evidence has appeared in the veterinary literature about this drug. It does not apparently induce any toxic side effects, however, documented evidence of efficacy is still lacking as well. The current recommended dosage for both dogs and cats is 10 to 15 mg/kg once daily orally (300 mg capsules, \$1.96 ea in 1998).

Drugs to Control Hepatic Fibrosis

One of the most significant pathologic changes occurring in chronic liver diseases is the development of fibrosis. Both increased synthesis and decreased degradation of collagen occurs in cirrhosis. If causative agents can be identified early in the course of chronic diseases, fibrosis may be completely reversible. However, at some point in the progression of chronic liver diseases, fibrosis becomes self-perpetuating, even if the causative agent is removed. Immunologic factors appear to play a role in the development and progression of fibrosis in many chronic liver diseases.

Colchicine

Of all the experimental antifibrotic drugs available, colchicine appears to have the most potential. Colchicine is an alkaloid, antimetabolic agent. This drug has unique anti-inflammatory properties but is only licensed for use in gouty arthritis. It binds to microtubule protein and interferes with the function of mitotic spindles, which can arrest cell division. Colchicine prevents transcellular movement of collagen in fibroblasts and stimulates a two- to 10-fold increase in collagenase activity. Preliminary clinical trials in human cirrhotics indicate that histologic progression was halted and mortality was decreased by 25 per cent over a 53 month period of study. In addition, serum albumin concentrations consistently increase in cirrhotic humans receiving colchicine. Therapeutic trials in primary biliary cirrhosis also show benefit. Serum albumin concentrations again increase, while those of bilirubin, cholesterol and ALT decreased, and mortality was reduced by 50 per cent after 4 years. Only one clinical report of its use in dogs has been published. A 4 year old cirrhotic dog was treated for 7 months (0.014 mg/lb/day or 0.03 mg/kg/day orally). The dog had deteriorated with the administration of steroids but improved clinically after colchicine was started. No toxicity was observed. Reported signs of acute toxicity in humans include nausea, vomiting, diarrhea and abdominal pain. These signs may be reduced by administering the drug intravenously. Chronic toxicity

includes agranulocytosis, aplastic anemia, myopathy and alopecia. The author has evaluated colchicine in several dogs with severe chronic liver disease. They showed no clinical improvement, but periods of evaluation were less than one month.

D-penicillamine

D-penicillamine is another drug which may be used to modify hepatic fibrosis. Large dosages given to cirrhotic rats (140 mg/lb/day or 300 mg/kg/day) induced significant reductions in hepatic fibrosis. This dose is much higher than currently recommended for the dog (5 to 7 mg/lb/day or 10 to 15 mg/kg/day), and would not likely be tolerated.

THERAPY FOR COMPLICATIONS OF HEPATIC FAILURE

A number of potentially serious complications of hepatic failure may develop in any given patient. It is often one or more of these complicating factors that causes the death of the patient. It is important for clinicians to recognize these complications early in their course and manage them vigorously if any degree of success is to be obtained.

Hepatic Coma

Hepatic coma is a serious complication of hepatic failure. It is seen most often in young dogs and cats with congenital portal systemic shunts. Occasionally, an older dog or cat with chronic liver failure will manifest encephalopathic signs as well. In adult animals, signs of encephalopathy are much less dramatic and often are those of depression, lethargy, vomiting and diarrhea. The goal of therapy is to control the pathophysiologic mechanisms responsible for inducing the encephalopathy, while the liver attempts to regenerate sufficient tissue to maintain life. This is accomplished by reducing the entry, production and absorption of gastrointestinal "toxins" and by administering systemic drugs which counteract the effects of the absorbed toxins.

The mainstays of therapy for encephalopathy involve reduction of protein intake, suppression or elimination of urease containing intestinal bacteria, and catharsis. In addition, steps must be taken to recognize and eliminate any precipitating factors which may have induced the encephalopathy. For animals exhibiting signs of encephalopathy all oral intake of food should cease until CNS signs abate. This is particularly important for protein. Cessation of food intake eliminates dietary sources of ammonia, toxic amines, aromatic amino acids, and short chain fatty acids which induce encephalopathy. Next, complete catharsis of the colon should be undertaken. Emptying the colon rapidly decreases numbers of colonic bacteria and removes potentially toxic by-products of bacterial metabolism. Although warm water enemas are most often used, a more effective method combines substances which impair ammonia production or absorption in the enema solution. Using a 10 per cent povidone iodine solution as the enema fluid, or adding liquid neomycin sulfate (22 mg/kg) to the enema fluid, results in more efficient, rapid suppression of colonic bacteria, which generate the majority of the blood ammonia. Enemas should be repeated until no fecal material is evident in the evacuated fluid.

Another drug which is highly effective in lowering blood ammonia concentrations when added to enema fluid is lactulose (1-4-beta-galactosidofructose (Cephulac). Lactulose is a semisynthetic disaccharide which is not metabolized by mammalian intestinal disaccharidases. When this undigested sugar reaches the colon, intestinal bacteria hydrolyze it to lactic, acetic and formic acids, which dramatically lower colon pH. In addition to the pH effect, when large

quantities of unabsorbed solutes are produced in the colon an osmotic diarrhea results. Blood ammonia concentrations are lowered because of several unique attributes of lactulose. By-products of lactulose fermentation produce what is termed ionic trapping of ammonia within the colon. In an acid environment, ammonia (NH_3) accepts a proton to form ammonium (NH_4^+). Ammonium is much less diffusible than ammonia. Thus, ammonium ions remain within the colon and are excreted rather than being absorbed. This effect occurs at colon pH's of 6.2 or less and is most noticeable if the colon pH is 5.0 or lower.

In addition to ionic trapping, lactulose apparently inhibits ammonia generation by colonic bacteria through a process known as catabolite repression. By providing a carbohydrate source to intestinal bacteria, less proteolysis, peptide degradation and deamination of bacterial proteins occurs. This results in significantly less ammonia being generated by colonic bacteria than they would produce under other circumstances, and this effect is independent of the pH effect. Lactulose containing enemas are much more effective than warm water enemas in reducing blood ammonia concentrations and improving clinical signs. Lactulose is diluted with warm water (30 per cent lactulose, 70 per cent water) and given as a retention enema. Approximately 10 to 15 ml/lb (22 to 33 mg/kg) is infused and retained in the colon for 20 to 30 minutes before evacuation. The pH of the evacuated fluid is measured and if greater than 6.0, another lactulose enema should be administered. Improvement in neurological status can occur in 2 hours in humans.

As soon as patients are able to tolerate oral liquids, attempts should be made to "sterilize" the gut. Non-absorbable intestinal antibiotics are used to suppress potent urea splitting intestinal flora, which contribute significantly to blood ammonia concentrations. The antibiotic used most commonly for this purpose is neomycin sulfate, although kanamycin, vancomycin, and paromomycin may be used interchangeably. The recommended dose for use in dogs and cats is ten mg/lb (22 mg/kg) three to four times daily. Other beneficial effects of the use of oral antibiotics are to decrease bacterial deamination of amino acids, and reduce the production of aromatic amino acids, circulating false neurotransmitters, and short chain fatty acids by gut bacteria. Occasional rare complications to the chronic use of neomycin are oto- and nephrotoxicity, severe diarrhea, and intestinal malabsorption. A number of other systemically absorbed antibiotics may be used in animals with hepatic failure as alternatives to aminoglycosides. One which has received a great deal of interest is metronidazole (Flagly). Metronidazole is active against many of the urease-positive, gram negative anaerobes which are potent generators of ammonia in the intestinal tract. Most clinical studies have indicated that metronidazole is equal in effectiveness to neomycin in controlling blood ammonia concentrations. The recommended dose is nine mg/lb (20 mg/kg) given every eight hours. Toxicity to metronidazole in man, includes nausea, ataxia, dizziness and paresthesias, and in dogs CNS signs may develop as well. Because of the potential for neurotoxicity and decreased elimination in liver failure, and it may be preferable to administer metronidazole at 5 mg/lb (10 mg/kg) TID to animals with encephalopathy. Many animals will also respond to other antibiotics such as ampicillin, which are effective against intestinal anaerobes. These animals improve clinically while receiving antibiotics but develop signs of illness when antibiotics are stopped. This likely corresponds to the effects the drug has on GI flora, an effect that stops soon after it is discontinued.

Oral lactulose may be used as an alternative to, or in conjunction with, intestinal antibiotics in the management of hepatic coma. Most surveys indicate that lactulose alone or neomycin alone provides clinical improvement in 80 per cent of humans with chronic encephalopathy. An additional group of patients will benefit from the combination of neomycin

and lactulose since these are sometimes synergistic. Because these two drugs control intestinal ammonia formation by different mechanisms, this should not be surprising. It is interesting, that neomycin does not impair the effectiveness of lactulose in most patients. Since lactulose requires metabolism by intestinal bacteria and neomycin kills bacteria, one would think that oral antibiotics would be contraindicated for maximal effectiveness of lactulose. This is not the case. Neomycin inhibits bacterial degradation of lactulose in less than one-third of patients. Lactulose is degraded by lactulophilic bacteria of which *Bacteroides* spp predominate. *Bacteroides* spp are fairly resistant to the effects of neomycin. To determine whether lactulose degradation is occurring in animals receiving both drugs, measure stool pH after 7 to 14 days of combined therapy. If the stool pH is lower than 6.0 then the lactulose is being metabolized and neomycin is not impairing its effectiveness. If the stool pH remains around 7.0, lactulose will be ineffective and should be discontinued. Lactulose is dosed so that a decrease in fecal pH is produced, but diarrhea is avoided. Usually cats require 2.5 to 5 ml three times daily and dogs require 2.5 to 25 ml three times daily. If watery diarrhea develops, the dosage should be reduced.

Alternative methods of controlling hepatic encephalopathy may be tried, but are not likely to be as effective as lactulose and neomycin. Attempts may be made to repopulate the colon with lactose fermenting, nonurease containing bacteria such as lactobacilli. Unfortunately, supplementing the diet with lactobacillus-containing drugs or yogurt in quantities sufficient to maintain desirable flora in adequate numbers has not had much clinical success.

Specifically formulated intravenous solutions containing primarily branched chain amino acids as the nitrogen source have been marketed for use in the therapy of acute hepatic encephalopathy (Hepatamine). These solutions are designed to help normalize plasma amino acid patterns by decreasing muscle catabolism. Decreasing muscle breakdown reduces the concentration of circulating aromatic amino acids which are considered to be important in the genesis of hepatic encephalopathy. Experimental work in encephalopathic dogs indicated that use of these preparations resulted in marked improvement in neurological status. However, the majority of the published results in humans with chronic encephalopathy does not support that it provides significant benefit over other well balanced amino acid solutions. Clinicians must be extremely cautious when using inexpensive intravenous protein hydrolysates in animals in hepatic coma. Such solutions have extremely high ammonia concentrations, 1500 to 1900 ug/dl, and may rapidly worsen the clinical status of the patient. Stored blood may also be dangerous in this regard.

Another drug which may be considered for use in encephalopathic dogs or cats that fail to respond to traditional therapy is l-dopa (Larodopa, Roche). L-dopa is a precursor to norepinephrine and dopamine, and when given orally, it raises cerebral dopamine concentrations. It has been used with some success in humans with acute hepatic coma. Patients usually respond by regaining full consciousness in 6 to 12 hours. Unfortunately, responses may be transient even though therapy is continued. The recommended dosages, based on those used in man, would be an initial dose of 15 mg/lb followed by 3 mg/lb every 6 hours. No information regarding the safety or efficacy of l-dopa in animals is available.

A new parenteral benzodiazepine antagonist, flumazenil (Mazicon, 0.1 mg/ml, 5 ml vials, \$6.00/ml, Hoffmann-LaRoche), has recently become available for clinical use. It is primarily used in humans to treat benzodiazepine overdose. However, since some of the signs of hepatic encephalopathy appear related to binding of "neurotoxins" to the benzodiazepine-barbiturate-GABA receptors in the CNS, this drug may reverse the "down regulation" of neural receptors associated with PSE. It is indicated for the acute management of encephalopathy, not, long-term control. Current dosage recommendations are **0.03** mg/kg IV as needed to reverse signs of

encephalopathy.

Oral cation exchange resins such as cholestyramine have been used in humans and experimental animals to decrease the absorption of endotoxins from the intestines. Reticuloendothelial function of the liver is known to be impaired in cirrhosis and predisposes patients to bacterial infections. Cholestyramine binds bacterial endotoxin and prevents it from being absorbed systemically. No dosage is available for dogs and cats.

Additional supportive measures may be necessary in the management of animals with hepatic encephalopathy. Parenteral fluid therapy is often required for several days in patients with hepatic failure, and the fluid you choose to use can be an important therapeutic decision. Animals with chronic liver failure are often hypokalemic, alkalotic and prone to sodium retention. The ideal fluid should be supplemented with potassium, be low in sodium and be non-alkalinizing. Sodium bicarbonate is given only if metabolic acidosis develops and is severe (pH is less than 7.1). Fluids containing lactate may be ineffective as alkalinizing agents since the liver is the site of conversion for lactate to bicarbonate and glucose. Either half-strength saline (0.45 per cent), or half-strength saline plus 2.5 per cent dextrose are good choices for fluid needs in the liver failure animal. These fluids should be supplemented with approximately 20 meq/l of potassium chloride. Glucose supplementation is beneficial in preventing hypoglycemia, in decreasing peripheral catabolic processes, and in decreasing brain ammonia concentrations.

Ascites and Edema

Ascites is a fairly common complication of chronic hepatic failure, while peripheral edema is very infrequent. Ascites, although varying in severity, is not necessarily harmful. Moderate amounts have minimal physiologic importance. When ascites is severe (marked by the presence of respiratory distress or hypotension), therapy should be directed at reducing the volume pharmacologically or mechanically, and also towards measures that will improve hepatic function. Patients with advanced hepatic failure and ascites may not have significant diuresis until improvement in hepatic function occurs.

Low sodium diets and diuretics are the most commonly used means of controlling ascites formation. If these methods fail, mechanical measures such as peritoneovenous or portal caval shunting procedures may be tried. Low sodium diets and diuretics form the basis for management of most cases. Salt restriction must be severe in cirrhotic animals in order to effectively manage ascites, and may require reductions in sodium intake that are much below those used in congestive heart failure. Commercially available low sodium diets (k/d, h/d, Hills Prescription Diets) may be tried initially, but if a poor response is noted, home-formulated diets should be tried. Ultra low sodium intake is on the order of 7 mg/lb/day (15 mg/kg/day) in dogs.

Active sodium reabsorption by the kidney plays a major role in the development and perpetuation of cirrhotic ascites. Potent "loop" diuretics are useful in many cases in preventing this reabsorption and inducing a diuresis. Either furosemide (1 to 2 mg/kg every 8 to 12 hours) or ethacrynic acid may be used. If a significant diuresis does not develop in 4 to 7 days, the initial dose is doubled. If there is no response to this increased dose, an aldosterone antagonist should be added to the therapy. A number of complications can develop following furosemide administration in cirrhotic patients, nearly all of which are dose related. The most important are electrolyte disturbances (hypokalemia, hypochloremia, and hyponatremia), hypovolemia, and hepatic coma. Periodic serum electrolyte profiles need to be evaluated in animals receiving potent diuretics for any period of time. In addition, animals must be monitored carefully to avoid inducing dehydration.

Some animals fail to respond to furosemide. This probably reflects the fact that serum aldosterone levels are very high in many cirrhotics. Hyperaldosteronism causes significant reabsorption of sodium in the distal tubules. Since furosemide promotes sodium excretion primarily from the loop of Henle, much of the sodium that reaches the distal tubules is reabsorbed under the influence of aldosterone, negating furosemide's diuretic effect. Aldosterone antagonists should be used in animals whose ascites is refractory to furosemide. Ascitic human cirrhotics who are refractory to furosemide, nearly all respond when spironolactone (Aldactone or Aldactone-A) or triamterene are added to the diuretic regime. Spironolactone should be administered at 0.5 to 1 mg/lb twice daily. Response may take several days to be noted. If neither a diuresis nor a decrease in ascites is noted, the dosage of spironolactone should be doubled. In humans, dosages of spironolactone may be 6 to 20 times the usual recommended doses before an appropriate diuresis is produced.. In humans, it is possible to predict those that are likely to need large doses of spironolactone by measuring the U_{Na}/U_K ratio. Patients likely to respond poorly to low dosages of aldosterone antagonists have U_{Na}/U_K ratios of less than 1.0, while in those that have good initial responses, the ratio is greater than 1.0. Potassium supplements should not be given to patients receiving aldosterone antagonists as this may lead to hyperkalemia.

Do not attempt to remove ascites through pharmacologic means too vigorously. Ascitic fluid has a maximal rate of mobilization of 700 to 900 ml/day in humans. Any net fluid loss beyond this is at the expense of plasma water. Patients are not normally allowed to lose more than 200 to 300 ml of net water loss per day (0.2 to 0.3 kg/day weight loss). Diuretics should be stopped once ascites is no longer clinically evident. If it reoccurs after drug withdrawal, the lowest dosage necessary to control ascites build-up should be continued indefinitely. If serum albumin concentrations can be raised, ascites will often spontaneously regress.

If two weeks of salt restriction and appropriate diuretic use do not result in significant reductions in the degree of ascites present, more heroic measures should be considered. Such measures include intermittent paracentesis, surgical implantation of some type or peritoneovenous shunt, or creating a surgical portocaval shunt. Paracentesis for removal of ascites should generally be avoided except as a temporary measure to provide immediate relief for a dyspneic or painful patient, or for patients in which aggressive medical therapy has been unsuccessful. Small quantities may be removed for diagnostic purposes. Complications associated with paracentesis of patients in hepatic failure include albumin depletion, peritonitis, hypovolemia, hepatic coma, and oliguria.

Two surgical procedures have been used clinically in man and experimentally in dogs, to control chronic, diuretic resistant ascites. The first is the LaVeen shunt, initially developed in 1972. The LaVeen shunt is a one-way pressure actuated valve. The valve is inserted into the peritoneal cavity and connected by subcutaneous tubing to the jugular vein. Ascitic fluid is propelled into the venous system by the pumping action of the diaphragm. Such surgical drainage systems have been well tolerated by experimental dogs. These shunts are often successful in controlling ascites in humans; however, their use is associated with many major complications. Shunt failure due to clogging of the valve occurs in 10 per cent of cases. An alternative surgical procedure for ascites management is the creation of a portal-systemic venous shunt. Such shunts decompress the portal system and relieve portal hypertension. If portal hypertension can be alleviated, ascites may disappear. Unfortunately, this procedure is associated with high surgical mortality and patients are prone to develop hepatic coma. The trade-off lies in whether the ascites is a worse problem than managing the encephalopathy.

Intercurrent Infections

Intercurrent infections are one of the most frequent complications of hepatic cirrhosis. Gram-negative septicemias often develop in humans, with the bowel being the presumed source of the infection. Because many cases of chronic active liver disease are associated with a non-specific fever, an infection tends to be overlooked and must be guarded against. The normal dog liver harbors anaerobic gram-positive organisms that may proliferate if hypoxic conditions develop within the liver. The addition of prophylactic antibiotics to the therapeutic regime of animals with acute hepatic failure is justified in such cases.

Malabsorption

Clinically significant malabsorption associated with chronic hepatic and biliary tract diseases is uncommon in animals. Steatorrhea due to reduced bile salt excretion probably occurs in many cholestatic liver diseases but its magnitude has not been assessed. Several products may help alleviate or reduce the severity of the problem. Oral bile salts may increase the emulsification of triglycerides and aid in the digestion and absorption of intestinal fats (Decholin). These products contain unconjugated fractions that are irritating to the bowel and may cause diarrhea. Neutral fats may be added to the diet in the form of water soluble medium chain triglycerides (Portagen), which do not require the action of lipase or bile salts for absorption. This preparation may increase caloric intake and promote weight gains, but it has the risk of aggravating hepatic encephalopathy because it contains significant quantities of short chain fatty acids. Lastly, occasional cases of biliary tract disease with steatorrhea may benefit from the addition of pancreatic enzymes to the diet.

Hemorrhage and Anemia

Coagulopathies associated with hepatic disease are common, but clinical bleeding associated with the coagulopathy is rare, except in acute fulminant hepatic failure or chronic end stage liver disease. Abnormalities associated with prothrombin deficiencies are frequent. Prothrombin synthesis is impaired in any hepatic disease that compromises the ability of the liver to synthesize prothrombin from dietary precursors. Chronic cholestatic diseases or prolonged bile duct obstruction can induce vitamin-K deficiencies due to impaired absorption of fat soluble vitamins. If overt hemorrhage occurs secondary to a coagulopathy, fresh whole blood is necessary to provide clotting factors and red blood cells. Injections of parenteral vitamin-K₁ 0.5 mg/lb/day (1.1 mg/kg, Menadione) will reverse hypoprothrombinemia associated with bile duct obstruction, but is of no benefit when hemorrhage is secondary to hepatic functional failure. Disseminated intravascular coagulation (DIC) can occur in severe hepatic failure and is very difficult to manage successfully. If evidence for DIC exists, the patient should be transfused and heparin therapy instituted, 50 units/lb/SQ, three times daily (110 mg/kg). Frequent monitoring of coagulation parameters must be done when heparin is given. Bleeding into the gastrointestinal tract is particularly devastating to patients in hepatic failure. Blood is a highly effective protein source for inducing hepatic coma. If bleeding is secondary to gastric or duodenal ulcers patient should be given cimetidine (Tagamet) at 2.5 mg/lb (5 mg/kg) every 8 hours, or ranitidine (Zantac) at 0.25 mg/lb (5 mg/kg) every 12 hours. In addition, ulcer protective agents such as sucralfate (Carafate) can be given at 1 gm/27 kg every 6 hours. Anemia of liver failure is multifactorial. Blood loss, lack of production secondary to malnutrition, and sequestration and

destruction of red blood cells all may play a role. If bleeding tendencies can be controlled and the liver disease stabilized or reversed, these anemias will resolve. In most animals the degree of anemia is not severe and the patient will not need transfusions.

Fulminant Hepatic Failure

Fulminant hepatic failure (FHF), is a syndrome associated with acute, massive necrosis of parenchymal cells and with sudden severe impairment of hepatic function. This syndrome is uncommon in small animals. The causes are variable, but most cases are associated with viral infections (rare), or exposure to drugs or toxins. The author has observed a number of cases in Bedlington terriers with copper toxicosis. Occasional cases occur following severe abdominal trauma or prolonged hypotension. Before beginning intensive therapy, it is important to be sure the situation is acute and that the patient is not in end stage chronic liver failure. This is because acute severe failure is potentially completely reversible, while the outcome of animals with chronic failure is invariably death. The primary goals of therapy are supportive and symptomatic. The animal is supported long enough for sufficient repair and regeneration to occur to allow for survival.

Fulminant hepatic failure is associated with multiple organ system abnormalities that may need to be aggressively managed (Table 1). The majority of humans that die in fulminant failure do not succumb from the loss of hepatic parenchyma, rather, they most often die from cerebral edema, hemorrhage, or sepsis. Central nervous signs in FHF are due to both hepatic encephalopathy and cerebral edema. Cerebral edema is not seen in chronic hepatic failure. Cerebral edema of FHF is thought to be primarily of vasogenic origin. Permeability of the blood-brain barrier is altered, allowing circulating toxins and plasma proteins to egress from intracerebral capillaries into the extracellular space. The permeability of the blood-brain barrier is increased by ammonia, short chain fatty acids, and mercaptans, which are known to be increased in the circulation in FHF. If patients are hypoproteinemic, fluid transudation out of capillaries is also promoted. Determining whether cerebral edema is present and causing some of the CNS signs in these patients is difficult. If the neurological status of the patient continues to deteriorate in spite of aggressive management of hepatic encephalopathy, it is best to treat for cerebral edema for 12 to 24 hours rather than do nothing. Steroids are ineffective in controlling cerebral edema in FHF. Mannitol (20 per cent solution) is given at 0.45 gm/lbIV (1 gm/kg/IV) over 30 minutes and is repeated every 4 hours if the patient does not improve neurologically. Furosemide is also given at 0.5mg/lb/IV (1 to 2 mg/kg/IV) every 8 hours for two or three doses. If patients are hypoproteinemic, plasma transfusions should be given, if available. Hypoglycemia can be severe in FHF and contribute to the CNS signs. Anorexia, depleted glycogen reserves and reduced hepatic insulin degradation all contribute to this effect. Intravenous glucose may have to be given as 10 or 20 percent solutions in order to maintain blood glucose concentrations in the normal range. Frequent blood glucose monitoring is essential.

Sepsis is responsible for the death of 10 to 15 per cent of humans with FHF. It is extremely important that great care be taken to maintain asepsis in catheter placement and to rapidly control any infections that develop. Broad spectrum antibiotics should be routinely administered.

Hemorrhage occurs early and often in FHF. Bleeding may be evident from any location in the body. Hemorrhage is usually secondary to decreases in prothrombin dependent clotting factors. Increasing gastric pH to greater than 4.0 with intravenous cimetidine or ranitidine significantly reduces gastrointestinal bleeding. Hemorrhagic tendencies are managed as

indicated previously. The use of injectable vitamin-K₁ is indicated because it may be rapidly incorporated into prothrombin by newly regenerating hepatocytes.

Renal failure occurs in up to 40 percent of patients with FHF and is termed hepato-renal syndrome. When present, the prognosis is usually very poor. This appears to be a result of intense renal vasoconstriction, which may cause acute tubular nephrosis. Therapeutic measures are often ineffective in reversing this problem. Prerenal components must be reversed rapidly. Hemodialysis is often necessary in humans to support patients with hepato-renal syndrome.

Glucocorticoids have been used for years in patients with FHF. Recent clinical trials in humans with viral induced FHF indicate they have no benefit and may be harmful. However, when methylprednisolone was given to rabbits with galactosamine induced FHF, significantly improved survival was noted when compared to control animals. Most cases of FHF in humans are viral induced and it was suggested that steroids may have benefit in non-viral FHF.

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DRUG INDEX

<u>Drug</u>	<u>Dose/Route/Frequency</u>	<u>Indications</u>
Allopurinol	9.9 mg/kg/os/q8h	Uric acid calculi
Ampicillin	10-20 mg/kg/os/q6-8h	Hepatic coma, sepsis
Cimetidine	5 mg/kg/os/q8h	GI ulcers
Colchicine	0.03 mg/kg/os/q24h	Antifibrotic agent
Dehydrocholic acid	10-15 mg/kg/os/q8h	Bile stasis ?
Diazepam	0.3 mg/kg/os/q8h	Anorexia in cats
Ensure-HN	1-kcal/ml	Liquid enteral diets
Impact		
Isocal		
Flumazenil	0.03-0.075 mg/kg IV	Hepatic coma
Furosemide	1-2 mg/kg/q8-12h	Ascites management
Heparin	23 units/kg SQ q8h	DIC in liver failure
Lactulose	2.5-5 ml/os/q8h (cats) 2.5-25 ml/os/q8h (dogs)	Hepatic coma
Metronidazole	10-15 mg/kg/os/q8h	Hepatic coma
Neomycin sulfate	22 mg/kg/os/q6-8h	Hepatic coma
Oxazepam	0.3-0.1 mg/kg/os/q 12h	Appetite stimulant, cat
Prednisone	1-2 mg/kg/q12h	Chronic hepatitis dogs, cholangitis-cats
Ranitidine	5 mg/kg/q 12h	GI ulcers
Spironolactone	1 mg/kg/q12h	Diuretic, ascites
Ursodeoxycholic acid	10-15 mg/kg q24h	Chronic cholestasis
Vitamin K ₁	1 mg/kg/day/os/IM	Bleeding, liver failure
Zinc sulfate	0.7-1 mg/kg/q 8h	Hepatic coma

Table 1: System Abnormalities Seen in Fulminant Hepatic Failure

Major Organ Failure

Hepatic coma

Cerebral edema

Circulatory failure

Respiratory failure

Renal failure

Pancreatitis

Metabolic Derangements

Jaundice

Hypoalbuminemia

Coagulopathies

GI bleeding (ulcers)

Hypoglycemia

Hypothermia

Electrolyte abnormalities

Acid-base disorders (alkalosis)

Sepsis