



WSAVA LECTURE

Balanced therapy for chronic liver disease

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KEY POINTS

- The availability of diverse medications has permitted clinical manipulation of inflammation, adverse immune-responses, fibrogenesis, oxidant damage, and cell replication and repair.
- A number of medications function as hepatoprotectants against a wide variety of recognized hepatotoxins.
- Balanced therapy requires confirmation of a definitive diagnosis and estimation of the extent of hepatic dysfunction.
- While nutritional support provides the cornerstone of medical management, use of micronutrients such as zinc, s-adenosylmethionine, and l-carnitine offer unique methods for manipulating intermediary metabolism.
- The common need for a “polypharmacy” approach requires familiarity with the pharmacology of prescribed medications, knowledge of the patient’s albumin concentration, renal function, and predictable drug interactions.

Introduction

Treatment of chronic liver disease requires careful consideration of the particular needs of an individual patient. Foremost among considerations, is an estimation of the patient’s body condition and requirements for a modified nutritional intake. Estimation of the severity of liver dysfunction is necessary in determining safe drug therapies and dosage recommendations. The common use of a polypharmacy approach requires intimate knowledge of the patient’s metabolic capabilities as well as a

working familiarity of the pharmacology of prescribed medications and predictable drug interactions. Selection of anti-inflammatory, immunomodulatory, or antifibrotic medications is considered on the basis of histological characterization of the type of liver injury.

This paper presents an overview of the benefits and recognized toxicities of medications in contemporary use for the treatment of liver disease in companion animals.

Nutrition

Patients with chronic liver disease are commonly malnourished as a result of impaired dietary intake derived from anorexia and nausea, inappropriate nutritional recommendations (protein restriction), nutrient maldigestion/malassimilation (cirrhosis and portal hypertension), and increased energy requirements, (1, 2, 3). Fat malabsorption may develop consequent to abnormal availability of enteric bile acids, mucosal insufficiency (edema/capillary injury), and portal hypertension (4, 5).

In severe hepatic failure, the central regulatory role of the liver in nutrient metabolism is lost. Normal, non-essential nutrients, synthesized, activated or stored by the liver, can become essential. Utilization of muscle glycogen and protein for energy results in reduced muscle tone and weakness. Since approximately 50% of the body ammonia pool is temporarily stored in skeletal muscle tissue, muscle wasting potentiates hyperammonaemia (6). Malnutrition/anorexia also may lead to hypoalbuminaemia which can increase access of encephalogenic substances to the CNS (7).

Advanced liver failure is associated with metabolic adaptations similar to starvation (8, 9). The quantity of protein required for maintenance, cell

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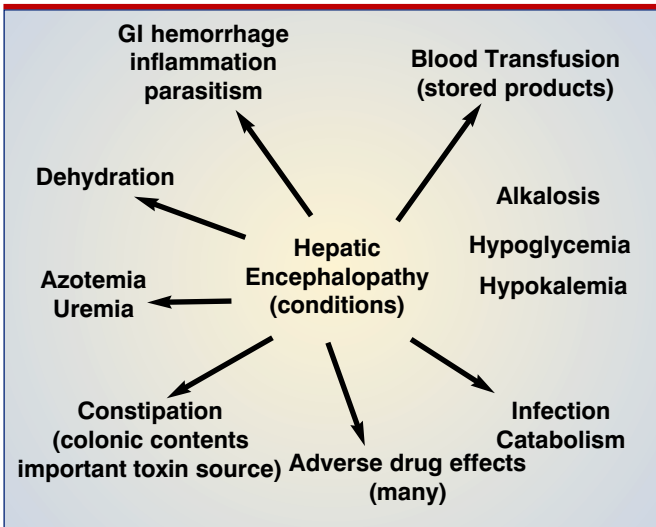


Figure 1 Systemic conditions known to cause or promote the syndrome of hepatic encephalopathy in patients with marked hepatic insufficiency. These conditions must be identified, eliminated, or effectively managed to improve patient status.

repair, and regeneration seems to vary with the type and severity of liver disease (10). A higher minimum protein intake is required in disorders characterized by inflammation and tissue regeneration. Although the type and severity of liver disease influences a patient's energy requirement, there is no absolute method by which these concerns can be quantitatively defined. Thus patients with chronic hepatic failure are considered hypermetabolic and those with acute inflammatory or necrotizing hepatic injury considered to require increased nitrogen (protein) and energy. Avoidance of a negative protein and energy balance is essential as these are

Table 1

Considerations important for optimising nutritional support in patients with hepatobiliary diseases

- 1. Provide adequate calories & protein**
Avoid negative nitrogen balance & catabolism
 feed protein at level of patient tolerance
 feed protein quality / quantity appropriate for type of liver disease
- 2. Provide essential & balanced nutrients:**
 amino acids, fatty acids, micronutrients: eg. zinc, l-carnitine, vitamins, water soluble, vitamin K, vitamin E
- 3. High diet palatability**
 ensure patient acceptance & adequate nutritional intake
- 4. Convenient diet preparations:**
 pre-formulated rations, encourage client compliance
- 5. Frequent feedings:**
 maximize caloric intake, optimize nutrient assimilation, prolong postprandial digestive interval
- 6. Monitor nutritional balance:**
Sequential body weight / Condition assessments
 behavior & mentation, weight, muscle mass, coat, behavior, activity level measure:
 serum albumin, fibrinogen, α -globulins
- 7. If ascites / edema:**
 sodium restriction: food, medications, diuretics inducing natriuresis (spironolactone & furosemida) – avoid hypokalemia, hypophosphatemia, azotemia
- 8. Adjunctive treatments:**
If hepatic encephalopathy:
 search for & eliminate underlying cause (Figure 1), increase dietary protein tolerance: lactulose, metronidazole, neomycin, soluble fiber, enemes
Control underlying liver disease:
 biopsy to attain definitive diagnosis for treatment: eg. medications: anti-inflammatory, immunosuppressant / immunomodulators, ursodeoxycholic acid, antioxidants, antibiotics

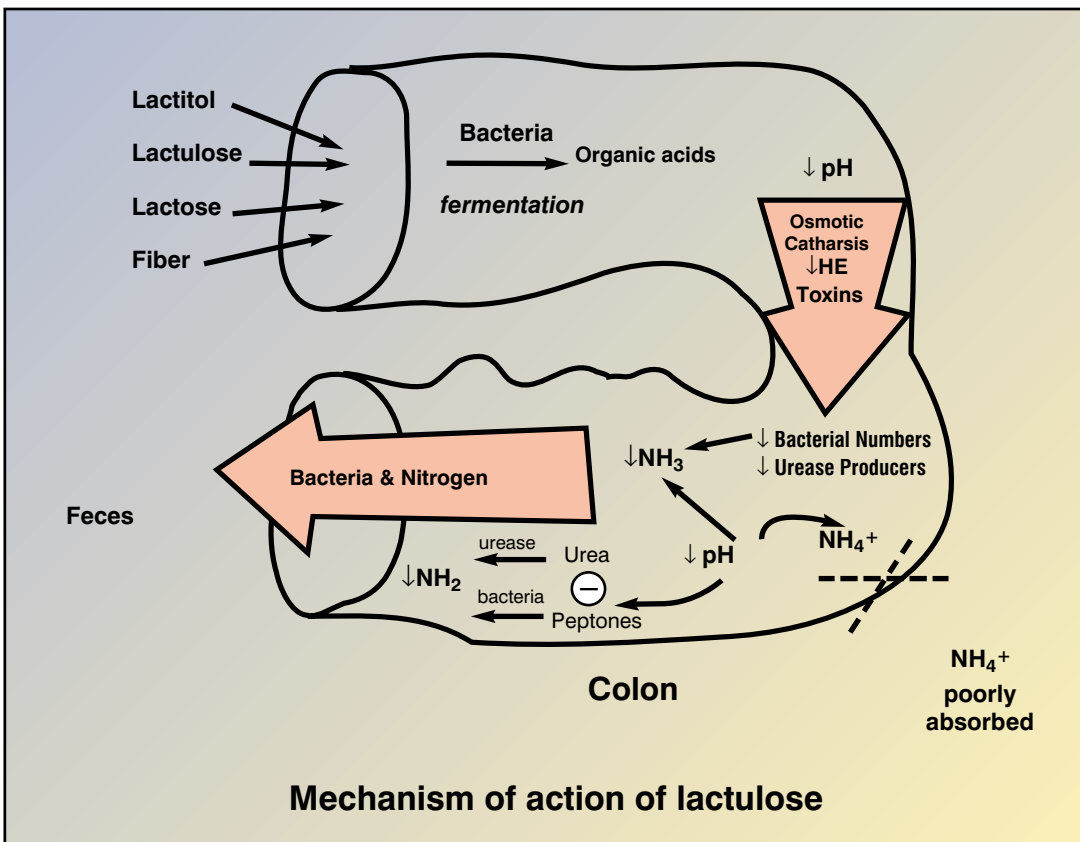


Figure 2 Mechanism of action of fermentable carbohydrates in reducing availability of enteric nitrogen for ammonia production. Formation of organic acids produces an osmotic catharsis mechanically reducing the hepatoencephalopathic toxins and urease producing bacterial organisms. Luminal acidification promotes formation of the ammonium ion, relatively impermeable to the mucosal surface. The presence of fermented carbohydrate products increases bacterial nitrogen fixation making less nitrogen available for ammonia formation.



Table 2

Hepatic encephalopathy treatment considerations

Dietary Modifications

reduce protein quantity & modify quality: dairy,
soy soluble fiber (metamucil, psyllium: reduces nitrogen intake)

Modification Enteric Microbial Population:

acidify colonic pH
antimicrobials

neomycin	22mg/kg PO	BID-TID
metronidazole	7.5mg/kg PO	BID
amoxicillin/clav	11mg/kg PO	BID

Modify enteric substrates: dietary nonabsorbable disaccharides & soluble fiber

lactulose	0.25-0.5ml/kg PO	BID-TID (achieve soft feces x2 daily)
lactose	slightly sweet solution or dairy products (see below)	BID
fiber	metamucil, psyllium	(achieve several soft stools each day)

Modify bacterial population (direct) with beneficial substrates:

lactobacilli live yogurt culture (dairy protein, lactose, organisms)

Elimination of Enteric Microbes, Substrates, Products: Enemas: mechanical vs retention

Mechanical Enemas	10ml/kg flush until clear of feces	
Retention Enemas		
Neomycin	15-20ml of 1% soin	BID-QID
Lactulose	5-15ml diluted 1:3	TID-QID
Metronidazole	7.5mg/kg (systemic dose)	BID (mixed with water)
Betadine	diluted 1:10 in water	TID (flush out after 10.15 minutes)
Activated Charcoal	liquid suspension	TID (administered & retained in crisis)
Vinegar diluted	1:4 in water	TID
Lactose	20-40gm in water	BID-TID

Quantity of Lactose Available in Different Products per 8 ounce (1 cup) serving:

Food item	Lactose (g)	Protein (g)	Calories (kcal)
Whole milk	11	8	157
Yogurt	11	8	139
Cottage Cheese	6	31	200
Cheddar Cheese	5	57	800

(1g/kg body weight lactose can produce osmotic diarrhoea in intolerant individuals)

Modified from: Center, S.A. (1996) *Chronic liver disease*. Eds. W.G. Guilford, S.A. Center, D.T. Stombeck, D.A. Williams, D.J. Meyer. *Strombeck's small animal gastroenterology*, W.B. Saunders, Philadelphia, USA, pp725

linked with abnormal immune responses, sepsis, and mortality (11).

Nutritional guidelines consider the extent of hepatic injury and dysfunction, and determination of whether the patient is protein or sodium intolerant (Table 1). In hepatic encephalopathy, the underlying or potentiating events must be discovered rather than immediately assuming that a diet change will solve the problem (Figure 1). Estimating appropriate nutritional intake requires repeated evaluation of patient body condition and nuances suggestive of hepatic encephalopathy. If signs of encephalopathy exist, the patient should initially receive a protein restricted diet as formulated for the patient with renal insufficiency. After 2 to 4 weeks of diet ingestion, serial physical and serum albumin assessments guide titration of protein and energy intake. In chronic hepatic insufficiency, a deficient capacity for carbohydrate storage and shift to protein utilization for energy is thwarted by frequent small meals which are thought to augment nitrogen balance and carbohydrate availability. Protein tolerance can be increased by co-administration of medications that alter enteric toxin production and availability (e.g. lactulose, neomycin, metronidazole), see Table 2, and by incorporation of soluble fiber in the diet; (e.g. psyllium, metamucil).

A high calorie: nitrogen ratio improves nitrogen tolerance as does maintenance of adequate muscle mass, which provides a temporary storage site of ammonia in glutamine. Lactulose increases nitrogen incorporation in bacteria eliminated in feces; its ammonia-lowering effect being

augmented by its enteric fermentation to organic acids (Figure 2)-12, 13). Colonic acidification impairs ammonia generation from urea and traps ammonia as the ammonium ion. Lactulose also imparts an antientotoxin effect (14).

To optimize nitrogen/protein tolerance, it is also imperative that the patient remain replete in zinc, water soluble vitamins, s-adenosylmethionine, and l-carnitine (1, 6, 15-20). Deficiencies of these nutritional cofactors are recognized in humans with chronic liver disease. Thus, zinc deficiency may compromise metalloenzymes essential for proper function of the urea cycle as well as cell repair and replication (21, 22). Thiamine deficiency produces a syndrome termed "Wernicke's Encephalopathy" subsequent to impaired cerebral energy metabolism (17). Vitamin B12 deficiency may provoke development of hepatic lipidosis in the cat presumably, as a result of impaired apolipoprotein synthesis, which impairs hepatic fat exportation as very low density lipoproteins (VLDL) (23). In humans with advanced cirrhosis, hepatocellular carnitine deficiency and hypocarnitinaemia reflects inadequate ingestion of carnitine, or its precursor amino acids (lysine and methionine), lost hepatic capacity to synthesize carnitine, or choline depletion which accelerates body carnitine turnover (24-27). Low plasma carnitine concentrations are especially prevalent in protein-calorie starved cirrhotics who are unable to synthesize adequate amounts of carnitine (25). These patients require support with presynthesized l-carnitine supplements.

Vitamin Supplementation:

Water Soluble Vitamins

Due to the variety of vitamin deficiencies that may develop in patients with liver disease and the inability to quantitatively appraise these changes, water soluble vitamins are empirically supplemented. Subnormal concentrations of vitamin B12 have been demonstrated in some cats with cholangiohepatitis and cats with hepatic lipidosis (28). When chronic inflammatory bowel disease (IBD) is a complicating problem, injectable vitamin B12 (1 mg every 14 to 28 days) may be required to successfully replete plasma concentrations in cats with cholangiohepatitis and IBD.

Adequacy of thiamine (vitamin B1) is of particular concern in cats. Clinical signs are inconsistent, confusing, and similar to HE (ventral neck flexion, dilated pupils poorly responsive to light, and sluggish posture corrections are observed)-29. The syndrome is easily averted by supplementation with a balanced vitamin formula. Consideration of possible thiamine deficiency is important because administration of glucose to such patients can potentiate brain thiamine depletion, intensifying neurologic signs (17). Treatment requires parenteral thiamine administration with an empirical dose; dogs and cats are each given 100 mg once or twice daily, initially.

Supplementation with additional vitamin C is not currently recommended without a liver biopsy, as ascorbate is believed to increase tissue damage due to transition metals, such as copper and iron (30).

Fat Soluble Vitamins

Malabsorption of fat soluble vitamins is of particular concern in patients with chronic bile duct occlusion, biliary cirrhosis, end stage cholangiohepatitis in the cat, or liver disorders coexistent with intestinal or pancreatic abnormalities causing steatorrhea. Any disorder that impairs enteric entrance of bile acids, their normal enterohepatic circulation, or fat absorption can reduce uptake of fat soluble vitamins A, D, E, and K (31). Induced deficiencies are more therapeutically urgent for vitamins K and E.

Deficiency of vitamin K is most easily recognized and occasionally catastrophic. Vitamin K deficiency is detected using an assay sensitive for non-carboxylated vitamin K-dependent procoagulants (PIVKA clotting time [Proteins Invoked by Vitamin K Absence])-32, 33. Normalization of prolonged clotting times after parenteral vitamin administration (vitamin K₁ 0.5 to 1.0 mg/kg IM or SQ initially, then given at 12 hour intervals for 2 doses) documents deficiency. In chronic conditions where vitamin K inadequacy is anticipated, dosing once every 10 to 28 days usually ensures vitamin repletion. Overdosage must be avoided in cats as it can cause oxidant injury to erythrocytes and haemolysis as well as hepatic necrosis.

Alpha-tocopherol is the most biologically active form of Vitamin E, a major antioxidant protecting cell membranes. Deficiency is permissive to hepatic injury since most forms of liver damage involve membrane oxidation (34). In disorders associated with severe cholestasis, failure of enteric bile acids to reach a critical micellar concentration results in vitamin E malabsorption (31). Since accumulation of vitamin E at critical sites in liver cell organelles (mitochondria) and Kupffer cells may optimize its cytoprotective capabilities, administration of the succinate form has been recommended as especially beneficial in humans with severe cholestasis (35). This form of vitamin E augments mitochondrial accumulation theoretically augmenting protection against mitochondrial derived oxidative radicals. Nevertheless, the acetate form of vitamin E is most commonly used, as this form may be effectively given per os or intramuscularly in patients with impaired enterohepatic bile acid circulation. Using α -tocopherol acetate, which has greater water solubility, and thus lower dependency on enteric micelle formation compared to other forms of vitamin E, a dose of 10 U/kg PO SID is usually recommended. If steatorrhea is a complicating

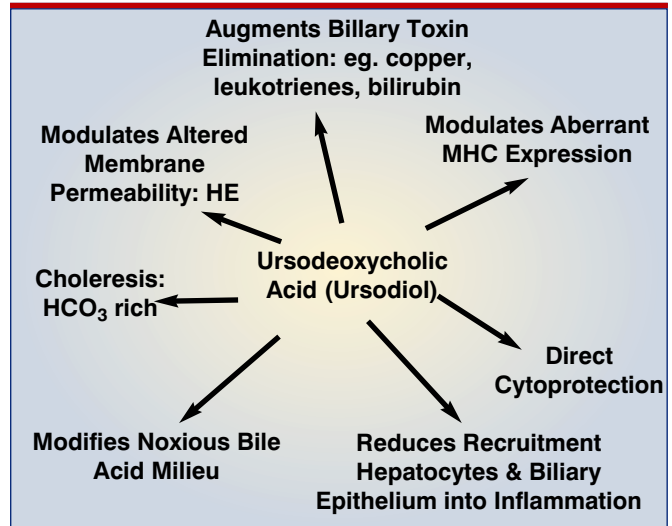


Figure 3 Summary of the recognized beneficial effects attributed to ursodeoxycholic acid in patients with cholestatic liver disease and hepatic insufficiency.

problem (gut disease or impaired bile flow into the gut), vitamin E deficiency may require 100 U/kg PO SID (31, 35). However, when high doses of vitamin E are used, it is important to remember that these may impair prothrombin activity in the circumstance of subnormal vitamin K availability (35).

Gastroenteric ulceration and vomiting:

Management of gastrointestinal ulcers, consequent to portal hypertension or glucocorticoid therapy, involves use of sucralfate and control of gastric acidity. Sucralfate is used for its cytoprotective and epithelotrophic effects, both for suspected ulcer formation and prophylactically when high dose glucocorticoids are initially prescribed (36). A histamine type 2 blocker such as famotidine, or an HCl pump inhibitor such as omeprazole, are used to reduce gastric acidity when enteric ulceration is suspected (Figure 4). In the event of intractable vomiting, metoclopramide is used by intravenous or subcutaneous administration, however, this drug is contraindicated in ascitic patients receiving spironolactone. Metoclopramide significantly reduces urinary output and sodium excretion while increasing plasma aldosterone concentration (37).

Ascites

The development of ascites requires investigation of factors dysregulating the homeostatic balance of water and sodium. A balanced approach for management of ascites incorporates sodium restriction (diet and medications), natriuresis, and sometimes, therapeutic abdominocentesis. Furosemide (1-4 mg/kg PO SID to BID) and spironolactone (1-4 mg/kg) are titrated to effect, starting with a low dose. Electrolytes and hydration status are monitored to avoid hypokalemia and dehydration which can worsen hyperammonemia and hepatic encephalopathy.

Immunomodulation

Ursodeoxycholic Acid (UDCA)

UDCA is used as a component of balanced therapy in patients with chronic



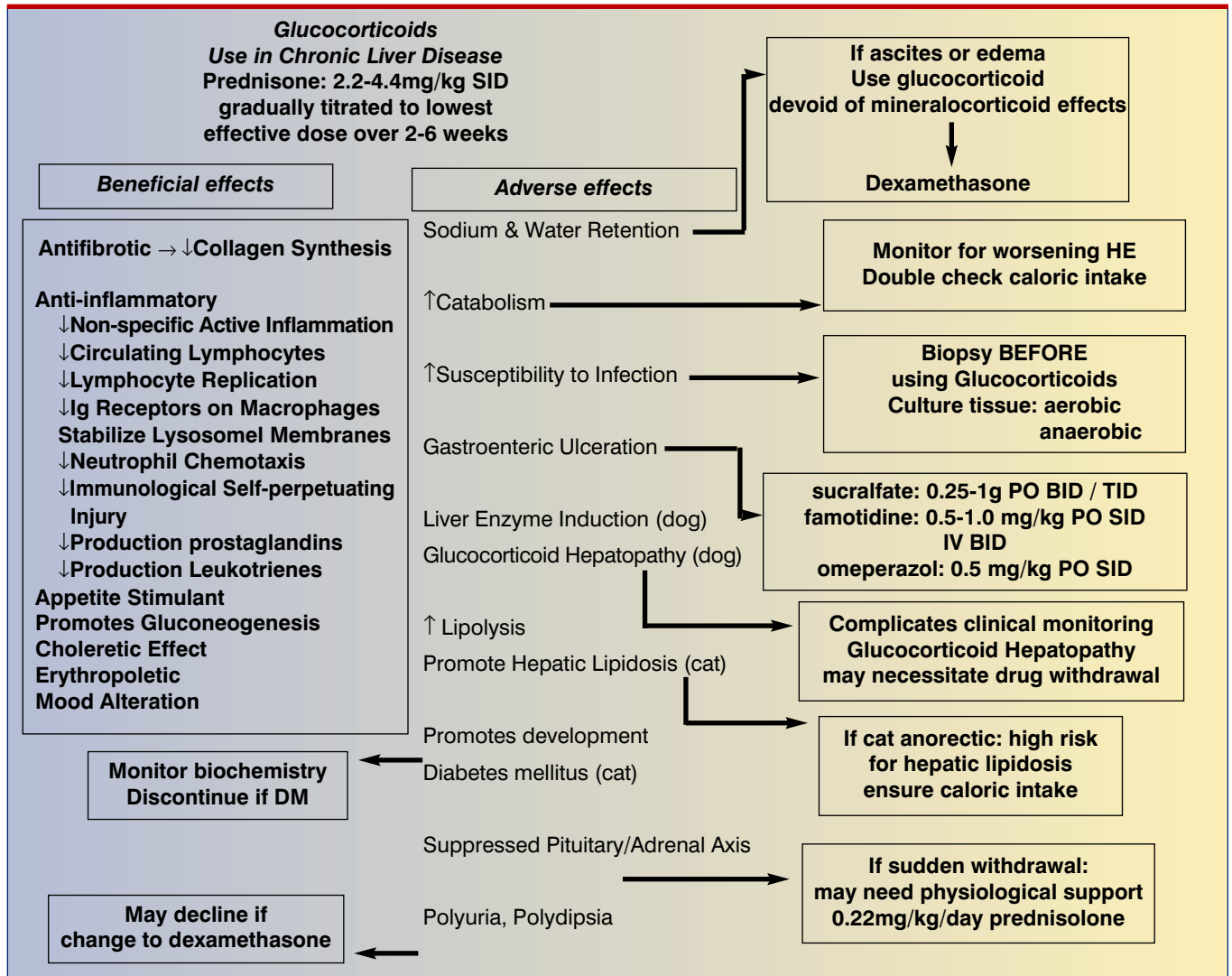


Figure 4 Summary of the Beneficial and Adverse effects derived from glucocorticoid administration in patients with severe hepatic disease. Adapted from Center, S. A. Chronic liver disease. In: Guilford, W. G., Center, S. A., Strombeck, D. R., Williams, D. A., Meyer, D. J. (eds.) Small Animal Gastroenterology, W. B. Saunders, Philadelphia, 1996:731.

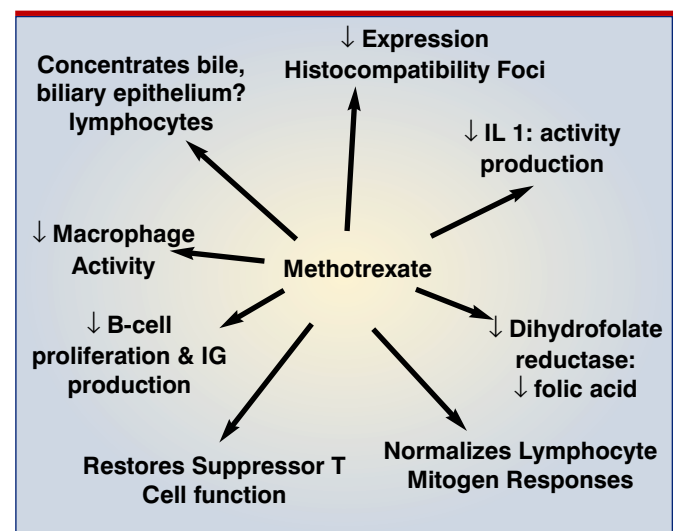
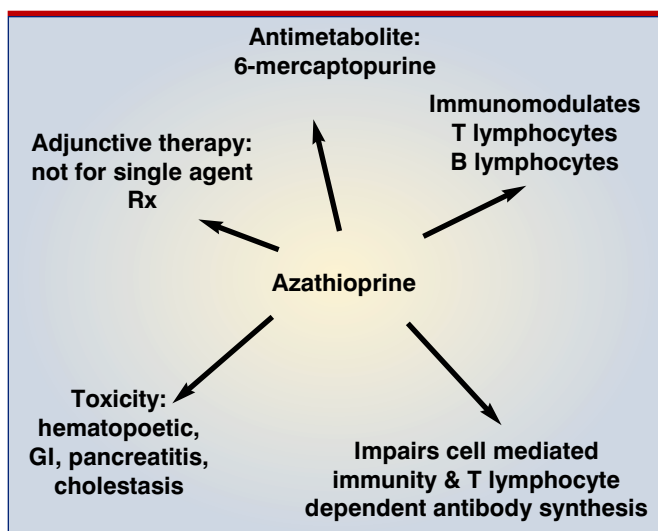


Figure 5 Summary of the recognized beneficial effects attributed to azathioprine in patients with non-suppurative inflammatory hepatobiliary disease.

Figure 6 Summary of the recognized beneficial effects attributed to methotrexate in patients with non-suppurative inflammatory hepatobiliary disease.

Table 3

Features of glucocorticoids important in inflammatory liver disease complicated by ascites**Indications for glucocorticoids**

Antifibrotic
 Anti-inflammatory
 Non-Septic Active Inflammation
 Immunologic-self-perpetuating injury
 Appetite Stimulant
 Promotes Gluconeogenesis
 Promotes Bile Flow
 Erythropoietic
 Mood alteration

Side effects of glucocorticoids:

Sodium retention
 Water retention
 Catabolism
 Susceptibility to Infection
 GI Ulceration (Gastric & Colonic)
 Suppressed Pituitary/Adrenal Axis
 Glucocorticoid Enzyme Induction (dogs only)
 Glucocorticoid Hepatopathy (dogs only)
 Hepatic Lipidosis (cats only)

Drug	Potency	Mineralocorticoid Activity	Plasma T _{1/2} in dogs (minutes, mean)	Duration of Action with PO dosing (hrs)
hydrocortisone	1-2	1-2	54	< 12
prednisolone	4	1	140	12-36*
prednisone	4	1	?	12-36*
triamcinolone	5	0	200	12-36*
betamethasone	25	0	7	> 48
dexamethasone	30	0	128	> 48

* = Appropriate for alternate day dosing to maintain pituitary adrenal axis

cholestatic and necroinflammatory liver disorders because it has a number of different beneficial effects (Figure 3), (38-41). The least controversial mechanism of action is its ability to modify the spectrum of injurious bile acids that accumulate in liver tissue, bile, and systemic blood in patients with severe liver disease, which damage membranes and promote a self-perpetuating cycle of tissue injury. UDCA also imparts a direct cytoprotective effect on hepatocellular membranes and possibly the blood brain barrier. One of its most impressive effects is a dampening of target foci that develop on hepatocytes and biliary epithelium (major histocompatibility foci). It also imparts a number of beneficial immunomodulatory effects as well as hydrocholerisis which may aid in toxin elimination.

Administration of UDCA is recommended for patients with chronic inflammatory and/or cholestatic liver disease and those with disorders complicated by "sludged" bile. Use in patients with bile duct occlusion is contraindicated unless biliary diversion is accomplished. If it is used after biliary tree decompression it reduces peribiliary inflammation and developing fibrosis associated with locally accumulated noxious bile acids and aberrant MHC expression. Clinical trials in human beings with a spectrum of liver disorders have demonstrated improvements in survival, biochemical parameters, patient well being, resolution of jaundice, but unfortunately no consistent improvement in histologic lesions. Use in an adjunctive capacity is advised based on a number of studies that has shown that UDCA for single agent therapy is relatively ineffective. Thus, appropriate use of UDCA involves its incorporation in a balanced therapeutic approach with other immunomodulatory and antifibrotic agents. If discovered, an underlying primary cause of liver damage should always be eliminated (e.g. drug toxicity, infectious disease).

Ursodeoxycholic acid exhibits no toxicity in the dog or cat although toxicity has been shown in a few other species (e.g. rabbits, Rhesus monkeys) and is thought to be associated with their reduced ability to sulfate noxious metabolites (e.g. lithocholate). A dose of 10 - 15 mg/kg per day PO SID or divided BID is recommended, given in gel caps or in as an aqueous suspension. Recent work suggests that severe extrahepatic cholestasis limits bioavailability of orally administered UDCA and that a BID dosing improves drug uptake (42, 43). Since UDCA is detected by the

conventionally run serum bile acid test, it will maintain raised bile acid concentrations in animals cholestatic disorders. It does not accumulate to detectable levels in animals with normal bile acids concentrations.

Glucocorticoids

Glucocorticoids are used when non-septic, non-suppurative inflammation and / or developing fibrosis are major components of liver disease, in an effort to control self-perpetuated inflammation. Although prednisone must be activated to prednisolone in the liver, studies have shown that prednisone still achieves adequate therapeutic effect due to contradictory influences on protein binding and hepatic metabolism (44, 45). Side effects of glucocorticoids should be carefully considered before they are used as some animals with compensated chronic hepatic insufficiency rapidly decompensate (Figure 4, Table 3). Thus, it is essential that only drugs with short term effects be used, for example, oral prednisone or prednisolone).

In the circumstance of ascites or edema, a glucocorticoid with minimal mineralocorticoid activity is preferred. If a glucocorticoid having a serum half-life and biologic effect > 24 hours is used, dosing is reduced to every third day. The initial dose of prednisolone or prednisone used is 2.2 mg/kg PO, SQ, IV tapered to every other day (EOD). Initial drug dose is maintained for 2 to 3 weeks depending on patient response and side effects. In most patients, glucocorticoids are used adjunctively with other treatment modalities aimed at controlling inflammation and fibroplasia. The glucocorticoid dose is tapered first (before other drugs) to reduce adverse side effects. Chronic therapy with prednisone is often possible with a dose tapered to 0.4 to 0.5 mg/kg daily, or twice this dose on an EOD basis. The lowest effective dose is therapeutically determined during a slow gradual titration using 25% current dose reduction in 2 to 4 week intervals, guided by serum biochemical changes. An EOD treatment regimen is assumed once a daily dose of 0.5 - 1.0 mg/kg is attained. Transition to EOD dosing is achieved by doubling the daily dose, and administering this on alternate days. Regular reexaminations are important and it is also necessary to monitor sequential biochemical parameters as a guide to therapy. Glucocorticoids can complicate biochemical monitoring of liver disease in



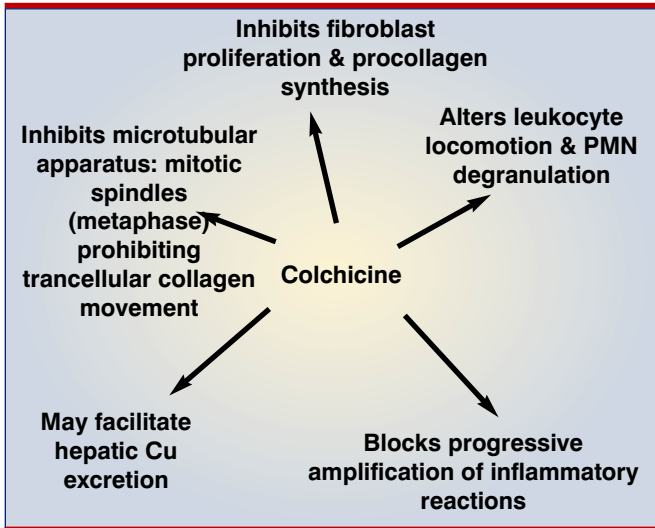


Figure 7 Summary of the recognized beneficial effects attributed to colchicine in patients with fibrosing inflammatory hepatobiliary disease.

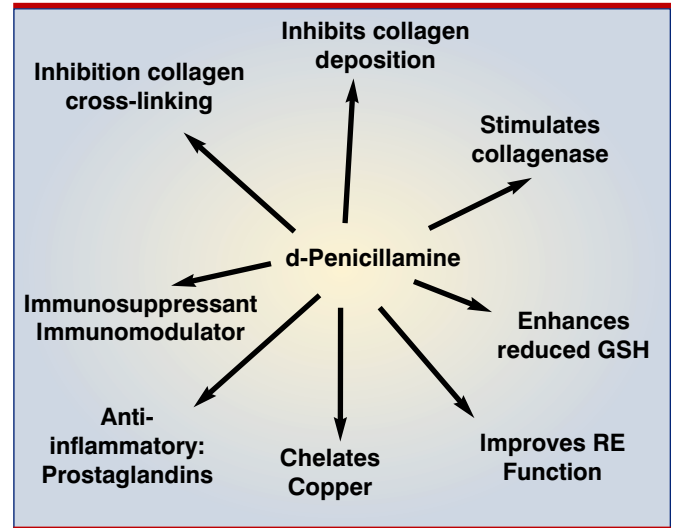


Figure 8 Summary of the reported theoretical benefits attributed to D-penicillamine in patients with non-suppurative inflammatory hepatobiliary disease. Unfortunately, side effects have curtailed use of this drug. In human beings, a lack of significant clinical improvement has been realised in different chronic inflammatory disorders.

dogs as a result of liver enzyme induction. However, most dogs with glucocorticoid responsive inflammation undergo a diminution in serum enzyme activity. Dogs developing a glucocorticoid vacuolar hepatopathy may develop raised alkaline phosphatase (ALP) and γ -glutamyl transferase (γ GT) activity. Cats treated with glucocorticoids for chronic cholangiohepatitis may develop a vacuolar hepatopathy due to hepatic lipid accumulation, deduced by examination of fine needle hepatic aspiration (28). In these cases, glucocorticoid dose reduction, treatment for developing hepatic lipidosis, and inclusion of an alternative immunomodulatory agent (e.g. methotrexate) are recommended.

Azathioprine

In dogs, liver disorders treated with glucocorticoids usually are adjunctively treated with azathioprine in an effort to modulate inflammation and immune response through a combination of pharmacologic mechanisms. Dual therapy permits a faster titration of glucocorticoid dose and lower dosages of each medication compared to their solitary use. However, efficacy of azathioprine in humans with liver disease remains highly inconsistent and controversial. Azathioprine is an antimetabolite which is converted to 6-mercaptopurine spontaneously in the circulation, as well as in the intestinal wall and hepatocyte (46). It is more effective in modifying T-lymphocyte than B-lymphocyte function, impairing both cell-mediated immunity and T-lymphocyte dependent antibody synthesis (47). A number of different benefits of azathioprine have been characterized which make it suitable for use in patients with non-suppurative inflammatory liver disease (Figure 5).

It is well tolerated by most dogs and appears to be more effective than cyclophosphamide in treatment of immune-mediated disorders in the author's clinic. Cats tolerate much lower dosages than dogs and require individual drug titration. Note that some do not tolerate azathioprine at any dose. Since azathioprine is an antimetabolite it can cause hematopoietic toxicity (leukopenia, thrombocytopenia), and gastrointestinal signs (vomiting and diarrhoea). Other occasional side effects include pancreatitis, dermatologic reactions, and rare hepatotoxicity (cholestasis and veno-occlusive disease in human beings) (48, 49). The WBC nadir (lowest WBC count) occurs between day 7 and 14 of first exposure. A CBC and biochemical profile should be performed every 2 to 3 weeks for the first 2 months of use (after the nadir is determined) and then monthly or bimonthly thereafter for the first 6 months. If acute hematopoietic toxicity

occurs (e.g. leukopenia, thrombocytopenia) treatment is stopped until hematopoietic recovery. A dose reduced by 25% is re-initiated with close monitoring for signs of acute toxicity. In some animals, marrow injury develops insidiously, resulting in aplastic anemia which may require months for recovery. Evidence of chronically acquired hematopoietic toxicity precludes further drug use.

The canine dose of azathioprine used in combination with prednisone / prednisolone is 1.0 - 2.0 mg/kg PO SID x 5-7 days (loading), then EOD. For cats, a dose no greater than 0.3 mg/kg PO EOD is used. The prednisolone dose is decreased at 2 week intervals by 25% each time, aiming at an alternate day treatment regimen with each drug. As clinical response is evaluated, the azathioprine dose may eventually be reduced by 50% using alternate day administration if clinical features are stable. However, an alternative approach is total withdrawal of glucocorticoids after solid disease remission (months of therapy), and use of a higher chronic dose of azathioprine (50). Patient response should be monitored no less than quarterly when azathioprine is chronically used. Liver enzymes and total bilirubin measurements are used to indicate disease activity and a CBC to evaluate adverse effects on bone marrow. As is true for humans, most patients requiring prednisone and azathioprine for chronic liver disease cannot be completely weaned off all drug therapy. Chronic therapy should be combined with UDCA.

Methotrexate

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, resulting in reduced folic acid availability, (51-54). Insufficient intracellular folic acid interferes with nucleic acid synthesis in cells that trap methotrexate (polyglutamate it). Methotrexate has poorly understood but significant anti-inflammatory immunomodulatory effects in a variety of immune-mediated disorders in human beings (e.g. primary biliary cirrhosis, sclerosing cholangitis, rheumatoid arthritis, psoriasis, severe inflammatory bowel disease), Figure 6. In clinical trials in humans with chronic hepatitis it improved biochemical parameters and liver function but showed variable histologic benefit (55). It has been used adjunctively with UDCA and prednisolone in the successful treatment of cats with sclerosing cholangitis, a severe form of cholangiohepatitis in which the small and medium sized bile ducts become involuted and diminished (28).

In cats a total daily dose of 0.4 mg divided into 3 treatments given at 0, 12, and 24 hours (0.13 mg per dose) given every 7 to 10 days, NOT DAILY. In cats resistant to oral medication, intramuscular injection of a single 0.2 mg dose may be administered, at 7 to 10 day intervals. Folate administration (0.25 mg/kg PO SID) is concurrently administered with methotrexate. Effects on hematopoiesis are monitored by evaluating a CBC at 7 to 10 day intervals during the induction month. In man, a variety of side effects observed with methotrexate given on a daily basis are obviated by the pulsatile weekly regimen (49, 53). Side effects of pulsatile therapy in cats are minimal but there is certain evidence that it is immunosuppressive; some treated cats have developed demodexosis, herpetic corneal ulcers, ascending urinary tract infections, and feeding tube associated infections. Consequently, high vigilance is required for complicating infections.

Metronidazole

Metronidazole is bactericidal, amoebicidal, trichomonocidal, and cytotoxic (49, 51, 56). It also has an immunosuppressive activity, via cell-mediated immune responses and it also exhibits a dose-dependent antioxidant effect. Adjunctive use with prednisone improves response compared to single agent therapy, especially in patients with chronic liver disease associated with inflammatory bowel disease. Metronidazole relies on hepatic metabolism (30-60%) and renal and fecal elimination (49, 51). It achieves adequate (good) concentrations in bile, bone, pleural or peritoneal effusions, CSF, and hepatic abscesses. An empirical 50% dose reduction based on recommendations made for humans, has been used in veterinary patients with good success. Common adverse effects of metronidazole include anorexia (unpleasant metallic taste sensation) and neurological effects encountered when excessive dosages are administered (57). Vestibular signs are most common and usually resolve within 1 week of drug discontinuation or dose adjustment. A dose of 7.5 mg/kg PO BID is used in patients with compromised liver function.

Antifibrotic Therapy

Hepatic fibrosis is an end product of multilevel regulation and elaboration of extracellular matrix (ECM) composition and turnover. This complicated process involves activators and inhibitors at every level. As further research into the mechanisms of fibrogenesis open wider avenues for therapeutic interventions, new medications will appear that specifically target steps in collagen deposition or its turnover (58). Medications presently available can intervene at a number of steps involved in this process. Some increase tissue collagenase activity, some reduce protein synthesis and product accretion, while others impair the transcellular movement and secretion of procollagen. Of special importance are colchicine and polyunsaturated phosphatidylcholine, used adjunctively with anti-inflammatory / immunomodulatory agents and antioxidants.

Colchicine

As an inhibitor of microtubular apparatus, colchicine has been used for arrest of hepatic fibrogenesis through its ability to interfere with transcellular movement of procollagen fibrils as well as its inhibitory influence on procollagen synthesis and fibroblast proliferation (59-61). Included among a myriad of benefits are its ability to induce collagenase activity, antiinflammatory effects via suppression of leukocyte locomotion and degranulation and facilitation of hepatic copper excretion, an effect valuable in cholestatic disorders complicated by hepatocellular copper retention (Figure 7). In humans with cirrhosis, chronic colchicine therapy has improved ascites, resolved jaundice, attenuated hepatic encephalopathy, and improved survival (60, 61). However, it does not appear to restrict development of fibrosis, cirrhosis, or the need for liver

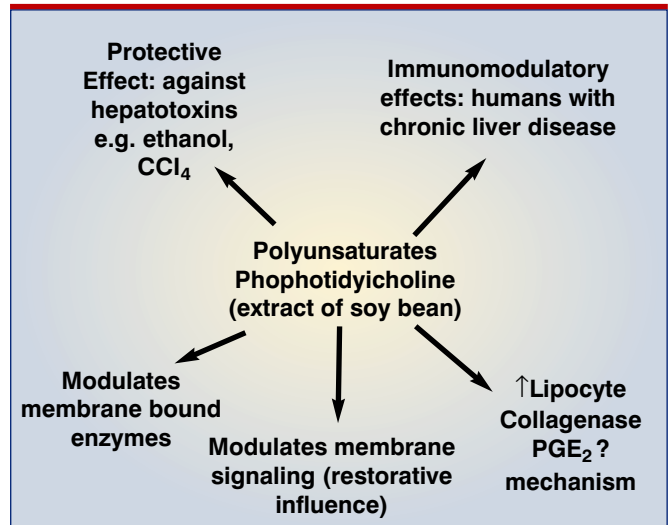


Figure 9 Summary of the recognized beneficial effects attributed to polyunsaturated phosphatidylcholine in patients with inflammatory hepatobiliary disease.

transplantation. The major side effect is hemorrhagic gastroenteritis. Less common adverse effects include bone marrow suppression, renal injury, and peripheral neuropathies (49). Nevertheless, in humans, colchicine is considered a safer therapeutic alternative than d-penicillamine or glucocorticoids.

Colchicine is commonly combined pharmacologically with probenecid, which increases its duration of action. The form without probenecid is preferred in dogs with liver disease since biotransformation and elimination of colchicine is in part dependent on the liver (62). Following a single IV bolus injection in humans, colchicine can be detected in urine for up to 10 days. Thus, there appears to be a body reservoir of the drug such that humans handling a treated animals urine have the potential for colchicine exposure. Colchicine administration is appropriate in cases where fibrogenesis is a prominent feature. It is used concurrent with UDCA and glucocorticoids or an alternative immunomodulatory agent. A dose of 0.025-0.03 mg/kg PO SID is used in dogs; there is no experience in cats.

D-Penicillamine

Has antifibrotic, immunosuppressant and immunomodulatory effects as well as an ability to inhibit fibrillar collagen deposition and to stimulate collagenase activity (49), Figure 8. It also is postulated to improve function of the mononuclear macrophage system, increasing host defense against antigenic and/or endotoxins derived from the portal circulation; to inhibit collagen cross linking, to enhance hepatocellular glutathione (GSH) stores, and to suppress inflammation. The most notable use of d-penicillamine in patients with hepatobiliary disease is as a copper chelator or detoxification mechanism. Benefit of d-penicillamine in humans with chronic liver disease remains controversial (63, 64). Side effects in humans include: acute hypersensitivity drug reaction (i.e. fever, malaise, rash, pruritus, lymphadenopathy), immune mediated disease of kidney and lung, Lupus-like syndrome, polyarthritis, Nephrotic syndrome, anorexia (altered taste sensation, nausea), leukopenia, thrombocytopenia, peripheral neuritis, a myasthenia-like syndrome, aplastic anemia, dermatitis, and hair loss (49). Since chronic d-penicillamine administration has been associated with pyridoxine deficiency, pyridoxine is concurrently given. In dogs, a d-penicillamine dose of 10 -15 mg/kg PO BID is used for copper chelation/detoxification when tissue copper values exceed 2500 ppm. If vomiting ensues, the dose is split and given at mealtime. There is no recommended feline dose.



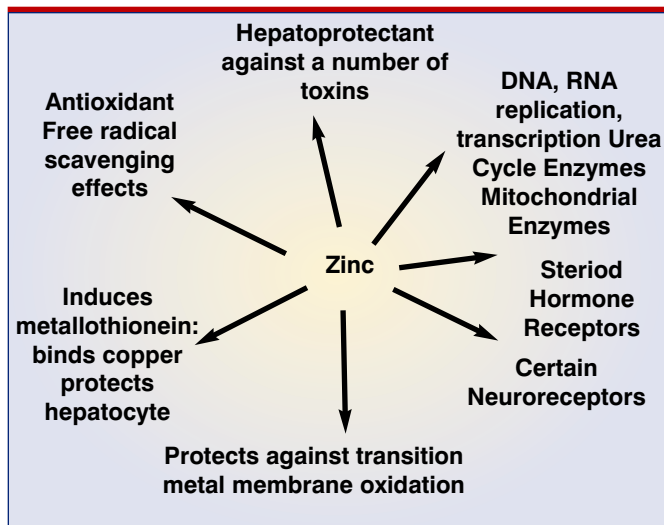


Figure 10 Beneficial attributes of zinc in patients with chronic hepatobiliary disease. While zinc deficiency is detrimental to these patients, overdosage with zinc can result in hemolytic anemia and systemic toxicity.

Polyunsaturated Phosphatidylcholine (PPC)

Myo-inositol, classified in the group of B-vitamins, is a lipotrope incorporated in the phospholipid phosphatidylinositol, an important membrane and lipoprotein component. PPC has diverse activities within membranes and has been shown to stimulate collagenase activity in cultured lipocytes (Ito cells), the source of collagen in hepatic fibrosis (65). It has been used to reduce fibrosis in humans with immune mediated hepatitis and alcoholic cirrhosis (66, 67). Beneficial aspects of PPC include immunomodulation, useful in chronic immune mediated hepatitis, and a glucocorticoid sparing effect when used adjunctively with prednisone and azathioprine; **Figure 9**. PPC, an extract of soy beans, is empirically dosed at 25-50 mg/kg based on experience in man (3 gm/day) and experimental animals. Pure lecithin is not an appropriate source of PPC and is ill advised in patients with hepatic insufficiency as this may impart encephalopathic signs. An alternative method of supplementing PPC is through use of s-adenosylmethionine (SAME), discussed below.

Zinc Acetate or Gluconate

Zinc is essential in numerous metalloenzymes and proteins important to intermediary metabolism (18, 21, 22, 68). Examples include its involvement in replication and transcription of DNA, RNA, mitochondrial enzymes, urea cycle enzymes, steroid hormone receptors, and certain neuroreceptors. Zinc imparts a number of beneficial effects considered important in liver patients, including an antioxidant effect protecting against metal induced membrane oxidation and an hepatoprotectant effect against a number of different hepatotoxins, **Figure 10**, (68). Zinc administration also has been shown to inhibit the accumulation of hepatic collagen in experimentally produced hepatic necrosis and to significantly improve neurologic signs in hepatoencephalopathic humans shown to be zinc deficient (68, 69). Zinc induction of the copper binding protein (metallothionein) in the gastrointestinal tract and hepatocyte, assists in the trapping and elimination of injurious copper (70). Thus, zinc can protect against the pathologic accumulation of copper in the liver, either as a consequence of an inborn error of metabolism as in the Bedlington Terrier, or as a result of cholestasis (71-73). Induction of copper binding protein in the hepatocyte also is believed to protect against lysosomal copper loading and subsequent cell autolysis. Humans with chronic liver disease develop reduced serum and

liver zinc concentrations; portosystemic shunting seems to produce the greatest deficiencies (74). The pathologic effects of accumulated iron in hepatic macrophages in necroinflammatory liver disease and copper in cholestasis may be attenuated by zinc therapy.

Zinc is commonly supplemented (as zinc acetate) in dogs with chronic liver disease with dose individually titrated. Generally, 50-200 mg of elemental zinc per day (> 15 kg sized dog) is given in 2 divided doses, 30 minutes before meals. Cautiously used smaller doses are carefully investigated in very small dogs. Plasma zinc is determined before treatment initiation and then 2-4 weeks after treatment commences. Although optimal plasma Zn concentrations are undetermined, baseline values should rise slightly but should not approach 800-1000 µg/dl as these cause hemolysis.

Antioxidants

Vitamin E, zinc, metronidazole: see above.

S-Adenosyl-L-Methionine (SAME)

SAME is a methyl group donor for transmethylation reactions, a precursor of sulphur-containing compounds (transsulphuration pathway), and source of polyamines (aminopropylation); **Figure 11** (19, 75-77). Since transmethylation is essential for biosynthesis of membrane phospholipids (e.g. phosphatidylcholine), SAME has important impact on membrane integrity, fluidity, and cell signaling. Other important methylation reactions involve: hormones, neurotransmitters, nucleic acids, proteins, and drugs. The transsulphuration pathway provides endogenous sulfur compounds, including glutathione (GSH) and taurine (not in the cat) essential for conjugation/detoxification reactions. Involvement in the polyamine pathway influences hepatocellular replication, DNA synthesis, and apoptosis. Since 85% of all transmethylation reactions occurs in the liver, SAME is integrally important to many different hepatic functions. It is well documented that the transsulphuration pathway becomes impaired in chronic liver disease, causing delayed methionine clearance. This derives from an inability to transform methionine into SAME as a consequence of low SAME synthetase activity (78).

SAME also has been suggested to impart cytoprotection, analgesia, and an antiinflammatory effect (19, 76). Hepatoprotection against drug induced injury has been shown with SAME in humans taking a variety of medications (e.g. anticonvulsants, acetaminophen, alcohol) and in lithocholate induced liver injury in cell culture (19, 79). Oral SAME administration in cirrhosis and patients with intrahepatic cholestasis replenishes hepatic GSH reserves in depleted patients improving their tolerance for free radical and reperfusion type cell damage (80-82). Administration of SAME also can beneficially modulate the immune response as DNA methylation is involved in regulation of genes signaled in activated lymphocytes. A dose of 20 mg/kg or higher is advised for dogs and of 200 to 400 mg/day in cats using enteric coated 200 mg tablets given on an empty stomach (58, 83). There are now commercially available enterically coated, stable SAME salt products which have no toxicity in dogs or cats.

Clinical work in dogs with glucocorticoid hepatopathy and in normal cats has shown that Denosyl-SD4® significantly increases liver tissue GSH and preserves or increases erythrocyte GSH. Recent work in clinical patients with severe liver disease has proven reduced hepatic tissue GSH concentrations in 45%; (unpublished information, College of Veterinary Medicine, Cornell University, S. Center). The only potential known adverse effect associated with SAME is an association between oncogene induced tumor growth and GSH availability.

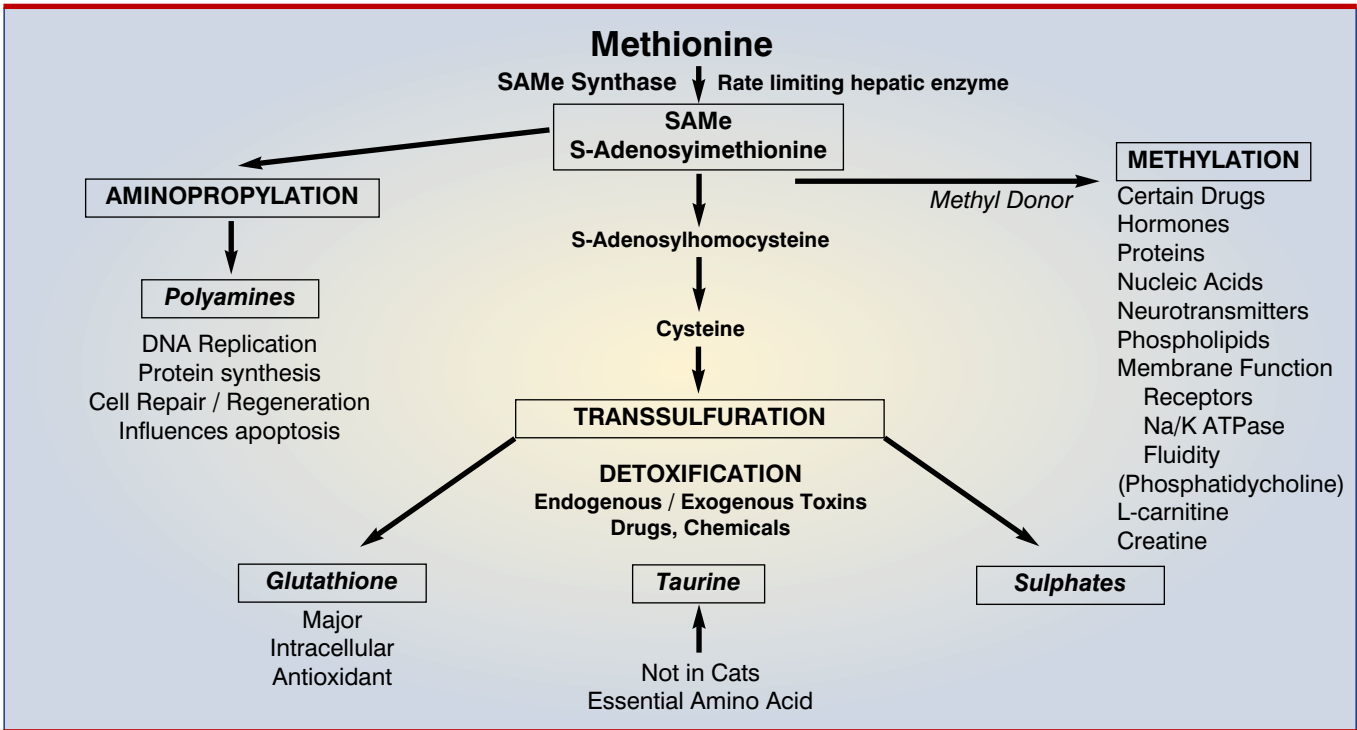


Figure 11 Simplified metabolic pathway and products derived from S-adenosylmethionine, the major donor of GSH.

Silibinin

This naturally occurring flavonoid extracted from milk thistle (silibinin), also referred to as silymarin (whole extract), has shown a protective influence in models of experimental liver intoxication (CCl₄, ethanol, acetaminophen, phenylhydrazone, mushroom toxicity) (84). Beneficial mechanisms include an antioxidant effect, protective influence on membrane phospholipids, a conservatory influence on hepatic GSH, an ability to enhance protein synthesis and hepatocellular regeneration, suppression of fibrogenesis and promotion of fibrolysis (85), **Figure 12**. Collectively, these effects conserve antioxidant protection while encouraging cell repair and replication and diminishing connective tissue deposition. Experimentally, silibinin improved functional markers of liver damage at an oral dose of 4-15 mg/kg in human beings with active cirrhosis (86).

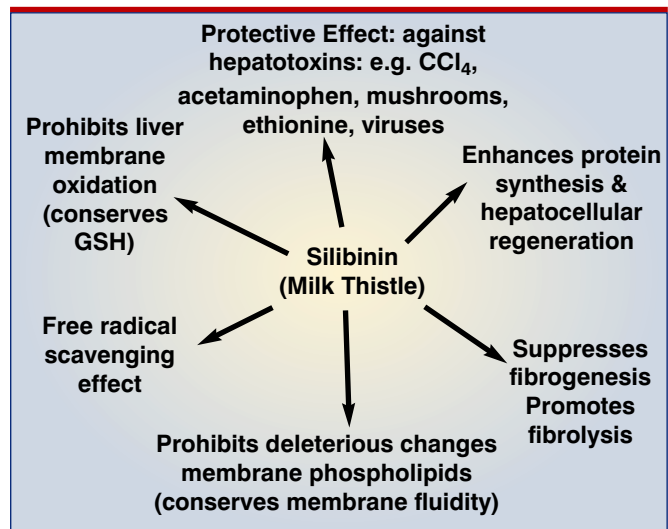


Figure 12 Summary of the recognized beneficial effects attributed to silibinin in patients with necrotizing and inflammatory hepatobiliary disease.



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