Nutritional Support for Dogs and Cats with Hepatobiliary Disease[1]

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ABSTRACT Nutritional intake in the patient with hepatobiliary disease provides the cornerstone of balanced medical care. Optimal recommendations require consideration of general nutritional principles, special species requirements and contemporary needs uniquely related to the patient's medical problem. Although general recommendations follow well-established guidelines developed to meet metabolic requirements for normal health, there is little information regarding altered requirements in animals that are ill. Consequently, recommendations for animals have been derived empirically from studies completed in humans, most work having been done in patients with end stage cirrhosis or liver failure complicated by hepatic encephalopathy. This is problematic because most veterinary patients with liver disease are not in hepatic failure and do not suffer from hepatic encephalopathy. Iatrogenic malnutrition can develop in patients when protein-restricted diets are inappropriately recommended. Insufficient energy intake and negative nitrogen balance can complicate a patient's condition, impairing tissue regeneration and recovery from disease. This paper reviews strategies that can be used to individualize nutritional management in small companion animals with hepatobiliary disease. Consideration is given to both the known and controversial issues regarding energy requirements, dietary energy distribution, vitamin and micronutrient supplementation, the special requirements of the cat with hepatic lipidosis, as well as strategies effective for palliation of hepatic encephalopathy. J. Nutr. 128: 2733S–2746S, 1998.

KEY WORDS: • *hepatobiliary disease* • *hepatic encephalopathy* • *nutrition* • *micronutrients* • *energy requirements*

The liver provides a myriad of biochemical, synthetic, excretory and regulatory functions important to intermediary metabolism. Consequently, effective treatment of hepatobiliary disease requires disease-directed interventions and adequate nutritional intake. Because it is difficult to estimate the degree of hepatic dysfunction, it has become common for veterinary practitioners to assume the worst-case scenario, treating each patient as if they needed protection from hepatic encephalopathy (HE).[2] This is inappropriate as the more common hepatobiliary disorders in dogs and cats (**Table 1**) are not associated with hepatic failure or HE. Important considerations relevant to nutritional support of the companion animal with hepatobiliary disease are summarized in **Table 2**.

Humans with chronic liver disease commonly are malnourished due to impaired dietary intake derived from nausea, anorexia and inappropriate nutritional recommendations (Kondrup et al. 1992, Merli et al. 1996). Nutritional deficiencies in cirrhosis and portal hypertension also develop because of nutrient maldigestion and malassimilation (e.g. pancreatic exocrine insufficiency or malabsorption of carbohydrates, fat and certain vitamins) (Silk et al. 1991). Reduced fat assimilation develops in dogs with surgically created portosystemic shunts (LaFlamme et al. 1993) and has been clinically recognized in cats with chronic cholangiohepatitis as well as animals with major bile duct occlusion. Fat malabsorption is multifactorial in origin, involving reduced availability of enteric bile acids, abnormal bile acid deconjugation and mucosal insufficiency secondary to edema, capillary injury and portal hypertension.

As the central regulatory role of the liver in nutrient metabolism declines, normally nonessential nutrients (synthesized, activated or stored by the liver) can become essential. Use of muscle glycogen and protein for energy reduces muscle mass. Because ~50% of the body ammonia pool is temporarily stored in skeletal muscle, tissue wasting potentiates hyperammonemia and HE (Lockwood et al. 1979). Consequently, muscle mass preservation through provision of a positive nitrogen balance is an important goal in patients prone to HE. Malnutrition and anorexia also promote hypoalbuminemia, which can increase the access of protein-bound encephalogenic substances such as tryptophan and benzodiazepines to the central nervous system (CNS). Negative protein and energy balance in cirrhotic humans has also been linked with abnormal immune responses, sepsis and mortality (O'Keefe et al. 1980).

CALCULATION OF ENERGY NEEDS

In humans with liver disease, energy requirements vary with the type of disorder (Heymsfield et al. 1990, Schneeweiss et al.

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Abbreviations used: AAA, aromatic amino acids; BCAA, branched-chain amino acids; CNS, central nervous system; GABA, γ-amino butyric acid; HE, hepatic encephalopathy; HL, hepatic lipidosis; MER, maintenance energy requirements; SCFA, short-chain fatty acids.

TABLE 1

Common hepatobiliary diagnoses in dogs and cats

Dogs (Rarely associated with hepatic encephalopathy)	Cats (Rarely associated with overt hepatic encephalopathy)
Vacuolar hepatopathy	Mild hepatic vacuolar change
Chronic stress	Hepatic lipidosis syndrome
Glucocorticoid therapy	Primary or "idiopathic"
Diabetes mellitus	Secondary (many underlying non-hepatic diseases can be associated with hepatic encephalopathy)
Hepatocutaneous syndrome	Cholangitis/Cholangiohepatitis
Chronic illnesses	Associated conditions:
Gastrointestinal inflammation	Pancreatitis
Pancreatitis	Inflammatory bowel disease
Neoplasia: lymphosarcoma	Major bile duct occlusion
other neoplasia	Primary or metastatic neoplasia
Chronic infections	Least common: (Associated with hepatic encephalopathy)
Severe dental disease	Biliary cirrhosis
Chronic active hepatitis	Portosystemic vascular anomalies
Major bile duct occlusion	
Primary or metastatic neoplasia	
Microvascular dysplasia	
Least common: (Associated with hepatic encephalopathy)	
Cirrhosis	
Portosystemic vascular anomalies	
Juvenile fibrosing liver disorders	

1990). There have been no comparable nutritional studies in dogs and cats with spontaneous hepatobiliary disease. Patients with acute inflammatory liver disease are more catabolic than those with cirrhosis and have higher maintenance energy requirements. Measurement of resting energy expenditures in end-stage liver disease associated with ascites demonstrated a mean 1.6-fold increase (1.1- to 2.0-fold range) when corrected for lean muscle mass (Shanbhogue et al. 1987). Increased protein turnover accounted for a substantial portion of the increased metabolic rate. This "hypermetabolism" resembles adaptations made in starvation. After a meal, there is increased protein storage and, between meals, increased protein degradation. The overall result is increased protein requirements for energy and nitrogen balance (Swart et al. 1988). When humans with end-stage liver disease were fed diets providing normal energy and protein intake, encephalopathic signs were not induced because increased protein consumption was accompanied by increased nitrogen retention. Because of the deficient capacity for carbohydrate storage and shift to protein utilization, frequent small meals are often prescribed to augment nitrogen balance and carbohydrate availability. The first consideration in diet formulation is an estimation of the patient's energy requirements. There are three levels of energy requirement relevant to healthy and ill animals: basal metabolic requirements, resting energy requirements and maintenance energy requirements (MER). Controversy exists among nutritionists regarding which formula(s) best predict baseline energy needs of clinical patients. Although extrapolations from human studies have been used to argue for application of basal and resting energy requirements, these formulas may underestimate maintenance needs. The safest course to follow clinically is to use MER, calculated with the use of contemporary methods that provide generous energy intakes, as a starting point (Earle and Smith 1991, Hill 1993).

Although the type and severity of liver disease influence energy requirements, there is no absolute method by which these concerns can be quantified. Patients with chronic hepatic failure are considered empirically to be hypermetabolic. Those with acute inflammatory or necrotizing hepatic injury are considered to have increased protein and energy requirements for tissue repair. There are no guidelines for estimated energy needs in dogs with vacuolar hepatopathies or cats with hepatic lipidosis (HL) other than clinical experience, which suggests that normal intakes are sufficient. Other variables influencing MER, including stress, the level of physical activity, the presence of anorexia and preexisting malnourishment, also should be considered. However, because adjustments in energy intakes are made empirically, there are unavoidable wide variations among recommendations. Each regimen therefore must be individually tailored to meet the circumstances of an individual patient.

HOW MUCH PROTEIN?

Humans with hepatic insufficiency show both quantitative and qualitative abnormalities in nitrogen metabolism. These patients may be protein depleted while concurrently showing signs of protein intolerance. Nitrogen balance is dependent on requirements for essential and nonessential amino acids and energy. Humans with severe hepatic insufficiency have normal requirements for essential amino acids but an increased requirement for nonessential amino acids. The majority of their plasma amino acids are derived from endogenous protein breakdown, which ranges between 5 (cirrhosis) and 12 (fulminant hepatic failure) times higher than levels derived from normal dietary intake.

Healthy adult cats require three to five times more dietary protein (~20–24% metabolizable energy) than adult dogs (NRC 1986). Protein restriction for the feline patient with HE should not exceed minimum values determined for cats with chronic renal insufficiency (3.3–3.5 g/kg body weight of high biologic value protein in a diet providing 70–80 kcal/(kg · d) [293–335 $\times$ 10^3 J(kg · d)]. Protein intake must not be reduced below this level because the cat is unable to conserve nitrogen efficiently after protein restriction (Rogers et al. 1977).

Minimal maintenance protein requirements for healthy dogs are estimated at 6–7% of metabolizable energy (NRC 1985). The minimum protein intake for healthy dogs is 1.25–1.75 g/kg; for dogs with chronic renal insufficiency it is 2.0–2.2

TABLE 2

Considerations essential for nutritional support of patients with hepatobiliary disease

1) Provision of adequate energy
2) Provision of adequate protein: AVOID negative nitrogen balance
   - Appropriate amount and quality for the type of hepatic disease
   - Avoid inappropriate dietary protein restriction
   - Individually optimize nitrogen balance
     - Reassess patient's body condition: Weight, muscle mass, coat, behavior, activity level
     - Measure: serum albumin, creatinine, α-globulins, plasma fibrinogen
3) Provision of essential nutrient components
   - Essential amino acids, fatty acids
   - Micronutrients: e.g., zinc, L-carnitine
   - Water-soluble vitamins, vitamin K, vitamin E
4) High diet palatability
5) Ease of diet preparation
   - Encourage client compliance
6) Frequent feedings
   - Maximize energy intake
   - Optimize nutrient assimilation
   - Prolong postprandial digestive interval
7) If ascites/edema
   - Sodium restriction
   - Adjunctive treatments: diuretics (spironolactone and furosemide)
8) Adjunctive treatments
   - Increase protein tolerance: lactulose, metronidazole, neomycin, dietary fiber
   - Control complicating conditions: enteric parasitism, infections, ulceration
   - Control underlying liver disease
     - Biopsy to attain definitive diagnosis
     - Definitive treatments:
       - Antiinflammatory drugs
       - Immunomodulators
       - Antifibrotic drugs
       - Antimicrobials
       - Ursodeoxycholic acid

g/kg body weight of high biologic value protein in a diet providing 70–110 kcal/(kg · d) [293–460 × 10^3 J/(kg · d)].

Diets formulated for chronic renal insufficiency have been successfully used to palliate HE in both dogs and cats. However, these diets are not considered optimal for most other liver patients. It is surmised that recovery from acute hepatic necrosis or ischemic damage requires a higher protein intake to maintain a positive nitrogen balance. Animals with chronic hepatitis are similarly thought to require protein intake exceeding maintenance values. If energy and protein metabolism of animals with cirrhosis resembles those of humans, these patients also have increased protein requirements, possibly two- or threefold minimal maintenance values (Elwyn 1987). In animals demonstrating HE, dietary recommendations must consider the balance between the amount of protein required to achieve a positive nitrogen balance and the amount of protein that produces adverse effects. Although clinically determining a particular patient's needs, protein tolerance can be increased by adjunctive treatments, including orally administered antibiotics (neomycin or metronidazole) and lactulose, provision of non-meat protein sources and diet supplementation with soluble fiber.

Protein-restricted diets containing high concentrations of lipids are inappropriate for recovery of most cats with HL (Biourge et al. 1994). Clinically, these cats recover optimally when consuming feline maintenance or high stress nutritional formulas providing ≥4.0 g/kg protein (Center 1998). Restricted-protein diets also are inappropriate for most cats with chronic cholangiohepatitis in which underlying inflammatory bowel disease and pancreatitis are inordinately common. High fat, protein-restricted diets also are ill advised in dogs with vacuolar hepatopathies because these patients may have underlying problems of lipid metabolism (e.g., schnauzers and Shetland sheepdogs), pancreatitis, inflammatory bowel disease or diabetes mellitus.

Similar to the situation in humans, it is likely that protein deficiency occurs in veterinary patients with liver disease as a consequence of decreased dietary intake derived from anorexia or inappropriate nutritional restrictions. Particularly at risk are patients with active necroinflammatory disorders and, possibly, those treated with glucocorticoids. In the absence of HE, efforts should be made to provide normal dietary intake in patients with chronic stable liver disease. Those with severe liver dysfunction and HE require dietary modification and protein restrictions. Because no single measurement is available for clinical identification of malnutrition, estimation of protein-energy malnutrition is based on sequential objective assessments including weight changes (unintentional weight reduction), serum concentrations of proteins produced by the liver (albumin, α-globulins, fibronectin, fibrinogen), body condition estimation and the serum creatinine concentration (Heymsfield 1983).

IMPORTANCE OF PROTEIN SOURCES IN HEPATIC ENCEPHALOPATHY

Diminished portal venous perfusion or critically reduced hepatic mass permits encephalogenic material derived from the gut, diet or endogenous metabolism to spill into the systemic circulation. Subsequent exposure to the blood-brain barrier allows access to the CNS. Although HE is believed to be multifactorial, it is well established that nutritional intake precipitates its expression and that palliation is achieved with therapeutic agents acting within the gut (Mullen and Weber 1991). It has long been clear that feeding a meat-based diet to dogs with experimentally created Eck fistulas produces HE. It is currently believed that vegetable or dairy protein performs better than meat, fish, or egg protein sources in humans susceptible to HE (Bianchi et al. 1993, Uribe 1989 and 1990). Changing a meat-based diet to a vegetable or dairy protein base yields better results than overall protein restriction in controlling subclinical HE and maintaining body condition. There is clinical and experimental evidence that similar nutritional manipulations may be beneficial in dogs with HE (**Table 3**).

Although a variety of toxins have been characterized in HE, the most common unifying factor is nitrogen, which is normally metabolized to ammonia and detoxified in the hepatic urea cycle. Ingestion of a meat-based high protein diet, gastrointestinal bleeding and azotemia are clearly the most common causes of HE in animals with severe liver disease or portosystemic shunting. Certain amino acids that are deaminated or deamidated in their metabolism are more ammoniogenic than amino acids that are transaminated (Rudman et al. 1970). Nevertheless, feeding diets restricted in these ammoniogenic amino acids will not block development of HE. Methionine, a sulfur-containing amino acid metabolized by gut bacteria and hepatocytes to a series of products termed mercaptans (dimethylsulfide, methanethiol and ethanethiol), is also implicated as an encephalopathic factor. However, its dietary restriction will not curtail development of HE. It has long been recognized that the molar ratio between the branched-chain amino acids (BCAA) and the aromatic amino acids (AAA) is abnormal in HE (Center 1996a). The AAA,

TABLE 3

Diets investigated in humans, dogs and rodents with portosystemic shunting: protein source, energy distribution (estimated) and clinical effects

Reference model	Primary components	Diet protein	Energy distribution			Clinical effects
			Protein	Fat	Carbohydrate	
		g/kg body weight		*%*		
Bianchi et al. 1993	Meat	NA	21	43	36	Induced hepatic encephalopathy (HE)
Human end-stage liver disease	Casein	NA	26	30	44	Better neurologic status
Uribe et al. 1982						
Human end-stage liver disease	Meat 40 g	NA	11	32	58	8.3 g fiber; induced HE
	Vegetable 40 g	NA	11	19	70	15.7 g fiber; better neurologic status
	Vegetable 80 g	NA	21	25	54	13.9 g fiber; better neurologic status
Thompson et al. 1986	Meat	3.4	27	53	19	Induced HE
Dog Eck fistula	Soy/Casein[1]	1.6	13	50	37	Better neurologic status and weight maintenance
Laflamme et al. 1993	Soy meal + BCCA[2]	1.8	14	9	78	Too low in available protein, weight loss
Dog Eck fistula	Soy mean + AAA	1.5	12	8	80	Too low in available protein, weight loss
	Soy meal + BCCA	3.6	29	8	63	Few adverse effects, weight maintenance
	Soy meal + AAA	3.5	28	8	64	No adverse effects, weight maintenance
Condon 1971	Meat	4.6	34	49	17	Induced HE
Dog Eck fistula	Casein	2.5	20	16	64	Better neurologic status
	Fish	6.1	49	23	29	Induced HE, less noxious compared to meat
Strombeck et al. 1983	Dairy/Wheat germ	1.4	11	46	44	Effective in clinical patients with HE long term
Dog clinical patients	Dairy	0.9	7	42	51	For short term use only
Schaeffer et al. 1986						
Dog Eck fistula	Soy isolate	2.0	16	54	30	Effective in clinical patients long term; lowers albumin after 18 wks, possibly due to low protein intake
Proia et al. 1984	Meat	NA	28	60	12	Induced HE
Rat Eck fistula	Casein	NA	23	64	13	Better neurologic status

[1] Isocal, Mead John Nutritionals, Evansville, IN.
[2] BCAA, branched chain amino acids; AAA, aromatic amino acids; NA, not available.

tyrosine (Tyr), phenylalanine (Phe) and tryptophan (Try) serve as substrates for amine synthesis in the brain and lead to the formation of encephalogenic "false neurotransmitters." The AAA increase in patients with hepatic insufficiency as a result of their dependency on hepatic extraction and metabolism. The BCAA, leucine (Leu), valine (Val) and isoleucine (Ile) serve as peripheral energy substrates and subsequently are maintained at low plasma concentrations. Although the AAA:BCAA ratio (Tyr + Phe/Leu + Val + Ile) exceeds 3 in patients with HE, this ratio also persists in the absence of HE, suggesting that it may be an epiphenomenon attributable to increased endogenous protein breakdown and reduced hepatic clearance/metabolism of AAA. Because BCAA are gluconeogenic, their increased utilization is aggravated by insufficient dietary intake of carbohydrates and energy. Together these circumstances increase the potential for AAA to access the blood-brain barrier because both AAA and BCAA share a common transporter.

Different proteins have variable potency in their influence on blood ammonia and plasma amino acid concentrations. Proteins containing heme groups are particularly implicated as encephalogenic. Diets containing dairy- and vegetable-quality protein are less encephalogenic and produce lower blood ammonia concentrations in humans and dogs with hepatic insufficiency compared with meat-based diets (Table 3) (Bessman et al. 1958, Rudman et al. 1970 and 1973). However, collective consideration of amino acid profiles, methionine concentrations and BCAA:AAA of these diets cannot predict their encephalogenic potential. For example, the BCAA and AAA content of a beneficial soy protein–based diet resembles that of encephalogenic meat-based diets (Hickman et al. 1992). Because similar benefits are achieved with diets having protein derived from dairy and vegetable sources, factors thought to be important likely involve dietary carbohydrate components. This specifically involves fermentable carbohydrates in each diet, i.e., fiber in the vegetable-based diet and lactose in the dairy-based diet.

Vegetable sources of protein successful in humans prone to HE include soy and amaranth. Soy protein (purified soy meal, tofu) has been used in many dogs with hepatic insufficiency and is well tolerated. However, soy protein has some important shortcomings as a major protein source (Kendall and Holme 1982, O'Donnell et al. 1981). Specifically, it is deficient in methionine; it substantially reduces enteric taurine availability and has relatively low digestibility unless highly processed. Digestibility of tofu ranges between 50 and 60% and soy protein meal between 76 and <90% (Huber et al. 1994, Neirinck et al. 1991). Low digestibility of some extracts is attributed to plant fiber or carbohydrate moieties having low gut degradation and to induced alterations in enteric bacterial

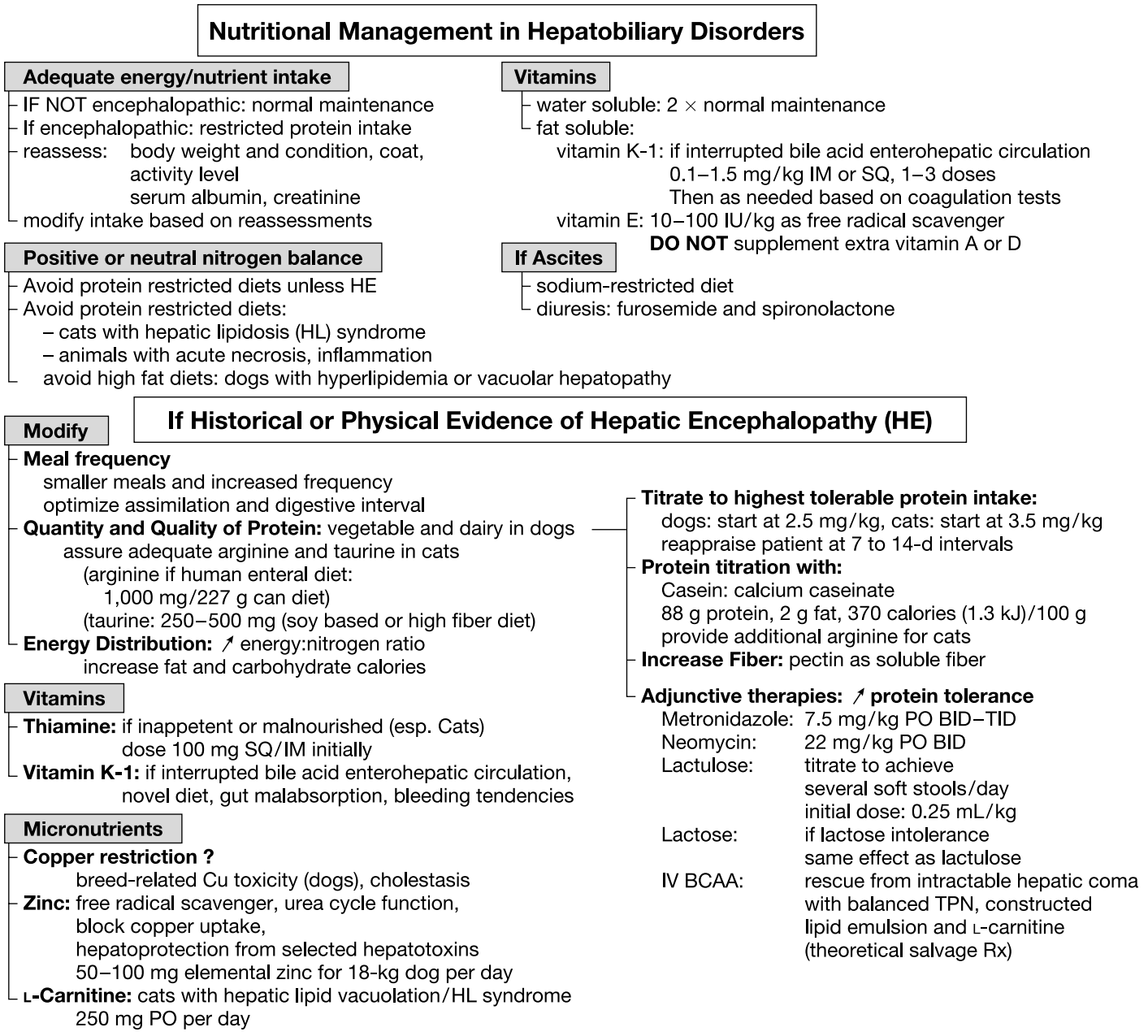

FIGURE 1 Algorithm for describing the clinical approach to nutritional management of dogs and cats with hepatobiliary disease with and without evidence of hepatic encephalopathy. Abbreviations used: IM, intramuscular; SQ, subcutaneous; PO, per os (by mouth); BID, twice a day; TID, three times a day; TPN, total parenteral nutrition.

activity. Digested soybean protein forms hydrophobic peptides that bind bile salts, thus preventing their reabsorption. Along with increased loss of bile acids in feces, the amino acid conjugate (glycine or taurine) is also wasted (Kim et al. 1995). This effect can be eliminated by oral administration of antibiotics or dietary supplementation with additional taurine (Kim et al. 1996). Because taurine is an essential amino acid in the cat and is required for bile acid conjugation, supplementation of taurine at a level of 1 g taurine/kg soy-based diet has been recommended.

The dried seeds of *Amaranthus hypochondrium* contain 5–7% hemicellulose as a nonsoluble fiber and 70% starch. This grain has been used widely as a food source in Mexico for centuries. Experience with amaranth protein in humans with hepatic insufficiency has been encouraging (Uribe 1990). There is no information available on its use in companion animals but seemingly, this protein could be adopted into home-prepared diets.

Casein as a protein source has been fed to both dogs and cats with liver disease. Because casein-based diets have the potential for low arginine concentrations, supplemental arginine is necessary when such diets are used in cats. Dietary arginine deficiency in cats can invoke hyperammonemia and encephalopathic signs within 30 min of consumption of a high protein diet (Morris 1985).

The ratio of nonprotein:protein energy is another important variable of dietary therapy in patients prone to HE. Increasing the energy:nitrogen ratio improves dietary protein utilization with a greater effect at higher protein intakes. This has great relevancy in clinical patients because provision of a

TABLE 4

Diets and recipes used in dogs with liver disease: protein source, protein provided (g/kg body weight) and energy distribution

Diet	Protein source	Diet protein[8]	Energy distribution		
			Protein	Fat	Carbohydrate
		g/kg body weight		*%*	
W- Low protein[1,2]	Corn, chicken, meat, liver, eggs	1.7	12	55	34
W- Medium protein[3,7]	Meat, chicken, rice	2.6	18	60	22
W- Hepatic support[1,3,4,7]	Corn, chicken, milk	2.0	15	25	60
H- Senior[3,7]					
(dry)	Corn, poultry by-product meal, rice, soy bean run	2.7	19	24	59
H- Geriatric[3,7]					
(canned)	Chicken, rice, corn, liver	2.2	15	31	54
(dry)	Corn, poultry by-products	2.4	17	24	59
H-Low protein[1,2]					
(canned)	Meat, liver, casein	1.6	11	49	40
(dry)	Rice, corn, egg	1.7	12	38	50
H-Low salt cardiac[2,7]					
(dry)	Corn, glandular meat, poultry by-products, egg	2.0	14	42	44
(canned)	Chicken, corn, rice, liver	1.9	13	52	35
H-Fiber supplemented[1,3,7]					
(canned)	Corn, chicken, egg, liver	2.3	16	30	54
(dry)	Corn, chicken, casein	2.7	19	19	62
Homemade diets					
Diet A[5]	Dairy/wheat germ	1.4	11	46	44
Diet B[5]	Dairy	0.9	7	42	51
Diet C[5]	Egg, rice	1.1	9	22	70
Diet D[3,7]	Meat, egg, rice, bread	2.3	18	26	56
Diet E[3,7]	Meat, rice	2.7	21	21	56
Diet F[1,3,7]	Dairy, egg, farina	3.3	26	39	35
Diet G[1,3,7]	Casein, egg, chicken	2.4	19	26	55
Diet H[1,3,7]	Tofu, casein	2.9	23	45	32
Diet I[6,7]	Casein, egg	2.2	15	55	30

Diet indications:

[1] Chronic liver disease accompanied by episodic HE.

[2] Chronic liver disease complicated by ascites; sodium-restricted diets moderately protein restricted.

[3] Chronic liver disease, no HE. Alternatively use a good quality maintenance canine ration.

[4] Diet is formulated with high biologic value, restricted quantity protein, with additional fiber (crude fiber 3.9 g/400 kcal) and zinc specifically for support of dogs with hepatic disease.

[5] Initial presentation with severe HE; short term use, followed with titration to maximal tolerable protein.

[6] Copper restricted for dogs with severe copper storage hepatopathy unable to accept chronic zinc therapy for control of enteric copper uptake.

[7] Active necroinflammatory liver disease: Diets should have protein content providing ≥2.0 g/kg if not encephalopathic.

[8] Calculations done assuming dietary protein has 85% availability, in a 17 kg dog requiring 1000 kcal (4.19 MJ) ME per day.

Homemade diets: Diet A: 3 cups nonfat dry milk, $1\frac{1}{8}$ C wheat germ (raw), 3 cups cornstarch, $1\frac{1}{2}$ cup safflower oil, $\frac{1}{2}$ cup animal fat, $\frac{2}{5}$ cup blackstrap mollasses, 1/5 cup bone meal, $1\frac{1}{2}$ tsp iodized NaCl (Strombeck et al. 1983). Diet B: 2 lb (lowfat) cottage cheese, 1lb, 3 T sugar, 1 lb 5 T cornstarch, $\frac{1}{4}$ cup safflower oil, $\frac{1}{4}$ lb animal fat, $1\frac{1}{3}$ oz bone meal, 2 tsp iodized NaCl, $3\frac{1}{4}$ t iodized KCl (salt substitute) (Strombeck et al. 1983). Diet C: 1 hard cooked egg, $2\frac{1}{2}$ cup cooked rice, 2 T safflower oil $\frac{1}{4}$ tsp calcium carbonate, $\frac{1}{4}$ tsp iodized NaCl (Bauer and Schenck 1989). Diet D: 1 hard cooked egg, 2 cups cooked rice, 3 slices white bread, $\frac{1}{4}$ lb regular ground beef (braise, retain fat) (Bauer and Schenck 1989). Diet E: 2 cups cooked rice, 1 T safflower oil, $\frac{1}{4}$ (lean) ground beef (braise, retain fat), 2 tsp dicalcium phosphate Marks et al. (1994), (Bauer and Schenck 1989). Diet F: 1 hard cooked egg, $1\frac{1}{2}$ cup creamed cottage cheese, $\frac{1}{2}$ cup cooked farina, 3 T sugar, 1 T safflower oil, 1 t dicalcium phosphate, 1 tsp calcium carbonate, 1 tsp iodized KCl (salt substitute) (Bauer and Schenck 1989). Diet G: $\frac{2}{3}$ cup raw rice, $\frac{1}{2}$ cup low fat cottage cheese, 1 egg, $\frac{1}{4}$ cup diced poultry, 2 T animal fat, 1 T vegetable oil (safflower), 1 tsp bone meal, $\frac{1}{2}$ tsp salt substitute (Marks et al. 1994). Diet H: 1 lb tofu, 2 lbs cottage cheese, 4 cups cooked rice, 6 T safflower oil, $1\frac{1}{2}$ tsp salt substitute, 6 tsp dicalcium phosphate, 1-$1\frac{1}{2}$ tsp pectin. Can use a strong low salt cheese to flavor. (Center S. A., Reynolds, A., College of Veterinary Medicine, Cornell University, Ithaca, NY, 14853). Diet I: $\frac{2}{3}$ cup raw rice, $\frac{1}{4}$ cup cottage cheese (low fat), 2 hard boiled eggs, 3 T animal fat, 1 T vegetable oil, 1 tsp bone meal, $\frac{1}{4}$ tsp lite salt, 1 multi-vitamin and mineral tablet. Puppies receive 1 cup homemade diet or 1 cup of dry Prescription DietCanine u/d (Hills Pet Products, Topeka, Kansas) to one of the following: 1 cup cottage cheese, 1 cup hamburger, or 2 hard-boiled eggs (Marks et al. 1994). Each diet is supplemented with 1 multivitamin tablet per day. If unspecified, supply bone meal or dicalcium phosphate and calcium carbonate to maintain calcium/phosphorus adequacy.

W-Low protein: Waltham low protein diet, WALTHAM Centre for Pet Nutrition, Waltham-on-the-Wolds, Melton Mowbray, Leicestershire, UK. W-Medium protein: Waltham Medium Protein Diet. W-Hepatic Support: Waltham Hepatic Support Diet. H-Senior: Hills Canine Senior Science Diet, Hills Pet Products, Topeka, Kansas. H-Geriatric: Hills Geriatric Diet. H-Low protein: Hills k/d Diet. H-Low salt cardiac: Hills h/d Diet. H-Fiber supplemented: Hills w/d Diet.

TABLE 5

Examples of diets used in cats with liver disease

Product prescription diets	Protein source	Diet protein	Energy distribution		
			Protein	Fat	Carbohydrate
		g/kg body weight		%	
H- Maintenance 1					
(canned)	Rice, chicken, corn, liver	6.2	32	54	14
(dry)		5.1	26	47	26
H- Maintenance 2					
(canned)[1]	Meat, liver, egg, soy, chicken	6.8	35	57	8
H- Protein restricted					
(canned)	Meat, liver, corn	3.7	19	65	15
(dry)	Rice, chicken, yeast	4.1	21	50	29
W- Protein restricted					
	Chicken, meat, liver	3.9	20	80	NA
Feline homemade diets					
Diet A	PC (30 g supplemental casein)	7.0	35	41	24
Diet B	Meat	6.4	33	54	13
Diet C	Meat, egg	3.5	18	29	53
Diet D	Chicken, casein	4.9	25	27	48
Diet E	Liver, cottage cheese	3.1	16	35	51

[1] Diets used to recover cats with hepatic lipidosis.

Diets calculated for a 4 kg cat requiring 320 kcal (1339×10^3 kJ)/d at 85% energy availability. Feline homemade diet ingredients: A: Pulmocare 8-oz can, micropulverized casein (30 g), KCl (5 g), vitamin B complex (2 mL), L-citrulline (1 g), choline (500 mg), taurine (250 mg), L-carnitine (250 mg) (Biourge et al. 1991). B: 1 lb ground beef braised, $\frac{1}{4}$ lb liver, 1 cup cooked rice, 1 tsp safflower oil, 1 tsp calcium carbonate (Bauer and Schenck 1989). C: $\frac{1}{4}$ lb liver, 2 hard-cooked eggs, 2 cups cooked rice, 1 T safflower oil, 1 tsp calcium carbonate (Bauer and Schenck 1989). D: $\frac{2}{3}$ cup raw rice, $\frac{3}{4}$ cup low fat cottage cheese, 1 egg, $\frac{1}{2}$ cup diced poultry, 1 T animal fat, 1 T vegetable oil (safflower), 1 tsp bone meal or equivalent dicalcium phosphate and calcium carbonate, $\frac{1}{2}$ tsp salt substitute, 1 multivitamin table (Marks et al. 1994). E: $\frac{1}{4}$ lb (115 g) liver (diced and braised, retain fat), $\frac{1}{2}$ cup creamed cottage cheese, 2 cups (350 g) cooked rice (no salt), 1 T (15 g vegetable oil), 1 T (15 g) chicken fat, $\frac{1}{2}$ cup 2% milk, Taurine 50–100 mg/d, 1 tsp pectin, $\frac{1}{2}$–1 tsp bone meal or equivalent dicalcium phosphate and calcium carbonate. Modified from Lewis, L. D., Morris, M. L., Jr., Hand, M. S. (1987) Small Animal Clinical Nutrition III. Mark Morris Associates, Topeka, KS.

HE, hepatic encephalopathy; NA, not available.

H-Maintenance 1: Feline c/d, Hills Pet Products, Topeka, KA.

H-Maintenance 2: Feline p/d, Hills Pet Products.

H-Restricted protein, Hills Pet Products.

PC, Pulmocare, Ross Laboratories, Columbus, OH.

W-Restricted protein, Waltham low protein, WALTHAM Centre for Pet Nutrition, Waltham-on-the-Wolds, Melton Mowbray, Leicestershire, UK.

protein-restricted diet (as for renal insufficiency) coupled with a failure to provide adequate energy increases dietary protein intolerance and worsens an already negative nitrogen balance. Arguments have been made for fat, carbohydrates and specifically for fructose as energy sources promoting nitrogen utilization (Zieve and Zieve 1987). In humans, caution is warranted to avoid exclusive feeding of glucose to patients with HE because this will raise the blood ammonia concentration and increase the influx of AAA into the CNS (Schlienger and Imler 1978). However, adding glucose to a balanced diet reduces cerebral AAA uptake and stimulates uptake of ammonia by muscle.

An overview of nutritional management of dogs and cats with liver disease is summarized in **Figure 1**. Diets clinically used in veterinary patients with liver disease are summarized in **Tables 4** and **5**. Patients showing signs of HE initially require a protein-restricted diet. Intervention with treatments palliating HE are concurrently administered (e.g., lactulose, neomycin or metronidazole). If the patient becomes neurologically asymptomatic, the level of protein in the diet is cautiously increased in 7- to 14-d intervals. This can be done with the addition of micropulverized casein. Attention must be given to ensure that energy intake is adequate and that cats receive supplemental arginine and taurine. For patients not showing HE, histologic or cytologic diagnoses of the underlying liver disease will assist in estimating desirable energy and protein intakes.

STUDIES OF NUTRITIONAL MANAGEMENT OF ANIMALS WITH HEPATIC INSUFFICIENCY

There are few investigations concerning nutritional support for animals with liver injury. Most work has involved dogs with surgically constructed portosystemic shunts (Eck fistulas) as models for the study of HE. As early as 1971, Condon used dogs with Eck fistulas to evaluate the effect of three different isocaloric isonitrogenous diets with protein sources derived from meat, milk and fish. Each dog was offered at least 7 g dietary protein/(kg body weight · d) and energy midway between adult maintenance and growing dog needs (unspecified amounts) (Table 3). Findings clearly determined that meat protein was encephalogenic and that milk protein (casein) was better tolerated. Dogs fed the milk-based diet lost the least amount of weight and survived longest (100 d). Unfortunately, the dietary formulations were not equivalent in energy distribution, with carbohydrate contents ranging between 6 and 30% (sucrose) and fat ranging between 1 and 12% (suet and corn oil). Dogs consuming the meat-based diet received the highest protein and lowest carbohydrate and fat percentages. Dogs consuming the milk-based diet received the highest

TABLE 6

Liquid critical care nutritional rations: protein source, protein provided (g/kg body weight) and energy distribution[1]

Product	Protein source	Diet protein[2]		Energy distribution			Energy density (1 kcal = 4.185 kJ)
		Dog	Cat	Protein	Fat	Carbohydrate	
		g/kg body wt			*%*		*kJ/mL*
Human enteral products							
PC[3]	Casein	2.1	2.9	17	55	28	6.28
PC[3,4]	mixed with 30 g micropulverized casein and 1 g L-citrulline, 250 mg taurine	NA	6.0	35	41	24	
TC[3]	Casein, amino acids	2.1	2.9	17	55	28	6.28
IHCN[3]	Casein, soy	1.9	2.6	15	45	40	8.37
I[3,5]	Soy, casein	1.6	2.2	13	37	50	4.44
E-HN[4]	Soy, casein	2.1	2.9	17	30	53	6.28
E[3]	Soy, casein	1.8	2.4	14	32	54	4.44
C[3]	Casein	1.8	2.4	14	3	83	4.44
Veterinary products							
CC (dog)	Casein, egg yolk	3.1	NA	25	59	16	4.19
CC (cat)[4]	Casein, egg yolk	NA	5.1	30	45	25	4.19
Ad[4]	Liver, chicken Corn, casein	4.5	6.0	36	51	13	5.44
NR[4]	Chicken, fish	2.9	3.9	23	26	51	8.79

[1] All diets and calcium caseinate are available over the counter.

[2] Protein availability: estimated at 0.85 from each diet. For cats: calculated for a 4-kg cat requiring 320 kcal (1,339 kJ)/d. For dogs: calculated for a 17-kg dog requiring 1000 kcal (4.19 MJ)/d.

[3]Casein used to bring dietary protein to 3.5 g/kg/day to meet feline protein requirements. Supplemental arginine or citrulline added to diets based on casein or soy for feline ammonia detoxication; 1 g added per 8 oz (240 mL) mixture. Supplemental taurine (300 mg/1000 kcal [4.185 MJ] total energy) added to diets used for cats to ensure taurine availability. NA, not applicable.

[4] Diets used to recover cats from hepatic lipidosis; with additional L-citrulline or arginine, and other supplements (see Table 7).

[5] I: contains MCT, avoid use in cats. Calcium caseinate: 88 g protein, 1.6 g calcium, 120 mg sodium, 2 g fat, 370 kcal (1.55 MJ) per 100 g.

Human enteral products. PC: Pulmocare, Ross Laboratories, Columbus, OH. TC: TraumaCal, Mead Johnson Nutritionals, Evansville, IN. IHCN: Isocal-HCN, Mead Johnson Nutritionals. I: Isocal, Mead Johnson Nutritionals. E-HN: Ensure HN, Ross Laboratories. E: Ensure, Ross Laboratories. C: Criticare, Mead Johnson Nutritionals.

Veterinary products. CC (dog): Clinical Care, Pet-Ag, Elgin, IL. CC (cat): Clinical Care, Pet-Ag. Ad: A/d, Hills Pet Products, Topeka, KS. NR: Nutritional Recovery, The Iams Company, Dayton, OH.

carbohydrate and fat percentages and thus a relatively energy-dense diet.

The effect of a liquid diet containing sodium caseinate and soy protein sources (Isocal, Mead Johnson Nutritional, Evansville, IL; 13% crude protein, 37% fat and 50% carbohydrate) compared with a standard dry dog food (25% crude protein, 8% fat and 50% carbohydrate) was also studied in dogs with Eck fistulas (Thompson et al. 1986). Dogs maintained on standard food lost considerable body weight, developed HE and became hypoalbuminemic. Dogs given Isocal gained weight, maintained their serum albumin concentrations, did not become encephalopathic and survived in good condition until killed at 6 wk. The major weakness in this study was that dogs receiving the standard canine diet ingested inadequate energy and protein to meet maintenance requirements once they became encephalopathic. Important nutritional information was lost due to the failure to maintain isonitrogenous and isocaloric intakes between groups.

The long-term biochemical and physiologic effects of surgically created portosystemic shunts were studied in dogs maintained on a diet containing 16% vegetable protein (isolated soy protein), 44% carbohydrate (cornstarch), and 40% fat (chicken fat) with other essential micronutrient and vitamin supplements (Schaeffer et al. 1986). Monitored for 50 wk, all dogs maintained body weight and were neurologically stable. Serum albumin concentrations gradually declined after 18 wk and became subnormal by 38 wk. It was not clear whether this was a result of suboptimal protein intake or a natural progression of hepatic injury. A similar diet with protein derived from casein and wheat germ was effective in clinical patients with hepatic insufficiency showing signs of HE (Strombeck et al. 1983).

A study of dogs with experimentally established portosystemic shunts evaluated the influence of portal circulatory deviation and hepatocellular atrophy on apparent dietary protein requirements (11 and 24% crude protein were evaluated) (Laflamme et al. 1993). This study also examined whether a 20% shift in enteric nitrogen derivation from either AAA or BCAA had a measurable effect. A diet comprised of ground brewer's rice, dehulled soybean meal, an amino acid premix and soybean oil was used. The low protein diet did not contain soybean meal because protein was derived exclusively from the amino acid premix. Portosystemic shunting did not alter canine protein requirements. Nutritional support with at least 2.1 g crude protein/(kg body weight · d) was recommended. There was no benefit gained by shifting dietary protein composition to a 20% contribution of BCAA. The common beneficial effect of the diets described above is the high energy: protein content. Either carbohydrate or fat was used to increase energy content of each diet. Protein intake (calculated on the basis of an estimated 85% availability) in these studies ranged between 1.6 and 2.5 g/(kg body weight · d).

High levels of fat in some of these diets were well tolerated by dogs with portosystemic shunting despite a mildly reduced fat assimilation shown in one study (LaFlamme et al. 1993). It appears that for dogs with portosystemic shunting, protein intake of 2.2–2.5 mg/kg is appropriate as a starting point. This value is titrated upward if an animal's tolerance is good and sequential evaluations of body condition, serum albumin or creatinine concentrations suggest a negative nitrogen balance.

A variety of commercial diets and enteral solutions containing different amounts of protein (amino acids), carbohydrate (glucose), fat, micronutrients and electrolytes are available (**Table 6**). No single formulation is ideal for all patients. Meal-replacement formulas developed for humans, such as Isocal (Mead Johnson) and Ensure Ross Laboratories, Columbus, OH), may be used in patients retaining normal proteolytic and lipolytic digestive capabilities. These are polymeric mixtures containing proteins, fats and carbohydrates in high-molecular-weight form, lower in osmolality than elemental formulas (Michel et al. 1984). At least 30% of calories in meal replacement formulas are commonly provided by fat. Protein sources include casein, soy or egg albumin. Elemental diets are not necessary in liver patients unless there is complicating bowel disease or pancreatic enzyme insufficiency. Isocal can be used for initial nutritional support in an encephalopathic dog, but the protein content is too low for chronic maintenance if catabolic tendencies coexist. If used in cats, supplemental arginine or citrulline, micropulverized casein and taurine are necessary (Table 6). Based on collective data in humans, the recommendation has been made for provision of some protein (25%) as BCAA if HE develops at an insufficient protein intake. However, only limited study of the effect of orally administered BCAA in dogs (a single study) and no studies in cats have been completed.

VITAMINS IN LIVER DISEASE

Humans with chronic liver disease and poor nutritional intake can develop serious vitamin deficiencies (Russell 1979). Acute severe hepatic necrosis can result in a critical loss of vitamins stored in liver parenchyma. If vitamin intake or supplementation is inadequate, vitamin deficiencies can develop acutely. Liver tissue from humans with chronic liver disease (cirrhosis) contains less folate, riboflavin, nicotinamide, pantothenic acid, vitamin B-6, vitamin B-12, vitamin A, zinc and cobalt than normal tissue (Leevy et al. 1970). Reduced vitamin storage results from hepatocyte degeneration, tissue fibrosis, fatty infiltration and altered hepatocyte function. Vitamin deficiencies are amplified by their increased use in regenerative processes, intestinal malabsorption, reduced metabolic activation or increased urinary losses. A state of "functional vitamin deficiency" develops consequent to impaired use or transport of a vitamin to its receptor or end organ. Complex interrelated abnormalities may also develop, as exemplified by vitamin A in which availability depends on the adequacy of protein synthesis and zinc sufficiency.

Water-soluble vitamins. Established daily minimal vitamin requirements are inadequate for humans with active liver disease. Due to the variety of vitamin deficiencies that may develop and the inability to quantitatively appraise these changes, water-soluble vitamins are empirically supplemented at a doubled daily dose. Subnormal concentrations of vitamin B-12 have been demonstrated in some cats with cholangiohepatitis associated with chronic inflammatory bowel disease. Injectable vitamin B-12 (1 mg every 7–28 d) has successfully repleted plasma vitamin concentrations.

Of particular concern is adequacy of thiamine (vitamin B-1), which relies on intracellular activation and hepatic storage. Thiamine is an essential coenzyme in intermediate carbohydrate metabolism, functioning as a coenzyme in the pentose-phosphate pathway (transketolase) and tricarboxylic acid cycle (pyruvate decarboxylase and α-ketoglutarate). Deficiency induces a syndrome known as Wernicke's encephalopathy, which is easily avoided by supplementation with a balanced vitamin formula (Reuler et al. 1985). Clinical signs are attributed to impaired cerebral energy metabolism and synaptic transmission, which can be potentiated by glucose administration without vitamin repletion. Clinical signs are inconsistent and confusing, and resemble HE. Cats may be more susceptible than dogs to thiamine deficiency. Affected cats develop ventral neck flexion, dilated, poorly responsive pupils and sluggish postural corrections (Jubb et al. 1956). In dogs with experimentally created thiamine deficiency, abrupt onset of neurologic signs (depression, vestibular signs, profound muscle weakness, exaggerated spinal reflexes, head ventroflexion, and deficits in supporting reflexes and menace response) terminated in death within 1 wk (Read and Harrington 1981). As in humans, Wernicke's encephalopathy is a clinical diagnosis and should be treated if suspected because response to vitamin supplementation is acute and dramatic. Treatment requires parenteral thiamine administration with an empirical dose; dogs and cats are each given 100 mg once or twice daily.

Supplementation with additional vitamin C is not currently recommended for humans with hepatobiliary disease associated with retention of copper or iron. Experimental evidence suggests that vitamin C may augment free radical membrane injury in this circumstance (Sokol 1996).

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

Deficiency of vitamin K is most easily recognized and occasionally catastrophic. This condition is detected using assays sensitive for noncarboxylated vitamin K–dependent procoagulants. The most sensitive test is the PIVKA clotting time (proteins in vitamin K absence assay). Determination of prolonged clotting times and their normalization after parenteral vitamin administration (vitamin K-1, 0.5–1.0 mg/kg intramuscularly or subcutaneously) documents vitamin deficiency. In chronic conditions in which continued vitamin K inadequacy is anticipated, dosing once every 10–28 d usually ensures vitamin repletion. Caution must be given to avoid overdosage with vitamin K in cats because oxidant injury to erythrocytes can cause clinically significant Heinz body hemolytic anemia. Because multiple factors can influence vitamin K availability, the circumstances of an individual case must be carefully reviewed. Use of vitamin K-2, passively absorbed in the colon, can avoid the influence of bile acid availability on enteric vitamin uptake.

Vitamin E has importance in protection against ongoing free radical or oxidant injury in the liver. When enteric bile acids fail to reach a critical micellar concentration, vitamin E absorption is markedly impaired (Sokol 1994). In humans, vitamin E deficiency can cause neurologic effects, mild hemolytic anemia and abnormal immune function. Vitamin E deficiency is permissive to hepatic injury associated with cholestasis, because both accumulation of hepatic copper and

hydrophobic bile acids promote free radical injury. When enteric absorption of vitamin E is impaired, parenteral vitamin supplementation is required. A dose ranging between 10 and 100 IU/(kg · d) is advised; the upper limit of this dose range was derived from studies of children with severe cholestatic liver disease and vitamin E malabsorption (Sokol 1994). Although an oral form of vitamin E absorbed in the absence of enteric bile acids has been developed, it is commercially unavailable. There are no commonly realized toxic effects derived from vitamin E supplementation.

Deficiencies of vitamin A or D also have been shown in humans with severe chronic cholestatic liver injury. Vitamin A is partially metabolized in the liver where the majority of its storage is maintained. Because excess vitamin A can cause liver injury, no supplemental therapy is recommended aside from quantities available in balanced multivitamin preparations. Because the 25- hydroxylation of cholecalciferol occurs in the liver, severe parenchymal insufficiency can reduce active Vitamin D availability. Nevertheless, deficiencies of this vitamin in humans are not recognized for years after the onset of chronic liver disease. Because supplementation entertains the risk of iatrogenic hypercalcemia, careful scrutiny of a patient's clinical circumstance is required before such treatment is undertaken. Ingestion of a balanced vitamin supplement appears to obviate vitamin D insufficiency.

FIBER

Current dietary recommendations are contrary to the old adage that a low residue, low fiber diet should be used in patients with hepatic insufficiency to minimize residual colonic debris and toxin generation. Investigations in humans with end-stage liver disease have shown that diets high in either vegetable or dairy protein and fiber are advantageous (Herrmann et al. 1987, Uribe 1990, Weber et al. 1985). Enteric fermentation of fiber increases a patient's nitrogen tolerance through a variety of mechanisms (Cummings et al. 1978, Royall et al. 1990, Tetens et al. 1996). Fiber-supplemented rations in veterinary patients with hepatic insufficiency have permitted diet variation without induction of HE.

Soluble fiber derived from pectin, gums, mucilages and psyllium are fermented in the colon. This type of fiber has a great capacity to retain water, thus increasing fecal viscosity/bulk. Various other influences imparted by soluble fiber ingestion include an increase in the unstirred water layer adjacent to the enterocyte, an ability to alter intestinal transit time, to bind enteric toxins, to stimulate enteric IgA production and to alter the resident enteric flora. The last-mentioned effect results from by-products of bacterial metabolism of fiber that can influence the ecosystem of other organisms in the vicinity (Rolfe 1984, Talarico et al. 1988). Alteration of gut flora by favoring acidophilic organisms (e.g., *Lactobacillus*) may reduce enteric ammonia production, increase fermentation of fiber and lactulose, as well as production of beneficial SCFA. The influence of fiber on intestinal transit rate varies with the species, the type of fiber and study criteria of the reported investigation. Insoluble fiber, such as cellulose and lignin, is fermented and degraded to a lesser degree than soluble fiber, depending on the colonic microflora, as well as fiber type, particle size and the quantity presented. Insoluble fiber, like soluble fiber, adds bulk to stool, which can mechanically assist the defecation reflex and elimination of encephalogenic toxins produced within the distal bowel. Like soluble fiber, insoluble fiber also increases fecal bile acid excretion. This effect involves fecal wasting of chenodeoxycholate and shift in the bile acid ratio as a result of increased synthesis of less toxic trihydroxy bile acids. Increased dietary fiber can reduce the uptake of ursodeoxycholic acid (a therapeutic bile acid) (Sauter et al. 1995).

Soluble fiber components are metabolized by anaerobic bacteria producing SCFA (Cummings 1984, Floch 1990). Although SCFA were once considered important factors contributing to HE, they are no longer considered primary or single encephalogenic agents. The SCFA, including acetic, propionic and butyric, are rapidly absorbed in the large bowel and contribute to a number of metabolic functions. Butyrate is essential for normal colonic mucosal health, comprising its major energy source and trophic influence.

Because ~25% of endogenous urea diffuses into the alimentary canal, it comprises an important source of enteric ammonia. Bacterial degradation of fiber and the influence of metabolic products generated in this process reduce enteric ammonia production and enhance fecal nitrogen elimination. Specifically, these effects have been shown with ingestion of pectin (Herrmann et al. 1987). Enteric acidification as a result of fiber fermentation may favor less ammoniogenic anaerobic organisms (*Lactobacilli*), and promote ammonia trapping within the enteric lumen as the ammonium ion (NH_4^+). These effects significantly influence enterohepatic cycling of nitrogen, reducing enteric ammonia production and absorption. In many ways, these effects mimic therapeutic benefits derived from lactulose. Similar benefits are not realized with insoluble forms of dietary fiber (cellulose or lignin).

Adverse effects of fiber that may have importance in hepatic insufficiency include its impedance of nutrient ingestion and absorption. Too much dietary fiber can result in early satiety (gastric distention) and interfere with nutrient digestion and absorption. The latter effect is related to reduced mucosal-nutrient contact, thickening of the unstirred water layer (deterring monosaccharide absorption), reduced mucosal enzymes essential for carbohydrate and protein digestion, and "chelation" of important micronutrients. Digestion and absorption of sugars, fats, amino acids, minerals and certain vitamins (B-12) may be reduced. Impaired absorption of taurine would be of special concern if high fiber diets were used in cats being fed novel protein sources (soy protein), which also may impair uptake and retention of this essential feline amino acid (Hickman 1991, Kim et al. 1995). Such formulations have been considered for cats showing signs of HE.

Although nutritional recommendations for dogs with congenital portosystemic vascular anomalies have typically focused on protein restriction (as for renal failure), dietary combination of soluble and insoluble fiber has permitted feeding diets with a higher protein content. In fact, fiber-supplemented commercial canine maintenance diets and geriatric diets are routinely used in nonencephalopathic dogs with chronic "active" hepatitis and cirrhosis in the author's clinic as opposed to protein-restricted diets. Supplementation of soluble fiber to a diet naturally low in fiber can be accomplished by the addition of psyllium or citrus pectin 5–10 mL to ~150–200 kcal ($628–837 \times 10^3$ J) for dogs (Twedt 1993, Willard 1988). Addition of insoluble fiber, at a dose of 15–45 mL of dry coarse bran, and 45–60 mL of bran cereals to ~500 kcal (2093×10^3 J), has been recommended for modification of colonic transit time and fecal evacuation in dogs (Twedt 1993, Willard 1988).

MICRONUTRIENTS

Liver dysfunction can create disturbances in micronutrient homeostasis. Although a thorough discussion of micronutrient metabolism is beyond the scope of this paper, categories hav-

ing special importance in the patient with liver disease include zinc, copper and L-carnitine.

Hepatic metabolism is pivotal to trace metal balance because liver tissue serves as a storage depot for enterically absorbed minerals and potentially toxic metals (McClain et al. 1991). Hepatic production of transport proteins (e.g., albumin or ceruloplasmin) determines the bioavailability, tissue distribution and toxicity of many minerals. Maintenance of normal biliary excretion is important in avoiding toxic tissue accumulations of copper.

Zinc. Zinc is essential to >200 metalloenzymes involved in a multitude of biochemical processes. Included among the numerous physiologic functions influenced by zinc are maintenance of membrane stability, neurologic health, immune functions, vision, reproductive function, wound healing and protein metabolism (McClain et al. 1991, Prasas 1979, Vallee and Falchuk 1993). In humans and in animals not fed commercially formulated diets, zinc ingestion correlates with protein intake, absorption occurring mainly in the small intestines and excretion occurring mainly in feces. Most commercially formulated pet diets contain additional zinc concentrations. Zinc metabolism may become disrupted in patients with liver disease. Zinc deficiency has been documented in humans with a variety of different disorders (e.g., viral associated chronic hepatitis, chronic active hepatitis, cirrhosis due to alcoholism or other disorders). In particular, acquired portosystemic shunting has been correlated with an increasing zinc deficit (Scholmerich et al. 1983). Among the mechanisms leading to zinc insufficiency are reduced intake (anorexia, consumption of a protein-restricted diet), impaired intestinal absorption associated with cytokine-induced metallothionein synthesis and portal hypertension, and abnormal protein binding and transport of zinc resulting in increased urinary losses. In most cases, the most important factor is lack of food consumption or intake of a nutritionally deficient diet. Intestinal uptake of zinc is regulated by the presence of metallothionein, a low-molecular-weight metal binding protein present in the enterocyte. Synthesis of this protein is induced by exposure to normal or high serum/tissue zinc concentrations, endotoxemia (known to complicate the health of patients with liver disease) and cytokines. Increased quantities of metallothionein irreversibly bind zinc and copper, resulting in their excretion within effete enterocytes. In the circumstance of low serum/tissue zinc concentrations, metallothionein synthesis is low and zinc/copper uptake from the alimentary canal unimpaired. Because normal to slightly increased tissue zinc concentrations stimulate metallothionein production, deterring enteric copper absorption, zinc supplementation is therapeutically used in patients with hepatic copper storage disorders (Brewer and Yuzbasiyan-Gurkan 1989).

There are many consequences of zinc deficiency in patients with liver disease. Most important is its influence on nervous tissue, neurotransmitters and ammonia storage and detoxication. Central nervous system functions altered by zinc deficiency include sensory processing, memory, cortical association and response to neurotransmitters [including γ-amino butyric acid (GABA), glutamate and benzodiazepines). Zinc deficiency reduces activity of key enzymes involved with normal nitrogen storage and detoxification (glutamate dehydrogenase in muscle and ornithine transcarbamylase in the urea cycle). The latter enzyme can be limiting to urea cycle function. Giving zinc to zinc-deficient humans with HE is beneficial likely because of improved brain zinc concentrations and urea cycle function (Marchesini et al. 1996). Because zinc deficiency is known to deter activity of thymidine kinase, a key enzyme in DNA synthesis, a severe consequence of deficiency is reduced tissue healing. Zinc given to humans with cirrhosis has also been shown to reduce systemic glucagon concentrations associated with hyperammonemia.

An additional benefit of zinc supplementation is its protective influence against a variety of hepatotoxic agents (e.g., bromobenzene, acetaminophen, carbon tetrachloride, pyrrolizidine alkaloids or copper) (McClain et al. 1991) These effects likely are derived from zinc-induced membrane stabilization, free radical scavenging or antioxidant activity, maintenance of hepatocellular metallothionein or modulation of specific cytochrome oxidases (e.g., p450 cytochromes).

Dietary supplementation with zinc in patients with severe hepatobiliary disease or portosystemic shunting is done empirically with doses similar to those used in dogs with copper storage hepatopathy (Brewer et al. 1992). Dosing is based on elemental zinc with a dose of 50–100 mg elemental zinc/d given to a 14- to 18-kg dog. Although zinc acetate, gluconate or sulfate can be used, zinc acetate is best tolerated. Although serum zinc concentrations do not accurately reflect body zinc excess or deficit, they will reflect systemic toxicity. Serum zinc concentrations are measured before supplements are initiated and then at 7–14 d, and 2 and 6 mo after treatment is started to guard against iatrogenic zinc toxicity. Chronic dietary supplementation with zinc acetate at the recommended dosage has been used in many dogs in the author's clinic without adverse effects. It is rare for a patient not to tolerate zinc supplementation in any form.

Copper. Copper is an essential component of many different metalloenzymes (McClain et al. 1991). Approximately 30–60% of dietary copper is absorbed in the small intestine where uptake is largely regulated by metallothionein. Body copper balance is determined by dietary intake and the adequacy of hepatic function (biliary excretion being most important). Liver tissue is a major site for deposition of excess body copper, and excessive stores are hepatotoxic. Injurious effects are derived from mitochondrial lipid peroxidation, damaged cytosolic proteins, impaired cellular protein synthesis and lysosomal dysfunction resulting in organelle membrane instability. In addition to the well-recognized inherited copper storage disorder in Bedlington terriers, occasionally mixed-breed and other purebred dogs develop a similar syndrome. Because severe cholestasis permits accumulation of liver copper, quantitative determinations assist in differentiating primary copper storage disease from secondary copper retention due to cholestasis (Center 1996b).

Dietary copper restriction in animals with copper-associated liver injury will not sufficiently deter copper intake and will induce other nutritional deficiencies if strictly adhered to. Preferred treatment consists of orally administered zinc. Metallothionein induction in hepatocytes and other hepatoprotective benefits are concurrently derived. Ingestion of copper-rich foods should be avoided (e.g., nuts, shellfish, organ meats, mushrooms, legumes or cereals high in copper). Animals with severely increased tissue copper stores (>5000 μg/g dry weight liver) should receive 2 mo of chelation with D-penicillamine or 2,2,2-tetramine before chronic zinc therapy is initiated (Brewer et al. 1992).

L-Carnitine. Carnitine is an essential cofactor for transport of long-chain fatty acids into mitochondria for β-oxidation. It also enables removal of excess mitochondrial acetyl-CoA that limit efficient fatty acid utilization. Accumulation of free fatty acids in mitochondria may augment development and persistence of excessive hepatic triglyceride in the feline HL syndrome. Carnitine is either synthesized endogenously (liver, kidney or brain) or is derived from the diet (especially from meat or dairy quality protein) (Brehmer 1983, Goa and

Brogden 1987). Several substrates are essential and limiting to carnitine production, including methionine, lysine, niacin, iron, vitamin C and pyridoxine. Lysine, an essential amino acid, and methionine are the most limiting factors. Because niacin is not readily synthesized by cats, dietary niacin deficiency (anorexia) could impair feline carnitine synthesis. A number of systemic conditions, including severe parenchymal disease in either the liver or kidney, and chronic total parenteral nutrition have been associated with an acquired carnitine deficiency in humans. In patients with severe liver disease, deficient *S*-adensolymethionine synthetase limits production of the intermediate carnitine precursor *S*-adenosylmethionine (Friedel et al. 1989). Nutritional deficiencies related to inappetence, nausea, vomiting or feeding of poorly balanced novel diets make the patient with hepatobiliary disease at special risk for development of acquired carnitine deficiency.

Increased synthesis of L-carnitine is initiated whenever hepatic triglyceride concentrations increase. This requires the capability for hepatic protein synthesis. Measurements of liver tissue, plasma and urine carnitine moieties in cats with HL have shown normal to high concentrations of free carnitine and acyl-carnitines (Center et al. 1991, Jacobs et al. 1990). An increased liver to plasma efflux of acyl-carnitines is reflected in the increased acyl-carnitine excretion in urine. Although the genesis of HL is considered multifactorial, severely affected cats are believed to have reduced protein synthesis. This could curtail not only synthesis of L-carnitine, but also of apoprotein B-100 necessary for hepatic dispersal of VLDL. The serious implication that an acquired or relative carnitine deficiency may augment the feline propensity for HL has led to the therapeutic administration of L-carnitine to affected cats. L-Carnitine is given to cats at a dose of 250 mg/d along with administration of a diet containing adequate energy and protein. These cats also receive other supplements and supportive care, as discussed in the following section. Although there have not been any rigorous placebo-controlled clinical trials evaluating the benefits of L-carnitine in these patients, the clinical impression is one of faster recovery and increased survival rates. Preliminary evaluation of the metabolic effects of L-carnitine in obese cats undergoing rapid weight loss suggests that it can increase β-oxidation of fatty acids (Center et al. 1997). In this circumstance, L-carnitine may provide a protective influence against development of HL, which has been shown to coincide with inappetence and weight loss in obese cats.

SPECIFIC NUTRITIONAL AND THERAPEUTIC CONCERNS IN CATS WITH HEPATIC LIPIDOSIS (HL)

The feline HL syndrome is a serious condition in which >50% of hepatic weight is attributable to retained triglycerides. Severe hepatocellular vacuolation with triglyceride distorts the cytosolic compartment and collapses canaliculi (Center et al. 1993b). Approximately 50% of cats have an underlying primary disease causing inappetence. Affected cats develop increased liver enzymes, particularly alkaline phosphatase activity, and are hyperbilirubinemic and jaundiced. Increased serum bile acid concentrations precede jaundice. Most cats develop abnormal erythrocyte morphology (irregular shapes, poikilocytes) with acanthocytes being most common. There are no consistent changes in the leukogram or other biochemical abnormalities. Some cats develop a vitamin K-1 responsive coagulopathy. Many cats become hypokalemic and some develop hypophosphatemia severe enough to produce hemolysis. Hypokalemia must be judiciously corrected as soon as possible because this electrolyte abnormality is associated with a poor prognosis. A unique difference in liver enzyme activity contrasting with other feline cholestatic liver disorders is the relative inactivity of γ-glutamyltransferase compared with alkaline phosphatase. This feature, coupled with the typical ultrasonographic appearance of a diffusely hyperechoic hepatic parenchyma, has high diagnostic utility.

TABLE 7

Dietary supplements routinely used with balanced feline rations or stress formulas in cats with severe hepatic lipidosis

L-Carnitine	250–500 mg/d PO[1]
Taurine	250–500 mg/d PO
Balanced vitamin supplement	1 tablet/d PO
Thiamine	100–200 mg/d IM / PO
Potassium	
KCl	IV with fluids initially: sliding scale
K gluconate	PO with diet as appropriate
Zinc (elemental)	7–8 mg/d
Vitamin E (α-tocopheryl acetate)	20–100 IU/d PO
Optional	
Fish oil[2]	2000 mg/d

[1] PO, per os; IM, intramuscular; IV, intravenous.
[2] Supplies (n − 3) polyunsaturated fatty acids.

Affected cats require aggressive nutritional and fluid support. In most cases, initial feeding is achieved using nasogastric intubation. When the cat attains hydration and resilience to survive, sedation/anesthesia and alimentary intubation via either an esophagostomy or gastrostomy route are secured. Provision of a nonstressful method of alimentation reduces the chance of acquired food aversion and continued undernutrition. The metabolic rate and nitrogen requirements of cats with HL have not been quantified. However, in a small group of obese cats with HL induced by food deprivation, recovery was facilitated by feeding a diet supplemented with protein-based vs. lipid- or carbohydrate-based energy (Biourge et al. 1994). Although cats with HL are stressed by illness and hospitalization, which should increase both their energy and nitrogen requirements, their relative inactivity complicates requirement estimations. Considering all variables involved and the feline inability to down-regulate protein turnover, normal energy and protein intake has been fed to most patients that have recovered. A variety of veterinary and human diets have been used to feed cats with HL as shown in Table 6. If human enteral diets are prescribed, supplements (protein, arginine, taurine) are necessary to meet feline nutritional needs. In the rare patient demonstrating signs of HE, a restricted protein diet can be used as long as it meets minimal protein requirements for healthy cats. However, recovery with consumption of protein-restricted diets is poor as is recovery in patients demonstrating overt evidence of HE. All patients with HL receive supplemental water-soluble vitamins, extra thiamine, L-carnitine, taurine, vitamin E and vitamin K-1 (1–3 doses) in the author's clinic (**Table 7**). Taurine is supplemented because of the loss incurred with bile acids in urine and because very low serum taurine concentrations have been documented in cats with HL (Center et al. 1991). If a soy-based diet is used, dietary taurine supplementation is especially essential. The adequacy of vitamin E is of concern in cats with HL because this disorder resembles the human condition of kwashiorkor (Doherty et al. 1991). In children, death from kwashiorkor is believed to be related to antioxidant deficiency. Vitamin E is therefore supplemented for its value as a free radical scavenger. A low dose of elemental zinc is provided to

maintain hepatic zinc stores, to ensure that zinc deficiency does not impair urea cycle function and to provide hepatoprotective influences previously described. Additional arginine is supplemented only if a novel diet, such as a human elemental soy- or a casein-based diet, is fed. Some clinicians additionally supplement fish oil because feeding n-3 fatty acids may reduce production of interleukin-1, tumor necrosis factor and prostaglandin E_2 related to an underlying condition.

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