Chapter 68

Hepatobiliary Disease

Hein P. Meyer
David C. Twedt
Philip Roudebush
Elizabeth Dill-Macky

"Life loves the liver of it."
Maya Angelou

CLINICAL IMPORTANCE

Among the most challenging problems in medicine are those that involve failure of a metabolically active organ such as the liver. The liver is the second largest organ of the body and performs an estimated 1,500 essential biochemical functions (Zakim, 1985). In addition to its role in drug metabolism, the removal of environmental and endogenous noxious substances and synthesis of important substances (e.g., albumin and blood clotting factors), the liver plays a key role in food digestion and nutrient metabolism. The liver influences nutritional status through its elaboration of bile salts and central role in intermediary metabolism of protein (amino acids), carbohydrate, fat and vitamins. **Table 68-1** lists the most important hepatic functions.

Patients with hepatobiliary disease are often seen in companion animal practice. An estimated 2 to 3% of all animals presented at a veterinary teaching hospital have some form of hepatobiliary disease (Meyer, 2000). Hereditary portosystemic shunts (PSS), tumors (metastasis, malignant lymphoma and primary liver tumors) and chronic hepatitis account for more than 60% of these patients (Rothuizen and Meyer, 2000). Hereditary PSS occur in 2 to 5% of investigated breeds (Meyer et al, 1995). The liver may also be damaged secondarily by other disease processes. Resultant changes are often classified as a reactive hepatopathy. Because the liver plays an essential role in the metabolism of protein, carbohydrate and fat, nutritional support plays an essential role for many patients with hepatobiliary disease.

The liver has tremendous storage capacity, functional reserve and regenerative capabilities. All of these functions protect the body from profound metabolic alterations. However, these same characteristics complicate the clinical recognition of serious liver disease. Consequently, hepatobiliary disease must be severe before clinical signs occur. As a result, the patient may be suffering longstanding and profound metabolic alterations by the time a diagnosis is made and an appropriate management plan is implemented.

The liver is also unique in that it derives its nutrient blood supply from venous and arterial sources (Anderson and

Table 68-1. Major hepatobiliary functions related to nutrient digestion and metabolism.

Metabolic functions
Converts glucose to glycogen and triglycerides during absorptive state
Converts glycogen to glucose in postabsorptive period
Synthesizes glucose from glucogenic precursors such as glycerol and amino acids in postabsorptive period (gluconeogenesis)
Transforms amino acids (transamination and deamination), synthesizes nonessential amino acids as needed for metabolism
Synthesizes triacylglycerols and secretes them as lipoproteins
Synthesizes and releases cholesterol into blood
Forms ketones from degraded fatty acids during fasting
Synthesizes urea from ammonia (sole site in body)
Synthesizes plasma albumin, fibrinogen and various other coagulation factors
Biliary functions
Synthesizes bile salts from cholesterol, which are secreted into bile for lipid emulsification and absorption in the small intestine
Secretes a bicarbonate-rich solution to help neutralize acid in the duodenum
Secretes plasma cholesterol into bile
Conjugates and excretes bilirubin in bile
Detoxifies substances by biotransformation before biliary excretion
Excretes endogenous and foreign organic molecules in bile
Storage functions
Stores glucose as glycogen and triglycerides
Stores vitamins, particularly A but also D, E, K, B_{12} and to a lesser extent other B vitamins
Stores minerals such as iron, copper, manganese and zinc
Stores blood, especially with pressure increases in the hepatic vein or posterior vena cava
Endocrine functions
Activates (partial) vitamin D by dehydroxylation
Converts thyroxine to triiodothyronine
Secretes IGF-1 in response to growth hormone
Metabolizes (deactivates) and excretes hormones
Miscellaneous functions
Removes bacteria and food antigens that regularly cross the intestinal epithelial barrier (Kupffer cells of mononuclear-macrophage system in the sinusoids)

Anderson, 1994). The portal vein provides 70 to 75% of total hepatic blood flow (Center and Strombeck, 1996). Portal venous blood is nutrient rich in the absorptive state but oxygen poor. The hepatic artery provides about 25 to 30% of blood flow with oxygen-rich blood (Center and Strombeck, 1996). Hepatotropic factors especially from portal venous blood modulate the functional and structural integrity of the liver (Diehl, 1991). Concentrations of several hormones, including hepatocyte growth factor, insulin, glucagon, glucocorticoids, thyroid hormones, parathyroid hormone, calcitonin, α- and, β-adrenergic agents and insulin-like growth factors I and II, increase after hepatic injury or resection and affect the ensuing hepatic regenerative growth (Bucher and Malt, 1971; Stolz et al, 1999; Nishino et al, 2008).

Unlike most terminally differentiated cells, hepatocytes in adult liver retain the capacity to proliferate. After partial (70%) hepatectomy, compensatory hyperplasia begins within minutes of resection and is typically completed within two weeks in rats and in less than one month in people (Higgins and Anderson, 1931; Francavilla et al, 1990). The unique regenerative ability of the liver should be a consideration in the management of many hepatic diseases (Bauer and Schenck, 1989).

Hepatobiliary diseases can be categorized depending on their cause (**Table 68-2**). (See Common Hepatobiliary Diseases below.) Irrespective of the primary liver disease, the hepatic reaction pattern is similar; thus, most of these disorders, if severe and/or longstanding, often lead to a few syndromes with potentially serious metabolic consequences (e.g., cholestasis, icterus, portal hypertension, ascites and hepatic encephalopathy [HE]). **Table 68-3** lists the frequency distribution of liver diseases in dogs and cats.

Cholestasis is decreased bile flow and can happen at any level of the complex interplay of bile formation, excretion, hepatic re-uptake or intracellular transport. Cholestasis is present to some degree in most patients with hepatobiliary disease. Severe cholestasis becomes apparent as icterus. Moreover, deposition of increased amounts of extracellular collagen and reorganization of the hepatic architecture (i.e., cirrhosis) may lead to an increase in hepatic vascular resistance, which results in portal hypertension. Portal hypertension in turn may lead to formation of multiple portosystemic collaterals and ascites. Portosystemic shunting in combination with a decrease in functional liver mass may lead to the development of HE, the complex of neurologic and behavioral signs due to gastrointestinal (GI) toxins bypassing the liver.

Malnutrition is a common finding in patients with advanced hepatic disease and is an independent risk factor for predicting clinical outcome in human patients with chronic hepatic disease (Qiao et al, 1988). In human patients with nonalcoholic cirrhosis, 14% had significant weight loss (O'Keefe et al, 1980), 50% had mild to moderate steatorrhea and 40% had deficiencies of fat-soluble vitamins (Morgan et al, 1976). Food intake was normal and was unrelated to the degree of malnutrition, suggesting that factors other than decreased food intake are involved in the malnutrition of human patients with hepatic disease. Potential causes of malnutrition in animals with hepat-

Table 68-2. Diseases of the liver and biliary tract commonly seen in dogs and cats.*

Disease categories	Etiology
Liver	
Hepatitis**	Immune mediated
	Viral
	Bacterial
	Drug induced
	Reactive
	Toxins
	Lobular dissecting
Storage disorders**	Copper toxicosis
	Lipidosis
	Amyloidosis
	Steroid-induced hepatopathy
Circulatory disorders**	Hereditary portosystemic shunt
	Portal vein hypoplasia
	Portal vein thrombosis
	Arteriovenous fístula
Neoplasia	Metastases
	Malignant lymphoma
	Hemangiosarcoma
	Hepatocellular carcinoma
Biliary tract	
Cholangitis**	Bacterial/immune mediated
(Neutrophilic/lymphocytic)	Drug induced
Cholecystitis	Bacterial
Choleliths	Bilirubin
	Cholesterol
Neoplasia	Cholangiocarcinoma
Extrahepatic cholestasis	Pancreatitis
(Not covered by above)	Pancreatic/intestinal tumor

*Adapted from Meyer HP. Hepatic encephalopathy: An overview. In: Proceedings of the Hill's European Symposium on Canine and Feline Liver Disease, Amsterdam, 2000, ISBN 0-9540567-0-1, pp 24-28.
**Hepatic encephalopathy may be present.

Table 68-3. Frequency distribution of liver diseases in dogs and cats.

Dogs*	Frequency (%)
Reactive hepatitis	25
Chronic hepatitis/cirrhosis	17
Portosystemic shunts	16
Liver tumors (primary, metastases)	14
Malignant lymphoma	14
Other conditions	12
Extrahepatic cholestasis	2
Cats**	
Lipidosis (idiopathic and secondary)	26
Cholangitis	25
Neoplasia (malignant and benign)	20
Reactive hepatopathies	16
Other conditions	8
Vascular anomalies	5

*Adapted from Rothuizen J, Meyer HP. History, physical examination, and signs of liver disease. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat, 5th ed. Philadelphia, PA: WB Saunders Co, 2000; 1272-1277.
**Twedt DC. 175 consecutive liver biopsies in cats: Unpublished data. College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colorado.

Table 68-4. Clinical signs that most often accompany primary liver disease in dogs.*

Signs	Frequency of occurrence (%)
Apathy and listlessness	60
Reduced appetite	59
Vomiting	58
Weight loss	50
Polydipsia/polyuria	45
Diarrhea	27
Reduced endurance	27
Ascites	25
Neurologic signs	12
Icterus	12
Acholic feces	7

*Adapted from Rothuizen J, Meyer HP. History, physical examination, and signs of liver disease. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat, 5th ed. Philadelphia, PA: WB Saunders Co, 2000; 1272-1277.

ic disease include: 1) anorexia, nausea and vomiting, 2) impaired nutrient digestion, absorption and metabolism, 3) increased energy requirements and 4) accelerated protein catabolism with impaired protein synthesis (Marks et al, 1994).

Nutritional management of hepatobiliary disease is usually directed at clinical manifestations of the disease rather than the specific cause. The goals of nutritional management for hepatobiliary disease include: 1) maintaining normal metabolic processes and homeostasis, 2) avoiding and managing HE, 3) providing substrates to support hepatocellular repair and regeneration, 4) decreasing further oxidative damage to damaged liver tissue and 5) correcting electrolyte disturbances (Center, 1998; Blackburn and O'Keefe, 1989).

PATIENT ASSESSMENT

History and Physical Examination

Recognition of liver disease based on history and clinical signs is usually difficult. Signs are often nonspecific and few indications of liver disease are found on physical examination. Consequently without appropriate laboratory evaluation, liver disorders are often overlooked and either the patient recovers without treatment or becomes worse despite symptomatic treatment. This section considers the expected clinical signs of liver disease and the difficulties in interpreting them.

Table 68-4 lists the most important clinical signs and the frequencies with which they occur in primary liver diseases. These signs occur in a variety of combinations in many liver diseases. Physical findings are often similar and include lethargy, neurologic signs, low body condition score (BCS), icterus and ascites.

GI abnormalities include anorexia, vomiting and diarrhea (Center, 1995). Ptyalism (hypersalivation) is especially common in cats (**Figure 68-1**) with HE. Hematemesis suggests GI ulceration, which can also be a complication of hepatobiliary disease. The anorexia, GI disturbances and metabolic alterations associated with liver disease often contribute to chronic

Figure 68-1. A 14-year-old Persian cat with ptyalism due to liver disease.

Figure 68-2. An eight-month-old Himalayan cat with clinical signs of aggression associated with hepatic encephalopathy due to a congenital portosystemic shunt.

weight loss. Bleeding tendencies (which are rarely noted clinically) may develop due to a decrease in hepatic production of clotting factors, to consumption coagulopathy (disseminated intravascular coagulation) (Rothuizen and Meyer, 2000) or malabsorption of vitamin K, which is essential for production of vitamin K-dependent factors in patients with prolonged extrahepatic bile duct obstruction (Center, 1995). Subclinical blood clotting abnormalities may become clinically evident during liver biopsy procedures or surgery. Icterus may be observed with severe cholestasis. Acholic feces due to total bile duct obstruction occur rarely in dogs and cats. Consequently, serious disturbances in fat digestion and absorption, which rely on functional biliary excretion, are rare in hepatobiliary disease (Rothuizen and Meyer, 2000).

Neurobehavioral signs of HE develop in animals with portosystemic vascular anomalies and a decreased functional liver mass. Typical signs include aggression (cats) (**Figure 68-2**), aimless wandering, manic barking (dogs), ataxia, lethargy, episodic weakness, ptyalism (cats especially), altered consciousness (disorientation, stupor or rarely coma), head pressing (**Figure 68-3**), sudden blindness, circling, pacing and seizures (Center, 1995). These signs may be episodic and may be linked to meals, dietary changes, GI hemorrhage or some other event.

A normal liver can be difficult to palpate in dogs and cats; the edges are normally sharp and the liver resides cranial to the ribcage. Hepatomegaly, however, is readily palpated in most cases. Hepatomegaly may be caused by passive venous congestion, inflammation, neoplasia, nodular hyperplasia and infiltration by fat, amyloid or glycogen. On the other hand, reduced liver size is difficult to palpate in dogs and cats. Abdominal enlargement associated with ascites usually develops slowly and insidiously. Small amounts of effusion may go undetected, whereas moderate to severe abdominal effusion becomes obvious. Hyperadrenocorticism may also cause distention from abdominal wall muscle weakness and hepatomegaly from steroid hepatopathy.

When liver disease is included in the differential diagnosis based on one or more of the historical or physical findings, additional diagnostics are required. **Figure 68-4** presents a diagnostic algorithm for liver diseases.

Laboratory Evaluation

It is beyond the scope of a nutrition textbook to discuss in detail, specific laboratory tests and imaging techniques (i.e., ultrasound, nuclear imaging techniques, laparoscopy) used to detect and confirm hepatobiliary disease. Readers are referred to small animal internal medicine, GI and surgical texts for these details. However, routine tests that help establish parameters for developing feeding and reassessment plans are summarized below.

Liver disease is most often discovered during hematologic, serum biochemistry and urine tests performed either as part of a routine wellness screen or diagnostic evaluation of sick dogs and cats. Hematologic changes may include anemia, abnormal erythrocyte morphology, reduced platelet numbers or function and detection of icteric or lipemic plasma (Center, 1995, 1996e; Dial, 1995). A regenerative anemia caused by blood loss due to GI hemorrhage and/or a bleeding diathesis may by present. More commonly, a nonregenerative anemia is found and is associated with chronic disease, chronic blood loss, malnutrition and reduced erythrocyte survival (Center, 1995, 1996e). Target cells, poikilocytes and spur cells, Heinz

bodies (cats) and microcytosis are erythrocytic abnormalities seen in animals with liver disease (Center, 1995, 1996e; Dial, 1995). Erythrocyte microcytosis is associated with acquired and congenital portosystemic vascular shunts in dogs.

Measurement of plasma enzyme activities (usually but not entirely correctly called "liver enzymes") is based on the concept that certain enzymes are released and enter the bloodstream when changes occur in the liver or bile ducts. The most important enzymes for dogs and cats are discussed below.

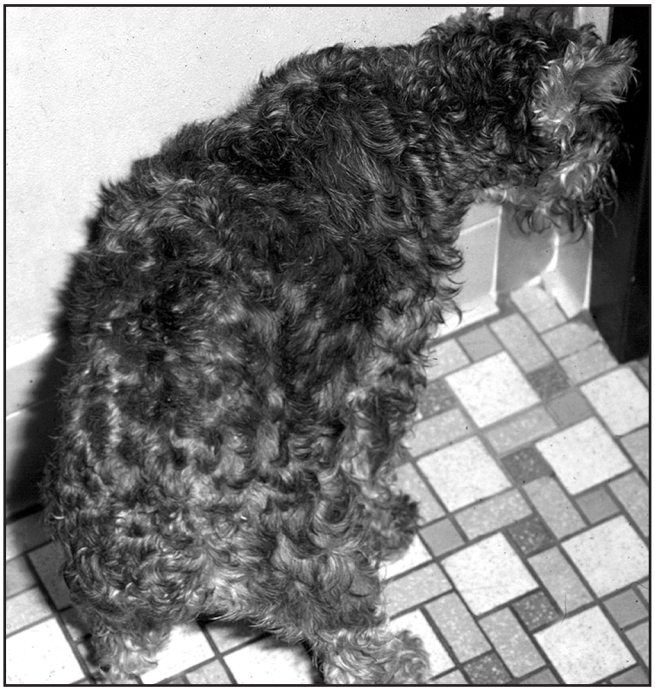

Figure 68-3. A miniature schnauzer with head pressing due to hepatic encephalopathy as a result of chronic hepatitis and cirrhosis.

Alkaline Phosphatase

Alkaline phosphatase (AP) is found in almost all organs but primarily in bone, liver, kidney, small bowel mucosa, placenta and bile duct epithelium. The plasma half-life of intestinal, renal and placental AP is only a few minutes; their contribution to total serum AP is negligible. In dogs, measurable serum AP arises from bone, liver or corticosteroid induction.

The half-life of AP from liver and bone in dogs is about 70 hours. Bone AP increases from osteoblastic activity in young growing dogs or occasionally from osteoblastic bone tumors. AP increases from cholestatic disorders resulting in induction of a liver AP and subsequent enzyme solublization and elution from damaged membranes into the blood (Gary and Twedt, 2009). Abnormal bile acid concentrations may play a role in AP production and release. Thus, significant extrahepatic cholestasis usually causes very high plasma AP activity. Finally, in dogs but not cats, corticosteroids, either endogenous or exogenous, can induce specific corticosteroid AP isoenzyme produced in the liver, leading to higher AP activity. The corticosteroid fraction of AP can be determined by heating plasma to 65°C (149°F) for two minutes, which inactivates AP of liver and bone origin, but not that induced by corticosteroids. Clinically determining the percent fraction arising from corticosteroids is generally not helpful in determining hyperadrenocorticism from other diseases.

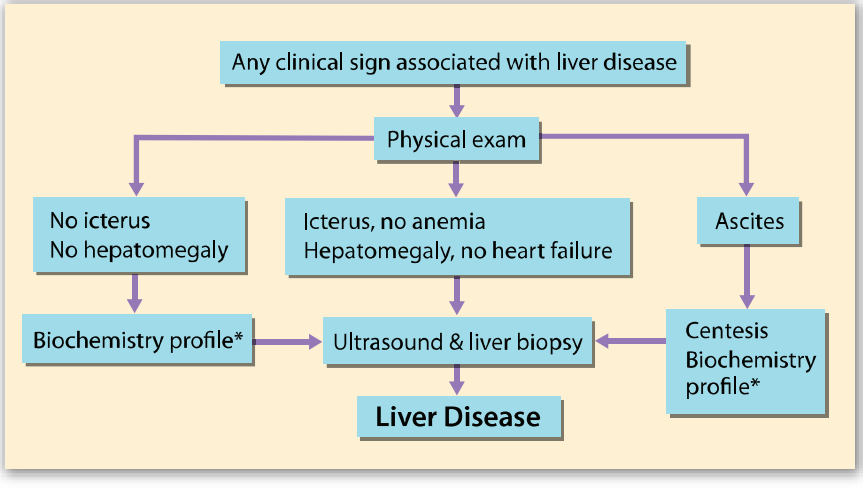

Figure 68-4. Algorithm for the diagnosis of hepatobiliary disease. (Adapted from Rothuizen J, Meyer HP. History, physical examination, and signs of liver disease. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat, 5th ed. Philadelphia, PA: WB Saunders Co, 2000; 1272-1277.)
*Alkaline phosphatase, alanine aminotransferase, bile acids, ammonia.

In cats, AP is of less diagnostic importance because the half-life is very short (i.e., 5.8 hours); thus, it is only elevated in severe hepatobiliary diseases. In addition, feline hepatic AP concentrations are low; therefore, the sensitivity of AP in detecting feline liver disease is low. The highest concentrations of plasma AP in cats often occurs with hepatic lipidosis.

Gamma Glutamyl Transferase

Hepatic γ-glutamyl transferase (GGT) is associated with hepatocyte canalicular membranes and bile ducts. Highest concentrations generally are associated with disease of biliary epithelium such as bile duct obstructions or cholangitis. Cats with cholangitis, biliary tract disease or hepatobiliary disease generally have higher GGT concentrations than AP. GGT concentrations are usually only mildly elevated in feline idiopathic hepatic lipidosis (Center et al, 1986).

Alanine Aminotransferase and Aspartate Aminotransferase

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were known in the older nomenclature as GPT and GOT, respectively. They are often collectively referred to as "hepatic leakage" enzymes. ALT is very liver-specific in dogs

and cats. It is localized in the cytoplasm of hepatocytes and released with even mild damage to cell membranes. Hepatocytes, however, do not need to be irreversibly damaged and a number of metabolic or systemic conditions can alter membrane function without being a primary liver disorder. The biologic half-life of ALT is about two and one-half days in dogs and approximately six hours in cats (Webster and Cooper, 2009). ALT is fairly sensitive and specific in dogs and cats and thus a good parameter for use in screening for liver disease.

AST is not liver specific. In dogs, it is mainly present in cardiac and skeletal muscle and other tissues and to a lesser degree in the liver. In cats, AST is more limited to the liver. Although not liver specific, AST is useful because it is chiefly located in the mitochondria and thus only released by cell death. The half-life of serum AST in dogs is five to 12 hours and 77 minutes in cats (Webster, 2005). Increased activities of AST and ALT generally indicate more severe hepatocellular damage than does an increase in ALT alone. However, this reasoning has proved to have no real diagnostic meaning, hence AST is not used.

Other Blood Examinations

Laboratory tests found in most biochemistry profiles that can reflect, in part, hepatic function include bilirubin, albumin, cholesterol, glucose and urea nitrogen. Other specialized tests of hepatic function include serum bile acid concentrations. Because the liver is involved in a multitude of functions, no single test can reflect its functional state and interpretation of function must be made in light of the clinical and laboratory testing results. Chronic hepatic dysfunction can cause hypoalbuminemia and clotting disorders. The liver exclusively produces albumin and coagulation factors except factor VIII. A number of non-hepatic conditions cause hypoalbuminemia; however, albumin synthesis declines with the loss of approximately 70% of hepatic function. Serum albumin concentrations may fall even lower with concurrent ascites and third-spacing in the ascitic fluid. The biologic half-life of albumin is approximately two weeks. Glucose and clotting factor concentrations decline when more than 75% of hepatic function is lost.

Abnormal blood coagulation generally reflects significant hepatic dysfunction due to reduced protein synthesis. Rarely, chronic bile duct obstruction can deplete intestinal bile acid concentrations required for adequate vitamin K absorption and can result in depletion of hepatic production of vitamin K-dependent clotting factors (factors II, VII, IX and X). When this situation occurs, clotting times are quickly corrected following parenteral vitamin K administration.

Ammonia is an important parameter to consider when HE is suspected. Elevated ammonia concentrations generally reflect the presence of portosystemic circulation abnormalities (e.g., congenital PSS or acquired shunts from portal hypertension). Plasma ammonia concentration is less sensitive and specific in reflecting hepatocellular function but is the method of choice when HE is suspected. Most in-house dry chemical methods provide reliable results (Sterczer et al, 1999). Care should be taken when handling samples because a number of factors may interfere with accurate results. When results are equivocal, an ammonia tolerance test can be performed. Bile salts (primarily taurocholate in dogs and cats), also erroneously called bile acids, are produced by the liver and excreted in the bile. After uptake in the portal blood, the liver re-extracts bile salts (i.e., enterohepatic circulation). Concentration of bile salts increases in the systemic circulation in cholestasis (either intrahepatic or extrahepatic), hepatocyte dysfunction (failure to extract bile acids from the sinusoidal circulation) and when vascular portosystemic shunting is present. Thus, determination of the venous concentration of total bile salts is a specific and an early, sensitive indicator of liver function. Bile salts are stable and easy to measure (Webster and Cooper, 2009). An eight-hour fasted sample should be obtained followed by a postprandial sample two hours later in dogs and cats. After hemolysis has been ruled out, bilirubin elevations reflect hepatic or extrahepatic cholestasis. The ratio between conjugated and unconjugated bilirubin fractions is not useful for differentiating among various hepatic disorders; other diagnostic testing is required. Also, urinary urobilinogen concentrations have a very low diagnostic accuracy for supporting a diagnosis of extrahepatic cholestasis.

Imaging the Liver

Radiographs are useful to determine the size and shape of the liver and to identify other concurrent abdominal disorders. Advanced studies of the hepatobiliary system include ultrasonographic imaging (Szatmari and Rothuizen, 2006). Hepatic ultrasonography is useful for initially identifying disease and monitoring its progression (Partington and Biller, 1995, 1996; Barr, 1990; Nyland et al, 1995; Lamb, 1998). Ultrasonography can detect and differentiate focal and diffuse hepatic parenchymal disorders and changes in the hepatobiliary (gallbladder and bile ducts) system. The evaluation should also include the hepatic vascular system because portosystemic anomalies are extremely common. Ultrasonography is highly operator dependent and imaging expertise takes time to develop. Readers are referred to diagnostic imaging textbooks and manuals for detailed descriptions and classifications of hepatic lesions identified by ultrasonography (Barr, 1990; Nyland et al, 1995; Partington and Biller, 1996; Lamb, 1998).

Nuclear imaging procedures (e.g., hepatic scintigraphy) and magnetic resonance imaging are used to further assess hepatic structure and vasculature or measure the degree of portosystemic vascular shunting. These techniques are usually only available at specialty referral centers.

Liver Biopsy

Histopathologic tissue examination is essential for definitive diagnosis of hepatobiliary disease (Center, 1995; Meyer, 1996; Kerwin, 1995). Liver biopsy is an invasive procedure that must be carefully considered before implementation. Common options for securing liver tissue include ultrasonographic-guided needle biopsy, "blind" biopsy techniques, laparoscopic needle or pinch biopsy and celiotomy for wedge biopsy (Center, 1995). A minimum of three full 16-gauge needle samples should be collected if a needle procedure is used. Small sample size decreas-

es the diagnostic accuracy of the histologic diagnosis (Rothuizen et al, 2006). One study showed a poor histologic correlation when only two 18-gauge needle biopsy specimens were compared to a wedge biopsy (Cole et al, 2002).

The advantage of fine-needle aspiration cytology (**Figure 68-5**) is decreased risk of complications or bleeding. However, a representative sample might not be obtained with this technique because of the very small amount of tissue that is obtained and the fact that liver architecture is not left intact during fine-needle aspiration procedures. Interpretation of hepatic cytology should be used in light of all clinical findings because hepatic cytology does not always correlate with histopathology. Ideally, liver tissue should be submitted for histopathologic and cytologic evaluation, aerobic and anaerobic bacterial cultures and copper quantification when copper toxicosis or chronic hepatitis is suspected. Specific stains for collagen, lipid, copper, iron and infectious agents may be required in some cases (**Figure 68-6**).

Abnormal concentrations of copper can occur from either a primary metabolic defect in copper metabolism reported to occur in certain dog breeds or secondarily as a result of chronic cholestatic liver disease. Abnormal copper levels damage hepatocytes. Hepatic copper content can be determined using either fresh or formalin-fixed liver tissue (Meyer, 1996; Thornburg et al, 1985). Most laboratories require one gram or less of tissue for analysis (Center, 1996a; Thornburg et al, 1990, 1996, 1985a). Normal canine hepatic copper concentrations should be 400 µg/g dry weight (DW) or less. Concentrations ranging from 750 to 2,000 µg/g DW may result from primary or secondary causes. The disease most likely results from a breed-associated copper accumulation disorder when hepatic copper concentrations exceed 2,000 µg/g DW. Hepatic copper concentrations can also be subjectively estimated using a histochemical copper stain grading system. Copper grading ranges tends to correlate with quantitative copper analysis (Teske et al, 1992).

Fine-needle aspiration of the liver using special copper staining correlates with histochemical grading but the extent of liver pathology cannot be adequately determined (Stockhaus et al, 2004). Genetic markers have been made available for testing Bedlington terriers (Yuzbasiyan-Gurkan et al, 1997).

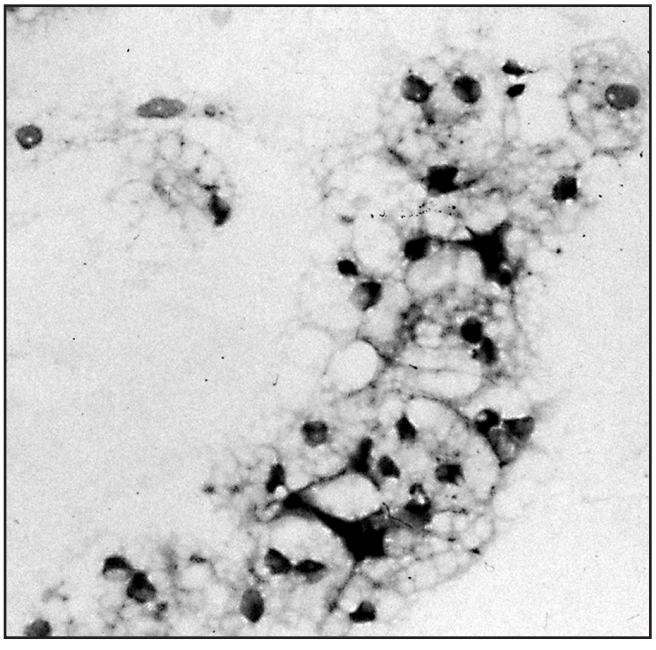

Figure 68-5. A cytologic specimen obtained by fine-needle aspiration of the liver from a cat with hepatic lipidosis. Note the lipid-laden hepatocytes. (Photograph courtesy Dr. Joseph Taboada, Louisiana State University, Baton Rouge.)

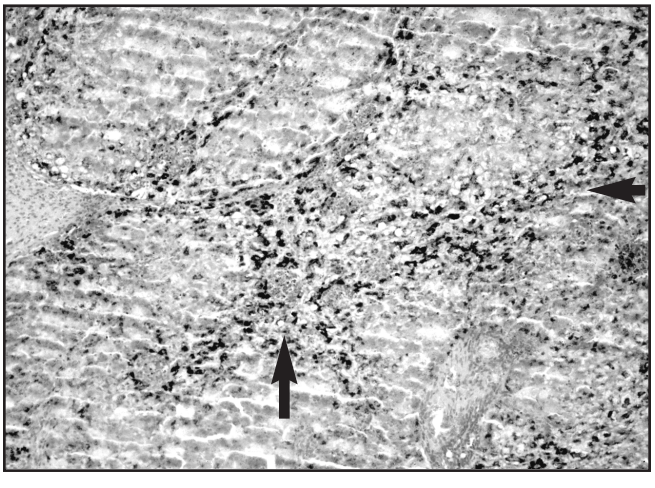

Figure 68-6. Photomicrograph of a liver biopsy specimen from a Doberman pinscher with chronic hepatitis. Note the accumulation of copper (arrows) as detected with rubeanic acid stain. In such cases, the hepatic copper content should be determined by quantitative methods.

Common Hepatobiliary Diseases

Feline Hepatic Lipidosis

Hepatic lipidosis in cats is a well-recognized syndrome characterized by accumulation of excess triglycerides in hepatocytes with resulting cholestasis and hepatic dysfunction (**Figures 68-7** and **68-8**) (Biourge et al, 1990, 1993; Center et al, 1993; Cornelius and Jacobs, 1989; Dimski and Taboada, 1995). Lipidosis can occur secondary to diabetes mellitus, diseases resulting in anorexia and weight loss (such as pancreatitis or inflammatory bowel disease) or as an idiopathic disorder of unknown etiology. Cats with idiopathic hepatic lipidosis often present with a history of prolonged anorexia after a stressful event. The biochemical mechanisms responsible for inducing hepatic lipidosis during fasting are not completely understood (Biourge et al, 1990, 1994; Center, 1996c). Potential causes include protein deficiency, excessive peripheral lipolysis, excessive lipogenesis, inhibition of lipid oxidation and inhibition of the synthesis and secretion of very low-density lipoproteins. The prognosis for this life-threatening disorder has improved dramatically during the past several years as a result of long-term enteral feeding (i.e., three to eight weeks or longer) (Biourge et al, 1990, 1994a; Dimski and Taboada, 1995). Hepatic lipidosis is a reversible process but resolution of hepatic lipidosis secondary to pancreatitis, infection or other causes depends on the success of treating the underlying disorder (Cornelius and Jacobs, 1989) and providing appropriate nutritional support.

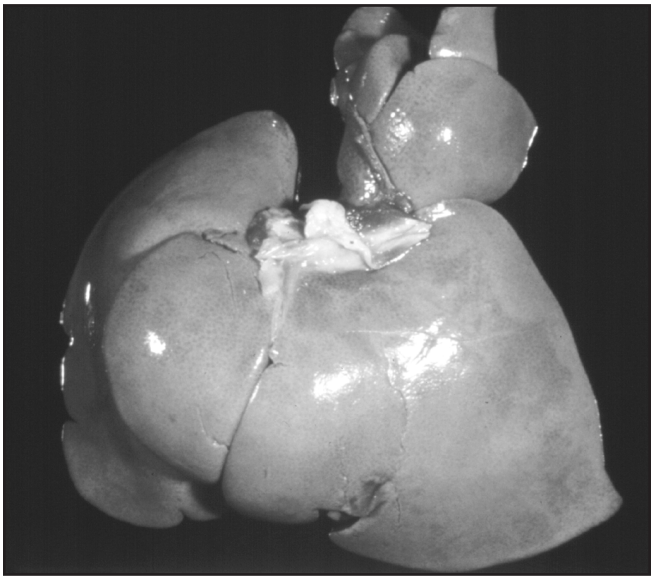

Figure 68-7. An enlarged, pale yellow liver from a cat with hepatic lipidosis.

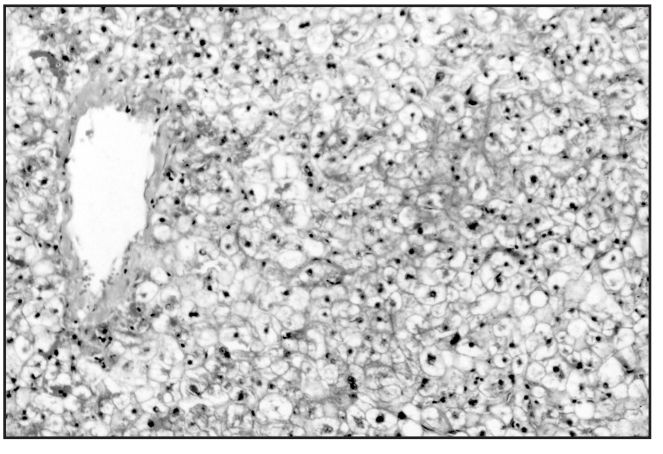

Figure 68-8. Photomicrograph of a liver specimen from a cat with hepatic lipidosis. Hepatocytes containing lipid appear empty with an inconspicuous nucleus when processed routinely with formalin fixation and hematoxylin and eosin stain.

Canine Chronic Hepatitis and Cirrhosis

Chronic hepatitis in dogs is a poorly defined group of clinicopathologic entities characterized by parenchymal necrosis, particularly piecemeal and/or bridging necrosis, with associated lymphoplasmacytic inflammation (Meyer, 1996; Thornburg, 1998; Speeti et al, 1998). Chronic hepatitis can result from many different causes including copper accumulation (See below.), infectious diseases, drugs, breed-associated hepatitis and possibly autoimmune disease. An etiology is never determined in most cases (Watson, 2004).

Lymphoplasmacytic inflammation suggests an immune-mediated mechanism. Autoantibodies have been recognized in dogs with chronic hepatitis but it is unknown if such an immune reaction is the cause or result of the disease (Weiss et al, 1995; Andersson and Sevelius, 1992; Thornburg, 1998). The insidious onset contributes to the poor understanding of the pathogenesis because most patients have an advanced stage of the disease when it is recognized.

Hepatic fibrosis is an accumulation of extracellular collagen and connective tissue within the liver (Center, 1996c) and is a sequela to hepatic inflammation. Fibrosis not only results in distortion of normal hepatic architecture, but also becomes a barrier to movement of substances back and forth between blood and hepatocytes. Cirrhosis is defined as fibrosis with loss of normal acinar liver architecture and with regenerative nodules (**Figure 68-9**) (Meyer, 1996). The architectural changes in cirrhosis impair blood and bile flow and nutrient exchange, thus perpetuating hepatocellular injury.

Canine Copper-Associated Hepatotoxicosis

Hepatic copper storage disease was first described in the Bedlington terrier breed. The disease has some similarities to Wilson's disease in people (Hultgren et al, 1986). It is an inherited autosomal recessive trait that impairs biliary excretion of copper (Su et al, 1982, 1982a). Affected dogs progressively accumulate copper. Evidence of hepatic necrosis is observed when copper concentrations exceed approximately 2,000 ppm (μg/g) DW liver (normal copper concentrations are <400 μg/g DW (Twedt et al, 1979; Twedt, 1990). As copper concentrations increase, damage progresses to chronic hepatitis and ultimately cirrhosis (Hultgren et al, 1986; Twedt et al, 1979; Twedt, 1990). Rarely, massive widespread hepatic necrosis can result in some dogs presenting with acute liver failure. Without appropriate treatment with dietary management and copper chelation, affected dogs usually succumb to their liver disease by approximately seven to 10 years of age (Hultgren et al, 1986; Twedt et al, 1979; Twedt, 1990). The gene responsible for this defect has been identified (Van De Sluis et al, 2002) and it has become possible to distinguish affected, homozygous normal and carrier Bedlington terrier dogs using DNA markers (Yuzbasiyian-Gurkan et al, 1997). It was once estimated that about 25% of Bedlington terriers were affected with copper toxicosis and another 50% were carriers. Now, through genetic testing and responsible breeding programs, the incidence of this disease is significantly lower.

Hepatic mitochondria are important intracellular targets of copper toxicosis. Functional abnormalities of mitochondria associated with oxidative injury (i.e., lipid peroxidation) have been documented to occur in people, rats and Bedlington terriers with copper-induced hepatic injury (Sokol et al, 1993, 1994). Oxidative injury and abnormal hepatic mitochondrial respiration may be involved in the pathogenesis of copper toxicosis. This theory forms the basis for using vitamin E and other antioxidants as potential therapeutic agents in addition to chelation therapy.

The role of copper in hepatic diseases observed in other dog breeds is less clear. Abnormal concentrations of copper in the liver can result secondary to cholestatic liver disease (Center, 1996c; Haywood et al, 1988; Johnson et al, 1982) or as a primary defect in hepatic copper excretion resulting in hepatic

injury (Thornburg et al, 1984, 1985, 1986, 1996). Breeds that are currently thought to have primary copper-associated hepatopathies include Skye terriers (Haywood et al, 1988; McGrotty et al, 2003), West Highland white terriers (Thornburg et al, 1996), Doberman pinschers (Specti et al, 1998), Dalmatian dogs (Webb et al, 2002) and Labrador retrievers (Hoffman et al, 2006).

The liver diseases in these dogs are distinct from copper toxicosis in Bedlington terriers in that hepatic copper concentrations are generally lower and do not always increase with age. Other factors may be responsible for hepatic damage in some breeds. The exceptions might be Doberman pinschers and Dalmatian dogs because they tend to accumulate hepatic copper in concentrations similar to Bedlington terriers, suggesting defects in hepatic copper excretion (Mandigers, 2005).

Cholangitis in Cats

Cholangitis (i.e., inflammation of the biliary ducts, especially the intrahepatic ducts and the surrounding liver tissue) is the most common feline inflammatory liver disease (Gagne et al, 1999; Armstrong et al, 1997; Day, 1995). The World Small Animal Veterinary Association Liver Pathology Standardization Working Group categorized the two most common forms of cholangitis into neutrophilic and lymphocytic forms (2006). Bacterial infection from enteric bacteria (especially *Escherichia coli*) ascending through the bile ducts is thought to be the cause of most neutrophilic forms, whereas immunologic mechanisms may be involved in the lymphocytic type. Chronic cholangitis may progress to biliary cirrhosis.

Many cats with cholangitis develop significant cholestasis and may have sludged or inspissated bile, causing partial or complete biliary obstruction (Armstrong et al, 1997; Day, 1995). Concurrent cholecystitis, pancreatitis and inflammatory bowel disease are common in feline cholangitis patients (Armstrong et al, 1997; Day, 1995).

Portosystemic Shunts in Dogs and Cats

PSS are vascular communications between the portal and systemic venous circulation. PSS can be either congenital or acquired. Congenital shunts can be further subdivided into intrahepatic shunts, occurring mostly in large-breed dogs or extrahepatic shunts, occurring mostly in smaller dog breeds and cats. Intrahepatic shunts are the remnant of a ductus venosus that did not completely close after birth. Extrahepatic shunts are seen as anomalous embryonic vessels between the portal vein and the systemic circulation (mostly to caudal vena cava or azygos vein) (Moon, 1990; Lamb, 1998; Center, 1996b). A hereditary basis for congenital shunts has been established in Irish wolfhounds (Meyer et al, 1995) and a number of other breeds have a significant risk for development of congenital shunts, supporting a hereditary etiology. Acquired PSS may develop as multiple shunts in response to portal hypertension caused by cirrhosis or other causes (e.g., tumors or portal vein thrombosis). Both congenital and acquired PSS are more common in dogs than in cats.

Primary portal vein hypoplasia (also referred to as microvascular dysplasia) is a second congenital vascular anomaly occurring in dogs, but rarely in cats. This anomaly is a consequence of portal vein hypoperfusion that results in hepatic arterialization in the portal triad and the development of microscopic intrahepatic shunts. Commonly affected breeds include cairn terriers, Yorkshire terriers and Maltese (Schermerhorn et al, 1996). Affected dogs have abnormal bile acid concentrations and variable liver enzymes but rarely have clinical signs. A less common variant of portal vein hypoplasia associated with fibrosis in the portal triads results in portal hypertension, ascites and PSS (Christiansen et al, 2000; Bunch et al, 2001).

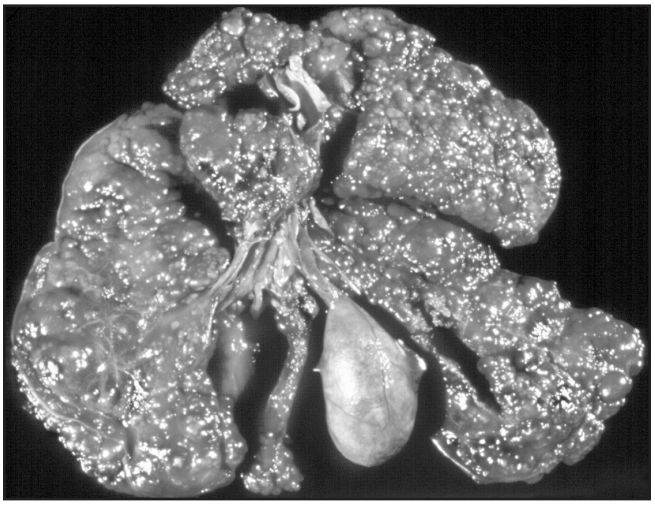

Figure 68-9. Cirrhotic liver from an eight-year-old female Doberman pinscher with chronic hepatitis. (Photograph courtesy Dr. Susan Johnson, The Ohio State University, Columbus.)

Clinical signs of HE usually predominate in patients with PSS (**Box 68-1**). Polydipsia and polyuria are also commonly seen. Ammonium urate and other purine uroliths occur in some animals because of high urinary excretion of ammonia and uric acid (Chapter 39). Stunted growth or failure to gain weight may occur in young animals with congenital shunts. Surgical closure is the treatment of choice for congenital PSS but not for acquired PSS. Dietary management is the cornerstone of successful case management and prevention of HE in the pre- and immediate postoperative phase and in partially closed shunts (Meyer and Rothuizen, 1996).

Neoplasia

The most commonly encountered hepatic malignancies in dogs and cats are metastases, lymphoma, hemangiosarcoma, hepatocellular carcinoma and cholangiocarcinoma (Cullen and Popp, 2002). The appearance may be localized or diffuse. Because the liver has such a tremendous reserve capacity, tumors, especially localized malignancies may be undetected for long periods. In advanced stages, tumors may be visible or palpable during physical examination. Severe liver dysfunction with icterus, coagulopathies and portal hypertension may occur especially in diffusely distributed malignancies (e.g., malignant lymphoma and hemangiosarcoma).

Box 68-1. Hepatic Encephalopathy.

Hepatic encephalopathy (HE) is a neurologic syndrome that may arise due to liver dysfunction and portosystemic shunting (**Figure 1**). HE is categorized as acute or chronic, based on duration of signs and relative importance of the two main etiologic factors. Striking differences exist in the pathogenesis of acute and chronic HE. Because acute HE occurs rarely in dogs and cats, this summary will focus on chronic HE. Chronic HE results from disturbances in various neurotransmitter systems caused by a variety of gut-derived toxins and compounds. These toxins and compounds reach the systemic circulation when liver function is compromised and collateral circulation develops (**Figure 2**).

The pathogenesis of HE remains partly unknown due to the complex interplay between various pathogenetic factors and neurotransmitter systems. However, there seems to be consensus that the main neurotransmitter systems involved in HE are the GABA-ergic (the most abundant inhibitory neurotransmitter system in the brain) and the glutamatergic (the most important excitatory neurotransmitter system in the brain). Other neurotransmitters that may play a role include catecholamines, serotonin and opioids. Without doubt, ammonia is the main causative agent behind neurologic changes. Other contributing factors may include accumulation of manganese (Mn), increased concentrations of neurosteroids and peripheral benzodiazepine receptor ligands and changes in the molar ratio between branched-chain amino acids (BCAA) and aromatic amino acids (AAA) in plasma and cerebrospinal (CSF) fluid.

An abundance of evidence suggests that GABA-ergic tone is increased in HE. Although the nature of this increase is partly unknown, ammonia plays a key role. The role of increased concentrations of endogenous benzodiazepine receptor ligands in HE, an attractive hypothesis postulated in the late 1990s, has been abandoned. However, neurosteroids, which increase in people with HE, may have a direct influence on the GABA-ergic tone.

Although total brain glutamate is decreased in HE, intrasynaptic glutamate is increased, leading to down regulation of various postsynaptic glutamatergic receptor types.

Methionine, degraded by gut bacteria to the mercaptans methanethiol and dimethyldisulfide, has been implicated in the pathogenesis of HE, alone or synergistically with ammonia and free fatty acids. However, previous diagnostic methods overestimated the importance of these compounds; in rats and dogs, there was no correlation between the severity of HE and the concentrations of methanethiol and dimethyldisulfide. Thus these compounds do not play an important role in the pathogenesis of HE. On the other hand, S-adenosylmethionine (SAMe), an important precursor of liver glutathione, may play a role in the treatment of chronic liver disease because liver glutathione, an important antioxidant compound, is depleted in liver disease.

In human HE patients, a relation was found between high Mn concentrations in blood and/or the globus pallidus and hyperintensity of the magnetic resonance imaging signal in the globus pallidus. High Mn concentrations in the globus pallidus were accompanied by a loss of dopamine binding sites. Binding of Mn to dopamine receptors may have resulted in auto-oxidation of dopamine and formation of free radicals that caused tissue damage. No studies have been done to confirm increased Mn concentrations in the brains of dogs and cats with HE.

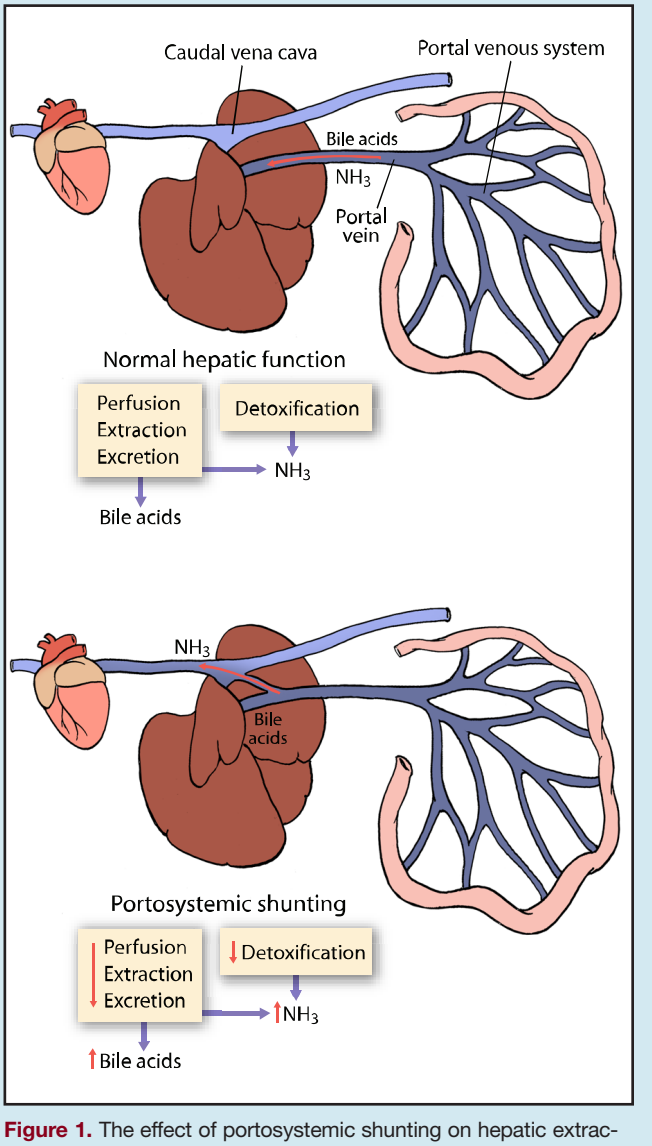

Figure 1. The effect of portosystemic shunting on hepatic extraction of bile acids and ammonia. (Adapted from Center SA. Hepatic vascular diseases. In: Guilford WG, Center SA, Strombeck DR, et al, eds. Strombeck's Small Animal Gastroenterology, 3rd ed. Philadelphia, PA: WB Saunders Co, 1996; 805, 813.)

Although a consistent decrease in the molar ratio between BCAA and AAA in plasma and in CSF has been reported in longstanding HE in many species, the importance of this molar ratio change in the pathogenesis of HE remains unclear. It may play a role in the reported dopaminergic dysfunction in HE, but others have not confirmed this hypothesis. The main beneficial effect of correction of the BCAA:AAA ratio by infusions or diet is reversal of the catabolic state in patients with HE.

Cats develop HE if fed foods deficient in arginine. Cats affected with hepatic lipidosis have low serum arginine concentrations. Because animal-origin protein is generally rich in arginine, most commercial cat foods and foods for stress and recovery are well

Box 68-1 continued

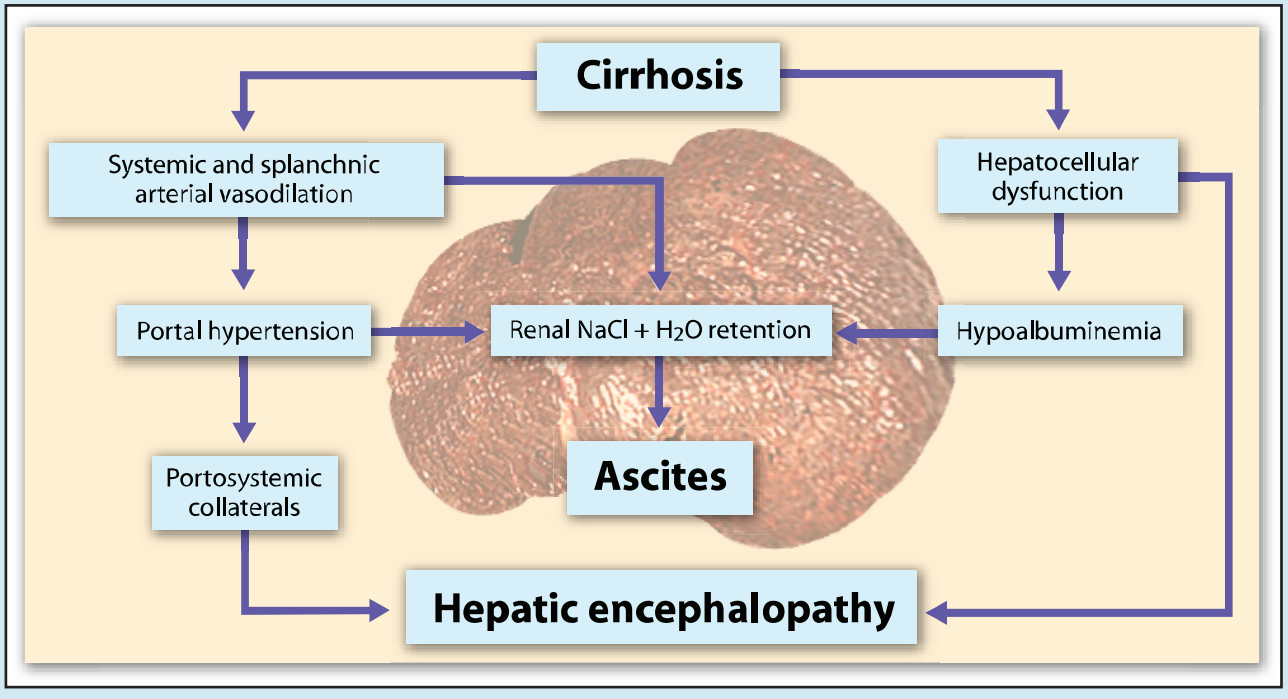

Figure 2. Interrelationships between the complications of cirrhosis. (Adapted from Abrams GA, Fallon MB. Cirrhosis of the liver and its complications. In: Andreoli TTE, Bennett JC, Carpenter CCJ, et al, eds. Cecil Essentials of Medicine, 4th ed. Philadelphia, PA: WB Saunders Co, 1997; 341.)

fortified with this amino acid. Homemade vegetable-based foods and human enteral foods fed to cats with encephalopathic clinical signs should be supplemented with arginine. Arginine levels in food should always be above the minimum dietary allowance for adult maintenance (>0.5% dry matter [DM] in dogs, >1.0% DM in cats). A dietary arginine level of 1.2 to 2.0% DM in dogs and 1.5 to 2.0% DM in cats seems appropriate for most patients with liver disease.

The Bibliography for **Box 68-1** can be found at www.markmorris.org.

Bile Duct Obstruction in Dogs and Cats

Extrahepatic bile duct obstruction, which is rarely seen in companion animals, can be caused by a number of conditions and pancreatitis is thought to be the most common cause in dogs (**Table 68-5**) (Neer, 1992). Cholestasis associated with occlusion of the major bile ducts leads to serious hepatobiliary injury within a few weeks (Center, 1996d). Obstructed bile flow and the resulting stagnation of bile acids and other compounds injure cell membranes and organelles. Bacterial cholecystitis may develop due to biliary reflux of intestinal bacteria or lymphohematogenous dissemination. Biliary injury is associated with cytokine-mediated inflammation and free radical injury. Long-term changes include biliary epithelial hyperplasia, cholangitis, multifocal parenchymal necrosis, fibrosis and cirrhosis (Center, 1996d). Coagulopathies associated with vitamin K deficiency may develop within three weeks.

Most patients with bile duct obstruction are candidates for exploratory celiotomy and corrective surgery. Enteral- or parenteral-assisted feeding is often used before and after surgery while the patient recovers (Chapters 25 and 26). Appropriate adult maintenance-type foods are generally indicated after recovery. Patients with inflammatory bowel disease, exocrine pancreatic insufficiency or concurrent pancreatitis may require a food with an altered nutrient profile (Chapters 57, 66 and 67, respectively).

Metabolic Alterations in Hepatocellular Dysfunction

Hepatocellular dysfunction is responsible for a number of metabolic disturbances that alter usage of various nutrients (**Table 68-6**). Changes in protein, carbohydrate and fat metabolism are particularly prominent in the fasting state (Marks et al, 1994; McCullough and Tavill, 1991; Latfi et al, 1991; Bauer, 1986, 1996; Chang et al, 1996). Attempts to correct these alterations by manipulating nutrient supply represent an important strategy in the management of patients with significant hepatic disease.

Impaired hepatic metabolism and storage may result in vitamin and mineral deficiencies. A combination of these metabolic and storage problems usually exists in patients with hepatic

Table 68-5. Causes of extrahepatic bile duct obstruction.*

Cholelithiasis
Cholecystitis (choledochitis)
Neoplasia
Bile duct adenocarcinoma
Pancreatic adenocarcinoma
Malignant lymphoma
Local tumor invasion
Malformation (polycystic liver disease)
Parasitic (trematode infection)
Extrinsic compression
Lymph nodes
Pancreatic mass
Entrapment in diaphragmatic hernia
Fibrosis or stricture
Blunt trauma
Peritonitis
Pancreatitis
Iatrogenic (postsurgical)

*Adapted from Center SA. Diseases of the gallbladder and biliary tree. In: Guilford WG, Center SA, Strombeck DR, et al, eds. Strombeck's Small Animal Gastroenterology, 3rd ed. Philadelphia, PA: WB Saunders Co, 1996; 870.

disease; each problem should be considered before appropriate dietary therapy is begun.

Carbohydrate Alterations

The liver plays a key role in the metabolism of the major monosaccharides glucose, fructose and galactose (Owen et al, 1981). Glucose can be used for energy production or to synthesize other substrates (e.g., amino acids, fatty acids), or it can be stored as glycogen. Liver glycogen can be readily mobilized when glucose is in demand. Hepatic glycogen can normally meet glucose needs (primarily for the brain) for 24 to 36 hours (Center, 1996). In human patients with hepatic cirrhosis, glycogen stores are more rapidly depleted (in 10 to 12 hours), which results in premature protein catabolism to supply amino acids for gluconeogenesis (Zakim, 1982). Gluconeogenesis, the production of glucose from amino acids, glycerol or lactate, is carried out only in the liver and the renal cortex. Glycolysis is the pathway by which glucose can be metabolized anaerobically with production of ATP. Regulation of glycolysis in the liver is highly integrated with that of gluconeogenesis, lipogenesis, glycogen synthesis and glycogenolysis.

Fasting hypoglycemia is uncommon in patients with liver disease because euglycemia can be maintained with as little as one-fourth to one-third of normal liver parenchymal mass (Zakim, 1982). However, hepatogenic hypoglycemia can occur in dogs with cirrhosis, congenital portosystemic vascular anomalies, fulminant hepatic failure, septicemia and extensive hepatic neoplasia (Center, 1996).

Glucose intolerance is more common than hypoglycemia in people with severe hepatic dysfunction; as many as 80% of cirrhotic patients have this abnormality (Zakim, 1982). The importance and causes of glucose intolerance in dogs and cats with liver disease are poorly documented. Hyperglycemia has been observed in some dogs with cirrhosis and portosystemic vascular shunts and in some cats with hepatic lipidosis and cholangitis (Center, 1996).

Protein and Amino Acid Alterations

The liver synthesizes the majority of circulating plasma proteins. The most abundant is albumin, which represents 55 to 60% of the total plasma protein pool (Center, 1996). Albumin serves as a binding and carrier protein for hormones, amino acids, steroids, vitamins, calcium and fatty acids, as well as exogenous compounds, drugs, toxins, etc. Albumin also helps maintain normal plasma oncotic pressure. The other proteins synthesized and secreted by the liver are usually glycosylated proteins (i.e., glycoproteins) that function in hemostasis, protease inhibition, transport and ligand binding. Hypoalbuminemia and increased bruising/bleeding tendencies result from decreased plasma protein production due to liver disease and/or increased usage (consumption coagulopathy) (Center, 1996). Ascites results from a combination of hypoalbuminemia and portal hypertension.

Protein regulatory events in the liver include amino acid storage and deamination of amino acids for intermediary metabolism. Generally, the liver degrades essential amino acids (including the aromatic amino acids [AAA], but not the branched-chain amino acids [BCAA]) and some of the nonessential amino acids (Center, 1996; Skeie et al, 1990). When dogs and other omnivores consume a minimal amount of dietary protein, the activities of key degradative enzymes are typically down regulated to ensure amino acid availability for protein synthesis. Alternatively, when omnivores ingest excess dietary protein, the activities of these key metabolic enzymes rapidly increase. This down regulation does not occur in carnivores such as cats (Chapter 19). Amino acids not required for protein synthesis are deaminated and oxidized or will be converted to carbohydrate and lipid. In this way, the liver plays an important role in energy balance and regulation of plasma concentrations of important amino acids (Chapter 5).

The deamination of amino acids is linked to carbohydrate and lipid metabolism by a number of common intermediates. These intermediates (e.g., pyruvate, fumarate, succinyl-CoA, oxaloacetate and acetyl-CoA) are entry points for amino acid carbon skeletons into the tricarboxylic acid (TCA or Krebs) cycle after deamination (Chapter 5). Intermediates are used primarily for energy production, gluconeogenesis and storage of excess dietary energy as triglycerides.

Alterations in nitrogen metabolism are one of the most prominent biochemical changes in chronic liver failure. Hyperammonemia is a common finding and results from a combination of factors including: 1) impaired ureagenesis due to decreased functional mass, 2) inadequate delivery of ammonia to the liver because of portosystemic vascular shunting and 3) increased ammoniagenesis due to amino acid deamination and gluconeogenesis (Meyer, 1998) (**Box 68-2**).

Plasma amino acid concentrations may be altered in patients with liver disease (Center, 1996; Strombeck and Rogers, 1978; Strombeck et al, 1983, 1984; Rutgers et al, 1987; Aguirre et al, 1974). Plasma amino acid concentrations differ depending on

Table 68-6. Metabolic alterations in hepatic failure.*

Alterations	Mechanisms
Hyperglucagonemia	Portosystemic shunting
	Impaired hepatic degradation
	Increased plasma aromatic amino acid levels
	Hyperammonemia
Hyperinsulinemia	Increased peripheral insulin resistance
	Decreased insulin to glucagon ratio
	Impaired hepatic degradation
Increased plasma cortisol levels	Deranged feedback mechanism
Decreased liver and muscle carbohydrate stores	Accelerated glycogenolysis
	Impaired glycogenesis
Increased gluconeogenesis	Hyperglucagonemia
Hyperglycemia (fasting and postprandial)	Portosystemic shunting
	Increased gluconeogenesis
	Decreased insulin-dependent glucose uptake
	Decreased insulin-hepatic glycolysis
Increased plasma aromatic amino acid levels	Decreased hepatic clearance and incorporation into proteins
	Increased release into the circulation
Decreased plasma branched-chain amino acid levels	Hyperinsulinemia and excessive uptake
	Increased usage as an energy source
Increased plasma methionine, glutamine, asparagine and histidine levels	Decreased hepatic clearance

*Adapted from Marks SL, Rogers QR, Strombeck DR. Nutritional support in hepatic disease. Part I. Metabolic alterations and nutritional considerations in dogs and cats. Compendium on Continuing Education for the Practicing Veterinarian 1994; 16: 972.

the type of hepatic failure present. In health, the AAA (i.e., tyrosine, phenylalanine and tryptophan) are efficiently extracted from the portal circulation and metabolized by the liver. Reduced liver function is associated with an increase in circulating levels of AAA because of continued mobilization of amino acids for gluconeogenesis and impaired hepatic AAA metabolism (Center, 1996; Strombeck and Rogers, 1978). Plasma concentrations of BCAA (i.e., leucine, isoleucine and valine), and most other amino acids metabolized in peripheral tissues are reduced because of an increased rate of usage by muscle and adipose tissue (Center, 1996; Strombeck and Rogers, 1978). The molar ratio between BCAA and the AAA (BCAA:AAA ratio) in healthy dogs usually ranges between 3.0 to 4.0. This ratio is often reduced to 1.0 or less in dogs with portosystemic vascular anomalies and chronic hepatitis (Meyer, 1998; Center, 1996e; Strombeck et al, 1983, 1984; Rutgers et al, 1987). Conversely, massive, acute hepatic necrosis in dogs (which is a rare disorder in dogs and cats) increases the plasma concentrations of all amino acids except arginine (Strombeck and Rogers, 1978). Increased circulating catecholamines, insulin and glucagon concentrations are thought to contribute to the altered amino acid metabolism seen in patients with liver disease (Center, 1996; Strombeck et al, 1983). Because all neutral amino acids (which includes BCAA, AAA and glutamine) use the same carrier to cross the blood-brain barrier, the decreased BCAA:AAA ratio is even more pronounced in cerebrospinal fluid than in plasma. Alterations in plasma amino acid profiles may also play a role in the pathogenesis of HE (Fischer et al, 1975; Maddison, 1992; Meyer, 1998a). Increased cerebral AAA levels have been hypothesized to form "false neurotransmitters," leading to decreased dopaminergic tone. Dopaminergic disinhibition at the pituitary level has been documented to occur in dogs with PSS (Rothuizen and Mol, 1987). Attempts to show that normalization of the BCAA:AAA ratio in cerebrospinal fluid would restore dopaminergic inhibition at the pituitary level have failed in dogs with induced HE (Meyer, 1998a).

Lipid Alterations

Lipid metabolic processes in the liver include: 1) fatty acid and triglyceride synthesis, 2) phospholipid and cholesterol synthesis, 3) lipoprotein metabolism and 4) bile salt synthesis. The liver synthesizes fatty acids from carbohydrate precursors by converting these precursors to acetyl-CoA. Fatty acids are generally stored in the liver as triglycerides. After hepatic glycogen stores are depleted, fatty acids are mobilized from adipose tissue and their rate of hepatic oxidation increases. The ketone bodies produced are an important energy source for peripheral tissues (i.e., brain, skeletal muscle) and decrease the rate of glucose usage.

The liver is a site for β-oxidation of fatty acids, producing energy from fatty acid substrates (Chapter 5 and 6). L-carnitine functions to transport long-chain fatty acids across the inner mitochondrial membrane to the mitochondrial matrix for β-oxidation. The liver is also a major site of cholesterol synthesis from acetyl-CoA. Cholesterol is found throughout the body as a structural component of cell membranes, a substrate for synthesis of steroid hormones and is important in the liver as the precursor for bile acid synthesis. The liver secretes lipoprotein particles and is an essential organ for their uptake and metabolism.

The composition of plasma lipids and lipoproteins is altered in patients with liver disease. These abnormalities are associated with changes in lipoprotein and cholesterol synthesis, lec-

Box 68-2. Ammonia Metabolism and the Urea Cycle.

Ammonia is highly toxic and lethal. Therefore, excretion of excess ammonia is necessary for life. Animals have developed different approaches to this problem. Mammals use the urea cycle and glutamine synthesis as ammonia disposal mechanisms.

UREA SYNTHESIS

Urea is synthesized in the liver via the urea cycle (**Figure 1**). The initial step in urea production is synthesis of carbamoyl phosphate from bicarbonate and ammonia. Carbamoyl phosphate synthetase I catalyzes carbamoyl phosphate formation in mitochondria. This reaction requires free Mg^{++} and magnesium adenine triphosphate, the rate-limiting step of the urea cycle.

Next, citrulline is formed from carbamoyl phosphate and ornithine. Ornithine transcarbamoylase, another mitochondrial enzyme, catalyzes this reaction. This step is followed by the cytosolic portion of the urea cycle, beginning with a reaction catalyzed by argininosuccinate synthetase that combines citrulline with aspartate, a second nitrogen donor, to form argininosuccinate. Argininosuccinate is cleaved to arginine and fumarate via the action of argininosuccinate lyase. Finally arginine is cleaved by arginase to form urea and ornithine. Urea is released into the circulation and ornithine reenters the urea cycle.

THE UREA CYCLE IN NONCARNIVOROUS ANIMALS

In noncarnivorous mammals (i.e., herbivores and omnivores), the urea cycle is controlled by the activities of constituent enzymes, which in turn are controlled by the substrates they act upon. Additionally, during periods of normal protein intake, most enzymes involved in urea synthesis in noncarnivorous animals operate only at 20 to 50% capacity, allowing for adaptation to high or low protein foods. These mechanisms conserve nitrogen during periods of food deprivation, but slow the response time for ammonia detoxification after ingestion of a high protein meal.

The amino acid intermediates used in the urea cycle (i.e., ornithine, citrulline and arginine) are formed within the cycle itself and are provided by dietary sources of amino acids. In noncarnivorous mammals, amino acids for the urea cycle can be synthesized via alternative pathways; for example, rats can synthesize ornithine via proline or glutamate, a process that doesn't occur in obligate carnivores. Therefore, noncarnivorous animals can better adapt to foods containing protein of lower quality that may not contain all of the amino acids required for urea cycle function or foods that vary in protein content over time.

THE UREA CYCLE IN CARNIVOROUS ANIMALS

In contrast to noncarnivorous animals, carnivores (e.g., cats and ferrets) have not developed adaptive mechanisms to conserve nitrogen during periods of low protein intake. Only minimal changes in enzymatic activity are seen in cats fed either high or low protein foods. Thus, urea cycle enzymes act continuously, independent of dietary protein intake. Because enzymatic activity is constant, carnivores control the urea cycle via concentrations of urea cycle intermediates, which allows for rapid detoxification of ammonia.

Carnivores are also unable to synthesize ornithine from proline and glutamate. Therefore, ornithine for the urea cycle must be synthesized exclusively from arginine. Although the kidneys synthesize a small amount of arginine from citrulline, the high activity of

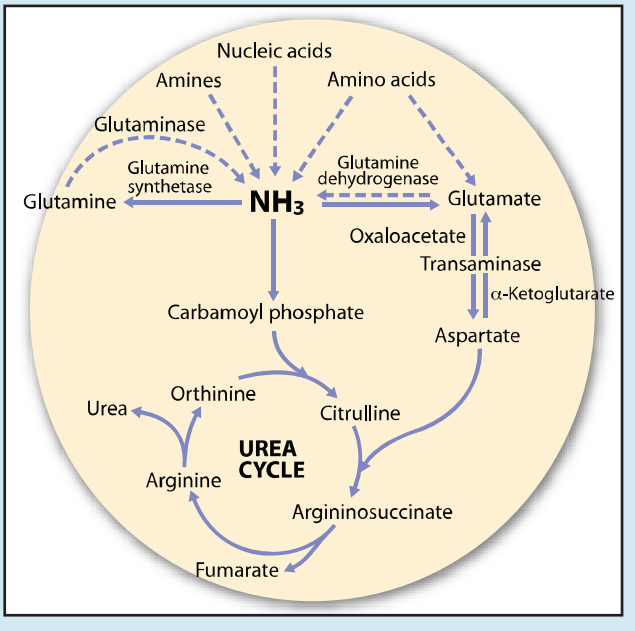

Figure 1. General scheme of hepatic ammonia metabolism, illustrating the pathways of ammonia usage (solid arrows) and ammonia formation (broken arrows). (Adapted from Ampola MG. The urea cycle: Enzymes and defects. In: Arias IM, Boyer JL, Fausto N, et al, eds. The Liver: Biology and Pathobiology, 3rd ed. New York, NY: Raven Press, 1994; 366.)

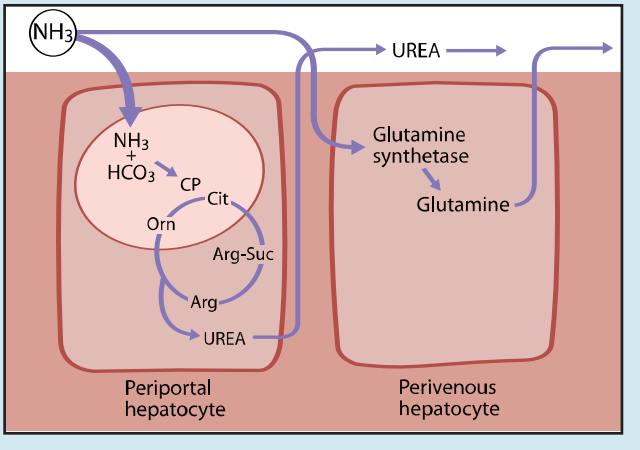

Figure 2. The scavenger role of perivenous hepatocytes. Most ammonia is metabolized to urea in the periportal hepatocytes. Ammonia not metabolized to urea is metabolized to glutamine by the perivenous hepatocytes (catalyzed by glutamine synthetase). This prevents ammonia from entering the systemic circulation and allows for uncoupling of urea production, which may be useful in acid-base regulation. Key: CP = carbamoyl phosphate, Cit = citrulline, Arg-Suc = argininosuccinate, Arg = arginine, Orn = ornithine. (Adapted from Dimski DS. Ammonia metabolism and the urea cycle: Function and clinical implications. Journal of Veterinary Internal Medicine 1994; 8: 75.)

Box 68-2 continued

hepatic arginase dictates that food primarily supply arginine for the urea cycle. To illustrate this point, adult cats and ferrets develop hyperammonemia and hepatic encephalopathy when fed foods devoid of arginine.

GLUTAMINE SYNTHESIS

Glutamine synthesis is the second primary mechanism by which mammals can metabolize excess ammonia. Hepatic glutamine synthetase is compartmentalized in a small area surrounding the centrilobular vein; thus, perivenous cells serve as "scavengers" for any ammonia that has not been converted to urea by periportal hepatocytes (**Figure 2**). Approximately one-third of the total ammonia from portal blood is detoxified by glutamine synthesis, although this percentage varies depending on acid-base status.

The glutamine synthetase pathway is a high affinity system, ensuring that ammonia does not reach the systemic circulation in toxic concentrations. In contrast, urea production is a low affinity, high capacity system for detoxifying ammonia. Thus, glutamine synthesis acts as a backup system for ammonia detoxification, allowing urea production to be decreased as required for acid-base regulation, while preventing hyperammonemia.

Glutamine synthetase activity is also high in brain astrocytes, which detoxify ammonia that may reach the brain. However, this system has limited capacity. Thus, increases in brain ammonia cannot be prevented in cases of severe hyperammonemia.

The Bibliography for **Box 68-2** can be found at www.markmorris.org.

ithin-cholesterol acyltransferase deficiency, defective lipolysis, abnormal recognition and uptake of lipoproteins by the liver and regurgitation of biliary lipids into plasma (Center, 1996). Obstructive icterus may lead to hypercholesterolemia and hypertriglyceridemia (Center, 1996). Hypocholesterolemia has been recognized in animals with portosystemic vascular anomalies and acquired hepatic insufficiency (Center, 1996). Hypotriglyceridemia has been recognized in dogs with PSS and hepatic necrosis (Center, 1996). Little is known about changes in lipoprotein fractions in dogs and cats with liver disease. Because the well-known relationship between plasma lipid and lipoprotein disturbances and cardiovascular disease in people is lacking in dogs and cats, the clinical relevance of the aforementioned disturbances in liver disease in these species may be limited.

Vitamin and Mineral Alterations

The liver serves as a storage reservoir for certain vitamins and minerals. Vitamin A can be stored in quantities sufficient for several months. The other fat-soluble vitamins (D, E and K) and vitamin B_{12} are also stored in the liver. The rest of the B vitamins are found in high concentrations in hepatic tissue, but the liver is not generally considered as their storage reservoir. Iron from dietary sources and from erythrocyte degradation is sequestered in hepatic tissue. Copper, manganese, selenium and zinc are trace elements normally present in high concentrations in the liver (Chapter 6).

Changes may occur in the patterns of storage and availability of all of these micronutrients in patients with significant liver disease. Malabsorption and alterations in hepatic blood flow may decrease availability and liver concentrations of certain vitamins and minerals. Vitamin B_{12} appears to be important in cats and subnormal concentrations of vitamin B_{12} have been reported in cats having liver disease. An adequate supply of B-complex vitamins is essential for the liver to perform a myriad of metabolic activities.

Copper is an essential trace metal required for diverse and numerous metabolic functions. The liver is essential for regulating copper concentrations and excreting excess copper via bile. Hepatic copper concentrations increase as a result of a primary metabolic defect in hepatic copper metabolism noted in some breeds of dogs. In dogs, the concentration of accumulated copper caused by cholestatic disease is less than the concentrations occurring from breed-associated copper hepatotoxicity (Spee et al, 2006). Subcellular damage to hepatocytes can result from significant copper accumulation. Copper is referred to as a transitional metal and is a catalyst (through the Fenton reaction). Free copper can directly damage hepatocyte mitochondria resulting in electron leak with free radical formation leading to lipid membrane peroxidation (Sokol et al, 1989).

Iron accumulates in the liver of canine patients with chronic hepatitis/cirrhosis, congenital portosystemic shunting and possibly other types of liver disease (Schultheiss et al, 2002; Simpson et al, 1997). Iron accumulation is thought to result from three mechanisms: 1) dietary iron uptake from the intestine, which is then deposited in the liver, 2) hepatic sequestration of iron released during hepatic inflammation and 3) abnormal hepatic retention secondary to cholestasis. Most hepatic iron is sequestered as hemosiderin and found in Kupffer cells or as lipogranulomas. Iron in hepatocytes occurs as ferritin or hemosiderin. Kupffer cell damage from iron results in cytokine release with subsequent inflammation and fibrosis. Because iron is a transition metal much like copper, abnormal levels of iron can catalyze the generation of free radicals and initiate lipid peroxidation of hepatocyte membranes and damage cellular proteins (Britton, 1996; Sokol and Hoffenberg, 1996).

Key Nutritional Factors

The specific nutrient requirements of patients with various naturally occurring hepatobiliary diseases are not well understood or documented. Most key nutritional factor recommendations for these patients are based on understanding normal hepatic function, studies in animals with experimentally induced disease, results in human patients with comparable diseases and

Table 68-7. Key nutritional factors for cats with hepatic lipidosis or cholangitis.*

Factors	Recommended levels
Energy density (kcal/g)	≥4.4
Energy density (kJ/g)	≥18.4
Protein (%)	30 to 45
Arginine (%)	1.5 to 2.0
Taurine (%)	≥0.3
Potassium (%)	0.8 to 1.0
L-carnitine (%)	≥0.02

*Nutrients expressed on a dry matter basis.

Table 68-8. Key nutritional factors for dogs and cats with hepatobiliary disease.*

Factors	Dogs	Cats
Energy density (kcal/g)	≥4.0	≥4.2
Energy density (kJ/g)	≥16.7	≥17.6
Protein (%)	15-20**	30-35**
Arginine (%)	–	1.5 to 2.0
Taurine (%)	≥0.1	≥0.3
Sodium (%)	0.08 to 0.25	0.07 to 0.3
Copper (mg/kg)	≤5	–
Zinc (mg/kg)	>200	>200
Iron (mg/kg)	80 to 140	80 to 140
Vitamin E (IU/kg)	≥400	≥500
Vitamin C (mg/kg)	≥100	100 to 200

*Nutrients expressed on a dry matter basis.
**For liver disease patients with signs of hepatic encephalopathy, dry matter dietary protein levels should be limited to 10 to 15% for dogs and 25 to 30% for cats until signs resolve.

clinical experience. The key nutritional factors discussed below support a common nutrient profile that will benefit most liver disease patients. However, it should be noted that due to the wide range of hepatobiliary diseases and their differing severity, one nutrient profile might not always be ideal for all patients. The following section will discuss these key nutritional factors in more detail and outline specific recommendations for the most common hepatobiliary disorders. **Tables 68-7** (feline hepatic lipidosis and cholangitis) and **68-8** (canine and feline hepatobiliary diseases) summarize these key nutritional factors.

Energy

Provision of adequate daily energy intake is the cornerstone of successful medical management of cats with hepatic lipidosis (Biourge et al, 1990, 1994a; Center, 1996c; Biourge, 1997; Marks et al, 1994a). An adequate supply of energy is needed to: 1) prevent catabolism of amino acids for energy, 2) inhibit peripheral lipolysis and 3) avoid excess energy consumption, which will promote hepatic triglyceride accumulation. Cats with hepatic lipidosis are often fed commercial veterinary therapeutic products via assisted-feeding techniques (Chapter 25). Foods with energy densities of at least 4.4 kcal metabolizable energy (ME/g) (18.4 kJ ME/g) (dry matter [DM]) are well tolerated by most cats and result in clinical improvement when fed in appropriate amounts. Energy density recommendations for cats with cholangitis are similar to those outlined for cats with hepatic lipidosis. Achieving this level of energy density typically requires at least 25% DM dietary fat.

Providing adequate daily energy intake is also important in managing dogs and cats with chronic hepatitis, portal hypertension and PSS and dogs with copper-associated hepatotoxicosis. An adequate supply of energy is needed to allow protein synthesis and prevent tissue catabolism that generates ammonia. Foods for patients with these diseases should provide at least 4.0 and 4.2 kcal ME/g DM (16.7 and 17.6 kJ ME/g), for dogs and cats, respectively.

The role of dietary fat in patients with hepatic disease has not been specifically determined. Dietary lipids are beneficial because they have a protein-sparing effect, reduce carbohydrate intolerance, augment fat-soluble vitamin absorption, enhance palatability and are an important source of energy and essential fatty acids.

A minor decrease in fat digestibility (i.e., from 92 to 85%) was found in dogs with experimentally created PSS (Laflamme et al, 1993). Other studies showed that dogs with experimental shunts tolerate foods containing 20 to 25% DM fat (Center, 1996b). Clinically significant impaired fat digestion may occur in animals with severe biliary disease with subtotal or total biliary obstruction.

There appears to be no reason for routinely restricting dietary fat in dogs and cats with liver disease. One of two different situations may be occurring if steatorrhea is a problem in patients with hepatobiliary disease. First, the patient may have concurrent disease that is contributing to fat malassimilation, such as exocrine pancreatic insufficiency. Second, the patient may have subtotal or total biliary duct obstruction.

Medium-chain triglycerides (MCT; i.e., carbon chain lengths <12) have theoretical advantages over long-chain triglycerides (LCT) for the treatment of GI and some forms of hepatobiliary disease (Guilford, 1996). MCT may be more easily hydrolyzed and absorbed than LCT; however, these advantages have yet to be proved. Caloric supplementation with MCT is useful for malnourished human cirrhotic patients with steatorrhea and those with advanced cholestatic hepatic disease (Munoz, 1991). Controlled clinical trials using MCT in animals with cirrhotic or cholestatic liver disease have not been reported.

The inflammatory component of hepatic disease may be attenuated by omega-3 (n-3) fatty acid supplementation. However, the specific amounts to include in foods and the optimal ratio of omega-6 (n-6) to omega-3 fatty acids have not been determined. Some veterinary therapeutic foods for liver disease are enhanced with omega-3 fatty acids (Remillard and Saker, 2005).

Protein and Amino Acids

Dietary protein and the amino acids arginine and taurine are important in cats with hepatic lipidosis. Cats are less efficient in sparing protein during fasting than other animals. As such,

protein deficiency may play a major role in the development of feline idiopathic hepatic lipidosis. Cats with hepatic lipidosis have signs of protein malnutrition include hypoalbuminemia, anemia, muscle wasting and negative nitrogen balance (Biourge et al, 1994; Barsanti et al, 1977). Specific amino acids (e.g., methionine and arginine) become limiting during fasting in obese cats (Biourge et al, 1994). Protein or amino acid deficiency may induce lipid accumulation in the liver by limiting lipoprotein synthesis needed for normal lipid metabolism and transport (Biourge et al, 1994). Protein supplementation at only one-fourth of the daily requirement (22 g protein/day) significantly reduced lipid accumulation in the liver and promoted positive nitrogen balance during long-term fasting in obese cats (Biourge et al, 1994a).

Cats with hepatic lipidosis will usually tolerate moderate amounts of dietary protein unless they are suffering from concurrent HE, which is uncommon. Commercial veterinary therapeutic foods containing 30 to 45% DM protein are well tolerated by cats with hepatic lipidosis and have been used successfully in many cases. Protein needs for cats with cholangitis are similar to those for cats with hepatic lipidosis.

Adult cats and ferrets developed hyperammonemia and HE when fed foods devoid of arginine (**Boxes 68-1** and **68-2**). Foods for cats with hepatic lipidosis should provide adequate arginine. Arginine levels in food should always be above the minimum dietary allowance for adult maintenance (≥0.77% DM [NRC, 2006]). More arginine is required in cat foods that contain more than 20% DM protein (NRC, 2006). Arginine levels in foods for cats with liver disease should be between 1.5 to 2.0% DM. Good quality commercial foods are typically adequate in arginine. Homemade vegetable-based foods and human enteral foods fed to cats with encephalopathic clinical signs should be supplemented with arginine.

Ensuring adequate taurine intake is important for anoretic cats with hepatic lipidosis. Cats and dogs primarily synthesize taurine in the liver and bile salts are mainly conjugated with taurine. Compared to cats, dogs have a high capacity to synthesize taurine; therefore, dietary taurine is usually not essential. Food-induced bile salt excretion into the gut can result in significant loss of taurine, particularly when normal enterohepatic recycling is interrupted. Taurine synthesis is limited in cats; therefore, dietary taurine is essential. Adequate taurine nutriture is important in patients with enterohepatic circulation abnormalities and possibly in liver disease. In certain species, taurine also stimulates synthesis and turnover of bile independent of its role as a bile acid conjugate. Taurine appears to aid choleresis in dogs and possibly cats. This role may explain the observation that taurine prevents cholestasis in certain models of liver disease. Most commercial cat foods and foods for stress and recovery for dogs and cats are fortified with taurine. However, homemade and human enteral foods fed to cats should be supplemented with taurine (250 to 500 mg/day) (Chapter 10). The minimum recommended allowance for dry expanded and moist foods for adult cats is 0.10 and 0.17% DM, respectively (NRC, 2006). Foods for cats with hepatic lipidosis and other liver diseases should probably contain at least 0.3% DM taurine. Although no minimum recommended allowances for taurine for healthy dogs have been defined, foods for dogs with liver disease should contain at least 0.1% DM taurine.

Appropriate amounts of high quality dietary protein are also important in patients with chronic hepatitis and/or cirrhosis, portal hypertension and dogs with copper-associated hepatotoxicosis. Hypoalbuminemia, which reflects depleted body stores and reduced protein synthesis, is a frequent and serious problem in patients with chronic liver disease. Protein plays a leading role in hepatic regeneration; therefore, patients with liver disease require adequate protein intake to remain anabolic and support regeneration of hepatocytes. On the other hand, dietary protein restriction may be important in patients with endstage cirrhosis, hyperammonemia and HE. Protein, or more accurately, nitrogen excess, is a major contributor to neurotoxic precursors formed when amino acids are metabolized to ammonia. For patients with liver disease, the goal is to provide adequate dietary protein to support hepatic regeneration while avoiding excess dietary protein that might contribute to HE.

The protein requirements for patients with PSS have been roughly estimated from a nutritional study in adult dogs with surgically created shunts (Laflamme et al, 1993). This study showed that ingestion of 2.11 g crude protein/kg body weight/day with an 80% or greater availability was adequate to maintain body protein reserves without producing HE. In the absence of other data, this recommendation for dietary protein intake seems appropriate. This equates to approximately 14 to 16% protein calories (15 to 20% DM protein) for dogs and 25 to 30% protein calories (30 to 35% DM protein) for cats. These protein levels are also appropriate for dogs and cats with most other forms of liver disease, except hepatic lipidosis (described above) and HE. Patients with evidence of HE will often need restricted dietary protein levels for the short term (10 to 15% DM for dogs and 25 to 30% DM for cats). For a point of reference, the minimum recommended protein allowances for foods for normal adult dogs and cats are 10 and 20% DM, respectively (NRC, 2006).

In addition to the absolute amount of protein fed, the amino acid profile and digestibility are important for optimal protein usage. Amino acids from poor-quality protein sources are deaminated and metabolized to a greater extent than amino acids from higher quality protein sources and exacerbate hyperammonemia. Intestinal bacteria may degrade poorly digested proteins and add to the body's ammonia burden.

The importance of the dietary protein source has been studied in human patients with HE and in several experimental studies in dogs with PSS (Center, 1996b). Vegetable and dairy protein sources have produced the best results in maintaining positive nitrogen balance with minimal encephalopathic signs in human patients with liver disease (Uribe, 1990; Bianchi et al, 1993; Weber et al, 1985). Foods containing soybean meal averted encephalopathic signs in dogs with experimentally created shunts (Center et al, 1997; Thompson et al, 1986; Schaeffer et al, 1986). In addition, dairy products (especially cottage cheese) have been recommended for use in homemade foods for dogs and cats with PSS and chronic hepatic insufficiency (Center,

Box 68-3. Adjunctive Use of Copper Chelating Agents for Patients with Hepatic Copper Toxicosis.

For Bedlington terriers with subclinical or clinical liver disease, in addition to selection of a low-copper (<5 mg/kg, [dry matter]) veterinary therapeutic food (**Table 68-11**), adjunctive treatment with copper chelating agents is clearly indicated. Chelator treatment is used for breeds of dogs with copper-associated chronic hepatitis and cirrhosis and other breeds in which copper accumulation is documented by liver histopathology and/or elevated hepatic copper concentrations (generally >1,000 to 2,000 ppm dry weight).

Adjunctive treatment of hepatic copper toxicosis involves use of zinc or copper chelating agents such as D-penicillamine or trientine (**Figure 1**). Zinc blocks copper absorption. Chelating agents bind to copper and increase its excretion in urine. D-penicillamine, the copper chelating agent most frequently recommended for use in dogs, should be given at a dosage of 10 to 15 mg/kg body weight twice daily, on an empty stomach. Vomiting is the most common side effect in dogs, but can be alleviated by giving the agent more frequently in reduced doses. D-penicillamine therapy also has been associated with pyridoxine deficiency in people. However, this problem has not been recognized in dogs.

Trientine[a] (2,2,2-tetramine) is another chelating agent. In a clinical trial, chelation results with trientine (10 to 15 mg/kg body weight, per os, twice daily) were comparable to those of D-penicillamine and fewer side effects were noted. Modification of 2,2,2-tetramine to 2,3,2-tetramine increases the potency as a copper chelating agent. Use of 2,3,2-tetramine in affected Bedlington terrier dogs significantly reduced liver copper concentrations after 200 days of treatment at a dose of 15 mg/kg body weight. This drug is not commercially available but can be obtained from chemical supply companies in the form of N,N'-bis(2-aminoethyl)-1,3-propanediamine and prepared as a salt for oral administration.

Oral zinc therapy blocks copper absorption from the intestine. In early human studies, therapy with combined zinc and copper chelators found no benefit over single chelator therapy suggesting the chelator most likely binds zinc in the intestinal tract. However, more recently, human patients having Wilson's disease who are intolerant to penicillamine are sometimes treated with a combination trientine and zinc regimen with apparently good results. Affected dogs should be fed copper-restricted foods and be given the faster acting copper chelator. When hepatic copper concentrations approach normal levels, switching to zinc therapy alone may prevent further copper accumulation.

The initial report in dogs used 100 mg of elemental zinc acetate b.i.d. for one to two months during an induction phase followed by a maintenance dose of 50 mg of elemental zinc b.i.d., thereafter. Serum zinc concentrations should be monitored with a goal of approximately a twofold increase in serum concentrations (<200 µg/ml). Hemolysis can occur if serum zinc concentrations increase significantly (>750 µg/ml). Zinc can be given as an acetate, sulfate, gluconate or methionine salt but should be administered on an empty stomach to ensure adequate absorption. Common problems encountered with zinc therapy include anorexia, nausea and vomiting shortly following administration. If concurrent chelator therapy is used, dosing should be staggered to ensure adequate absorption of the chelator.

ENDNOTE

a. Syprine. Merck & Company, Inc., Rahway, NJ, USA.

The Bibliography for **Box 68-3** can be found at www.markmorris.org.

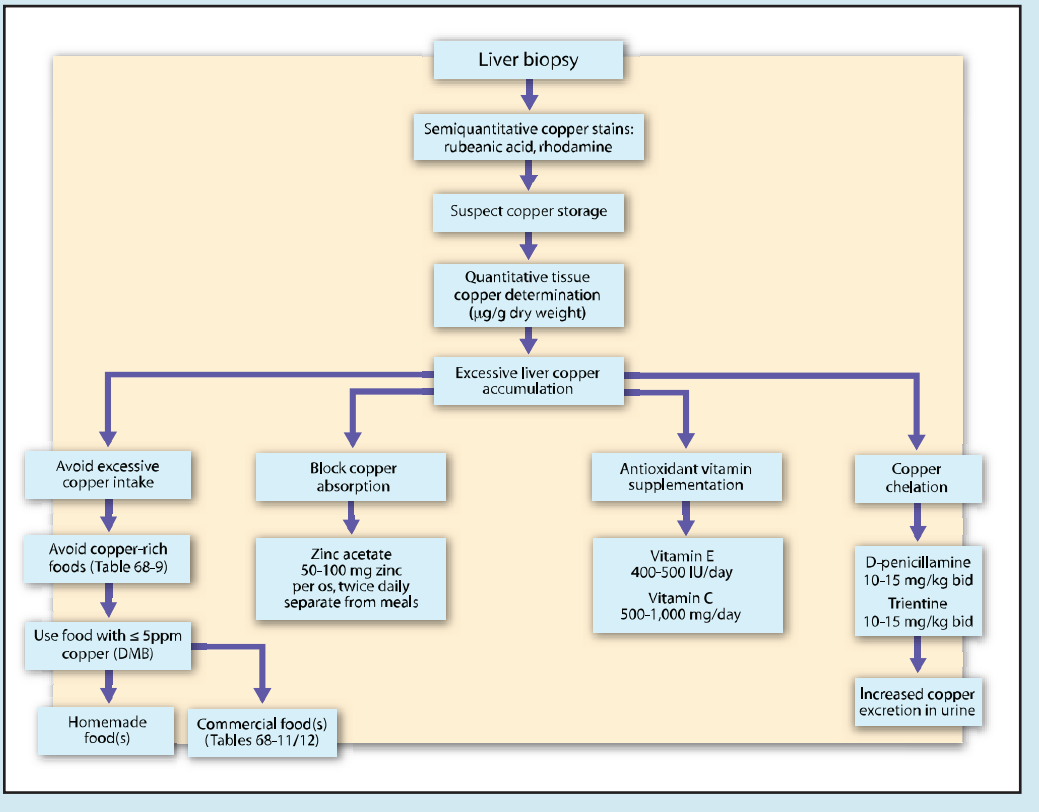

Figure 1. Algorithm for treating copper hepatotoxicosis in dogs. (Adapted from Center SA. Chronic liver diseases. In: Guilford WG, Center SA, Strombeck DR, et al, eds. Strombeck's Small Animal Gastroenterology, 3rd ed. Philadelphia, PA: WB Saunders Co, 1996; 749.)

1996b; Marks et al, 1994a). The amino acid composition of these protein sources is not significantly different from that of meat sources, suggesting that other food factors such as digestibility and levels of digestible (soluble) carbohydrate and fermentable fiber are important. Fermentable carbohydrates increase microbial nitrogen fixation, reduce intraluminal ammonia production in the gut and promote colonic evacuation (Center, 1996b). (See Fiber below.)

Superficial necrolytic dermatitis (hepatocutaneous syndrome) is an uncommon skin disease associated with systemic metabolic disease. Afflicted dogs commonly have concurrent skin erosions and ulcerations with alopecia, exudation and thick adherent crusts on the footpads and around mucocutaneous junctions. The hepatopathy grossly has the appearance of macronodular cirrhosis but is characterized by regenerative hyperplastic nodules separated by fibrous septa containing ductular structures and is void of inflammation. Some authors believe this condition results from exaggerated amino acid catabolism and the resultant hypoaminoacidemia is responsible for the skin and liver lesions (Gross et al, 1990, 1993). Most affected dogs also have low plasma amino acid concentrations and parenteral amino acid replacement with nutritional protein supplementation may resolve the skin lesions (Gross et al, 1993). In these cases, high protein foods, various protein supplements and intravenous amino acid solution administration is recommended. Note that rapid amino acid infusion can result in HE. Repeated amino acid infusions are given weekly as needed if a clinical response is observed using this protocol.

Potassium

Cats with hepatic lipidosis may develop hypokalemia due to inadequate potassium intake, vomiting, polydipsia and polyuria, magnesium depletion and concurrent chronic renal failure. In one study, hypokalemia was present in 19 of 66 cats (29%) with severe hepatic lipidosis (Center et al, 1993). Hypokalemia was significantly related to nonsurvival in this group of cats. Dogs with chronic liver disease and HE also frequently develop hypokalemia due to vomiting and alkalosis (Meyer, 1998). Hypokalemia is exacerbated by ascites due to activation of the renin-angiotensin-aldosterone axis. Hypokalemia, especially in combination with alkalosis (which is also a common feature in the same patients due to decreased use of bicarbonate in the urea cycle and vomiting), is dangerous because it may prolong anorexia and exacerbate expression of HE. This is due to intracellular trapping of ammonia in hypokalemic alkalosis. Foods for cats with hepatic lipidosis should be potassium replete (0.8 to 1.0% DM potassium), or potassium supplementation (2 to 6 mEq potassium gluconate per day) should be considered.

Sodium and Chloride

Excessive dietary sodium chloride should be avoided in liver disease patients with ascites, portal hypertension and/or significant hypoalbuminemia. Dietary sodium chloride restriction to levels recommended for patients with renal and cardiac failure is appropriate. Thus, sodium levels should be restricted to 0.08 to 0.25% DM for dogs and 0.07 to 0.3% DM for cats. Recommended DM chloride levels are typically 1.5 times sodium levels (NRC, 2006).

Table 68-9. Relative copper content of selected human foods.

Foods with very high copper content
Liver
Shellfish
Foods with high copper content
Cocoa
Heart
Kidney
Legumes
Mushrooms
Nuts
Skeletal muscle (meat)
Foods with low copper content
Cheese
Cottage cheese
Rice
Tofu

Copper

Avoiding excessive copper intake is important for dogs with copper-associated hepatotoxicosis, especially when serious hepatic injury has not yet occurred. The minimum recommended allowance for dietary copper in foods for healthy adult dogs is 6 mg/kg DM (NRC, 2006). However, studies have shown that Bedlington terriers achieve copper balance when consuming approximately 0.4 mg copper/day (Brewer et al, 1989). This equates to approximately 2.6 mg/kg of food. Foods for dogs with suspected or confirmed copper-associated hepatotoxicosis should not provide more than 5.0 mg/kg DM copper from an available copper source. Hepatic copper content is also increased (although not to the levels found in patients with inherited copper-related hepatotoxicosis) in patients with cholestasis. Therefore, moderate copper restriction is recommended for most patients with cholestatic liver disease. The role of copper in cats with liver disease has not been adequately investigated but it is generally considered that copper plays a minimal part, if any, in feline liver diseases.

Feeding selected commercial veterinary therapeutic (i.e., those formulated for patients with liver disease) or homemade foods to patients with liver disease can control copper intake, especially those with cholestasis. For patients with copper-associated hepatotoxicosis, copper restriction should be more aggressive and copper chelating agents (**Box 68-3**) or dietary zinc supplementation (See below.) should be used. Dogs should not be fed supplements containing copper or table foods that have a high copper content (**Table 68-9**). Certain fiber sources and minerals in food inhibit copper absorption (Chapters 5 and 6). The appropriate levels of these nutrients in foods for patients with copper toxicosis have not been determined. Zinc supplementation is important for blocking copper absorption and is discussed below.

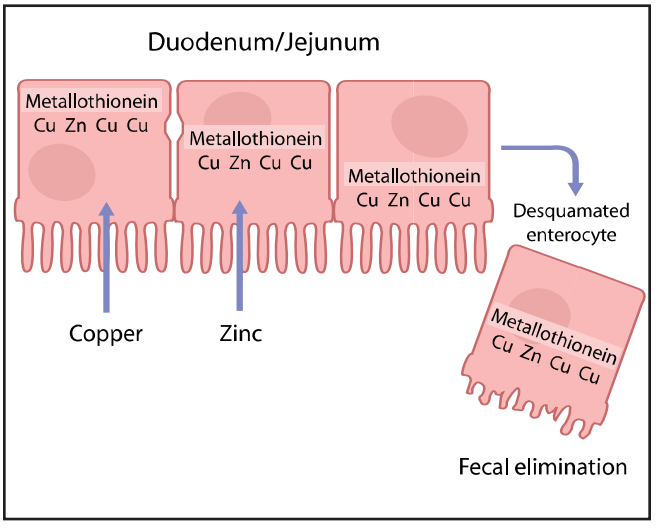

Figure 68-10. Diagrammatic representation of zinc and copper interaction in the intestine. Copper hepatotoxicosis is often treated with zinc supplementation. Zinc appears to induce synthesis of intestinal metallothionein, which has greater affinity for copper than for zinc. Metallothionein binds zinc and copper making them unavailable for systemic absorption. The metals are excreted in the feces with desquamated enterocytes. (Adapted from Center SA. Pathophysiology of liver disease: Normal and abnormal function. In: Guilford WG, Center SA, Strombeck DR, et al, eds. Strombeck's Small Animal Gastroenterology, 3rd ed. Philadelphia, PA: WB Saunders Co, 1996; 596, 599.)

Zinc

Zinc is an important metal involved in intermediary metabolism, enhanced ureagenesis, glutathione concentrations and immune function. The direct hepatoprotective effects of zinc include inhibition of lipid peroxidation and destabilization of lysosomal membranes. Zinc reportedly has antifibrotic activities (Brewer et al, 1992).

Zinc deficiency probably occurs in people with chronic hepatic disease (Riggio et al, 1991). Some dogs with chronic hepatitis or cirrhosis also have subnormal hepatic zinc concentrations (Schultheiss et al, 2002). Urea synthetic capacity may be reduced in zinc-deficient patients because of decreased hepatic ornithine transcarbamoylase activity and increased muscle glutamine synthetase activity (Marks et al, 1994). Zinc deficiency could adversely affect multiple aspects of ammonia metabolism (Mullen and Weber, 1991). Foods for patients with liver disease should contain more than 200 mg/kg DM zinc (Marks et al, 1994). This inclusion level is approximately three times the minimum recommended allowance for foods for healthy dogs and cats (60 and 74 mg/kg DM, respectively) (NRC, 2006), but is probably safe. A study in dogs and cats fed 80 and 200 mg zinc/kg body weight/day, respectively, for several months found no ill effects (Drinker et al, 1927; NRC, 2006). The levels of zinc intake in this study would be at least 60 times higher than would occur with the recommended amount for foods for dogs with liver disease. Similarly, the level is more than 100 times higher than would occur with the recommended amount for foods for feline patients with liver disease.

Dietary zinc blocks intestinal absorption of copper in dogs with copper-associated hepatotoxicosis. Animal and human studies have shown that zinc induces synthesis of intestinal metallothionein, which has greater affinity for copper than for zinc (Brewer, 1993; Friedman, 1993; Yuzbasiyian-Gurkan et al, 1992). In enterocytes, metallothionein acts as an intracellular ligand binding zinc, copper, mercury and cadmium to form mercaptides, thereby rendering them unavailable for systemic absorption. Thus, these metals are excreted in the feces with desquamated epithelial cells (**Figure 68-10**). In people with Wilson's disease, intestinal metallothionein concentrations were significantly elevated during zinc therapy when compared with the concentrations in patients not receiving zinc therapy (Friedman, 1993; Yuzbasiyian-Gurkan et al, 1992). A marked increase in intestinal metallothionein levels was observed in two human patients within a few days after zinc treatment was initiated. This finding was accompanied by suppression of copper uptake (Friedman, 1993; Yuzbasiyian-Gurkan et al, 1992). Discontinuation of zinc therapy was associated with progressive decreases in intestinal metallothionein concentrations and increased copper uptake. Thus, foods for canine patients with copper-associated hepatotoxicosis should also contain more than 200 mg/kg DM zinc, or the food should be supplemented with zinc gluconate (3 mg/kg body weight/day) or zinc sulfate (2 mg/kg body weight/day) divided into three doses (Marks et al, 1994).

Iron

Iron loading by hepatocytes and Kupffer cells has been recognized in some patients with inflammatory liver diseases and hepatic iron content is increased in dogs with cholestasis. Iron is a potent catalyst of oxidative processes (Fenton reaction) and iron-associated hepatic injury may involve lipid peroxidation of membranes and damage to organelles (Center, 1996c). Foods for dogs with chronic hepatitis and those with secondary hemosiderosis documented by evaluation of liver biopsy specimens should avoid excessive iron levels. The minimum recommended iron allowances for foods for normal adult dogs and cats are 30 and 80 mg/kg DM, respectively (NRC, 2006). Iron levels of 80 to 140 mg/kg DM meet the dietary allowance without providing excessive intake. This range is recommended for patients with liver disease. Injectable or oral supplements containing iron should be avoided in these patients.

On the other hand, iron deficiency may also occur in some liver patients with GI ulceration and hemorrhage associated with chronic hepatitis, portal hypertension or bile duct obstruction. Microcytosis, an erythrocyte abnormality associated with iron deficiency, also develops in dogs with portosystemic vascular shunts despite increased hepatic iron stores (Center, 1995, 1996b; Laflamme et al, 1994).

Iron supplementation is only indicated when serum iron concentrations are low, hypochromia is recognized and chronic gastroenteric bleeding or another source of chronic blood loss is recognized (Center, 1996a). Homemade foods, depending on the recipe, may require iron supplementation.

Antioxidant Vitamins E and C

Lipid peroxidation may be involved in the pathogenesis of some forms of acute liver injury and chronic hepatitis (Scalfani et al, 1986). Free radicals are an important component of most forms of liver damage. Abnormal concentrations of bile acids and the accumulation of heavy metals, such as copper and iron, cause free radical generation in the liver (Sokol and Hoffenberg, 1996; Sokol et al, 1994; Twedt et al, 1998). Activated inflammatory cells, damaged hepatocyte mitochondria and release of cytochrome P450 enzymes contribute to the production of reactive oxygen species. As the cascade proceeds, further hepatocyte damage occurs due to subsequent oxidation of cellular lipids, proteins and DNA. Oxidative stress may also activate pro-apoptotic protein kinases, proinflammatory transcription factors and modulators of apoptosis (Medina and Moreno-Otero, 2005).

Vitamin E functions as a cellular membrane-bound antioxidant that protects membrane phospholipids from oxidative damage. Results of vitamin E supplementation studies in human liver disease patients have been inconsistent. Vitamins E and C improved fibrosis scores in patients with nonalcoholic steatohepatitis (Harrison et al, 2003). Results of animal studies have also been mixed, perhaps due study design issues. However, in a study using a rat model of steatocholestasis, subcutaneous vitamin E provided significant protection against bile acid-induced hepatic injury, including a reduction in the release of apoptosis-inducing factor. Bile acid-induced necrotic hepatocyte injury was responsive to vitamin E therapy (Soden et al, 2007). Bedlington terriers with copper-associated hepatopathy have oxidative damage in their mitochondria and reduced mitochondrial vitamin E concentrations (Sokol et al, 1994). Vitamin E has a protective effect in the liver from copper-related oxidant damage and bile acids (Gaetke and Chow, 2003; Sokol et al, 1998). In a study using 20 dogs with naturally occurring chronic hepatitis fed a vitamin E-supplemented food for three months, increases in serum and hepatic vitamin E concentrations were accompanied by an increased hepatic reduced glutathione to oxidized glutathione (GSH:GSSG) ratio, suggesting an improved hepatic redox status. However, no changes in clinical or histologic scores were noted (Twedt et al, 2003).

Vitamin C is an important soluble intracellular antioxidant that helps convert oxidized vitamin E back to its reduced, active form. Vitamin C is also necessary for the synthesis of L-carnitine, which is important for transport of long-chain fatty acids across the mitochondrial membrane. People with liver disease often have low hepatic vitamin C concentrations, in part because human beings are unable to synthesize vitamin C, unlike dogs and cats. Although vitamin C supplementation may be beneficial in treating liver disease, supplementation with excessive amounts of vitamin C may be deleterious in patients with increased hepatic copper or iron concentrations.

No specific dosages of vitamins E and C have been documented to be safe and effective for dogs with liver disease. However, 50 to 400 IU vitamin E/day and 500 to 1,000 mg vitamin C given per os daily have been recommended as supplements for dogs with inflammatory liver disease (Rolfe and Twedt, 1995).

Alkenals (malondialdehyde and 4-hydroxyalkenals) in blood or tissues indicate lipid peroxidation, which may be a result of in vivo oxidative reactions. Alkenals are sometimes measured to determine the effectiveness of antioxidant interventions. Although dietary levels of antioxidant vitamins needed to reduce serum alkenal levels in dogs and cats with liver disease have not been established, a study found that food levels of 445 and 540 IU of vitamin E/kg (as fed basis) were necessary to reduce serum alkenal concentrations in apparently healthy dogs and cats, respectively (Jewell et al, 2000). Until more specific data are available, foods for canine and feline liver patients should provide at least 400 and 500 IU/kg DM, respectively.

Vitamin C is important for regenerating oxidized vitamin E. Foods for canine liver disease patients should contain at least 100 mg vitamin C/kg DM; foods for feline liver disease patients should contain 100 to 200 mg vitamin C/kg DM. This recommendation is based on the vitamin E levels in foods for dogs and cats with liver disease and data that show vitamin C regenerates vitamin E at about a 1:1 molar ratio (Barclay et al, 1985). Also, this range is not a risk for urinary oxalate production (Yu and Gross, 2005).

The earlier antioxidants are used to manage the oxidative damage that accompanies acute and chronic hepatobiliary disease, the more likely they are to be effective.

L-Carnitine

Food and hepatic biosynthesis are the primary sources of L-carnitine for animals. L-carnitine transports long-chain fatty acids across the inner mitochondrial membrane into the mitochondrial matrix for β-oxidation. L-carnitine also removes potentially toxic acyl groups from cells and equilibrates ratios of free CoA/acetyl-CoA between the mitochondria and cytoplasm.

Obesity is a risk factor for feline hepatic lipidosis; several studies have investigated the relationship between L-carnitine, weight loss in obese cats and feline hepatic lipidosis. Mean concentrations of L-carnitine in plasma, liver and skeletal muscle were significantly greater in cats with idiopathic hepatic lipidosis than in control cats (Jacobs et al, 1990). These findings suggest that systemic L-carnitine deficiency does not appear to contribute to the pathogenesis of feline idiopathic hepatic lipidosis. However, other studies have shown that feline foods supplemented with L-carnitine benefit obese cats undergoing rapid weight loss. Dietary L-carnitine supplementation protected obese cats from hepatic lipid accumulation during caloric restriction and rapid weight loss (Armstrong et al, 1992). Foods supplemented with L-carnitine can safely facilitate rapid weight loss in obese cats (Center et al, 1997). Based on these studies, the use of L-carnitine supplements or L-carnitine supplemented foods seems appropriate for obese cats undergoing weight reduction.

Besides being of value in preventing hepatic lipidosis, L-carnitine supplementation may also benefit cats with hepatic lipidosis (Center, 1996c). One author has recommended a dose of 250 to 500 mg L-carnitine/day for cats with hepatic lipidosis (Center, 1996c). Others have found that lower doses

(7 to 14 mg/kg body weight) also benefit weight loss, obesity prevention and hepatic lipidosis (Blanchard, 1998). Foods for cats with hepatic lipidosis should provide at least 0.02% DM L-carnitine.

Other Nutritional Factors

Depending on the type of hepatobiliary disease, some of the following nutritional factors may also be important.

Carbohydrate

Patients with clinical evidence of HE should receive adequate carbohydrate intake. Studies suggest that feeding foods with a high carbohydrate component is advantageous (Zieve and Zieve, 1987). Providing at least 30 to 50% of dietary calories in the form of easily digested, complex digestible carbohydrate (e.g., corn, rice, wheat, barley) may help avert encephalopathic clinical signs (Center, 1996b). Thus, the recommendations for DM digestible carbohydrates in foods for dogs and cats with liver disease are 45 to 55% and 30 to 40%, respectively.

Fiber

Foods with increased dietary fiber levels may benefit patients with hepatobiliary disease. Dietary fiber reduces the availability and production of nitrogenous wastes in the GI tract. Although highly digestible foods were previously advocated to maximize digestion and absorption and reduce colonic residues, considered a major source of encephalopathic toxins, this practice is currently not recommended. Increased amounts of fermentable fiber encourage nitrogen fixation by enteric bacteria, resulting in reduced quantities of nitrogenous substances available for absorption. Increased dietary fiber may bind noxious bile acids, endotoxins and other bacterial products. Dietary fiber is also useful in maintaining euglycemia (Chapter 29) and altering the pH of colonic contents. Total dietary fiber levels should be between 3 and 8% and be primarily soluble fiber. However, pet food labels and available product information list fiber content as crude fiber rather than total dietary fiber. Crude fiber analyses do not represent the soluble or fermentable fiber content of foods. Thus, for all practical purposes, this recommendation cannot be readily evaluated. Crude fiber levels in combination with knowledge of the soluble content of the fiber sources obtained from the foods' ingredient lists could provide imprecise guidelines. Commercial and homemade foods can be supplemented with psyllium husk fiber (1 tsp/5 to 10 kg body weight, added to each meal). If loose stools occur, reduce the supplemental fiber by half.

Branched-Chain Amino Acids

The abnormal plasma amino acid profile in patients with hepatic disease can be improved by feeding a protein with an amino acid composition high in BCAA and low in AAA, or by an intravenous amino acid infusion with a similar profile. However, a causal relationship between a deranged BCAA:AAA ratio in plasma and cerebrospinal fluid and HE has yet to be elucidated. Plasma ammonia levels decrease in dogs with HE after administration of BCAA-enriched intravenous infusions (Meyer, 1998a). The same effect could not be reproduced by feeding a BCAA-enriched food vs. an isonitrogenous control food in dogs with HE. This finding may have been due to reduced consumption of the test diet, leading to a severe catabolic state and increased endogenous ammonia production (Meyer, 1998a). The primary positive effect of dietary and intravenous BCAA enrichment may be the normalization of nitrogen balance, rather than a direct effect on neurotransmitter imbalances per se (Meyer, 1998a).

Vitamins

Vitamin deficiencies are common in patients with chronic hepatic disease. Deficient dietary intake and malabsorption are the principal causes of vitamin deficiency, although decreased storage, metabolic defects and increased requirements also may be involved (Marks et al, 1994).

Deficiency of water-soluble vitamins may occur due to inadequate intake, vomiting and urinary losses. Hepatic concentrations of folate, riboflavin, nicotinamide, pantothenic acid, pyridoxine and vitamin B_{12} are decreased in people with cirrhosis (Leevy et al, 1982). Commercial pet foods usually contain sufficient quantities of water-soluble vitamins to meet the needs of most patients with liver disease. Supplementation with water-soluble vitamins is indicated in patients: 1) receiving aggressive diuretic therapy for ascites, 2) with profound polydipsia and polyuria, 3) with prolonged anorexia and 4) eating homemade foods.

Abnormal blood coagulation tests and excessive bleeding reflect impaired hepatic synthesis, activation of clotting factors and/or a consumptive coagulopathy. Vitamin K stores in the liver are limited and can be rapidly depleted when dietary sources are inadequate or lipid (and therefore fat-soluble vitamin) malabsorption is severe. Among other functions, vitamin K catalyzes the activity of several clotting factors and normally is recycled in the healthy liver back to its active form (this step of vitamin K metabolism is sensitive to inhibition by dicumarol).

Vitamin K deficiency may develop in patients with hepatobiliary disease for several reasons. Oral antibiotic therapy may destroy the intestinal microflora that normally synthesize vitamin K. Chronic bile duct obstruction can interfere with enterohepatic circulation of bile acids causing intestinal bile acid deficiency and fat-soluble vitamin (including vitamin K) malabsorption. Inadequate intake of vitamin K may be a component of overall vitamin K deficiency, particularly if the patient has experienced prolonged anorexia (cats with hepatic lipidosis).

Coagulation abnormalities are common in dogs and cats with hepatobiliary disease. In dogs with naturally occurring liver disease, 50 and 75% had an abnormal prothrombin time (PT) and activated partial thromboplastin time (APTT), respectively. More than 90% of dogs had at least one abnormality (Center, 1996; Webster, 2005). At least one coagulation abnormality was present in 82% of cats with liver disease. Prolonged PT was noted in 73% of cats and factor VII activity was below reference range (<60%) in 68% of cats. When classified according to underlying pathogenesis, vitamin K deficiency was the most common abnormality found (11/22). Other abnormalities were less common and included hepatic

Table 68-10. General therapy for patients with hepatobiliary disease.*

Fluid therapy	
Maintain hydration	Give appropriate parenteral fluid therapy
Prevent hypokalemia	Add KCl to maintenance fluids
Maintain acid-base balance	Use potassium-replete food or potassium supplement
Prevent or control hypoglycemia	Avoid alkalosis in patients with hepatic encephalopathy Add dextrose to parenteral fluids as needed
Nutritional support	
Maintain caloric intake	Ensure that daily energy requirement is being met; if not, begin assisted feeding
Provide adequate vitamins and minerals	Add B vitamins to fluids or give as injection
Modify feeding plan to control complications	Use complete and balanced food See specific complications below
Control hepatic encephalopathy	
Modify food and prevent formation and absorption of enteric toxins	Avoid excess dietary protein Use retention enemas q6h containing lactulose or povidone iodine solution Give lactulose orally
Control GI hemorrhage	Treat GI parasites, treat gastric ulcers, avoid drugs that exacerbate GI hemorrhage (e.g., aspirin, glucocorticoids)
Correct metabolic imbalances	See fluid therapy above
Avoid drugs or therapies that exacerbate hepatic encephalopathy	Do not administer sedatives, analgesics, anesthetics, diuretics, stored blood or methionine-containing products
Control seizures	Use appropriate anticonvulsant drugs (e.g., potassium bromide)
Control infection	Give systemic antimicrobials (see below)
Control ascites and edema	Avoid excess dietary sodium chloride Administer diuretics (e.g., furosemide, spironolactone)
Control coagulation defects and anemia	Give vitamin K_1 parenterally Give fresh plasma or blood transfusion as needed
Control GI ulceration	Give H_2 blockers (e.g., ranitidine) or cytoprotective agents (e.g., sucralfate)
Control infection and endotoxemia	Give systemic antibiotics (e.g., penicillin, ampicillin, cephalosporins, aminoglycosides, metronidazole) Give intestinal antibiotics (e.g., neomycin)
Manage cholestasis	Give bile "altering" or choleretic drugs (e.g., ursodiol) Correct extrahepatic bile duct obstruction

*Adapted from Johnson SE, Sherding RG. Diseases of the liver and biliary tract. In: Birchard SJ, Sherding RG, eds. Manual of Small Animal Practice. Philadelphia, PA: WB Saunders Co, 1994; 730.

synthetic failure (3/22), indeterminate (3/22) and disseminated intravascular coagulation (1/22). Increased AP activity was the only biochemical abnormality statistically correlated with coagulation abnormalities ($p = 0.23$). Cats with marked increases in AP activity were more likely to have coagulation abnormalities than those with only mild increases in AP activity (Lisciandro et al, 1998). Despite the common presence of coagulation test abnormalities, spontaneous hemorrhage in liver disease patients is rare. However, it should be assumed that liver disease patients have a higher than normal risk of bleeding.

At the very least, foods for patients with liver disease should contain the minimum recommended allowance of vitamin K (menadione) for foods for normal adult dogs and cats: 1.63 and 1.0 mg/kg DM, respectively (NRC, 2006). Supplementing foods with active vitamin K (vitamin K_1) is expensive and the vitamin would likely not survive the heat of processing. The water-soluble form of menadione, menadione sodium bisulfite, is much less expensive, is heat stable and is passively absorbed from the small intestine and colon. However, menadione is biologically inactive, as is vitamin K_1, and requires alkylation by gut microorganisms or animal tissues to biologically active menaquinone-4 (NRC, 2006).

FEEDING PLAN

The universal goals for dietary management of hepatobiliary disease are directed at clinical manifestations of the disease rather than the specific cause itself. The goals of nutritional management for hepatobiliary disease include: 1) maintaining normal metabolic processes and homeostasis, 2) avoiding and managing HE, 3) providing substrates to support hepatocellular repair and regeneration, 4) decreasing further oxidative damage to liver tissue and 5) correcting electrolyte disturbances (Blackburn and O'Keefe, 1989; Center, 1998).

The therapeutic goals for patients with HE also include: 1) recognizing and correcting precipitating causes of encephalopathy (e.g., hypokalemic alkalosis), 2) reducing intestinal production and absorption of neurotoxins, with special emphasis on ammonia and 3) finding the balance between providing too much and too little protein, both of which increase ammonia generation.

Dietary therapy is only beneficial when performed in conjunction with proper medical and surgical management of the specific hepatobiliary disease involved. Medical management often includes use of antiinflammatory agents, immunomodu-

Table 68-11. Levels of key nutritional factors in selected commercial veterinary therapeutic foods marketed for canine patients with hepatobiliary disease compared to recommended levels.*

Dry foods	Energy density (kcal/cup)**	Energy density (kcal ME/g)	Protein (%)***	Taurine (%)	Sodium (%)	Copper (mg/kg)	Zinc (mg/kg)	Iron (mg/kg)	Vit. E (IU/kg)	Vit. C (mg/kg)
Recommended levels	**–**	**≥4.0**	**15-20**	**≥0.1**	**0.08-0.25**	**≤5**	**>200**	**80-140**	**≥400**	**≥100**
Hill's Prescription Diet l/d Canine	399	4.4	18.1	0.08	0.22	4.9	301	170	385	116
Medi-Cal Hepatic LS 14	342	na	17.6	na	0.2	na	300	na	na	na
Medi-Cal Vegetarian Formula	317	na	20.9	na	0.4	na	na	na	na	na
Purina Veterinary Diets EN GastroENteric	397	4.2	27.0	na	0.60	na	na	na	577	na
Royal Canin Veterinary Diet Hepatic LS 14	333	4.4	17.6	0.22	0.21	4.4	253	187	725	na

Moist foods	Energy density (kcal/can)**	Energy density (kcal ME/g)	Protein (%)***	Taurine (%)	Sodium (%)	Copper (mg/kg)	Zinc (mg/kg)	Iron (mg/kg)	Vit. E (IU/kg)	Vit. C (mg/kg)
Recommended levels	**–**	**≥4.0**	**15-20**	**≥0.1**	**0.08-0.25**	**≤5**	**>200**	**80-140**	**≥400**	**≥100**
Hill's Prescription Diet l/d Canine	472/13 oz.	4.5	17.6	0.10	0.20	4.2	258	118	693	190
Iams Veterinary Formula Stress/Weight Gain Formula Maximum-Calorie	333/6 oz.	5.8	41.8	0.33	0.24	na	na	na	na	na
Medi-Cal Vegetarian Formula	319/396 g	na	26.4	na	0.5	na	na	na	na	na
Purina Veterinary Diets EN GastroENteric	423/12.5 oz.	4.0	30.5	na	0.37	na	260	na	505	139

Key: ME = metabolizable energy, Vit. E = vitamin E, Vit. C = vitamin C, na = information not available from manufacturer.
*From manufacturers' published information or calculated from manufacturers' published as fed values; all values are on a dry matter basis unless otherwise stated.
**Energy density values are listed on an as fed basis and are useful for determining the amount to feed; cup = 8-oz. measuring cup. To convert to kJ, multiply kcal by 4.184.
***For liver disease patients with signs of hepatic encephalopathy (HE), dietary protein levels should be limited to 10 to 15% dry matter until signs resolve. In these cases, several commercial veterinary therapeutic foods designed for patients with kidney disease that provide less protein than the foods intended for liver disease may be appropriate (Chapter 37). If these foods are used, the patient should be transitioned to the selected food specifically formulated for liver disease after signs of HE have subsided.

lators, nonabsorbable disaccharides and bile "altering" agents (**Table 68-10**). In acute hepatic failure, correction of fluid and electrolyte imbalances and treatment of other complications such as metabolic acidosis, excessive bleeding, hypotension, hypoglycemia, cardiac dysfunction, renal failure, cerebral edema and infections take precedence over nutritional support. Surgical management can include partial or total ligation of congenital PSS, correction of bile duct obstruction or removal of focal liver masses.

Assess and Select the Food

A wide variety of foods are typically used or recommended for patients with hepatic disease (Marks et al, 1994a; Michel, 1995). **Tables 68-11** and **68-12** list the recommended levels of key nutritional factors for canine and feline hepatobiliary disease patients, respectively, and compare them to the key nutritional factor content of selected veterinary therapeutic foods. This information will help the veterinary health care team select the best food for patients with liver disease. Special consideration should be given to young patients with congenital PSS.

Although the total protein content of some veterinary therapeutic foods formulated for patients with liver disease is lower than that of regular commercial pet foods, protein quality and digestibility are usually high. Also, as discussed above, these foods still exceed minimum requirements. Thus, these foods provide adequate protein to support hepatic function and hepatocyte repair and regeneration while avoiding higher protein levels that exacerbate hyperammonemia. However, further short-term protein reduction may be necessary in patients with HE. In these cases, some commercial veterinary therapeutic foods designed for patients with renal disease that provide less protein than the foods intended for liver disease may be appropriate (Chapter 37). If these foods are used, the patient should be transitioned to the selected food specifically formulated for liver disease after signs of HE have subsided (**Tables 68-11** and **68-12**). Lactulose may be considered for patients with HE. **Box 68-4** provides information about lactulose products, their use and their mode of action.

Supplemental treatment should also be considered for dogs with hepatic copper toxicosis. Copper is considered a key nutritional factor for liver disease in dogs and the recommended DM level in foods is less than 5 mg/kg. This level may still provide too much copper for some patients with hepatic copper toxicosis. In these instances, adjunctive use of copper chelating agents should be considered. Copper chelating agents are discussed in **Box 68-3**. **Box 68-5** reviews other cytoprotective

Table 68-12. Levels of key nutritional factors in selected commercial veterinary therapeutic foods marketed for feline patients with hepatobiliary disease, compared to recommended levels.*

Dry foods	Energy density (kcal/cup)**	Energy density (kcal ME/g)	Protein (%)***	Arginine (%)	Taurine (%)	Sodium (%)	Zinc (mg/kg)	Iron (mg/kg)	Vit. E (IU/kg)	Vit. C (mg/kg)
Recommended levels	**–**	**≥4.2**	**30-35**	**1.5-2.0**	**≥0.3**	**0.07-0.30**	**>200**	**80-140**	**≥500**	**100-200**
Hill's Prescription Diet l/d Feline	505	4.5	31.8	1.98	0.53	0.27	305	173	267	109
Medi-Cal Mature Formula	355	na	29.2	na	0.4	0.4	na	na	na	na
Medi-Cal Reduced Protein	440	na	28.1	na	0.4	0.3	na	na	na	na
Medi-Cal Renal LP 21	409	na	24.7	na	0.2	0.2	na	na	na	na
Purina Veterinary Diets EN GastroENteric	572	4.4	56.2	na	0.32	0.64	na	na	232	na
Royal Canin Veterinary Diet Modified Formula	432	4.7	27.1	1.51	0.23	0.23	320	241	380	na

Moist foods	Energy density (kcal/can)**	Energy density (kcal ME/g)	Protein (%)***	Arginine (%)	Taurine (%)	Sodium (%)	Zinc (mg/kg)	Iron (mg/kg)	Vit. E (IU/kg)	Vit. C (mg/kg)
Recommended levels	**–**	**≥4.2**	**30-35**	**1.5-2.0**	**≥0.3**	**0.07-0.30**	**>200**	**80-140**	**≥500**	**100-200**
Hill's Prescription Diet l/d Feline	183/5.5 oz.	4.7	31.6	2.00	0.52	0.20	336	212	836	124
Medi-Cal Mature Formula	205/170 g	na	41.5	na	0.3	0.3	na	na	na	na
Medi-Cal Reduced Protein	265/170 g	na	33.9	na	0.3	0.2	na	na	na	na
Medi-Cal Renal LP	125/85 g pouch	na	29.3	na	0.8	0.6	na	na	na	na
Royal Canin Veterinary Diet Modified Formula	256/170 g 596/396 g	6.1	34.7	2.07	0.28	0.28	208	545	178	na

Key: ME = metabolizable energy, Vit. E = vitamin E, Vit. C = vitamin C, na = information not available from manufacturer.
*From manufacturers' published information or calculated from manufacturers' published as fed values; all values are on a dry matter basis unless otherwise stated.
**Energy density values are listed on an as fed basis and are useful for determining the amount to feed; cup = 8-oz. measuring cup. To convert to kJ, multiply kcal by 4.184.
***For liver disease patients with signs of hepatic encephalopathy (HE), dietary protein levels should be limited to 25 to 30% dry matter until signs resolve. In these cases, several commercial veterinary therapeutic foods designed for patients with kidney disease that provide less protein than the foods intended for liver disease may be appropriate (Chapter 37). If these foods are used, the patient should be transitioned to the selected food specifically formulated for liver disease after signs of HE have subsided.

agents that are sometimes considered for liver disease patients.

Anorectic cats with cholangitis or hepatic lipidosis will need to be fed via assisted-feeding techniques until they resume eating on their own. This dictates the use of nutrient-dense foods with textures intended for assisted feeding (Chapter 25). These patients should be fed a food intended for dietary management of other hepatic diseases after they start eating (**Table 68-12**).

Another criterion for selecting a food that may become increasingly important in the future is evidence-based clinical nutrition. Practitioners should know how to determine risks and benefits of nutritional regimens and counsel pet owners accordingly. Currently, veterinary medical education and continuing education are not always based on rigorous assessment of evidence for or against particular management options. Still, studies have been published to establish the nutritional benefits of certain pet foods. Chapter 2 describes evidence-based clinical nutrition in detail and applies its concepts to various veterinary therapeutic foods.

Assess and Determine the Feeding Method

Sick, anorectic and severely malnourished patients with hepatobiliary disease should be hospitalized to initiate supportive care and assisted-feeding techniques. Early tube feeding via nasogastric or gastrostomy tube remains the cornerstone of therapy for feline patients with hepatic lipidosis and all other anorectic patients with liver disease. Chapter 25 details foods and enteral feeding techniques commonly used in dogs and cats. Patients that are eating enough food to meet their daily energy requirement (DER) can usually be managed at home.

The DER for cats with hepatic lipidosis should be at least the resting energy requirement (RER) for ideal body weight when cats are managed in the hospital and 1.1 to 1.2 x RER when managed at home. The DER of canine liver disease patients managed at home should be approximately 1.2 to 1.4 x RER. Young patients with congenital shunts may be stunted or underweight. DER calculations for these patients should be based on ideal rather than current body weight. These calorie values can be converted to an amount of food to eat by dividing the energy density of the food (as fed basis) by the DER. The as fed energy density (in cups or cans) of foods for liver disease can be found in **Tables 68-11** and **68-12**.

Multiple daily feedings rather than one or two large meals may benefit patients with hepatobiliary disease. Multiple daily meals minimize the release of free fatty acids from adipose tissue, improve digestibility and reduce the quantity of ingesta at any one time that enters the colon where bacterial fermentation

Box 68-4. Adjunctive Lactulose for Patients with Hepatic Encephalopathy.

Administration of lactulose is considered one of the treatments of choice for hepatic encephalopathy (HE). Lactulose is a synthetic disaccharide that is hydrolyzed by colonic bacteria principally to lactic and acetic acids. Lactulose probably exerts its beneficial effects by: 1) increasing intraluminal nitrogen retention by increasing the colonic flora, 2) increasing intestinal transit rate due to its cathartic properties and 3) decreasing ammonia generation from glutamine in the intestinal wall by providing acetic acid as an alternative energy source. The dosage required to achieve these goals varies greatly, with a range of 2.5 to 25 ml, three times daily for dogs and 1.0 to 3.0 ml, three times daily for cats. The dosage should be titrated to produce a "porridge-like" stool and should be reduced if watery diarrhea develops.

Lactulose also is highly effective when added to water (30% lactulose and 70% water) and given as a retention enema. Approximately 20 to 30 ml/kg body weight are infused and retained in the colon for 20 to 30 minutes before evacuation. Lactulose requires intestinal bacteria for activation. Although neomycin and other nonabsorbable antibiotics are used in the treatment of HE in people, their use is limited to cases that do not respond to lactulose alone. Furthermore, patients should be monitored carefully. Moreover, evidence of their effectiveness in the treatment of dogs and cats with HE is lacking.

The Bibliography for **Box 68-4** can be found at www.markmorris.org.

occurs. Studies involving people with hepatic failure have shown that nitrogen balance can be improved if the food is divided into small, frequent meals, including a snack at bedtime (Swart et al, 1989). Nauseated patients may also better tolerate multiple small meals.

Appetite stimulants and force feeding moist food can be used to encourage caloric intake, but these strategies often fail to ensure enough food is consumed to meet the patient's nutrient requirements and typically frustrate the owner. Appetite stimulants such as anabolic steroids and benzodiazepine derivatives are not recommended and should be used cautiously in patients with hepatic disease, because of the potential for hepatotoxicity and, benzodiazepines may possibly be involved in the pathogenesis of HE (Wilson, 1990; Meyer, 1998).

Many patients may develop learned aversion to the foods they are offered if GI disturbances accompany liver disease. This is the classic scenario in cats with hepatic lipidosis. Cats that refuse to eat a food they associate with nausea may continue to avoid that food even after a complete recovery. Therefore, tube feeding should be started in cats immediately after a diagnosis of hepatic lipidosis is made. Such an approach is preferred to offering several commercial foods and possibly having the cat develop an aversion to them. The prognosis for hepatic lipidosis is influenced largely by the ability of the veterinarian and owner to aggressively meet the nutrient requirements of the cat via enteral feeding.

Managing cats with hepatic lipidosis that are starved or severely malnourished can be complicated by a refeeding syndrome, a condition that results in metabolic electrolyte disturbances that can lead to neurologic, pulmonary, cardiac, neuromuscular and hematologic complications. Cats with hepatic lipidosis often have hypophosphatemia and hypokalemia from low food intake, decreased intestinal absorption or increased renal loss. With the introduction of food and a sudden shift to carbohydrate metabolism, stimulation of insulin secretion promotes intracellular uptake of phosphorus, potassium, magnesium, water and glucose and further lowers serum electrolyte levels within 12 to 72 hours after feeding. Hypophosphatemia can result in muscle weakness, hemolytic anemia, leukocyte dysfunction, platelet dysfunction and decreased tissue oxygenation as a result of decreased levels of 2,3,-diphosphoglycerate. Electrolyte abnormalities should be corrected before feeding hepatic lipidosis patients. Approximately one-fourth of the patient's caloric needs should be provided by tube feeding on Day 1, then the amount should be gradually increased to provide the caloric need within the first week of feeding (Justin and Hohenhaus, 1995; Center et al, 1993).

REASSESSMENT

The owner and veterinarian should monitor the appetite, body weight and condition of the patient, while observing the frequency and severity of GI disturbances (i.e., vomiting, diarrhea), icterus and neurobehavioral signs. One of the most important clinical findings is improvement in the patient's attitude and activity level. This finding is highly correlated with nutritional success. Serial laboratory evaluations (every few days to weeks) of serum liver enzyme activity, bile acids and potassium and blood ammonia concentrations are useful. Serial hepatic biopsy specimens (i.e., every four to six months) can be evaluated for hepatic copper concentrations and assessed for inflammatory hepatopathies. Body weight, abdominal configuration and ultrasonography can be used to monitor patients with ascites.

Assisted-feeding tubes for cats with hepatic lipidosis and/or cholangitis can often be removed after several weeks to months. Enteral tubes are usually removed after the cat has shown clinical improvement and has begun eating two-thirds to three-fourths of its normal DER on its own. Many of these patients can be fed typical adult maintenance-type foods after hepatobiliary disease is resolved. These include patients that have recovered from an acute hepatic insult or hepatic lipidosis and patients that have undergone successful (partial or total) closure of PSS.

Box 68-5. Hepatocytoprotective Agents Considered for Use in Dogs and Cats with Hepatobiliary Disease.

In liver disease, numerous drugs and vitamins could be considered cytoprotective including copper chelators and vitamins E and C. Other cytoprotective agents, such as s-adenosylmethionine (SAMe) and silymarin, are being evaluated for use in dogs and cats with liver disease. Both are reviewed below. Hopefully, in the future, well-designed clinical trials using these and other cytoprotective agents in canine and feline liver disease patients will provide even more evidence regarding their efficacy.

S-ADENOSYLMETHIONINE

The naturally occurring molecule SAMe is synthesized in all living cells, is essential in intermediary metabolism and has hepatoprotective and antioxidant properties. SAMe is produced from the amino acid methionine and subsequently initiates one of three metabolic pathways: 1) The transmethylation pathway is essential in phospholipid synthesis, which is important in membrane structure, fluidity and function. Most (85%) of the SAMe generated, is used in this pathway. 2) The trans-sulfuration pathway generates sulfur-containing compounds, such as glutathione, which participates in many metabolic processes and plays a critical role in cellular detoxification mechanisms. Depletion of glutathione can indirectly cause toxic effects in hepatocytes by increasing oxidative stress. 3) The aminopropylation pathway yields products that have antiinflammatory effects and polyamines important in DNA and protein synthesis.

The liver normally produces abundant SAMe, but evidence also suggests conversion from methionine to SAMe is hindered in liver disease and results in the depletion of glutathione concentration. Orally administered SAMe (but not oral glutathione) increases intracellular glutathione levels in hepatocytes and prevents glutathione depletion when the liver is exposed to toxic substances. Thus, SAMe, in part, acts as an antioxidant by replenishing glutathione stores. Preliminary studies suggest that SAMe supplementation increases hepatic glutathione concentrations in normal cats and prevents glutathione depletion in dogs with steroid-induced hepatopathy. SAMe treatment following acetaminophen administration prevented hepatic glutathione depletion.

SILYMARIN

Silymarin, a flavonolignan from "milk thistle" (*Silybum marianum*), has been used for centuries in human patients with liver disease. Silymarin represents a group of several closely related flavonoids and thus has antioxidant properties. They include silybin, isosilybin, silydianin and silychristin. Among them, silybin is the most active and most commonly used. Silymarin also has antiinflammatory and antifibrotic qualities. In addition, it can increase hepatocyte protein synthesis and accelerate hepatocellular regeneration via increased gene transcription and translation and enhanced DNA synthesis. Silymarin can modulate hepatocyte transport, which is important in its ability to promote choleresis.

Studies in human patients with a wide variety of liver diseases have resulted in conflicting results, probably because of the broad issue of study design problems. As work continues to determine the value of silymarin in the management of human liver disease, better studies will likely bring more cohesive results. However, silymarin has been used successfully in the management of intoxications with acetaminophen and the mushroom toxin phalloidin, both of which exert toxic effects by oxidation. Silymarin appears to be protective against these toxins, which leaves little doubt about its potential therapeutic benefit.

The hepatocytoprotective effects of silymarin (and silybin, an isomer of silymarin) have been shown in a number of in vitro studies as well as studies in animals, including dogs, with induced liver damage. The results have been promising. Studies in dogs with carbon tetrachloride toxicity and dogs with phalloidin toxicity showed that silymarin was protective.

Silymarin, thus far, has been shown to be safe. No serious side effects have been noted in human or animal studies. However, because in vitro studies have shown silymarin to inhibit cytochrome P450 enzyme activities, in the event of concurrent drug therapy, potential adverse interactions should be considered. Unfortunately, the purity of the various commercial products and the ideal therapeutic dose are unknown. Suggested doses for dogs and cats are extrapolated from research in other species.

The Bibliography for **Box 68-5** can be found at www.markmorris.org.

Vomiting is often a problem in patients with hepatobiliary disease, especially cats with hepatic lipidosis or HE. Small frequent meals, continuous tube feeding and antiemetics may be helpful. More aggressive medical treatment of HE may also be needed, such as the use of lactulose.

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REFERENCES

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CASE 68-1

Intermittent Vomiting in a Miniature Schnauzer

Deborah J. Davenport, DVM, MS, Dipl. ACVIM (Internal Medicine)
Hill's Science and Technology Center
Topeka, Kansas, USA

Patient Assessment

A three-and-one-half-year-old, neutered female miniature schnauzer was examined for a two-year course of intermittent vomiting. The vomitus rarely contained food and was usually described as a yellow or clear fluid. No diarrhea had been noted. The owners reported that the dog became depressed and lethargic during these vomiting episodes. Antiemetic treatment by another veterinarian had partially controlled the vomiting. Laboratory evaluation, abdominal radiographs and gastrointestinal (GI) contrast radiography four and six months before admission revealed no abnormalities.

Physical examination revealed a thin, nervous dog (body condition score [BCS] 1/5; body weight 7.1 kg). No other abnormalities were noted (**Figure 1**).

A complete blood count revealed erythrocyte microcytosis (i.e., decreased mean corpuscular volume) without hypochromia or anemia. Abnormal results of a serum biochemistry profile included a low serum urea nitrogen level (7 mg/dl, normal 10 to 25 mg/dl), hypoproteinemia (total protein 5.9 g/dl, normal 6.0 to 7.2 g/dl), hypoalbuminemia (2.4 g/dl, normal 3.0 to 4.5 g/dl) and mildly increased alkaline phosphatase activity (125 IU/l, normal 10 to 75 IU/l). Bilirubinuria and many ammonium biurate crystals were found on urinalysis. The stomach appeared cranially displaced radiographically, which suggested a small liver.

The clinical, laboratory and radiographic changes suggested the presence of a portosystemic shunt. Bile acids were elevated (18.6 µmol/l [fasting], 246.1 µmol/l [two hours postprandial]) and an ammonia tolerance test demonstrated elevated baseline and challenge blood ammonia levels.

Abdominal ultrasound demonstrated a small liver and a single large shunt between the portal system and the caudal vena cava external to the liver (**Figure 2**). The final diagnosis was a portocaval shunt with intermittent episodes of hepatic encephalopathy.

Surgical attenuation of the shunt was recommended based on detectable hepatic portal blood flow and the extrahepatic location of the portocaval anastomosis. At the owners' request, the procedure was scheduled for three weeks later.

Assess the Food and Feeding Method

Several dietary changes had been made over the past two years in an effort to control the intermittent vomiting. The most recent food was a commercial dry veterinary therapeutic food for GI problems (Prescription Diet i/d Canine[a]). This food was offered in multiple small meals throughout the day.

Questions

1. What are the key nutritional factors to consider for this dog during the next three weeks?
2. Outline a treatment and feeding plan for this patient before surgery.

Answers and Discussion

1. Numerous key nutritional factors should be considered for patients with portosystemic shunts (**Table 68-8**). Providing adequate daily energy intake is the cornerstone of successful medical management of dogs with hepatobiliary disease, especially underweight animals such as this patient. With respect to protein, the goal is to provide adequate dietary protein to support hepatic regeneration while avoiding excess that might contribute to hepatic encephalopathy. The amount of protein needed by patients with portosystemic vascular shunts has been roughly estimated from a study in dogs with surgically created shunts. This study showed that ingestion of 2.11 g crude protein/kg body weight/day with an 80% or greater availability is adequate to maintain body protein reserves without producing hepatic encephalopathy. The protein should be high quality (i.e., high biologic value) and easily assimilated. Feeding a food with a high carbohydrate to protein component was shown to be advantageous to dogs with experimentally created shunts.
2. A commercial or homemade food that avoids excess dietary protein while providing adequate non-protein calories from fat and carbohydrate is recommended. Foods formulated for renal failure and liver patients generally meet these criteria. The daily energy requirement (DER) should be initially calculated at 1.2 to 1.4 x resting energy requirement (RER) for the estimated ideal body weight (10 kg). Administration of nonabsorbable disaccharides (e.g., lactulose) is also recommended in patients with hepatic encephalopathy. Colonic bacteria hydrolyze lactulose to lactic and acetic acids. Lactulose seems beneficial for several reasons. It: 1) lowers colonic pH with subsequent trapping of ammonium ions, 2) inhibits ammonia generation by colonic bacteria and 3) increases intestinal transit rate via cathartic properties. Neomycin and metronidazole can also be used to decrease ammonia production by inhibiting intestinal bacteria.

Progress Notes

The food was changed to a commercial dry veterinary therapeutic product (Prescription Diet k/d Canine[a]) that contained reduced levels of high quality and easily digested protein while providing a good source of non-protein calories (14.5% dry matter [DM] protein, 19.0% DM fat, 61.1% DM digestible carbohydrate). DER was calculated to be 1.2 x RER for an estimated optimal body weight of 10 kg (DER = 440 kcal [1.84 MJ]). The food was to be offered in at least three separate meals throughout the day. Additional therapy consisted of oral lactulose syrup[b] (10 ml, three times daily).

Three weeks later, the dog had gained 1.2 kg body weight. The owners reported a marked decrease in the number of vomiting episodes and periods of lethargy and depression. No new physical findings were noted. The hypoproteinemia, hypoalbuminemia and ammonium biurate crystalluria persisted. Results of clotting studies done before surgery were normal. During surgery, an anastomotic vessel was easily visualized at the level of the right kidney. This vessel was partially ligated. The dog was released from the hospital five days later with instructions for the owners to continue feeding the veterinary therapeutic food and administering lactulose, as described before surgery.

The dog was reassessed one month later. Body weight had increased to 8.6 kg, the BCS was 2/5 and the owners reported no episodes of malaise or vomiting. The serum urea nitrogen, total protein and albumin concentrations were normal, and ammonium biurate crystals were absent from the urine. The liver size was increased radiographically. Because of the apparent return of normal hepatic function and size, the owners were instructed to change the food to a regular adult maintenance product (25% DM protein, 15.4% DM fat, 53.3% DM digestible carbohydrate) and discontinue the lactulose. The food dosage was continued at 1.2 x RER (440 kcal [1.84 MJ]).

Five months later the dog was examined again. Body weight was 10 kg with a BCS of 3/5. The owners reported that the higher protein food had not precipitated any clinical signs. No changes in foods or feeding methods were recommended.

Figure 1. A three-and-one-half-year-old, neutered female miniature schnauzer with chief complaints of intermittent vomiting, depression and lethargy with weight loss and poor body condition.

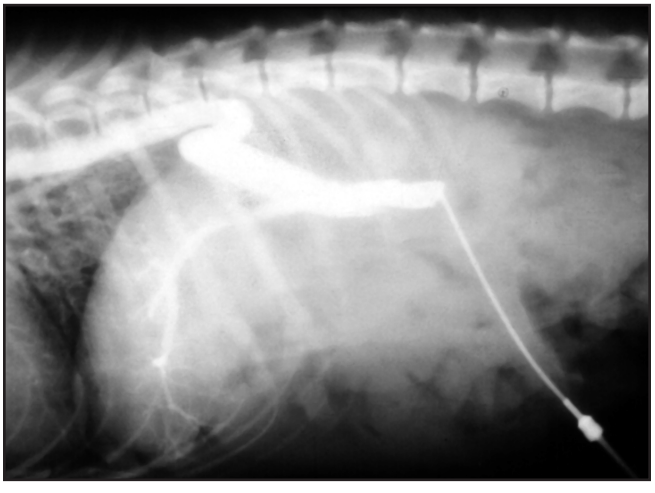

Figure 2. A lateral radiograph showing the results of an injection of positive-contrast medium into the mesenteric vein. A large vascular shunt is communicating from the portal vasculature to the caudal vena cava.

Endnotes

a. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
b. Cholac. Alra Laboratories, Gurnee, IL, USA.

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CASE 68-2

Vomiting in a Miniature Poodle

Philip Roudebush, DVM, Dipl. ACVIM (Small Animal Internal Medicine)
Hill's Scientific Affairs
Topeka, Kansas, USA

Patient Assessment

A seven-year-old male miniature poodle was examined for lethargy, excessive panting, elevated liver enzyme activity and intermittent vomiting of six weeks' duration. The vomitus was usually yellow foam or partially digested food. Elevated liver enzyme activity was noted on laboratory work obtained by the referring veterinarian (**Table 1**, Days 0 and 12). A two-week course of oral amoxicillin failed to improve the patient's problems. The dog received a single 2-mg intramuscular injection of triamcinolone[a] for generalized pruritus. The lethargy, panting and vomiting were first noted shortly thereafter.

Physical examination revealed a bright, alert dog that weighed 5 kg, appeared slightly overweight (body condition score [BCS] 4/5) and panted continuously. Other findings included a few subcutaneous lipomas, mild periodontal disease, hepatomegaly, bilateral lenticular sclerosis, right patellar luxation and no evidence of testicles in the scrotum. The owners were given the dog as a young puppy and denied that it had been castrated.

Evaluation of these problems included a complete blood count (mild leukocytosis), heartworm check (negative), serum biochemistry profile (normal except for elevated liver enzyme activity [**Table 1**, Day 19]), urinalysis (normal), fecal flotation (hookworms) and abdominal radiographs. Survey abdominal radiographs revealed an extremely enlarged liver that displaced the axis of the stomach dorsocaudally and displaced the small bowel caudally. Ultrasound demonstrated a segment of terminal jejunum or ileum with a thickened bowel wall. Retained testicles were also identified. Prothrombin and activated partial thromboplastin times were normal. Examination of an ultrasound-guided fine-needle aspirate of the liver revealed vacuolar changes in hepatocytes consistent with steroid hepatopathy. An anthelmintic was administered for the hookworm infection.

The dog was reexamined one week later for an ACTH response test with determination of resting and post-ACTH plasma cortisol concentrations. An exploratory celiotomy was also planned to obtain liver and intestinal biopsy specimens and remove the retained testicles.

The resting cortisol concentration was subnormal and failed to increase after intramuscular administration of ACTH gel (**Table 1**, Day 19). During surgery, a diffusely enlarged, pale liver with rounded margins was noted; biopsy specimens were obtained from the liver, distal small intestine and colon; the retained testicles were identified and removed. Histopathologic examination of these specimens revealed diffuse testicular atrophy, normal intestinal structure except for mild dilatation of lacteals and multifocal hepatic vacuolar change consistent with steroid hepatopathy.

The tentative diagnosis was secondary hypoadrenocorticism and hepatopathy associated with parenteral administration of corticosteroids.

Assess the Food and Feeding Method

The dog was normally fed a combination of commercial grocery brand moist food mixed with broiled chicken and cottage cheese. The commercial food and table food were mixed in approximately a 50:50 ratio. An unspecified amount of this mixture was offered twice daily. The dog preferred to drink either ice water or iced tea.

Questions

1. What are the key nutritional factors to consider for this patient?
2. Outline a feeding plan for this dog including food and feeding method.
3. What other therapy should be considered?
4. How should this dog be monitored for response to therapy?

Answers and Discussion

1. The key nutritional factors for patients with mild to moderate hepatic disease that is expected to be self-limiting are listed in **Table 68-8**. The food should contain appropriate amounts of these key nutrients and other essential nutrients based on the patient's current lifestage. Dramatic changes are not necessary in the nutrient levels of food for patients with mild to moderate hepatic disease and no evidence of hepatic failure, portosystemic vascular shunts, ascites or hepatic encephalopathy.
2. A commercial dog food formulated for older dogs (i.e., senior or geriatric food) would be appropriate for this patient. Such a food would be more balanced and avoid the probable excess protein and fat provided by the current diet of 50% moist commercial grocery brand food and 50% chicken and cottage cheese. The daily energy requirement (DER) should be calculated to maintain current body weight until the liver disease has resolved. The food and water should be offered in multiple small meals throughout

Table 1. Laboratory data from a miniature poodle with steroid hepatopathy.

Parameters	Day 0	Day 12	Day 19	Day 56	Day 110	Day 142	Day 214	Reference values
Alkaline phosphatase (IU/l)	4,990	4,960	3,080	>400	313	106	26	10-80
Alanine aminotransferase (IU/l)	1,380	1,600	1,450	>500	184	236	45	10-70
Cortisol, resting (µg/dl)	na	na	0.3	<1.0	1.8	1.4	12.3	0.5-4.0
Cortisol, post-ACTH (µg/dl)	na	na	0.5	<1.0	1.9	1.7	17.5	8.0-20.0

Key: na = information not available.

the day to help control nausea and vomiting.

3. Physiologic doses of oral hydrocortisone may be given to alleviate glucocorticoid deficiency (and control clinical signs such as lethargy and vomiting) while not exacerbating the liver disease. The patient should also avoid stressful environmental situations because it cannot respond normally to these events.
4. Serum liver enzyme activity and plasma cortisol concentrations (resting and post-ACTH) should be monitored every two months until they return to normal. The clinical signs of lethargy, vomiting and hepatomegaly should resolve as biochemical parameters improve.

Progress Notes

The dog made an uneventful recovery from surgery and was discharged to the owners' care three days later. Other than the single triamcinolone injection, no other sources of exogenous corticosteroids were identified.

In the hospital, the dog began eating a moist specialty brand dog food formulated for senior dogs (Science Diet Canine Senior[b]). This food was nutritionally balanced compared with the combination of commercial dog food, chicken and cottage cheese offered at home. The DER was estimated to be 1.2 to 1.4 x resting energy requirement (RER) for an ideal weight of 4.5 kg (250 to 290 kcal [1.0 to 1.2 MJ]; two-thirds to three-fourths can daily). The food was offered in small frequent meals throughout the day. The owners were also instructed to add water to the food or warm the food in a microwave oven if it was necessary to encourage acceptance.

No other treatment was given because the secondary hypoadrenocorticism and steroid hepatopathy were expected to resolve as the effects of the injectable triamcinolone decreased over the next several months. Recheck examinations over the next six months documented clinical improvement and gradual reduction in liver enzyme activity (**Table 1**, Days 56 to 214). Plasma cortisol concentrations returned to near normal by Day 214. The dog remained normal for the next three years before it died from complications of immune-mediated thrombocytopenia.

Endnotes

a. Vetalog Parenteral. Solvay Animal Health, Mendota Heights, MN, USA.
b. Hill's Pet Nutrition, Inc., Topeka, KS, USA. This food is currently available as Science Diet Mature Adult 7+ Canine.

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CASE 68-3

Anorexia and Icterus in a Domestic Shorthair Cat

Rebecca L. Remillard, PhD, DVM, Dipl. ACVN
MSPCA Angell Animal Medical Center
Boston, Massachusetts, USA

Patient Assessment

A six-year-old neutered female domestic shorthair cat was referred for a one-month history of weight loss and a week-long history of vomiting, icterus and anorexia. The cat was kept exclusively indoors. The family had relocated to the state two months before the cat was presented to the referring veterinarian. The referring veterinarian treated the cat with intravenous fluids.

Physical examination revealed a depressed, cachectic cat (body weight 3.1 kg, body condition score [BCS] 1/5). The cat's mucous membranes, sclera, inner pinnae, lips and nose were icteric. Mild hepatomegaly was detected by abdominal palpation. Dehydration

(approximately 5%) was evident based on abnormal skin turgor and tacky mucous membranes.

Results of a complete blood count were consistent with a stress leukogram and mild microcytic normochromic anemia. Results of a serum biochemistry profile included hyperbilirubinemia, elevated liver enzyme activities, mild hyperglycemia, hypoproteinemia, hypoalbuminemia and mild hypokalemia (**Table 1**). Urinalysis results were normal except for marked bilirubinuria. A blood coagulation profile revealed slightly prolonged prothrombin time (13.4 seconds, normal 8.5 to 10.5 seconds). Vitamin K_1 therapy was started (phytonadione, 5 mg/kg body weight, subcutaneously, q12h).

Ultrasonographic evaluation of the liver revealed hepatomegaly with a diffuse increase in echogenicity and no evidence of intrahepatic masses. Hepatic tissue was obtained by ultrasonographic-guided needle biopsy. The hepatic tissue was brown, soft and floated in 10% formalin. Cytologic evaluation revealed an increased number of bile casts, increased amount of bilirubin within hepatocytes and all hepatocytes contained vacuoles filled with lipid. These findings were interpreted as hepatocyte lipid accumulation and cholestasis. Bacterial culture of a portion of the liver biopsy specimen was negative. A diagnosis of feline hepatic lipidosis was made.

Assess the Food and Feeding Method

Historically, since the cat was neutered at nine months of age, it had been slightly overweight (BCS 4/5). Therefore, for several years the cat had been fed a dry commercial specialty brand food with a reduced caloric density (Science Diet Feline Maintenance Light[a]). The food was offered free choice. The exact amount of food consumed by the cat over the last month was unknown but markedly less than normal. A 4-lb bag of food usually lasted a month, but the owners had not purchased a new bag within the last two months. During the past week, the referring veterinarian had been giving vitamin-B supplements and force-feeding an unknown amount of a commercial recovery food (Prescription Diet a/d Canine/Feline[a]) per os. The cat was still vomiting three to four times per day.

Questions

1. Outline an appropriate fluid and feeding plan (food, amount and method of administration) for this cat.
2. What other medical therapy may be appropriate for cats with idiopathic hepatic lipidosis?
3. How should the patient's response to therapy be monitored?

Answers and Discussion

1. Severe dehydration and electrolyte and acid-base disturbances should be corrected with appropriate parenteral fluid therapy before initiating the feeding plan. The single most effective means of treating feline patients with hepatic lipidosis is providing fluid and nutritional support with assisted feeding. This is most easily accomplished using liquid foods administered through a nasoesophageal tube or homogenized/blended foods administered by esophagostomy or gastrostomy tube (Chapter 25). These tubes are well tolerated by cats and help ensure adequate caloric intake and, if necessary, owners can continue feeding the cat at home. A variety of commercial liquid and blended enteral products have been used successfully in patients with hepatic lipidosis.

   Energy requirements, and therefore the daily amount of food, should be calculated to meet the resting energy requirement (RER) for the cat's current body weight. The amount of food should be divided into multiple small feedings (four to six meals daily). Most cats can initially tolerate at least 30-ml bolus feedings and can be given 50- to 80-ml meals after a few days of refeeding. However, vomiting cats, especially those that have not eaten for weeks, may not tolerate bolus feedings initially, but will tolerate continuous rate infusion of a liquid food.

   Vitamin K_1 therapy should be used in cats with abnormal coagulation tests. Some clinical investigators have advocated L-carnitine supplementation for improving recovery based on results in experimental models of feline hepatic lipidosis. At the present time there are no clinical studies demonstrating the effectiveness of L-carnitine supplementation in cats with naturally occurring disease.
2. Vomiting is a common complication of enteral feeding in cats and can be managed with antiemetic drugs given 15 to 30 minutes before each feeding. Cats with hepatic lipidosis rarely develop hepatic encephalopathy. If they do, lactulose, enemas and oral antibiotics may also be needed. Cats that do not eat voluntarily may be given appetite stimulants.
3. The amount of food given each day should be carefully recorded to ensure that an appropriate caloric intake is being achieved. Complications of tube feeding should be monitored. These include epiphora (nasoesophageal tubes), displacement of the tube, vomiting, diarrhea and infection at the site of tube placement. Decreasing icterus, serum bilirubin concentrations, liver enzyme activities and improved activity and mental attitude mark clinical improvement in the hospital. Long-term weight gain, improved body condition and a return of normal appetite indicate improvement. In general, one to three weeks of assisted feeding are necessary, but some patients may require three to seven months of tube feeding. Many patients can be managed at home until normal appetite returns. At home, food and water should be readily available and offered before each tube feeding. Decreasing the amount fed or discontinuing the number of daily tube feedings is recommended when the cat begins to show interest in food again. The feeding tube may be removed when the cat voluntarily consumes an amount equal to its RER for two to three consecutive days.

Progress Notes

An intravenous catheter and nasoesophageal tube were placed the day of hospital admission. The cat was given fluid and nutritional therapy concurrently with vitamin K_1 therapy as diagnostic procedures were performed. Because the cat was still vomiting three to four times per day, a liquid food (CliniCare Feline[b] containing 1 kcal [4.2 kJ]/ml) was given by continuous rate infusion. The cat's RER was 163 kcal (682 kJ)/day [$70(3.1)^{0.75}$]. Fluid requirements were 200 ml/day (3.1 x 60 ml/kg body weight + 5% + ongoing losses). Therefore, the cat initially received 163 ml of liquid food via nasoesophageal tube and 37 ml of Plasmalyte A (with 30 mEq KCl/l), intravenously per day. Dehydration and hypokalemia were corrected, and vomiting ceased by Day 2 of hospitalization. The cat tolerated the continuous rate infusion given by nasoesophageal tube, and its prothrombin time returned to within normal limits after four treatments with vitamin K_1.

A gastrostomy tube (G-tube) was placed on Day 3 of hospitalization. Twelve hours after the tube was placed, the cat began receiving 30-ml bolus feedings of a blended commercial veterinary recovery food (Prescription Diet a/d Canine/Feline) (2 cans plus 50 ml water = 1 kcal/ml). The cat had no problems with the G-tube or the blended food and was discharged to the owners' care on Day 4 with instructions to offer the cat food (Science Diet Feline Maintenance[a]) first and, if the cat did not voluntarily eat, to then feed 55 ml of the blended recovery food followed by a 12-ml water flush, three times daily. This feeding regimen provided the cat with 165 kcal (690 kJ) and 200 ml of water daily.

The owners returned with the cat 11 days later. The G-tube was in place, body weight was 3.3 kg and the cat was more alert with less intense icterus. A complete blood count showed no evidence of anemia. The serum biochemistry profile revealed normoglycemia, increased serum total protein and albumin concentrations and decreased serum total bilirubin concentration. The liver enzyme activities had almost returned to normal (**Table 1**). The cat was still not eating spontaneously; therefore, an appetite stimulant (cyproheptadine[c]) was prescribed (2 mg per os, twice daily). The cat continued to receive 80 ml of the blended food twice daily via the G-tube. The cat began eating the adult maintenance-type food spontaneously after four days of receiving the appetite stimulant. The G-tube was removed three days after the cat began eating voluntarily and the recommendation was made to continue feeding the maintenance-type food free choice until the cat achieved an ideal BCS (3/5) and body weight (approximately 5.0 kg). The owners were instructed to monitor the cat's appetite, body weight and body condition closely and, after the cat had achieved an optimal BCS, to change the feeding method from free choice to meal feeding a specific quantity of food (approximately one-fourth cup, twice daily) to maintain optimal body weight and condition.

Table 1. Laboratory data from a domestic shorthair cat with icterus.

Parameters	Day 1	Day 15	Reference values
Packed cell volume (%)	27.5	31.7	30-45
Hemoglobin (g/dl)	9.2	10	10-15
Glucose (mg/dl)	150	89	70-110
Total protein (g/dl)	5.9	7.2	6.5-7.7
Albumin (g/dl)	2.2	2.4	2.5-4.0
Alanine aminotransferase (IU/l)	264	80	10-33
Alkaline phosphatase (IU/l)	110	45	14-43

Endnotes

a. Hill's Pet Nutrition Inc., Topeka, KS, USA. These foods are available as Science Diet Light Adult Feline and Science Diet Adult Feline.
b. Abbott Laboratories, North Chicago, IL, USA.
c. Periactin. Merck & Company, Inc., Rahway, NJ, USA.

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CASE 68-4

Polydipsia/Polyuria in a Doberman Pinscher[a]

Philip Roudebush, DVM, Dipl. ACVIM (Small Animal Internal Medicine)
Hill's Scientific Affairs
Topeka, Kansas, USA

Patient Assessment

A five-year-old neutered female Doberman pinscher was examined for polydipsia and polyuria. The dog's history was uneventful except for treatment of a recurrent interdigital cyst. Physical examination was normal. Body weight was 28.6 kg with a body condition score (BCS) of 3/5. The dog had weighed 32 kg during an examination five months earlier. Blood was obtained for a complete blood count and serum biochemistry profile. Urine was obtained for a urinalysis.

Results of the complete blood count were normal. Serum biochemistry profile abnormalities included elevated liver enzyme activity (**Table 1**, Day 1). Results of the urinalysis were normal except for dilute urine (specific gravity = 1.005). Radiographs of the abdomen were normal except for a small liver silhouette.

Liver specimens were obtained using an ultrasound-guided biopsy needle. Histopathologic changes were consistent with moderate, diffuse, subacute hepatitis. Most of the inflammatory cells were neutrophils and macrophages. Macrophages and some hepatocytes contained focal accumulation of granular pigment. Special stains were positive for accumulating copper, but the quantity of copper was not determined. Bacterial culture of one of the biopsy specimens recovered a coagulase-negative *Staphylococcus* spp. This organism was considered normal flora or an opportunistic pathogen; it was sensitive to most commonly available antibiotics except ampicillin.

Assess the Food and Feeding Method

The dog was normally fed four cups of a dry specialty brand dog food (Iams Minichunks[b]) once daily in the evening.

Questions

1. What is the most likely diagnosis for this patient?
2. Outline an appropriate feeding plan for this dog.
3. In addition to the feeding plan, what other medical therapy is appropriate for this patient?
4. How should the response to therapy be monitored?

Answers and Discussion

1. Middle-aged female Doberman pinscher dogs may develop an aggressive form of chronic hepatitis. Affected dogs may present in fulminant hepatic failure, or the disorder may be detected early based on elevated serum enzyme activity found on routine screening biochemistry profiles. Dogs with advanced liver disease present with weight loss, anorexia, polydipsia/polyuria, icterus, ascites, bleeding tendencies, severe depression and/or signs of hepatic encephalopathy. Dogs presenting in reasonable condition when first examined survive longer. These dogs are typically bright and responsive, have minimal weight loss and do not have ascites or hepatic encephalopathy. Typical laboratory findings include hypoalbuminemia, elevated liver enzyme activity, hyperbilirubinemia, elevated fasting bile acid concentrations and prolonged coagulation studies.

   Histopathologic features of chronic hepatitis in Doberman pinschers include variable degrees of degeneration and necrosis of periportal hepatocytes and mixed inflammatory cell infiltrates. Portal fibrosis may be mild to severe; hepatic cirrhosis occurs in severely affected dogs. The livers of affected dogs have moderately increased copper and increased iron concentrations. The role of copper is not understood but may be associated with cholestasis. Iron accumulation may be associated with hepatic necrosis, hemorrhage and inflammation. Excessive copper and iron accumulation may aggravate ongoing hepatic inflammation.
2. General recommendations for the nutritional management of patients with chronic hepatitis include feeding foods that are energy dense, contain adequate levels of potassium, avoid excess levels of protein, copper, iron, sodium and chloride and contain some fermentable fiber. These goals can be met with either commercial veterinary therapeutic or homemade foods. Highly palatable, energy-dense foods offered in multiple small meals throughout the day may help overcome the nausea and gastrointestinal (GI) complications often associated with liver disease.
3. Definitive medical management of dogs affected with chronic hepatitis is not well established. Medical therapy often includes antibiotics, antiinflammatory and immunosuppressive drugs (e.g., prednisone, azathioprine), choleretic or bile "altering" agents (e.g., ursodeoxycholic acid), vitamin E and other antioxidants, zinc supplementation and copper chelating agents (i.e., D-penicillamine, tetramine). Diuretics may be needed for patients with severe ascites. Hepatic encephalopathy should be treated with reduced protein intake, oral antibiotics, lactulose and retention enemas (**Table 68-10**).

Table 1. Body weight and selected laboratory values from a Doberman pinscher with hepatitis.

Parameters	Day 1	Day 49	Day 73	Day 108	Day 164	Day 288	Day 314	Day 350	Reference values
Body weight (kg)	28.6	28.4	27.3	30.5	30.5	30	29.5	na	na
Glucose (mg/dl)	101	120	95	109	85	132	114	155	60-115
Urea nitrogen (mg/dl)	6	2.5	5	10	5	4.1	3.3	11.6	10-25
Creatinine (mg/dl)	1.2	1.3	2.1	0.5	1.4	1.0	1.0	1.0	0.5-1.2
Total protein (g/dl)	6.4	6.9	6.6	6.6	7.4	6.8	6.7	na	5.5-7.2
Albumin (g/dl)	2.2	3.1	2.8	2.8	3.0	2.7	2.7	2.7	3.0-4.5
Total bilirubin (mg/dl)	0	1.2	2.3	0.4	0.4	0.4	0.2	0.4	0.0-0.6
Alkaline phosphatase (IU/l)	2,655	2,579	1,447	500	215	494	425	541	8.0-75
Alanine aminotransferase (IU/l)	1,080	707	747	417	158	115	136	155	6.0-70

Key: na = information not available.

4. Patients with chronic hepatitis should be monitored frequently (i.e., every few months) with serial physical examinations, body weight and body condition determinations and serum biochemistry profiles that include measurement of albumin concentration and liver enzyme activity. The owner should also be encouraged to document the amount of food eaten daily. If treatment is successful, the dog will maintain body weight, body condition and serum albumin concentrations, have gradually reduced liver enzyme activity and remain alert and active. Serial liver biopsy specimens (i.e., every six to nine months) can also be used to monitor pathologic changes and quantify hepatic copper concentrations.

Progress Notes

The dog was given 500 mg cephalexin, per os, twice daily for the possible secondary bacterial hepatitis. The food was changed to a veterinary therapeutic food that avoids excess levels of protein, sodium, chloride, copper and iron (Prescription Diet u/d Canine[c]). The daily energy requirement (DER) was estimated to be 1.4 to 1.6 x resting energy requirement (RER) for an ideal body weight of 32 kg (DER = 1,440 to 1,650 kcal [6.02 to 6.90 MJ]). The DER was met by feeding 4 to 5 cups of dry u/d Canine daily.

Evaluations six and 10 weeks later revealed slightly reduced liver enzyme activity, continued weight loss and mild hyperbilirubinemia (**Table 1**, Days 49 and 73). The dog was alert and active but not eating well according to the owner. The dietary management was not changed, but more aggressive therapy for liver inflammation and copper accumulation was initiated. This therapy consisted of a bile altering agent (ursodeoxycholic acid [ursodiol[d]] 300 mg per os, daily with food), prednisone (30 mg per os, once daily for two weeks and then 30 mg every other day), vitamin E (400 IU per os, daily) and zinc gluconate (100 mg elemental zinc per os, twice daily).

Further evaluations one month and three months later (**Table 1**, Days 108 and 164) revealed an alert, active dog that had gained weight. The owner reported that the dog seemed to be doing well. Dietary management and medical therapy were continued.

Eighteen weeks later (Day 288) the dog was examined for vomiting, diarrhea and fever. Two other dogs at home were also affected with the same clinical signs. Nonspecific gastroenteritis was suspected. Liver enzyme activity remained increased but lower than the original values (**Table 1**, Day 288). A liver biopsy was recommended to assess the extent of hepatitis, fibrosis and copper accumulation but was declined by the owner. Therapy was not changed.

One month later, the dog was examined because the owner was concerned about weight loss. Mild weight loss was documented, but the dog's serum biochemistry parameters remained stable (**Table 1**, Day 314). Therapy was not changed. Five weeks later the dog was presented in a comatose state. Serum biochemistry parameters were not significantly changed from previous values (**Table 1**, Day 350); however, a resting blood ammonia concentration was elevated (367 µg/dl, normal 0 to 98 µg/dl). Hepatic encephalopathy was diagnosed. The dog was euthanatized at the owner's request.

Endnotes

a. Thanks to Dr. Roy L. Davis, Red Bridge Animal Clinic, Kansas City, MO, USA, for providing the information about this patient.
b. The Iams Co., Dayton, OH, USA.
c. Hill's Pet Nutrition Inc., Topeka, KS, USA.
d. Actigall. CibaGeneva Pharmaceuticals, Summit, NJ, USA.

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CASE 68-5

Increased Hepatic Enzyme Activities in a Bedlington Terrier

David C. Twedt, DVM, Dipl. ACVIM (Internal Medicine)
College of Veterinary Medicine and Biomedical Sciences
Colorado State University
Fort Collins, Colorado, USA

Figure 1. A one-and-one-half-year-old female Bedlington terrier affected with inherited copper hepatotoxicity.

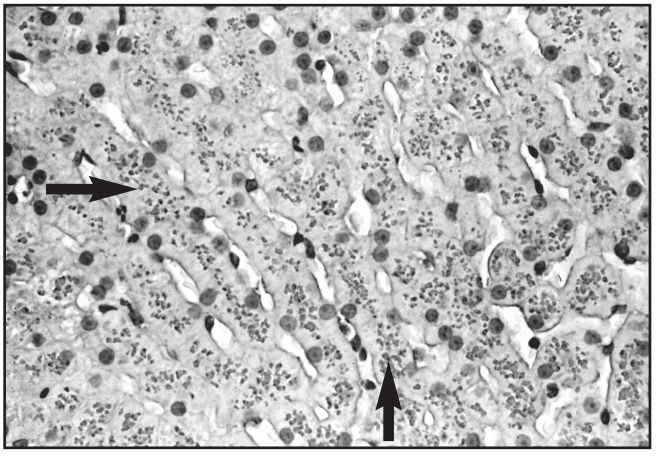

Figure 2. A photomicrograph of a liver specimen from a Bedlington terrier. Granules located in hepatocytes (arrows) stained positive for copper (rhodamine copper stain).

Patient Assessment

A one-and-one-half-year-old female Bedlington terrier (**Figure 1**) was evaluated because a littermate had recently been diagnosed with copper-associated hepatotoxicity. A serum biochemistry profile obtained by the referring veterinarian identified an abnormal alanine aminotransferase (ALT) activity of 161 IU/l (reference range 10 to 120 IU/l). The dog was considered to be normal by the owner and a physical examination was unremarkable. The dog weighed 6.6 kg and had normal body condition (body condition score [BCS] 3/5).

Another serum biochemistry profile confirmed an elevated ALT of 189 IU/l. Serum protein and bile acid concentrations, and clotting times were normal suggesting adequate hepatic function. The liver was grossly normal when biopsy specimens were collected at laparoscopy. Evaluation of the biopsy specimens revealed mild focal necrosis with many hepatocytes containing golden brown granules. These granules stained positive for copper using rhodamine copper stain (**Figure 2**). Hepatic copper quantitation was 4,901 μg/g dry weight liver (normal reference 120 to 400 μg/g dry weight liver). A diagnosis of inherited copper hepatotoxicity was made.

Assess the Food and Feeding Method

The diet was currently a mixture of a commercial dry grocery brand dog food (Purina Dog Chow[a]) and various commercial moist grocery brand foods with occasional table foods. The foods were mixed together at each meal so that approximately two-thirds of the volume came from dry food and one-third from moist food. The exact daily caloric intake was unknown. The patient was eating approximately the same amount of food and there had been no change in body weight during the last year.

Questions

1. What are the key nutritional factors to consider for this patient?
2. What nutritional supplements might benefit patients with copper hepatotoxicity?

Answers and Discussion

1. Key nutritional factors to consider in patients with copper-associated hepatoxicosis include energy, protein, copper, zinc and antioxidant vitamins. Providing adequate daily energy intake is important to allow protein synthesis and prevent tissue catabolism that generates ammonia. The exact caloric needs of these patients have not been determined but would be expected to be similar to those of other dogs of similar age and body condition.

   Most dogs with copper toxicosis develop clinical problems or liver disease is detected during adulthood (i.e., two to six years of age). Protein requirements have not been established for these dogs, but they would be expected to be similar to those of other adult dogs (15 to 30% dry matter [DM]). Patients with evidence of hepatic encephalopathy will often need more restricted dietary protein levels.

   Foods low in copper are recommended for affected dogs that accumulate hepatic copper. Restriction of dietary copper as the primary therapy probably does little to lower abnormal hepatic copper concentrations in diseased dogs. Copper-restricted foods have a minimal depleting effect for hepatic copper.

Commercial dog foods contain supplemental copper to meet or exceed dietary allowances established by the Association of American Feed Control Officials (AAFCO) or similar regulatory agencies. The AAFCO minimum allowance is 7.3 ppm copper (DM) or 2.1 mg copper/1,000 kcal (4.18 MJ) metabolizable energy. Most commercial dog foods exceed these levels of copper. These levels are appropriate for normal dogs but are excessive for dogs with copper-associated liver disease. For affected Bedlington terriers, foods with less than 5 ppm DM copper from available sources are appropriate. A few commercial veterinary therapeutic foods have low copper levels (**Table 68-11**).

Homemade foods can be prepared that do not contain excess copper (Chapter 10). These foods should exclude liver, shellfish, organ meats and cereals because of their high copper content. Vitamin-mineral supplements that do not contain a copper source are recommended. Treats and table food containing copper should also be avoided.

Decreasing the copper content of the food decreases the amount of copper that is absorbed through the intestine and enters the liver. Foods with low copper levels appear to be most useful for managing young dogs diagnosed with an inherited hepatic copper accumulation defect.

2. Oral zinc supplementation decreases intestinal absorption of copper. Zinc induces the increased synthesis of an intestinal mucosal metal-binding protein metallothionein. Copper that enters the intestine binds tenaciously to metallothionein, blocking the transfer of copper to the animal. The copper-metallothionein complex is lost in the feces during normal intestinal epithelial cell turnover.

Studies suggest that zinc supplementation will prevent copper accumulation and may actually decrease hepatic copper stores in affected patients. This "decoppering" method, however, is a slow process. Therefore, patients with high concentrations of hepatic copper should first receive copper chelating agents to reduce copper levels. Zinc supplementation alone may not be adequate for maintaining affected Bedlington terriers.

Zinc supplementation (i.e., as acetate, sulfate, gluconate or methionine) given at a dose of 5 to 10 mg/kg body weight every 12 hours has been recommended. Alternatively, 200 mg of elemental zinc given orally for several months for induction, then lowered to a maintenance dose of 100 mg daily, may be used. Serum zinc concentrations should be monitored with the goal of approximately doubling the serum zinc concentrations. Zinc should not be given with meals.

Experimental studies show that increased concentrations of hepatic copper catalyze hepatocellular oxidative damage and that therapeutic levels of antioxidants have protective properties. Vitamin E (d-α-tocopherol 200 to 400 IU/day) may be used as adjunct therapy. Vitamin C (ascorbic acid) has been suggested to decrease hepatic copper concentrations. However, this practice is not recommended because vitamin C promotes increased oxidative damage in the presence of high copper concentrations.

Table 1. Homemade food for a Bedlington terrier with copper hepatotoxicosis.

Ingredients*	Amounts (g)
Long grain brown rice, cooked	192
Cottage cheese, 4% fat	71
Margarine	8
Calcium carbonate	1
Iodized "lite" salt (KCl/NaCl)	1.7 (1/2 tsp)
Brewer's yeast	1
Other supplements	**

*Provides 350 kcal (1.46 MJ).
**Each day: 175 IU vitamin D, 28 mg iron, 8 µg vitamin B_{12}.

Progress Notes

A low-copper homemade food was recommended, but the owner wanted to continue feeding the dog commercial foods. No major changes to the current feeding plan were made other than eliminating table foods. The estimated daily energy requirement (DER) was 1.6 x resting energy requirement (RER) = 430 kcal (1.8 MJ). The foods were divided into equal portions and fed twice daily. A copper chelating agent, penicillamine[b] (125 mg, twice daily), was also given before meals.

Evaluation at six months found that the liver enzyme activities had returned to the normal reference range. A second liver biopsy was performed 12 months after therapy was instituted. The hepatic copper concentration had declined to 3,900 µg/g dry weight liver, and mild fibrosis, vacuolar degeneration and hepatic copper in centrilobular hepatocytes were evident histologically. Penicillamine therapy was continued.

An elective ovariohysterectomy was performed four years after the onset of penicillamine therapy and a liver biopsy specimen was obtained at that time. Both hepatic histology and hepatic copper concentration (125 µg/g liver) were normal. The penicillamine was discontinued and therapy with zinc gluconate (100 mg, twice daily, for a two-month induction period, followed by 50 mg, twice daily) and vitamin E (200 IU, twice daily) was instituted. Serum zinc concentrations were maintained between 200 and 300 g/ml, which were considered in the therapeutic range. Liver enzyme activities were evaluated at six-month intervals and were normal for three years. At that point, serum ALT concentrations began to increase and remained consistently abnormal when evaluated at six-month intervals for 18 months (i.e., ALT concentrations were 196, 275 and 278 IU/l, respectively). Zinc supplementation was thought not to be maintaining the patient. Therefore, a liver biopsy was suggested to obtain a specimen for evaluation of hepatic copper concentration. The owner declined the biopsy. Zinc therapy was discontinued and penicillamine therapy was reinstituted. The dog was also fed a homemade food, which probably had a lower copper content than the commercial foods that were being fed (**Table 1**). Vitamin-mineral supplements without copper were prescribed and the owner added small quantities of cooked ground beef, chicken or eggs to the basic homemade food recipe. One year following the change to the homemade food and reintroduction of penicillamine therapy, the ALT concentrations returned to the normal reference range.

Further Discussion

This case demonstrates that inherited copper hepatotoxicity can be managed and progression can be stopped by reducing hepatic copper concentrations, if the disease is detected early. The apparent failure of zinc therapy in this case suggests that therapy with copper chelating agents should be instituted in Bedlington terriers with this disease. Penicillamine and trientine[c] are both effective copper chelating agents. It remains unknown whether a low-copper food in conjunction with zinc therapy would have been beneficial in this case. Combination chelating agent and zinc therapy, essentially attacking the problem by two different mechanisms is intriguing, but there are no objective studies evaluating this form of therapy. It is possible that penicillamine may chelate zinc in the gastrointestinal tract making both drugs less effective.

Endnotes

a. Ralston Purina Co., St Louis, MO, USA.
b. Cuprimine. Merck & Company, Inc., Rahway, NJ, USA.
c. Syprine. Merck & Company, Inc., Rahway, NJ, USA.

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