The 2008 Nestlé Purina Veterinary Symposium on companion animal medicine

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Managing **vomiting in cats:** What's new for an old problem

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Vomiting is a frequent and potentially complex problem in cats. Adult cats often have a variety of different and more chronic causes of vomiting than kittens, and the condition remains one of the most common reason for cats to be presented to veterinarians for care.[1] Vomiting can be caused by both primary gastrointestinal diseases and extra-gastrointestinal diseases (*Table 1*, page 4). This wide spectrum of potential causes of vomiting in cats increases the difficulty for practitioners to make a definitive diagnosis. Nevertheless, it is important to carefully consider each of the potential differentials to prevent the problem from progressing to create further clinical deterioration.

One of the first steps in evaluating a vomiting cat is to determine as quickly as possible whether the vomiting is caused by a primary gastrointestinal problem or an extra-gastrointestinal disease. This determination helps to focus the diagnostic evaluation. The first and perhaps best way to help point clinicians toward the proper diagnostic approach is to obtain a thorough history of the diet and problem itself and perform a complete physical examination. These tools of the medical trade are often underestimated in their importance but can be invaluable to help clinicians refine and focus their diagnostic approach to the vomiting patient. As part of that process, one of the most important things to establish early on is whether the clinical sign reported by the owner is truly vomiting or if it represents regurgitation, a passive act of food reflux. If the cat is regurgitating food, the entire diagnostic and treatment plan will change dramatically. The most common causes of regurgitation are esophageal diseases, which typically require thoracic imaging or endoscopy for diagnosis and may be completely missed on routine evaluations of a vomiting cat.

The next step in evaluating the vomiting cat is based on whether it is a young cat with an acute onset of vomiting or an older cat with a chronic history of vomiting. In young cats, which are more likely to have parasitic, infectious, or dietary causes of vomiting (*i.e.*, primary gastrointestinal causes of vomiting), the clinician may elect to perform feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) testing, fecal flotation (or deworming), a diet change, or radiography to rule out a foreign body. However, in older cats (greater than 6 to 7 years of age), extra-gastrointestinal causes of vomiting are more prevalent, and the clinician should obtain a minimum database of routine blood work (*e.g.*, hematology, serum biochemistry profile, thyroid testing, gastrointestinal function

Managing vomiting in cats:
What's new for an old problem

Table 1. Common causes of vomiting in cats

Primary gastrointestinal

- *Helicobacter* gastritis
- Inflammatory bowel disease
- Parasitic gastritis (*e.g.*, *Physaloptera* spp., *Ollulanus tricuspis*)
- Mechanical diseases (*e.g.*, foreign bodies, trichobezoars, intussusception)
- Drug-related gastroenteritis (*e.g.*, from nonsteroidal anti-inflammatory drugs, steroids, or antibiotics)
- Nutritional causes (*e.g.*, dietary indiscretion, food allergy or intolerance).
- Neoplasia (*e.g.*, alimentary lymphoma).

Extra-gastrointestinal

- Endocrinopathies (*e.g.*, hyperthyroidism)
- Metabolic disease (*e.g.*, renal failure, hepatobiliary disease)
- Pancreatitis
- Systemic infections (*e.g.*, toxoplasmosis, feline infectious peritonitis [FIP])
- Heartworm disease.

testing, FeLV/FIV status testing) and imaging studies using radiography or ultrasonography. It is important to note that these tests may not always reveal the primary problem but often will identify many common systemic causes of vomiting in older patients.

In some cats, more invasive tests (*e.g.*, gastroduodenoscopy, exploratory laparotomy, biopsy) may be required to obtain the diagnosis, but in the majority of cats, these tests should not be pursued until the less invasive tests for systemic disease have been completed. Ultimately, the key is to develop a systematic, careful diagnostic process that allows the clinician to gradually—but eventually—rule out each of the extra-gastrointestinal and primary gastrointestinal causes until the problem is uncovered.

The purpose of this article is not to present a comprehensive review of all causes of vomiting. Instead, it will provide an overview of a few of the more common causes of vomiting in cats and discuss the best approaches for the diagnosis and treatment of these different problems. Where appropriate, the role of diet in both diagnosis and therapy of vomiting will also be considered.

Primary gastrointestinal disease

Adverse food reactions

Food allergy and food intolerance are the most common adverse reactions to food in adult cats.[2] In kittens and young cats, dietary indiscretion (*e.g.*, eating string, plants) and food intolerance are more common. Food allergy (also called food hypersensitivity) is an adverse reaction to a food or food additive with a proven immunologic basis. In other words, it is an immune response to an antigen, almost always a protein antigen, in the food. Food allergy typically occurs in young adult to middle-aged cats and can be associated with primary gastrointestinal signs, dermatologic signs, or a mixture of both. Food intolerance is a nonimmunologic, abnormal physiologic response to a food or food additive. This type of adverse food reaction can occur to any component of food and can occur without any prior sensitization and at any age. As with food allergy, vomiting is the most common presenting sign, but diarrhea can also be seen. Food poisoning, food idiosyncrasy, and pharmacologic reactions to foods also fall under this category of adverse food reactions.

The specific food allergens that cause problems in cats have not been well documented; only 10 studies describe the clinical lesions associated with adverse food reactions. In these reports, more than 80% of the reported feline cases were attributed to beef, dairy products, or fish. The incidence of food allergy vs. food intolerance in cats is unknown. However, a recent study suggested that 33% of cats with vomiting or other gastrointestinal signs had food sensitivity.[3]

The diagnosis of both food allergy and intolerance is based upon a dietary elimination trial. Practitioners should understand that a single diet trial does not eliminate all of the possible causes of dietary intolerance, so more than one trial is indicated. The intestinal flora may be disrupted by frequent diet changes (especially major changes in the type of food); thus, probiotic (*e.g.*, FortiFlora—Nestlé Purina) therapy

may be helpful when diet trials are being considered to reduce the risk of this complication.

The major difference between the diagnosis and treatment of these two types of adverse food reactions is the length of time on the appropriate diet that is required to achieve a response. Cats with food allergy require six to 12 weeks on the elimination diet before an improvement will be seen. Alternatively, in cats with food intolerance, resolution of signs may occur within days of the diet change (unless a concurrent bacterial floral disruption or other factor influences the response). In a recent study, greater than 55% of cats with gastrointestinal signs, especially vomiting but also diarrhea, completely responded to a change in diet to a highly digestible, high-protein, low-carbohydrate diet.[4] In most cats with dietary intolerance, it is not necessary to choose an elimination diet because they do not have a dietary allergy; they simply require elimination of the offending food substance (*e.g.*, carbohydrate type, coloring, flavoring, preservative) from their diet. In many cases, that can be achieved by feeding a high-quality, highly digestible diet. It should be noted that this does not necessarily require a novel antigen diet because many diets are formulated as highly digestible. Finally, in kittens with vomiting or diarrhea that is not due to parasites or other infectious causes, most nutritionists suggest that the most likely cause is food intolerance or a change in flora that has occurred due to multiple dietary changes. Thus, in many of these kittens, the addition of a probiotic or a change to a highly digestible, high-protein, low-carbohydrate diet (*e.g.*, Purina Veterinary Diets EN Gastroenteric Feline Dry) will result in resolution of gastrointestinal signs.

A variety of commercially available and homemade elimination diets, as well as diets formulated with hydrolyzed proteins, are available that may be used in cats with suspected food allergy. The key is to select a diet that has a novel or hydrolyzed protein source (based on a careful dietary history) and that is balanced and nutritionally adequate. Commercial diets are best for this; however, homemade elimination diets may be needed to find an appropriate test diet if the cat has had multiple protein sources. If a homemade diet must be used for long-term therapy, a complete and balanced diet containing the necessary protein sources should be formulated by a nutritionist. In most cats with food allergy, avoiding the offending antigen in the food is the most effective therapy and will result in complete resolution of clinical signs. However, short-term steroid therapy can be used to decrease the concurrent intestinal inflammation until the appropriate food sources can be identified. The most common therapy is methylprednisolone (4 mg/cat orally once daily) for two to four weeks. The key is to recognize that all cats with food allergy will improve when on the steroid therapy, but the condition will not resolve until the offending antigen source is removed. Finding the offending antigen can be difficult and time consuming, and it requires the owner's understanding and patience. It is not unusual for some cats with severe allergic disease to require multiple trials or homemade elimination diets for successful therapy. However, for the majority of cats, with appropriate dietary history and elimination trials, successful management of signs can be achieved without the need for long-term steroid therapy.

> "The addition of a probiotic or change to a highly digestible, high-protein, low-carbohydrate diet may result in resolution of gastrointestinal signs."

Extra-gastrointestinal disease

Feline pancreatitis

Feline pancreatitis, like many diseases in cats, is quite different than its counterpart in the dog. The most common form of pancreatitis in dogs is acute necrotizing pancreatitis, which is usually easy to recognize from its specific history and physical examination characteristics. The disease in cats is usually a lymphoplasmacytic disease, with less acute

Table 2. Dosages of selected antiemetic drugs used in cats*

Drug	Dosage	Potential side effects
Prochlorperazine	0.13 mg/kg intramuscularly every 12 hours, 0.15 to 1.5 mg/kg orally every eight hours	Sedation
Dolasetron (Anzemet—Aventis)	0.1 to 0.6 mg/kg intravenously or subcutaneously every 24 hours	None reported
Ondansetron (Zofran—GlaxoSmithKline)	0.5 to 1.0 mg/kg subcutaneously or intravenously every eight hours	None reported
Chlorpromazine	0.2 to 0.4 mg/kg subcutaneously, intramuscularly, or intravenously every six to eight hours	Sedation, may lower seizure threshold
Metoclopramide	0.1 to 0.3 mg/kg orally, subcutaneously, or intramuscularly every eight hours, 1 to 2 mg/kg intravenously every 24 hours as a continuous rate infusion	May cause behavioral changes
Diphenhydramine	2 to 4 mg/kg orally every eight hours, 1 mg/kg intramuscularly or intravenously every eight hours	Sedation
Dimenhydrinate (converted to diphenhydramine)	12.5 mg/cat orally, intravenously, or intramuscularly every eight hours	Sedation
Maropitant (Cerenia—Pfizer)	2 mg/kg orally every 24 hours or 1 mg/kg subcutaneously every 24 hours	Hypersalivation, lethargy, inappetence, diarrhea

* Most are not approved for use in cats.

inflammation and necrosis. Thus, cats with the disease have clinical signs that are much more subtle, with a tendency to wax and wane. Feline pancreatitis is also a very difficult disease to definitively diagnose antemortem (especially chronic cases or in cats that only vomit intermittently) compared with dogs. This is partly because of the lack of specific clinical signs in cats, but also because of the lack of a rapidly available, sensitive diagnostic test for the chronic form of the disease. Both of the available tests that have been routinely used to diagnose canine acute necrotizing pancreatitis (PLI and abdominal ultrasound) are significantly less sensitive and specific in feline pancreatitis due to the completely different nature of the feline disease.[5,6]

The signalment, history, and clinical signs of cats with pancreatitis are typically quite different from those of dogs. Acute pancreatitis is frequently encountered in obese dogs fed a high-fat diet, while affected cats are more likely to be underweight and high-fat diets do not appear to be an important predisposing factor. Cats of all ages, sexes, and breeds are affected, although Siamese cats are reported to have pancreatitis more frequently.[5] Finally, the clinical signs of pancreatitis in cats are usually very vague, with the most common signs being lethargy (reported in 100% of cats in one study[7]), anorexia, and dehydration. Vomiting and anterior abdominal pain, which are common clinical signs in dogs with acute pancreatitis, occur in only 35% and 25% of cats, respectively. Cats with severe

necrotizing pancreatitis may be icteric or in shock, have increased or decreased body temperature, and may have other concurrent conditions, including hepatic lipidosis, cholangiohepatitis, inflammatory bowel disease, interstitial nephritis, diabetes mellitus, or vitamin K-responsive coagulopathy. However, this form of pancreatitis in cats represents only about 15% of cases, and because the clinical signs in more typical pancreatitis cases in cats may be quite variable, this definitely complicates the diagnosis of the disease.

Hematologic findings in cats with pancreatitis are nonspecific but may include a nonregenerative anemia, leukocytosis, or leukopenia (less common). In a recent study, cats with pancreatitis consistently had elevated white blood cell counts (20,300 cells/µl) and mild decreases in platelet counts (mean = 180,000 platelets/µl).[7] Reported changes in the serum biochemistry profile include elevated serum alanine aminotransferase (ALT) activity, elevated serum alkaline phosphatase (ALP) activity, hyperbilirubinemia, hyper- or hypocholesterolemia, hyperglycemia, azotemia, and hypokalemia. In a recent study, the most common abnormalities in cats with severe pancreatitis were hyperglycemia (180 mg/dl), hyperbilirubinemia (2.5 mg/dl), hypocholesterolemia (130 mg/dl), and hypoalbuminemia (1.8 g/dl).[7] In cats with mild pancreatitis (determined by surgical biopsy), moderate liver enzyme activity elevations (*e.g.*, ALP, ALT, and gamma glutamyl transferase [GGT]) were more common. Hypocalcemia is less commonly observed but may be a poor prognostic sign when present in cats with severe pancreatitis or multiple organ dysfunction.[8] Serum lipase may be increased early in acute pancreatitis, but in a recent study, amylase and lipase were found to be of little diagnostic value in distinguishing normal cats from those with pancreatitis. These tests are not recommended as a means of confirming the disease in cats.[9] No changes in the urinalysis are consistently observed or specific for pancreatitis in cats.

The serum feline trypsin-like immunoreactivity (fTLI) assay was developed years ago as the definitive diagnostic test for exocrine pancreatic insufficiency, and the data and follow-up have confirmed its utility for this condition. In recent years, researchers have evaluated the fTLI as a diagnostic test for acute pancreatitis, working on the premise that elevated fTLI concentrations were due to pancreatic inflammation leading to leakage of enzymes into the bloodstream. They found that while an elevated fTLI concentration can be found in some cats with acute pancreatitis, a normal fTLI concentration does not rule out pancreatitis.[10] This is likely because the leakage of enzymes tends to decrease rapidly following an event or because the enzymes are inactivated and scavenged by the body's endopeptidases (*e.g.*, alpha$_2$-macroglobulin) within 12 to 24 hours following an acute insult. Further, in chronic or low-grade pancreatitis, which appears to be the most common form of the disease in cats, the leakage can be minimal—enough not to be detected by this assay. Thus, while an increase in fTLI concentration is specific for pancreatic enzyme leakage, it is not sensitive enough to be a definitive test for pancreatitis.

More recently, an ELISA for pancreatic specific lipase was developed by the gastrointestinal laboratory at Texas A&M University. This species-specific assay (fPLI in cats) used to detect elevations in serum pancreatic lipase concentration in clinical cases appeared to be more specific and sensitive for diagnosing pancreatitis in cats than the fTLI. However, the assay had a relatively low sensitivity (33%) and specificity (less than 80%) when a cut-off value of 100 µg/L was used for diagnosis.[10]

To improve upon this assay, a radioimmunoassay was developed and validated in 30 healthy cats. The sensitivity and specificity of this assay was tested in cats with mild pancreatitis and cats with moderate to severe pancreatitis.[11] The sensitivity in cats with mild pancreatitis was found to be 65% to 80%, while the specificity in healthy cats was 75%. However, in severe pancreatitis (determined by pancreatic biopsy), the sensitivity and specificity were both 100%.[9] These findings underscore the utility of this test in cats with acute pancreatitis; however, a problem still exists with the detection of low-grade or chronic pancreatic inflammation in cats.

Imaging studies are frequently used to help identify cats with

acute pancreatitis; however, the changes are not consistent and can be particularly subject to interpretation and operator expertise. The most common radiographic abnormalities in severe or necrotizing pancreatitis include a generalized or focal (upper right quadrant on the ventrodorsal view) loss of peritoneal detail, presence of a mass around the pancreas, hepatomegaly, dilated intestinal loops, or a fluid-filled duodenum. However, these findings are not specific for pancreatitis, and the sensitivity of radiography for diagnosing pancreatitis is extremely low in cats. In cats with acute necrotizing pancreatitis, ultrasonography may reveal a hypoechoic pancreas, hyperechoic mesentery, mass effect, or dilated common bile duct. In a recent study, ultrasonography had an 80% sensitivity and 88% specificity in cats with moderate to severe pancreatitis.[12] However, in that same study, mild pancreatitis was shown to be difficult if not impossible to diagnose via abdominal ultrasonography, with a sensitivity of 30%.[11]

The most reliable method for accurately diagnosing pancreatic disease remains direct visualization, biopsy, and histopathology. However, this can be expensive and increases the risk of complications, and the lesions may be missed on visual or histopathologic inspection in cases with focal lesions, which is common with chronic pancreatitis. In fact, pancreatic biopsy of cats is currently the only definitive means to diagnose the disease and to provide information on the best approach to therapy.[13] Further, many cats with pancreatitis have concurrent cholangiohepatitis, another disease for which biopsy is necessary for an accurate diagnosis. Thus, in cats with nonspecific signs and mild increases in liver enzymes, an exploratory surgery to obtain biopsies of both organs is strongly suggested.

Treatment of acute necrotizing pancreatitis in cats remains as for dogs: fluid therapy, especially colloid support to maintain pancreatic blood flow; antiemetics; and pain relief. In the most severe cases, antibiotic therapy may be indicated to reduce the risk of bacterial infection from translocation, and plasma is indicated if severe coagulation changes are occurring secondary to the inflammatory process. However, the major difference in therapy for cats is the need to feed them to prevent development of protein:calorie malnutrition, hepatic lipidosis, and gastrointestinal disturbances.[7] If the cat is vomiting, the best approach is to place a jejunostomy tube so that enteral nutrition can be administered distal to the stomach and pancreas. However, most cats do not vomit profusely, or the vomiting can be controlled with medication. In these cats, the easiest and quickest way to ensure appropriate nutrition is placement of an esophagostomy tube. Nutritional support in cats must be approached without delay; most cats have been anorectic for several days by the time of diagnosis, so aggressive and immediate plans to provide nutrition are essential for a successful outcome.

In cats with the most common form of pancreatitis, lymphoplasmacytic pancreatitis, anti-inflammatory therapy with steroids (methylprednisolone at 1 mg/kg/day orally) along with pain relief and appetite stimulants are the most important treatment choices. However, caution is advised in cats with chronic pancreatitis, as chronic steroid therapy can result in insulin resistance and diabetes, which in these cats can be extremely difficult to manage.

Feline hyperthyroidism

Hyperthyroidism, the most common feline endocrine disorder,[14] may present in a variety of ways. The cause of hyperthyroidism in cats remains somewhat controversial, but clinicians generally agree that this disease is likely multifactorial and associated with chemical or toxicologic environmental influences on the thyroid gland. The diagnosis of hyperthyroidism is based on identification of appropriate clinical signs, palpation of a thyroid nodule, and documentation of an increased serum total thyroxine (T_4) concentration or a positive radionuclide thyroid scan. Common clinical signs include weight loss, polyphagia, unkempt hair coat, patchy alopecia, polyuria, polydipsia, vomiting, hyperactivity, and aggressive or altered behavior.

Measurement of a baseline serum total T_4 concentration has been extremely reliable in differentiating the majority of hyperthyroid cats from those without thyroid disease. An elevated serum total T_4 concentration (*i.e.*, greater than 4.0 µg/dl) supports the diagnosis of hyperthyroidism,

especially if appropriate clinical signs are present, and a low serum total T_4 concentration (*i.e.*, less than 2.0 µg/dl) rules out hyperthyroidism, except in extremely uncommon situations where severe life-threatening nonthyroidal illness is present.

The challenge in diagnosing hyperthyroidism is in early or occult hyperthyroidism. Occult hyperthyroidism is defined as a hyperthyroid cat with mild clinical signs, a palpable nodule in the ventral region of the neck, and a serum total T_4 concentration that falls within the upper half of the reference range (*i.e.*, 2.5 to 4.0 µg/dl). Explanations for this phenomenon include the random fluctuations of endogenous T_4 concentration, which result in a normal serum total T_4 concentration. Alternatively, a decrease in serum total T_4 concentration as a consequence of concurrent nonthyroidal illness (*e.g.*, neoplasia, systemic infection, organ system failure) is also an important reason for a nondiagnostic serum total T_4 concentration test result in a hyperthyroid cat. The diagnosis of hyperthyroidism should not be excluded on the basis of one normal test result, especially in a cat with appropriate clinical signs and a palpable mass in the neck. Conversely, a diagnosis of hyperthyroidism should not be made on the finding of a palpable nodule in a clinically normal cat or a cat with a high or high-normal free T_4 concentration. If the serum total T_4 concentration test result is not definitive, the recommendation is to measure serum total T_4 and free T_4 concentrations using the modified equilibrium dialysis technique.

Baseline serum free T_4 concentration, as determined by the modified equilibrium dialysis technique, is a reliable means of assessing thyroid gland function because nonthyroidal illness has more of a suppressive effect on serum total T_4 than free T_4, and serum free T_4 is increased in many cats with occult hyperthyroidism and normal serum total T_4 concentration test results. Because of cost, measurement of serum free T_4 concentration is often reserved for cats with suspected hyperthyroidism when serum total T_4 concentrations are borderline or the results don't match with clinical signs and findings. In some cats, any concurrent illness may cause an increase in the serum free T_4 concentration, and this increase can exceed the normal reference range resulting in a misdiagnosis of hyperthyroidism. For this reason, serum free T_4 concentration should always be interpreted in conjunction with serum total T_4 concentration measured from the same blood sample. An elevated serum free T_4 concentration in conjunction with high-normal or increased serum total T_4 concentration is supportive of hyperthyroidism. An increased serum free T_4 concentration in conjunction with a low-normal or low serum total T_4 concentration is supportive of euthyroid sick syndrome, rather than hyperthyroidism.

In cats with no established diagnosis after the measurement of serum free T_4 concentration, the serum total T_4 and free T_4 tests can be repeated in four to eight weeks, a radionuclide thyroid scan can be evaluated, or a T_3 suppression test can be performed. If available, a radionuclide thyroid scan is preferable over the T_3 suppression test. Radioactive technetium-99m (pertechnetate) has a short physical half-life (six hours), is concentrated within functioning thyroid follicular cells, and reflects the gland's iodide-trapping mechanism. Scanning the thyroid provides a picture of all functioning thyroid tissue and permits the delineation and localization of hyperfunctioning thyroid tissue. The size and shape of the thyroid lobes and the radionuclide uptake by the thyroid and salivary glands are similar in a normal cat. This 1:1 ratio of salivary gland to thyroid lobe uptake is the standard by which to judge the thyroid status. Findings in most hyperthyroid cats are markedly abnormal and usually easy to interpret. The hyperfunctioning thyroid cells of cats with hyperthyroidism show increased uptake of technetium-99m compared with salivary tissue. Another finding in cats with hyperthyroidism on the radionuclide thyroid scan is that the atrophied normal thyroid cells do not take up technetium-99m and, therefore, are not visualized.

This test is also very helpful in treatment planning—whether surgery, radioiodine therapy, or medical management is contemplated. It is important to evaluate renal function in hyperthyroid cats before therapy.

Finally, clinicians should consider a number of other important extra-gastrointestinal causes of vomiting. A complete discussion of each of these subjects is not

possible, but remember to consider these possibilities when confronted with vomiting cats for which a definitive diagnosis is not yet made.

Nonspecific therapy

A number of antiemetic agents are available for use in vomiting cats (*Table 2*, page 6). Some are more commonly used in the hospital setting because they are injectable and may require frequent administration. The alpha$_2$-adrenergic antagonists (phenothiazines) and 5-HT3 antagonists appear to be the most effective antiemetic agents in cats. Dopaminergic antagonists (*e.g.*, metoclopramide) are less effective antiemetic agents in cats, and because they antagonize dopamine, they may potentially reduce pancreatic blood flow, although this effect has not been proven in cats with pancreatitis. However, metoclopramide is available in an oral preparation that can be used for therapy at home.

While nonspecific therapy may be indicated to control vomiting, it is important to remember to find the underlying cause of vomiting. Thus, antiemetic therapy should be used judiciously in the clinical setting and as an adjunct to therapy for the primary problem.

Dietary therapy

The use of diet to assist in the management of vomiting is not a new concept. Nevertheless, the type of diet used to help manage the problem has become an increasingly complex issue. In many—if not most—cases of uncomplicated vomiting and vomiting due to dietary indiscretion or intolerance, the best approach is to feed a highly digestible diet or to change the diet to one that does not contain the diet components believed to be associated with food intolerance, such as food coloring, flavorings, or other substances (*e.g.*, lactose). Highly digestible diets are designed to provide food ingredients that are easy to digest (digestibility of ingredients greater than 85% to 90%) with moderate to low fat, moderate to high protein, and moderate to low carbohydrates. In addition, they may have additives to improve intestinal health (*e.g.*, soluble fibers, omega-3 fatty acids, antioxidant vitamins) and contain no lactose, food coloring, or preservatives.

Many brands are available that fall under the highly digestible category, but they are not all alike. The highly digestible diets from different pet food manufacturers have a variety of formulations: different protein and carbohydrate sources, fat levels, and additives designed to promote intestinal health. Thus, when one diet from this category is not accepted by the cat, is ineffective, or seems to make the problem worse, clinicians should not assume that all diets in this category will be ineffective. If one type of highly digestible diet has been fed for at least one to two weeks with minimal response, then it is reasonable either to try another diet from a different source or try an entirely different dietary strategy (*e.g.*, high protein-low carbohydrate, novel antigen, hydrolyzed).

Another consideration is that the cat may improve by altering the amount or frequency of food fed. For example, feeding a canned food diet may improve gastric emptying—especially if the vomiting occurs immediately after eating. Alternatively, if canned food is not an option, feeding smaller meals more frequently may reduce vomiting that occurs in cats with altered gastric motility or reflux. Diets that are high in fiber may cause prolonged gastric emptying, so reducing the amount of fiber can improve gastric emptying and reduce vomiting in cats with gastric motility disturbances. Remember that dietary management is a trial and error process—no single diet will benefit all cats in all situations.

Conclusion

Vomiting is a common clinical problem in cats. The first step in the diagnostic process is to try to determine if the cat is vomiting because of a primary gastrointestinal disorder or a systemic or extragastrointestinal process. To accomplish this, careful observation and analysis of the history, clinical signs, laboratory data, imaging studies, and in some cats, more invasive procedures (*e.g.*, endoscopy or surgery) are needed to obtain the definitive diagnosis. But by narrowing the focus of the investigation, clinicians can be more specific in their approach to diagnosis and treatment of the vomiting and the underlying problem.

References

View this publication and a complete reference list online at www.advanstarvhc.com/c31.

Inflammatory bowel disease: More than a garbage can diagnosis

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Inflammatory bowel disease (IBD) is the most common cause of chronic vomiting and diarrhea in dogs and cats. IBD is an enteropathy characterized by the infiltration of gastrointestinal mucosa by inflammatory cells.[1] The cellular infiltrate is composed of variable populations of lymphocytes, plasma cells, eosinophils, macrophages, neutrophils, or a combination of these cells. Changes in the mucosal architecture, such as villous atrophy, villous fusion, villous fibrosis, and lacteal dilatation, frequently accompany the cellular infiltrates.

Etiology

The etiology of canine and feline IBD is poorly understood. However, evidence from clinical observations and animal models points to normal luminal bacteria or bacterial products as initiators of the disease. The role of enteric microflora in the pathogenesis of IBD in people is supported by clinical responses to fecal stream diversion treatment in patients with Crohn's disease[2] and antimicrobial therapy in patients with Crohn's disease or ulcerative colitis.[3] In addition, human IBD patients show an increase in circulating and intraluminal humoral and T-cell responses to the enteric microflora. Furthermore, genetic mutations in NOD2/CARD15[4] and toll-like-receptor-4 (TLR-4) in IBD human patients hinder the receptor's ability to detect bacterial components, resulting in defective responses to enteric microflora.[5]

Studying the composition of the intestinal microflora has been a challenge to researchers; however, recent work has focused on bacteria associated with the mucosal lining. A study of adherent mucosal bacteria in human IBD patients concluded that *Bacteroides fragilis* makes up more than 60% of the biofilm mass.[6] Dietary factors also appear to play a role in the etiopathogenesis of IBD in dogs and cats based on the clinical response to elimination or hypoallergenic diets in many of these animals.

Diagnosis

The diagnosis of IBD can be made after known causes of diarrhea, vomiting, and weight loss have been ruled out. Histologic confirmation of gastrointestinal mucosa infiltration by inflammatory cells and changes in mucosal architecture must also exist.

The standard workup for a dog or cat suspected of having IBD (*Figures 1* and *2*, pages 12 and 13) should include a detailed and accurate history, including a dietary history; comprehensive physical examination; and a minimum database consisting of a centrifugal fecal flotation, direct wet preparation, complete blood count, serum

Inflammatory bowel disease:
More than a garbage can diagnosis

Figure 1

Figure 1: A 4-year-old, severely emaciated German shepherd with severe inflammatory bowel disease and concurrent exocrine pancreatic insufficiency.

biochemistry panel, and urinalysis. Abdominal ultrasonography is also a valuable diagnostic tool in the evaluation process. It allows you to look at the gastric and intestinal wall for alterations in thickness and layering pattern (particularly the mucosa and muscularis layers); assess changes in mesenteric lymph node size and echo texture; and view the ultrasonographic appearance of the liver, pancreas, and adrenal glands.

Measurement of serum trypsin-like immunoreactivity (TLI) concentration is warranted in animals suspected of having exocrine pancreatic insufficiency. Veterinarians also commonly measure serum cobalamin and folate concentrations to evaluate the absorptive capacity of the ileum and jejunum, respectively, and to detect abnormal changes in the intestinal microflora. The limited diagnostic utility of measuring serum folate and cobalamin concentrations when diagnosing small intestinal bacterial overgrowth has been documented.[7]

Additional diagnostics to perform on a case-by-case basis include a serum thyroxine concentration, feline leukemia virus and feline immunodeficiency virus serology, fecal culture for *Tritrichomonas foetus*, fecal direct immunofluorescense assay (Merifluor DFA—Meridian Bioscience) or ELISA test for *Giardia* (SNAP *Giardia* Test—IDEXX Laboratories) and *Cryptosporidium* species, and a fecal enteric panel for enteropathogenic bacteria.

Endoscopy is another valuable procedure when diagnosing IBD or any other intestinal mucosal disorders associated with morphologic changes (*Figures 3* and *4*, page 14). However, endoscopy is limited by the working length of the scope, precluding endoscopic examination or biopsy of the jejunum. Regardless of the method used to procure intestinal biopsies (*e.g.*, endoscopy, laparotomy, laparoscopy), a high variation exists among recorded histopathologic evaluations of intestinal tissues from dogs and cats.[8] Endoscopically-obtained biopsies should be taken from an area perpendicular to the intestinal mucosa and must be carefully placed in a biopsy cassette to facilitate proper sectioning by the pathologist (*Figure 5*, page 14).

With the World Small Animal Veterinary Association's support, the Gastrointestinal Standardization Group has proposed to develop a standardized histologic evaluation system that would be used in all companion animal gastroenterologic disorders.

Treatment

IBD management requires a two-pronged approach, including both nutritional and pharmacologic therapy. Patients with mild to moderate IBD can often be managed with dietary modification and antimicrobial (*e.g.*, tylosin, metronidazole) administration. Dogs and cats that don't respond to more conservative therapy or patients with severe IBD (based on activity index scores reflective of the severity of clinical signs or histologic findings) should be managed with immunomodulatory therapy.

Nutritional management

Elimination protein diets. Antigenic determinants on proteins are often identified as causes in cases of IBD. This implies that feeding select protein diets containing a single, highly-digestible, novel protein source might be an effective tool in controlling IBD.[9]

Hypoallergenic diets. Hypoallergenic (hydrolyzed) diets are particularly useful in the diagnosis and management of food hypersensitivity. These elimination diets should be used when a patient appears to be allergic to multiple allergens, when a complicated dietary history makes it difficult to identify a novel protein, or when a patient has a severe case of IBD.[10]

Dietary fiber. The gelling and binding properties of fatty acids and deconjugated bile acids in soluble fibers may have a positive effect on certain gastrointestinal diseases.[11] The use of soluble, fermentable fiber instead of insoluble, nonfermentable fiber is generally recommended because most soluble fibers generate butyrate, the principal source of energy for colonocyte and other short-chain fatty acids. These fatty acids may lower the colonic luminal pH, impeding the growth of pathogens.[12]

Feeding oligofructose to dogs has been documented to decrease concentrations of fecal ammonia and amines and increase the amount of beneficial bifidobacteria in dog feces.[13]

Polyunsaturated fatty acids. To date, no published studies have demonstrated the efficacy of omega-3 fatty acid supplementation in managing canine or feline IBD. Fish oil has been reported to be beneficial in ulcerative colitis and Crohn's disease patients.[14] However, only a few studies found a significant decrease in rectal concentrations of the inflammatory leukotriene B_4, and others reported only clinical improvement with the use of fish oil.

Fat. Avoiding excessive fat can be instrumental in the management of canine IBD and various gastrointestinal diseases because fat delays gastric emptying in dogs and high-fat foods may contribute to osmotic diarrhea. Malabsorbed fatty acids exacerbate diarrhea and gastrointestinal protein and fluid losses because they are hydroxylated by intestinal bacteria and stimulate colonic water secretion.[15]

Vitamins and minerals. Water-soluble vitamins are often depleted by fluid losses associated with diarrhea, and fat-soluble vitamin loss can be significant in animals with steatorrhea. Magnesium and calcium deficiencies have been well documented in Yorkshire terriers with severe IBD and lymphangiectasia,[16] and cats with severe IBD frequently have subnormal serum cobalamin concentrations.

Vitamin B_{12} (cobalamin). Anemia is a relatively common finding on presentation and can result from blood loss or systemic suppression of hematopoiesis. In addition, severe iron-deficiency anemia has been reported in conjunction with IBD in dogs.[17] Low serum cobalamin has often been regarded solely in the context of its diagnostic utility in identifying dogs with small intestinal bacterial overgrowth. However, low serum cobalamin has been described in cats in association with a variety of gastrointestinal diseases, including IBD.[18] It is likely that mucosal repair is impeded in the initial management of IBD when cobalamin is deficient and its absorption impaired; however, this has not been investigated. Consideration should be given to cobalamin assays in the initial evaluation of dogs and cats with chronic intestinal disease, and parenteral administration of vitamin B_{12} should occur during the initial management of IBD if low serum cobalamin is identified.

Cats are typically supplemented with vitamin B_{12} at 500 µg per dose subcutaneously once weekly for five weeks, with re-evaluation of serum cobalamin concentrations every three to four months upon completion of a course of vitamin B_{12} administration. Dogs are typically supplemented with vitamin B_{12} at 500 to 1,000 µg per dose subcutaneously once weekly for five weeks.

Figure 2

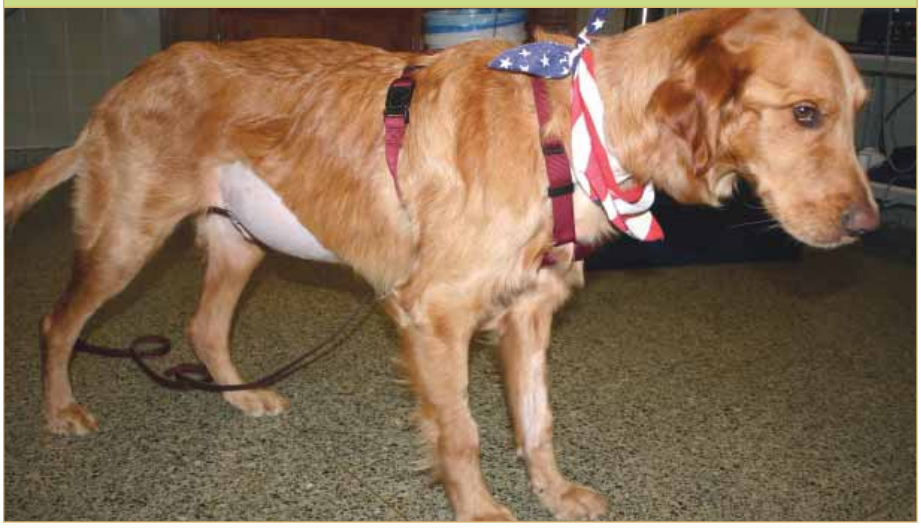

Figure 2: A 5-year-old golden retriever with a chronic history of diarrhea and weight loss secondary to inflammatory bowel disease with concurrent lymphangiectasia. The dog had ascites, which caused the abdominal distention.

Probiotics

Administration of probiotics to dogs and cats with IBD represents a novel alternative therapeutic modality that warrants further investigation. It has been demonstrated that colitis in both people and mice is associated with increased levels of certain cytokines, such as tumor necrosis factor-alpha, interleukin (IL)-6, IL-12p70, and IL-23.[19,20] Thus, a proper selection of probiotic strains for the treatment of IBD is crucial and should be based on the estimation of their capacity to induce an anti-inflammatory pattern of cytokines. Probiotics' antimicrobial actions on intestinal pathogens have a protective effect on the human gut's microflora.[21]

Probiotics have also been utilized to facilitate eradication of intestinal parasites. A recent study documented the ability of the probiotic organism *Enterococcus*

Inflammatory bowel disease:
More than a garbage can diagnosis

Figure 3

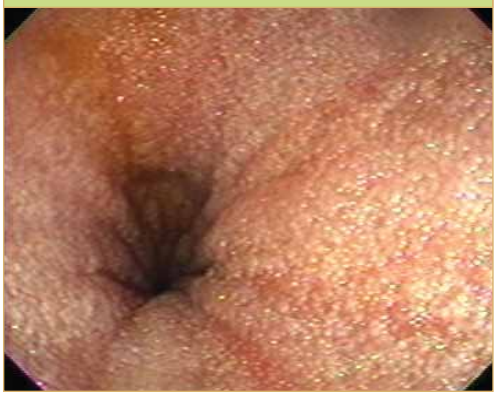

Figure 4

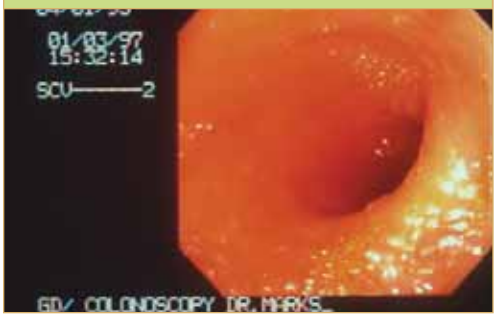

Figure 5

Figure 3: Endoscopic appearance of the duodenum from a dog with severe inflammatory bowel disease. The mucosa appears erythematous and cobble-stoned.

Figure 4: Endoscopic appearance of the colon in a dog with severe colitis. The colonic mucosa appears markedly erythematous and was extremely friable on biopsy.

Figure 5: Biopsy cassette with endoscopically-obtained intestinal biopsy samples. Note the correct placement of the specimens in the cassette.

faecium SF68 (FortiFlora—Nestlé Purina) to antagonize *Giardia intestinalis* infection in mice.[22] Oral feeding of *E. faecium* SF68 starting seven days before inoculation with *Giardia* trophozoites significantly increased the production of specific anti-*Giardia* intestinal IgA and blood IgG. This humoral response was mirrored at the cellular level by an increased percentage of CD4+ T cells in the Peyer's patches and in the spleens of *E. faecium* SF68-fed mice. The improvement of specific immune responses in probiotic-fed mice was associated with a decrease in active trophozoites in the small intestine, as well as decreased shedding of fecal *Giardia* antigens.

Pharmacologic management

Most dogs and cats with moderate to severe IBD require adjuvant pharmacologic therapy in combination with dietary management. IBD therapy must be tailored according to each patient's response.

Oral corticosteroids. Corticosteroids remain the cornerstone of pharmacologic IBD therapy, despite the lack of published controlled clinical trials documenting their benefit. The value of corticosteroids relates to their anti-inflammatory and immunosuppressive properties, although they also increase sodium and water absorption from the intestines, as well as regulate basal colonic electrolyte transport.

The dosage and duration of corticosteroid therapy is based on a variety of factors, including the severity and duration of clinical signs, severity and type of inflammation, clinical response, and tolerance to a particular drug. The initial dosage of prednisone for IBD therapy in dogs is 1 to 2 mg/kg every 12 hours. Most cats are usually managed with prednisolone at 5 mg/cat every 12 hours. The drug is gradually tapered over a 6- to 10-week period after clinical remission begins. Practitioners should combine this therapy with dietary therapy, azathioprine, or metronidazole so they can reduce prednisone dose. Parenteral corticosteroid therapy is reserved for vomiting patients or animals with severe, nonresponsive disease.

Budesonide, an oral corticosteroid structurally related to 16-alpha-hydroxyprednisolone, has high topical anti-inflammatory activity and low systemic activity because of its high affinity to the steroid receptor and rapid hepatic conversion to metabolites with minimal or no steroid activity. The typical dose for cats and toy-breed dogs is 1 mg/animal once a day and up to 3 mg/dog twice a day for large-breed dogs.

Azathioprine. The antimetabolite azathioprine is converted to 6-mercaptopurine in the liver and then to thioinosinic acid. The latter compound impairs purine biosynthesis, inhibits cellular proliferation, and reduces natural killer cell cytotoxicity.[23] The onset of these immunologic effects is slow and can require several months for maximum effectiveness.

Azathioprine is most useful in dogs as an adjunctive therapy in severe or refractory cases of IBD. It can also be used for its steroid-sparing effects when the adverse effects of prednisone are unacceptably high.

The dose for dogs is 50 mg/m^2 or 1 to 2 mg/kg once daily for two weeks, followed by alternate-day administration. Cats should receive 0.3 mg/kg every 48 hours.

The most significant side effect of azathioprine is bone marrow

suppression, particularly in cats. Others include anorexia, pancreatitis, and hepatic dysfunction.

Chlorambucil. The alkylating agent chlorambucil is beneficial for managing refractory cases of IBD, particularly in cats. Practitioners should monitor hematologic parameters every three to four weeks to assess the patient for neutropenia. Chlorambucil can be administered at 15 mg/m^2 orally once daily for four consecutive days and then repeated every three weeks (in combination with prednisone) or administered at 2 mg/cat every four days indefinitely. In dogs, chlorambucil is administered at 4 to 6 mg/m^2 every other day.

Cyclosporine. Research has shown cyclosporine to be effective in dogs with IBD when they previously had refractory responses to immunosuppressive doses of prednisone.[24] The dose of cyclosporine used was 5 mg/kg every 24 hours, and the drug was well tolerated. There is a paucity of information pertaining to the utilization of cyclosporine in cats with severe IBD, and most cats with severe disease are administered chlorambucil in combination with prednisolone.

Sulfasalazine. This drug consists of sulfapyridine linked to mesalamine (previously called 5-aminosalicylic acid) by an azo bond. The drug becomes effective only in the colon, when the bond is cleaved by colonic bacteria and the active moiety of mesalamine is released. Therefore, sulfasalazine is of no value in managing small bowel inflammation.

The sulfapyridine moiety is almost completely absorbed in the colon, metabolized in the liver, and excreted in the urine. The sulfapyridine moeity has no therapeutic effect. The mesalamine moiety is locally absorbed and inhibits the formation and degradation of inflammatory mediators, including leukotrienes, prostaglandins, thromboxane, platelet activating factor, histamine, and a number of other cytokines.

The initial dose for dogs is typically 20 to 40 mg/kg every eight hours for three weeks, followed by 20 to 40 mg/kg every 12 hours for three weeks and 10 to 20 mg/kg every 12 hours for three weeks. The drug should be used with caution and at a lower dose (10 to 20 mg/kg every 24 hours) in cats because it contains salicylates.

The most common side effects of sulfasalazine include anorexia, vomiting, cholestatic jaundice, allergic dermatitis, and keratoconjunctivitis sicca.

Antimicrobials. Metronidazole, an inhibitor of cell-mediated immunity,[25] has been frequently used as an adjunctive agent for IBD management. The dose of metronidazole in dogs and cats is 10 to 15 mg/kg every eight to 12 hours. Metronidazole tablets have a sharp, unpleasant, metallic taste when scored that can cause severe salivation. Side effects are rare, although metronidazole has been associated with a peripheral neuropathy in people and animals. Less common side effects include inappetence, nausea, vomiting, seizures, and reversible neutropenia.

Tylosin (Tylan—Elanco) is a macrolide antibiotic that has been reported to be effective and safe in managing canine IBD and antibiotic-responsive diarrhea.[26] The drug is used infrequently in cats with IBD predominantly because it is only available in powder form and is extremely bitter, necessitating its compounding before administration. Although the drug's mechanism of action is unknown, it appears to be effective in some dogs that had refractory responses to other forms of therapy. The dose in dogs and cats is 20 to 40 mg/kg every 12 hours.

Conclusion

IBD is a syndrome of exclusion and requires a comprehensive workup to rule out known causes of vomiting and diarrhea, followed by gastrointestinal biopsies to confirm the diagnosis. Dietary proteins and luminal bacteria or bacterial products are incriminated in initiating the disorder. IBD management involves a combination of dietary management and pharmacologic therapy.

The most common reasons for IBD treatment failure include:

1. Reliance on pharmacologic therapy alone
2. Poor dietary selection
3. Inadequate client education
4. Improper long-term maintenance of immunosuppressive or anti-inflammatory therapy
5. Misdiagnosis (*e.g.*, lymphoma)
6. Poor client compliance
7. Unmasking of a latent disease (*e.g.*, toxoplasmosis or histoplasmosis).

Ongoing studies seek to determine the potential benefit of probiotic and omega-3 fatty acid administration, although a paucity of clinical studies in dogs and cats document the clinical benefits of these products. The prognosis for most dogs and cats with IBD is favorable, providing that appropriate dietary and pharmacologic therapy are utilized.

References

View this publication and a complete reference list online at www.advanstarvhc.com/c31.

Growing old **gracefully:** An overview of healthcare management in the aging cat

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The definition of geriatric has changed over the last decade—not just in cats, but in other species as well. The government has raised the retirement age in an attempt to prepare for the financial and social policy onslaught of baby boomers. Life insurance companies have raised age limits for coverage. These changes reflect greater longevity in the human species and the benefits of improved health care and nutrition.

In cats, life expectancy has risen to 14 to 16 years of age. Practitioners today see the benefits of cat owners' acceptance and compliance with their recommendations for vaccination protocols; nutritional counseling and nutritionally balanced, feline-specific diets; and dental hygiene. And while we can always focus and expand our client education efforts, the veterinary community—and to a great extent industry—have done a good job at educating clients.

What is a senior or geriatric cat? In cats, senior ranges from about 9 to 12 years of age, and geriatric follows thereafter. These age ranges correlate roughly with human ages of 52 to 64 and 68 onwards.[1] A cat may begin to manifest serious age-related disorders (*e.g.*, renal insufficiency) at 8 to 9 years of age on average. This does not make that individual old or less treatable. Aging involves a set of predictable cellular changes that practitioners need to consider in their approach to health care, both preventive and therapeutic. In addition, at any age, changes and disorders exist that are particular to that age group or stage of progression.

Aging is a complex process reflecting increasing damage at the cellular and organismal level. Aging begins at the moment of conception, involves differentiation and maturation, and, at some point, leads to the progressive loss of functional capacity characteristic of senescence ending in death.[2] Organismal aging may be affected by genetics, social environment, nutrition, and the occurrence of age-related diseases. Cellular aging, on the other hand, includes progressive accumulation of sublethal injury (*e.g.*, free radical damage), resulting in either cell death or the cell's diminished capacity to repair itself. Practitioners can influence these changes to some degree through nutritional intervention.

Nutritional considerations of aging

What happens to body composition as cats age? Maintenance energy requirements vary with age, genetic potential, health

status, and gender (intact or altered). These requirements decrease with age in people, dogs, and rats. In cats, interestingly, some report no change, but when evaluated over longer periods, it has become apparent that the requirements decrease until about 11 years of age. After this point, however, maintenance energy requirements per unit body weight actually increase.[3-5]

Senior cats under 12 years of age tend to be overweight or obese as energy needs decrease without a concurrent decrease in energy intake. Lean body mass (*i.e.*, skeletal muscles, bones, skin, and organs) decreases in cats, just as it does in other species, with advancing age. As lean body mass is a primary driver of metabolism, all decreases in activity result in a reduction of maintenance energy requirements.

Studies in geriatric cats show that fat digestibility decreases with age.[6] Additionally, approximately 20% of cats over 14 years of age have reduced protein digestion. This is of clinical relevance when practitioners design an optimal nutritional regimen for older feline patients; protein and fat restriction may be contraindicated. Especially if they're underweight, older cats will benefit from a more energy-dense, highly digestible diet to help offset age-related digestive and metabolic changes.

The key to determining an appropriate diet is a nutritional assessment. This should include determining not only body weight at every visit, but also identifying body composition, most practically by using a body condition score. Determining the percentage weight change is helpful in detecting trends and alerting both the practitioner and client to incipient (or blatant) physiologic alterations. Using a simple diet history form provides important information by revealing not only food fed, but also brand, quantity, and treats or supplements that the patient receives (*Figure 1*, page 18).

Researchers have recently studied whether the use of dietary antioxidants (*e.g.*, vitamin E, beta carotene) alone or in combination with a prebiotic (chicory root) and a blend of oils to supplement omega-3 and omega-6 fatty acids benefit the health and longevity of healthy, older cats when compared with a complete and balanced diet.[7] Ninety cats over 7 years of age (grouped into 7 to 9, 10 to 12, and 13+ years of age at the start time) were studied in a controlled environment for five years. As expected, all cats lost weight as they aged, but cats in the fully supplemented group lost less weight than those in the other two groups. Other beneficial effects noted were improved lean body mass scores, improved fecal microflora, fewer diseases (notably gastrointestinal) during the study, and a longer life.

Weight loss in older cats can be a frustrating and worrisome change. While possibly normal in the older individual, it is of great importance to the cat and the client that the cause be determined (*Figures 2* and *3*, pages 20 and 21).

Optimizing oral and dental health cannot be over-emphasized, yet clients may express concern about anesthetizing elderly cats. Several studies have looked at risk factors for anesthesia. Properly staging the patient and taking appropriate precautions were found to minimize perianesthetic complications; age was not a risk factor (*ASA physical status classification system*, page 21).[8,9]

"Older cats may benefit from a more energy-dense, highly digestible diet to help offset age-related digestive and metabolic changes."

Reminding clients that the majority of anesthetic procedures in human medicine are performed on elderly patients may provide reassurance that safe anesthesia is possible—cats can benefit from dental or other procedures when practitioners perform appropriate preanesthetic evaluations and intraoperative monitoring.

The skinny older cat, especially if inappetent or anorectic, has a limited ability to conserve its

Figure 1. Diet history form*

Date: _____

Client's name: _____ Cat's name: _____

Breed: _____ Gender: M MC F FS

Age: _____ Body weight: _____ Body condition score: __ / 9

Activity level: High Medium Low Very Low

What food(s) are currently fed for the cat's main meal?

Dry: never occasional/small proportion about half mostly exclusively

If fed, what brands and amounts are fed most often: _____

Canned: never occasional/small proportion about half mostly exclusively

If fed, what brands and amounts are fed most often: _____

Home prepared: never occasional/small proportion about half mostly exclusively

If fed, please provide recipes used. _____

What treats and/or supplements are currently fed?

Commercial treats: No Yes

What brands and amounts are fed most often: _____

Fresh foods/table scraps: No Yes

What foods and amounts are fed most often: _____

Dietary supplements: No Yes

What supplements and amounts are fed most often: _____

Have there been recent changes in foods/brands fed? No Yes

If so, when and why? _____

How is your cat's appetite? Good Poor **Any recent changes?**_____

How frequently does your cat defecate? 0-1x/day 2-3x/day 4x or more/day Don't know

How would you characterize its stool? Firm/hard Formed but not hard Loose

Where does your cat spend most of its time? Indoors Outdoors About half in and half out

How much time does your cat spend exercising each day? <30 min/day 30-60 min/day More

Are there other pets in your household? Yes No

Do you have any questions regarding your cat's diet? _____

*Modified from: Laflamme DP. Nutrition for aging cats and dogs and the importance of body condition. *Vet Clin North Am Small Anim Pract* 2005;35:720.

body proteins. This results in a negative nitrogen balance, protein:calorie malnutrition, and the deterioration of protective mechanisms impacting immunity, red blood cell hemoglobin content, muscle mass, and tissue healing ability. Inappetence and anorexia must be dealt with promptly and adequately. Cats have limited storage of many nutrients and a restricted ability to down-regulate numerous metabolic processes. They were designed to eat multiple small meals per day that were high in protein and moderate in fat. Hepatic lipidosis is always a risk, especially in previously obese cats. It is essential to calculate daily caloric and protein requirements, just as one routinely calculates fluid needs as part of a therapeutic plan (calories: 50 kcal/kg ideal body weight/day; 4 g protein/kg ideal body weight/day). Appetite stimulants, including cyproheptadine (1 mg/cat orally twice a day) or mirtazapine (3 mg/cat orally every 72 hours), may help jump-start a cat's appetite, but practitioners must be wary not to lose sight of total calories consumed. If a cat is eating but not enough, practitioners must consider supportive feeding (*e.g.*, assisted syringe feeding, tube feeding). A large-bore feeding tube is preferable because it may be maintained for months if necessary and permits feeding complete, nutritionally balanced diets. Esophagostomy tubes can be placed quickly and provide a feeding route that is well tolerated by most feline patients.

For a patient with apparent maldigestion, such as seen with chronic small intestinal disease, folate and cobalamin supplementation has been beneficial (folate: 0.5 to 1.0 mg/cat/day orally for one month; cobalamin 250 µg/cat subcutaneously or intramuscularly once weekly for six weeks).[10,11]

Age-associated illnesses

In older cats, practitioners see a marked increase in problems associated with the urinary tract (*e.g.*, chronic renal insufficiency, pyelonephritis, ureteronephroliths, and certain forms of lower urinary tract disorders), disorders of the endocrine system (*e.g.*, hyperthyroidism, diabetes mellitus), arthritis, dental diseases, and neoplasia. Certain infectious diseases are more likely to be diagnosed in older cats (*e.g.*, feline infectious peritonitis). A decline in the function of the special senses occurs frequently and behavior changes suggestive of cognitive dysfunction may be seen in some cats.

Ophthalmologic aging changes include iris atrophy, melanin deposition on the irises, and lenticular sclerosis. While iris atrophy and melanin deposition on the irises do not appear to affect vision, lenticular sclerosis results in a decreased acuity that is most obvious in dim lighting. Impaired hearing is fairly common in older cats and affects selective frequencies, similar to that which occurs in older people. The result of these alterations in perception may be nocturnal yowling as the cat strives to orient itself with the help of cues from the caregiver. Other causes of this behavior include hyperthyroidism or hypertension (both presumably resulting in agitation), cognitive dysfunction, or pain.

Development of inappropriate elimination behavior may have several age-associated causes. Pain from arthritis may make getting to the litter box or getting into the box difficult. Past experiences of discomfort from cystitis or difficult stool passage may result in an aversion to use the litter box. Urge incontinence (urinary or fecal) may result in the inability to get to the box in a timely fashion, resulting in the development of an alternative location for eliminative behaviors. Hyperthyroidism may result in defecation of normal or diarrheic feces outside the litter box.

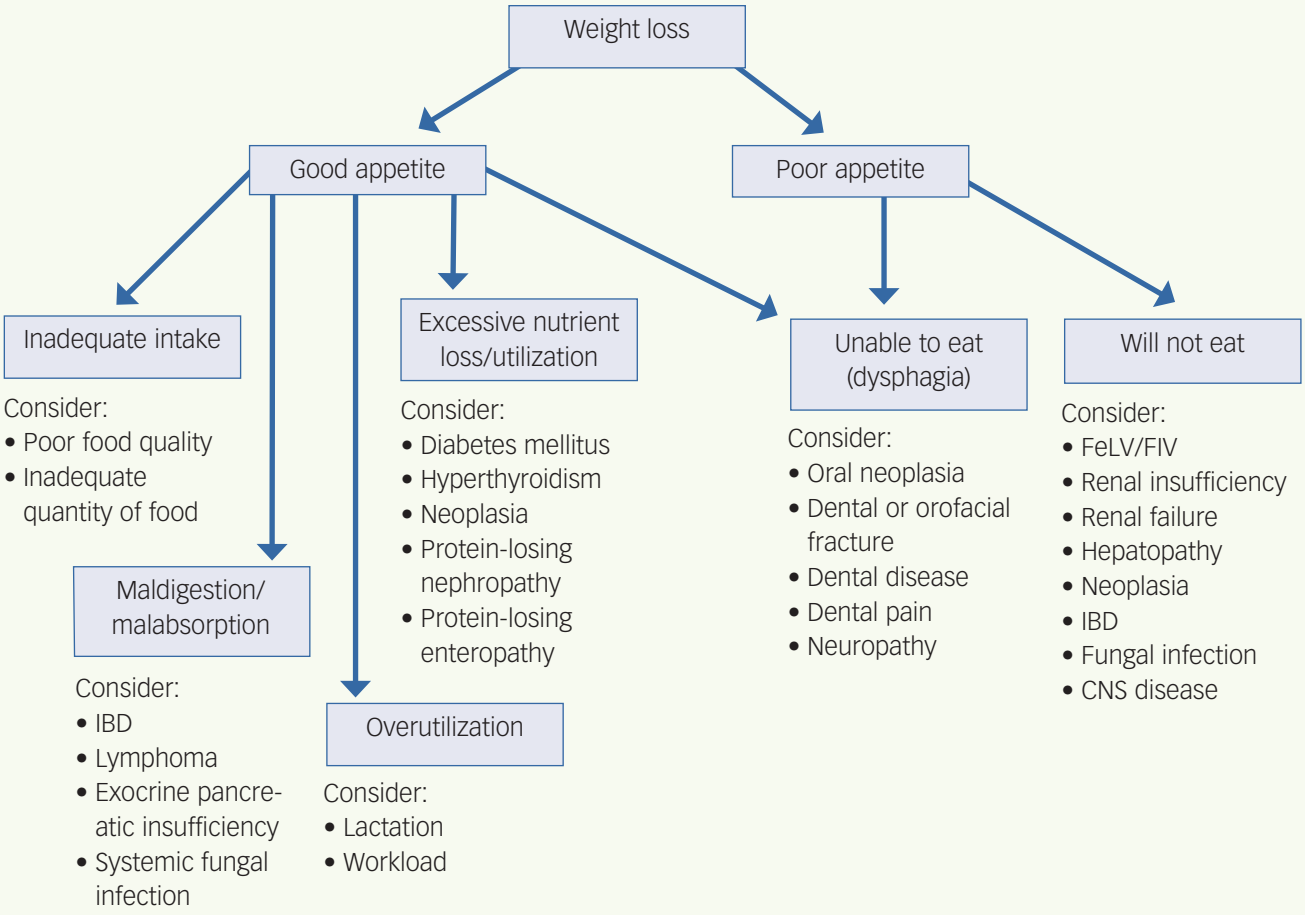
Practitioners also see conditions related to altered hydration and nutritional requirements, such as constipation. For the most part, constipation is a sign of dehydration. Cellular water content has priority over fecal water content; thus, practitioners should direct primary treatment towards rehydration and correction of the underlying cause(s) of the problem, rather than at the consistency of the stool and its movement. Use of promotility agents, laxatives, osmotic agents, and fiber-enriched diets should be used conservatively and once rehydration has been addressed.

Because most older cats have a reduced ability to reclaim water from their urine, practitioners should pay special attention to counseling clients about hydration. Circulating water fountains are accepted by many cats, as are flavored broths. Increasing the proportion of canned food

Growing old gracefully:
An overview of healthcare management in the aging cat

Figure 2. Differential diagnoses for weight loss in cats*

Recommended diagnostics will vary and may include CBC, serum biochemistry panel, serum thyroxine concentration, serum cobalamin and folate concentrations, complete urinalysis, microalbuminuria test, fecal flotation, FeLV/FIV test, thoracic and abdominal radiography, and abdominal ultrasonography. A gastrointestinal biopsy may also be necessary in some cases.



*Modified from: Laflamme DP. Nutrition for aging cats and dogs and the importance of body condition. *Vet Clin North Am Small Anim Pract* 2005;35:772.

fed and adding water to food are the easiest ways to address a cat's increased fluid needs. Subcutaneous fluids administered at home become part of daily maintenance care for many elderly cats.

Normal radiographic changes are seen in older feline patients, including an increase in the heart's sternal contact. A decrease in bone density may be seen in very elderly cats. Some minor calcific changes may occur in the pulmonary parenchyma of normally aging cats. Practitioners should look for spondylosis, especially of the lumbar vertebrae, but bony changes may be seen in any part of the spinal column as well as degenerative, proliferative, or lytic changes of the joints. Calcifications may be noted in the kidneys—these are often insignificant, representing calcification of old clots. Differentiation from nephroliths can be made with aid

of ultrasonography. Similarly, adrenal calcification should not be over-interpreted in cats, as it may be a normal, age-related change.

The pains of aging

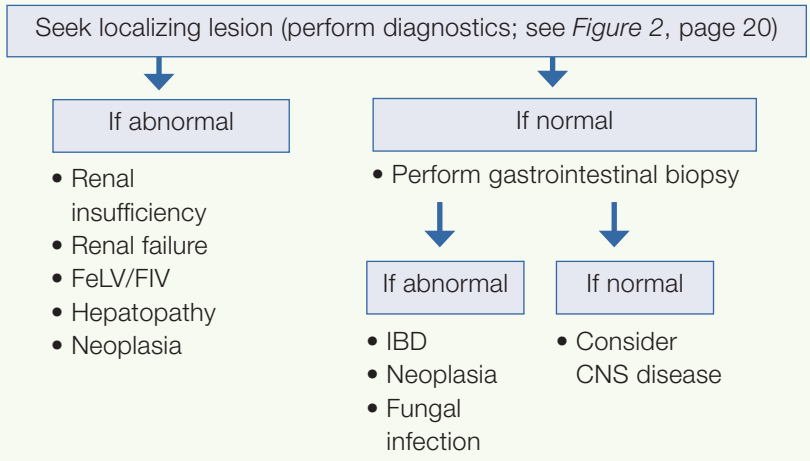
Oral diseases, such as periodontal disease, root exposure, odontoclastic resorptive lesions, stomatitis, and oral masses, are all potentially painful. Surgical manipulations of tissue result in inflammation as well as direct trauma and cell damage, which initiate the pain response. Similarly, common procedures (*e.g.*, blood collection, intravenous catheter placement, restraint of a thin or arthritic patient) may make patients uncomfortable. In addition, numerous chronic conditions can be potentially painful. Bacterial cystitis and pyelonephritis are frequent in older cats, while the incidence of interstitial or sterile cystitis and inflammatory bowel disease (IBD) is not different in older cats than in younger cats. The likelihood of neoplasia increases with age. Because of all these factors, practitioners must consider the need for analgesia as part of any treatment plan for older cats.

Recognition of chronic and arthritic pain is a relatively recent event. Osteoarthritis or degenerative joint disease appear to be much more common in aging cats that previously thought and is probably a major cause of discomfort. Secondary osteoarthritis may be caused by joint trauma (*i.e.*, fractures or ligamentous injuries); infectious or immune-mediated inflammation; compensation for congenital and developmental defects; and neoplastic, endocrine (diabetic), or metabolic conditions. Osteoarthritis involves a cascade of mechanical and biochemical events resulting in articular cartilage deterioration, synovial membrane inflammation, soft tissue changes, and osteophyte formation with bone remodeling.

In one study of the prevalence of degenerative joint disease in cats, researchers reviewed radiographs taken as part of a diagnostic workup for a variety of reasons in 100 cats over 12 years of age. They found that 90% of these cats showed evidence of degenerative joint disease.[12] Interestingly, in only four medical records of the 100 patients was a concern noted for degenerative joint disease. Does this mean that, as in dogs, the

Figure 3. Diagnostic algorithm

Use this diagnostic algorithm for anorectic cats with weight loss.



ASA physical status classification system

The ASA classification refers to the American Society of Anesthesiologists' classification system, based on the physical status of the patient. Five categories are defined as follows:

- **Class 1:** Normal, healthy patient
- **Class 2:** A patient with a mild systemic disease
- **Class 3:** A patient with severe systemic disease
- **Class 4:** A patient with a severe systemic disease that is a constant threat to life
- **Class 5:** A moribund patient not expected to survive without the operation

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clinical signs of osteoarthritis in cats do not correlate well with radiographic findings, or does this mean that practitioners are poor at recognizing the signs? Another researcher performed a retrospective radiographic study looking at cats of all ages.[13] This study showed radiographic changes suggestive of osteoarthritis in 22% of cats; in just 33% of this small group, clinical signs were noted. In a third study of 218 cats, the prevalence of radiographic signs of degenerative joint disease or osteoarthritis was 33.9%, and the prevalence of clinical signs was 16.5%.[14] Most of these cats were over 10 years of age.

Lameness is not a common clinical sign of this problem in cats. Rather, the signs are insidious or attributed to aging. They include eliminating inappropriately (often adjacent to the litter box), decreased grooming, developing antipathy for being combed, being reluctant to jump up or down, sleeping more, moving less, withdrawing from human interaction, and possibly hiding. When activity monitors have been attached to cats' collars, activity levels increased with nonsteroidal anti-inflammatory drug (NSAID) treatment, suggesting alleviation of musculoskeletal discomfort.[15]

Caring for elderly cats

Older feline patients have particular therapeutic and nursing needs. It is important to restrict hospital stays to as short as possible because older cats are less tolerant of the hospital environment and are more prone to depression and pining. Some problems may be masked and even undetectable with careful and thorough examination, yet they make their presence known when the patient is stressed. Many conditions that these special individuals develop require ongoing home care, such as subcutaneous fluid administration, frequent medication administration, and dietary manipulation.

Some cats prefer medications administered subcutaneously rather than orally; when the agent exists in a subcutaneous formulation, this is often an easier route for clients to use. Palatability of diets, especially in the face of declining senses, is especially important. Many older cats need an increase in biologically available protein rather than a decreased amount. Practitioners should give special thought to each elderly patient's need for analgesia. Slow, gentle persistence with acute and empathic observation are the best tools to care for and handle older cats.

A screening program for older cats is an excellent management tool. Offering such programs as part of a wellness program approach provides the best preventive medical care and can give the clinic a more predictable income base. At my clinic, the Mature Cat Program consists of a comprehensive physical examination; complete urinalysis; blood pressure determination; and blood panel consisting of a complete blood count with differential and serum biochemical screen, including a basal serum total T_4, amylase, lipase, and electrolyte concentrations. We recommend this annually for all cats from the age of 8 years onwards and twice annually for cats over 14 years of age or once abnormalities have been detected to assist in the management of these problems. With the introduction of the Healthy Cats for Life program sponsored by the American Association of Feline Practitioners and Fort Dodge Animal Health, the new recommendation of semiannual wellness exams in cats of all ages seeks to increase the opportunity to uncover illness in cats by teaching people the 10 subtle sign of sickness (www.healthycatsforlife.com). Client acceptance of this and other wellness programs is very good.

Finally, when is enough, enough? Although practitioners have the ability to help prolong life, the quality of life must be first and foremost in the practitioner's and client's mind. "Just because we can, doesn't mean we should." I recommend that all practitioners read the paper "Ethical issues in geriatric feline medicine."[16] Yes, we can help, but we also need to know when to stop.

We are very fortunate to practice in times that allow us to not only recognize changes and conditions associated with aging, but also influence the experience of growing older. With courage and perspective, we can improve the lives of our patients, making their older years more enjoyable for both them and their human companions.

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Treatment of liver disease in dogs and cats: The role of nutrition in patient management

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Few controlled studies have investigated treatments for liver disease in dogs and cats. Among the recommended therapies, most studies suggest the importance of providing adequate nutritional support. Managing hepatic encephalopathy and feline idiopathic hepatic lipidosis are prime examples of situations in which nutrition is critical.

The liver is paramount in metabolism and plays a key role in regulating protein, carbohydrates, fat, vitamins, and minerals. Metabolic derangements that occur with liver disease can lead to malnutrition, impaired hepatic regeneration, and the clinical consequences of hepatic insufficiency (*e.g.*, hepatic encephalopathy, ascites, gastrointestinal ulceration, coagulopathies, and immune suppression). The liver can regenerate following injury, and this process must be promoted through appropriate nutrition.

Figure 1 (page 24) lists my treatment goals for managing liver disease. The goal of nutritional management of liver disease is predominately supportive and requires a fine balance between promoting hepatocellular regeneration and providing nutrients to maintain homeostasis—without exceeding the metabolic capacity that will lead to accumulation of toxic metabolites.

This article will cover nutritional aspects of managing liver disease in small animals, including dietary composition, antioxidants, nutraceuticals, and feeding management for patients with hepatic encephalopathy and idiopathic hepatic lipidosis. In addition, this article will discuss a number of misconceptions and controversies regarding nutritional considerations when treating patients with liver disease.

Basic nutritional concepts

Anorexia and weight loss occur commonly in patients with liver disease, and consequently one of the most important aspects in liver disease therapy is ensuring the patient has appropriate energy intake to minimize catabolism. Adjustments to the diet are required when malnutrition is present. To this end, practitioners must first calculate the patient's caloric needs to ensure the patient's intake meets those calculations. Calculation of the basal energy requirements is based on the weight of the lean body mass; the weight of fat or ascites is not included in the calculation. *Figure 2* (page 25) explains how to calculate a patient's basal energy requirements.

The basal energy requirement can then be multiplied by an

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Figure 1. Liver disease treatment goals

When I treat liver disease, I address four treatment goals in every case:

1. Remove or correct the inciting etiology, if identified.
2. Provide adequate nutrition and prevent malnutrition.
3. Provide specific treatment of hepatic disease or related complications.
4. Provide an environment for optimal hepatic function and regeneration.

illness factor that is estimated to be between 1.0 to 1.4 to achieve daily caloric needs.[1] No comprehensive studies have looked at illness factors in dogs or cats with liver disease; however, studies have shown that people with cirrhosis have an energy intake comparable to normal controls.[2] In any event, energy requirements should be individually adjusted to maintain optimal body weight.

Palatability. It is important to ensure that poor palatability of the diet is not the reason the patient refuses to eat. Practitioners can offer the ideal diet for a particular condition, but if the patient is unwilling to eat it, it becomes essentially worthless. I would rather see patients eat almost any diet than nothing at all. When nutritional requirements are not being met by voluntary intake, practitioners should then consider enteral supplementation, which will enable the clinician to have better dietary control.

Fat. A misconception regarding fat content in the diet often exists when treating liver disease. This is especially true of nutritional management of feline hepatic lipidosis because some practitioners believe that affected patients should be fed lower-fat diets. However, dogs and cats with liver disease in general have a good tolerance for fat in their diet. Fat not only improves the palatability but also provides important energy density to the diet. In general, lipid restriction is not necessary for patients with liver disease; this even holds true for cats with idiopathic hepatic lipidosis.

Carbohydrates. It is suggested that carbohydrates should make up no more than 35% and 45% of the diet's total calories for cats and dogs, respectively.[3] Adequate carbohydrate intake is important to maintain glucose concentrations, especially in dogs with advanced liver disease or animals with portosystemic shunts where hypoglycemia is a concern. Feeding small yet frequent meals throughout each day may help maintain glucose concentrations. I have observed hyperglycemia in some dogs with cirrhosis and portosystemic shunts and some cats with hepatic lipidosis. This becomes especially true in cats also receiving steroids. Cats with glucose intolerance, or the tendency to develop hyperglycemia with feeding, in conjunction with liver disease (and sometimes concurrent steroid therapy) will require a lower-carbohydrate content diet. The best way to prevent hyperglycemia or hypoglycemia is to feed frequent yet small meals (four to six times a day). In general, I prefer to feed patients with liver disease an energy-dense, low-fiber diet. However, a role for fiber exists in the dietary management as it relates to the treatment of hepatic encephalopathy and will be discussed later.

Protein. A misconception also exists about protein content when feeding animals with liver disease. It was previously thought that patients with liver disease should be placed on a protein-restricted diet to reduce the liver's workload and the production of detrimental nitrogenous waste products. This is not well substantiated. Many veterinary nutritionists and gastroenterologists now believe restricting protein could be detrimental, especially if the patients have a negative nitrogen balance.[4] The goals of dietary protein intake are to adjust the quantities and types of nutrients to meet the patient's nutrient requirements and to avoid the production of excess nitrogen by-products causing hepatic encephalopathy. It is always important to provide the patient with a high-quality, highly digestible protein source.[5] Poor-quality proteins may aggravate hepatic encephalopathy and fail to promote hepatic regeneration.

In some instances, it is possible that the protein requirements for patients with liver disease may actually be greater than those of the normal animal. Most quality commercial or prescription diets are suitable for this purpose. As a general recommendation, dietary protein should represent 15% to 20% of the digestible kilocalories

(kcal) of the diet.[3] Clinically, protein restriction should only be instituted in patients that have evidence of protein intolerance; this is most often patients with portosystemic shunts or signs of hepatic encephalopathy.[6]

In these situations, lower protein content diets and diets with a milk- or plant-based protein source rather than a meat source are recommended to prevent hepatic encephalopathy and colonic production of excess nitrogen byproducts. Because cats have such a high protein requirement, I rarely—if ever—limit protein intake in cases of feline liver disease, such as lipidosis. I find hepatic encephalopathy an uncommon consequence in cats.

Trace minerals

With certain types of liver disease, changes occur in the hepatic trace mineral content. Most of the information available to practitioners deals with changes in copper and zinc as they relate to chronic hepatitis or cirrhosis.

Copper. Copper is an essential trace metal required for many metabolic functions. The liver is quintessential in regulating the concentration and excretion of excess copper through bile. Hepatic copper concentrations can increase in dogs either because of a primary genetic defect in hepatic copper metabolism noted in some breeds or diminished copper excretion secondary to cholestatic liver disease. Copper accumulation caused by cholestatic disease does not occur as frequently and copper concentrations are lower than in the breed-associated cases of copper hepatotoxicity.

With either mechanism of copper accumulation, subcellular damage in hepatocytes can result. It appears that damage from copper results in lipid peroxidation.[7] Copper-specific chelators (*e.g.*, penicillamine, trientine) are the standard therapies used to remove excess hepatic copper in cases of breed-associated copper hepatotoxicity. It is also important to feed diets with a lower copper content and to avoid nutritional supplements with additional copper. A restricted copper intake of about 1.25 mg/1,000 kcal of metabolizable energy is suggested.[3] Most diets list their copper content on the label; if not, the manufacturer can provide this information. If a homemade diet is used, exclude liver, shellfish, organ meats, and cereals, which are all high in copper content.

Zinc. Zinc is an essential trace metal involved in many metabolic and enzymatic functions of the body. Zinc is important in the intermediary metabolism involved in enhanced ureagenesis, glutathione concentrations, and immune function. The direct hepatoprotective effects of zinc include the inhibition of lipid peroxidation and destabilization of lysosomal membranes. Zinc also appears to have antifibrotic activities. Zinc deficiency occurs in many people with advanced chronic liver disease and seems to correlate with hepatic encephalopathy, which demonstrates zinc's importance in ureagenesis.[4]

Dietary zinc works by inducing an increased formation of a metal-binding protein (metallothionein) in intestinal epithelial cells. This protein binds dietary copper with a high affinity and prevents its transfer from the intestine into the blood. When the intestinal cells die and are sloughed into the intestinal tract, so is the copper.[8] I recently reviewed the metal content of a small group of dogs with chronic hepatitis or cirrhosis and found that two-thirds had a decreased hepatic zinc concentration. Zinc supplementation (*e.g.*, zinc acetate, sulfate, or gluconate) at a maintenance dose of 2 to 4 mg/kg/day is suggested for these cases.[3] Zinc acetate is reported to be effective in both decreasing and preventing hepatic copper accumulation in some breeds, associated with copper hepatotoxicity. Zinc acetate (Galzin—Gate Pharmaceuticals) is recommended for blocking copper absorption.

Zinc should be administered on

Figure 2. Caluclate a patient's basal energy requirements

For animals < 2 kg:
$70 \times [kg^*]^{0.75} = kcal/day$

For animals ≥ 2 kg:
$30 \times [kg^*] + 70 = kcal/day$

Nutritional requirements for most cats can also be expressed as 50 to 55 kcal/kg body weight.

* Of lean body mass

an empty stomach, and toxicity other than occasional vomiting is minimal. To block intestinal copper absorption, I use 50 mg zinc acetate twice a day as an induction dose for two months and 25 mg twice a day thereafter. It is suggested to monitor serum zinc concentrations during the early induction period to ensure zinc levels increase to about 200 µg/ml (ppm)—but take care to not approach a toxic range (>500 to 1,000 µg/ml).[9]

Vitamins

The liver is the major organ for vitamin metabolism. Both vitamin storage as well as the conversion of provitamins to their metabolically active state takes place in the hepatocytes of the liver. Consequently, practitioners must contemplate the vitamin status of patients with liver disease. The fat-soluble vitamins (*i.e.*, A, D, E, and K) are prone to be deficient because they require bile salts to form intestinal micelles for absorption. In cholestatic liver disease, bile acids abnormally excrete into the intestine, which affects the uptake of fat-soluble vitamins.[10] The water-soluble vitamins (*i.e.*, B vitamins, vitamin C) are generally found in high concentrations in the liver where many are stored as coenzymes. In patients with liver disease, an increased demand for these vitamins, altered conversion to the vitamin's active form, or decreased hepatic storage may occur.

Vitamin E. Vitamin E (alpha-tocopherol) functions as a cellular membrane-bound antioxidant. Evidence now shows that oxidative damage occurs during liver disease from free radical generation.[11] While cellular damage in liver disease is probably multifactorial, free radicals may play an important role in initiating or perpetuating this damage. Free radicals are molecules with an unpaired electron that form by the injurious effects of certain drugs or various other toxic agents or events. Abnormal concentrations of bile acids and the accumulation of heavy metals, such as copper and iron, have been shown to cause free radical generation in the liver. If not inactivated, free radicals damage cellular macromolecules via lipid peroxidation and thus participate in cellular injury when produced in excess.

Normally, an extensive system of cytosolic and membrane-bound enzymatic and nonenzymatic antioxidants prevent oxidative damage by scavenging or quenching free radicals that are formed. Vitamin E is a major membrane-bound intracellular antioxidant that protects membrane phospholipids from peroxidative damage when free radicals are formed. Evidence shows that dietary supplementation with vitamin E reduces oxidant injury to hepatic tissue.[11] Bedlington terriers with copper-associated hepatopathy have oxidant damage in their mitochondria and reduced mitochondrial vitamin E concentrations.[12] Vitamin E has also shown a protective effect in the liver from copper-related oxidant damage and bile acids.[13]

Vitamin E is inexpensive and safe when supplemented at a dose of 10 IU/kg/day. *d*-Alpha-tocopherol, the natural form of vitamin E, is recommended because of greater uptake, dispersion, and bioactivity compared with the more common synthetic *dl*-alpha-tocopherol formulation. *d*-Alpha-tocopherol is also retained in tissues by a two-to-one ratio over the synthetic formulation.[10] With significant cholestatic liver disease, I suggest a water-soluble formulation (Liqui-E—Twin Labs).

Vitamin C. Ascorbic acid (vitamin C) is an important soluble intracellular antioxidant that helps convert oxidized tocopherol radicals back to active alpha-tocopherol. Vitamin C is also necessary for the synthesis of carnitine, which is important for transport of fat into mitochondria. People with liver disease often have low hepatic vitamin C concentrations in part because people can't synthesize vitamin C, but dogs and cats can. Although vitamin C supplementation may be a beneficial adjunct in treating liver disease, supplementation of excessive amounts of vitamin C may be deleterious in patients with increased hepatic copper or iron concentrations. This is because ascorbate is believed to promote oxidative damage caused by these transition metals.[11]

Vitamin K. Vitamin K stores in the liver can become depleted with advanced liver disease and can result in serious coagulopathies. Deficiency can occur from reduced intestinal absorption from cholestatic liver disease or as the result of advanced liver dysfunction with a failure of

hepatic conversion to the vitamin K-dependant coagulation factors (*i.e.*, factors II, VII, IX, and X). This can result in prolongation of coagulation as measured by prothrombin time or activated partial thromboplastin time and can cause significant bleeding.

Vitamin K supplementation is warranted in patients with liver disease to maintain hepatic stores. With severe cholestasis or overt coagulation abnormalities, parenteral vitamin K_1 (phytonadione) at 0.5 to 2.0 mg/kg every 12 hours subcutaneously for two to three dosages (or until normalization of prothrombin time) is recommended for dogs and cats with hepatic disease. Vitamin K_1 supplementation is recommended for 24 to 36 hours before invasive procedures, such as hepatic biopsy or feeding tube placement.[6]

B vitamins. The water-soluble B vitamins are important in many metabolic functions and may become deficient in both dogs and cats with liver disease. However, deficiencies are difficult to diagnose or analytically document. Because the B vitamins are water-soluble, they are relatively nontoxic and supplementation is recommended in patients with liver disease.

Cats are particularly prone to B vitamin deficiency. Subnormal concentrations of vitamin B_{12} (cobalamin) is reported in cats with liver disease and, in particular, idiopathic hepatic lipidosis.[14] Cats with cholangiohepatitis frequently have concurrent inflammatory bowel disease or chronic pancreatitis and subsequent cobalamin deficiency. The recommended dose of cobalamin for cats is 250 µg given subcutaneously weekly until normal cobalamin concentrations are maintained. Thiamine (vitamin B_1) deficiency is also a concern in cats with poor nutritional intake. Adequate dietary supplementation prevents deficiency.

Nutraceuticals

A nutraceutical is not quite a foodstuff and not quite a drug—it appears to lie somewhere in between. The North American Veterinary Nutraceutical Council defined a nutraceutical as "a non-drug substance that is produced in a purified or extracted form and administered orally to patients to provide agents required for normal body structure and function and administered with the intent of improving the health and well being of animals."[15] Because nutraceuticals are not classified as drugs, they are not subject to Food & Drug Administration approval showing purity, safety, and efficacy. Many nutraceuticals available for use in animals are listed as nutritional supplements. Typical categories of nutraceutical products used in pets include antioxidants, omega fatty acids, amino acids, chondroprotective agents, herbals, and probiotics. Although some nutraceuticals have shown a potential for improving veterinary care, little information is known about the purity, dosage, safety, side effects, and effectiveness of the substance for the prescribed disease treated. The nutraceutical industry, with a few exceptions, has done little to answer these important questions. Below are some nutraceutical compounds used in the management of liver disease that have shown at least some scientific evidence for both effectiveness and relative safety.

S-adenosylmethionine. The naturally occurring molecule S-adenosylmethionine (SAMe) is synthesized in all living cells, is essential in intermediary metabolism, and has both hepatoprotective and antioxidant properties. SAMe is produced from the amino acid methionine and subsequently initiates one of three metabolic pathways. The transmethylation pathway is essential in phospholipid synthesis, which is important in membrane structure, fluidity, and function. 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 hepatic glutathione can indirectly cause toxic effects in these cells by increasing oxidative stress. The aminopropylation pathway yields products that have anti-inflammatory 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 concentrations.[16] Orally administered SAMe (but not oral glutathione) has been shown to increase intracellular glutathione levels in hepatocytes and prevent

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glutathione depletion when exposed to toxic substances.[17] Thus, SAMe in part acts as an antioxidant replenishing the glutathione stores. Preliminary veterinary studies suggest that SAMe supplementation increases hepatic glutathione concentrations in normal cats and prevents glutathione depletion in dogs with steroid-induced hepatopathy.[17] SAMe treatment following acetaminophen administration prevented hepatic glutathione depletion.[18]

SAMe (Denosyl—Nutramax Laboratories) is my preference for both dogs and cats. Because SAMe is easily oxidized when exposed to air, only foil-wrapped preparations should be used. Enteric-coated tablets should not be broken or crushed because of gastric acid inactivation. Further, the product purity can be quite variable from formulation to formulation, so it is advisable to use products only from reputable companies.

Phosphatidylcholine. Phosphatidylcholine is a phospholipid used as a nutritional supplement for its hepatoprotective effects. A building block for cell membranes, phosphatidylcholine is one of the components required for normal bile acid transport. It is thought to be hepatoprotective by improving membrane integrity and function. In vitro studies have shown phosphatidylcholine increases hepatic collagenase activity and may also help prevent fibrosis.[19] Clinical trials indicate that phosphatidylcholine protects the liver against damage from alcohol, viral hepatitis, and other toxic factors that operate by damaging cell membranes. In two animal studies using baboons given alcohol and supplemented with 60% phosphatidylcholine, both fibrosis and cirrhosis were largely prevented in the phosphatidylcholine-treated group.[19]

Several forms of phosphatidylcholine supplements are available, and no major side effects have been reported other than occasional nausea or diarrhea. Based on the multiple mechanisms of action of phosphatidylcholine, this nutrient may be beneficial for chronic liver disease because oxidative stress, cytokine alterations, and fibrosis ensue. Given the apparent safety of phosphatidylcholine and its acceptable cost, animal studies would appear to be worthwhile. Phosphatidylcholine is rapidly absorbed, enhances absorption of other compounds, and is included as a carrier in one silybin product (Marin—Nutramax Laboratories).

N-acetylcysteine. *N*-acetylcysteine, the acetylated variant of the amino acid L-cysteine, is an excellent source of sulfhydryl groups and is converted in the body into metabolites capable of stimulating glutathione synthesis, promoting detoxification, and acting directly as free radical scavengers. *N*-acetylcysteine has historically been used as a mucolytic agent in a variety of respiratory illnesses; however, it appears to also have beneficial effects in other conditions characterized by oxidative stress or decreased glutathione concentrations. *N*-acetylcysteine is currently the mainstay of treatment for acetaminophen-induced hepatotoxicity.[18] It also appears to have some clinical usefulness as a chelating agent in the treatment of acute metal poisoning, both as an agent capable of protecting the liver and kidney from damage and as an intervention to enhance elimination of the metals.

Although *N*-acetylcysteine is produced as a drug, it is also available as a nutritional supplement. The oral dose recommended for acetaminophen toxicity is 70 mg/kg three times a day. When given intravenously, a loading dose of 140 mg/kg is given and followed by the 70 mg/kg dosing. *N*-acetylcysteine is reported to have extremely low toxicity with few side effects.

Carnitine. L-carnitine is a vitamin-like substance found in most cells. Synthesis of carnitine is predominately in the liver, and, consequently, liver disease may result in deficiency states. The primary function of L-carnitine is to transport long-chain fatty acids across the inner mitochondrial membrane into the mitochondria for ß-oxidation to form acetyl CoA fragments. These fragments then enter the citric acid cycle for energy production.

Carnitine deficiency may result in hepatocyte triglyceride accumulation and lead to accumulation of toxic acetyl CoA metabolites that impair mitochondrial respiration and function. Clinically, carnitine deficiency has been associated with increased ammonia concentrations, hypoglycemia, and fatty livers.[20]

In a study where carnitine was given to obese cats undergoing rapid weight loss from caloric

restriction, researchers found it protected against hepatic triglyceride accumulation.[20] Some studies suggest that L-carnitine deficiency may play a role in the pathogenesis of idiopathic feline hepatic lipidosis; however, carnitine concentrations were higher in the plasma, liver, and muscle than in control cats.[21] A deficiency of carnitine may lead to impaired mitochondrial function; however, these studies failed to show carnitine deficiency in cats with hepatic lipidosis.[22] Supplementation is reported to be associated with better survival rates, but this is not well documented.

Silymarin. Milk thistle grows wild throughout Europe and has been used there for more than 2,000 years as a medical remedy for liver disease. The active extract of milk thistle is silymarin, which is classified as a nutraceutical in the United States. Mounting evidence suggests that milk thistle has medicinal benefits for various types of liver disease as well as a protective effect against hepatotoxins. A recent poll of liver patients at one U.S. hepatology clinic found that 31% were also using alternative agents for their disease and that milk thistle was the most commonly used nontraditional therapy.[23]

Silymarin is the active extract in milk thistle. A standard milk thistle extract is approximately 70% silymarin and contains four flavonoid stereoisomers—and the most biologically potent one is silybin. An abundance of both in vivo animal and in vitro experimental data shows the antioxidant properties and free radical scavenging properties of silymarin. Specifically, silymarin inhibits lipid peroxidation of hepatocyte and microsomal membranes and protects against gene damage by suppressing hydrogen peroxide, superoxide anions, and lipoxygenase. Silymarin also increases hepatic glutathione content and appears to retard hepatic collagen formation. Evidence also suggests that silymarin has hepatoprotective effects through the inhibition of Kupffer cell function by inhibiting leukotriene B_4 production and hepatotoxin binding to receptor sites on hepatocyte membranes, which provide additional stability against xenobiotic injury.[23]

Several human trials have assessed the efficacy of silymarin in the treatment of liver disease. The data are somewhat difficult to interpret because of the limited number of patients, poor study design, variable etiologies, and lack of standardization of preparations with different dosing protocols. However, compelling evidence in many studies suggests that silymarin has a therapeutic effect in acute viral hepatitis, alcoholic liver disease, cirrhosis, and toxin- or drug-induced hepatitis.[24] To date, limited clinical studies have evaluated the efficacy of silymarin in liver disease in dogs and cats. In one placebo-controlled experimental study of dogs poisoned with the *Amanita phalloides* mushroom, silybin had a significant positive effect on liver damage and survival outcome.[25]

The purity and potency of commercial milk thistle products vary by manufacturer, and the therapeutic dosage for dogs and cats is unknown. Suggested doses for silymarin range from 50 to 250 mg/day. Milk thistle is reported to have an extremely low toxicity and has been used extensively in clinical patients with little concern for side effects. When the active isomer silybin is complexed with phosphatidylcholine, oral uptake and bioavailability is greater.[26] I recently performed a pharmacokinetic study evaluating a commercially available silybin-phosphatidylcholine complex (Marin—Nutramax Labs) in normal cats, which found no clinical outward signs of toxicity at 5 mg/kg daily and showed evidence of some oxidative protection in red blood cells.

Nutritional management of specific hepatic conditions

Hepatic encephalopathy. Hepatic encephalopathy results from either portosystemic shunting of blood (congenital or acquired) or hepatocyte depletion from either acute or chronic liver disease. Many factors can cause hepatic encephalopathy, and most of these are derived from nitrogenous products produced in the gastrointestinal tract. Ammonia is only one of many substances that cause hepatic encephalopathy but is commonly used as its marker. Plasma amino acid concentrations may become altered in patients with liver disease. Increased levels of aromatic amino acids are hypothesized to form false neurotransmitters, leading to hepatic encephalopathy, while higher concentrations of branched-chain amino acids had a more protective

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Figure 3. Hepatic encephalopathy treatment goals

When I treat patients with hepatic encephalopathy, my therapeutic goals include:

1. Recognize and correct precipitating causes of encephalopathy.
2. Reduce intestinal production and absorption of neurotoxins, with special emphasis on ammonia.
3. Achieve the fine balance between providing too much and too little protein.

effect.[5] See *Figure 3* for the therapeutic goals of managing hepatic encephalopathy.

The importance of the dietary protein source has been studied in human patients with hepatic encephalopathy and in several experimental studies in dogs with portosystemic shunts.[27] Vegetable and dairy protein sources with lower concentrations of aromatic amino acids have produced the best results in maintaining a positive nitrogen balance with minimal encephalopathic signs.[5] Foods using soybean meal averted encephalopathic signs in dogs with experimentally created shunts,[27] and Purina Veterinary Diets HA Hypoallergenic formula could be an option in these cases. In addition, dairy products (especially cottage cheese) have been frequently recommended for use in homemade foods for dogs and cats with portosystemic shunts and chronic hepatic insufficiency.[3] However, the amino acid composition of these protein sources is not significantly different from that of meat sources, suggesting that other food factors (*e.g.*, digestibility, levels of soluble carbohydrate and fermentable fiber) are important.

Fermentable carbohydrates increase microbial nitrogen fixation, reduce intraluminal ammonia production in the gut, and promote colonic evacuation. Fermentable fiber added to the diet has been shown to decrease ammonia production.

The first step to managing hepatic encephalopathy is using enemas to clean the colon of both bacteria and protein substrates for ammonia production. Slightly acidic enemas will lower the pH of the colon, thus ionizing ammonia and reducing its absorption. Povidone iodine can safely be given by enema as a 10% solution (weak-tea color) that will both acidify the colon and have an antiseptic action reducing bacterial numbers.

Intestinal antibiotics are used to alter bowel flora and suppress urease-producing organisms important in forming factors that cause hepatic encephalopathy. Antibiotic suggestions include oral ampicillin, aminoglycosides (*e.g.*, neomycin, kanamycin, or gentamicin), or metronidazole. Metronidazole given orally at 7 to 10 mg/kg twice a day has been useful in controlling anaerobic urease-producing bacteria. Practitioners should monitor patients carefully because metronidazole is partially metabolized in the liver, and, therefore, the lower dose range is suggested.

A nondigestible disaccharide lactulose (Cephulac or Chronulac—Hoechst-Marion Roussel) given orally acidifies the colon, converts ammonia to ammonium that is poorly absorbable, and thus, traps ammonia in the colon. The fermentation products of lactulose will also act as an osmotic laxative and reduce colonic bacteria and protein substrates. Lactulose is not absorbed systemically and is considered safe. A dose of 1 to 10 ml orally three times a day is generally effective, but the dose should be adjusted to cause three or four soft stools a day. If diarrhea develops, the dose should be reduced. Lactulose can also be given by enema in treating severe cases of hepatic encephalopathy.

Commercial and homemade foods can be supplemented with various sources of soluble fiber, such as psyllium husk fiber or Metamucil (1 tsp per 5 to 10 kg body weight, added to each meal). If loose stools occur, reduce the supplemental fiber by half.

Feline idiopathic hepatic lipidosis. The therapy for idiopathic hepatic lipidosis requires aggressive management. Appropriate fluid and electrolyte replacement is critical, and the next step is to provide adequate nutrition. Hand-forced feeding may be used, but it is usually difficult to supply adequate caloric support through this method, which can become a major stressor to the cat. Therefore, tube feeding is the crux to the therapy in these cases. Esophageal or gastrostomy feeding tubes are ideal for most

cases because a blended diet and any medications and supplements can be administered through the tube without stressing the patient. Nasogastric tubes are thought to be less desirable than gastrostomy tubes because of the small size limit and consistency of food administered. I suggest placing an esophageal or gastrostomy feeding tube. I find esophageal tubes to be well tolerated with fewer complications than gastrostomy tubes, and they cost less.

In some cats, nutritionally managing patients 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 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 of the commencement of feeding.[28] 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.

The nutritional recommendations for idiopathic hepatic lipidosis are completely empirical and not well documented. Numerous reports suggest various diets (with a variety of protein and fat content recommendations) and various dietary supplements. Commercial feline diets or nutritional support diets formulated for tube feeding are generally used.

Some practitioners recommend L-carnitine supplementation for cats with hepatic lipidosis at 250 mg/cat/day, but additional studies are necessary to determine the benefit of this supplementation in cats with hepatic lipidosis.

Healthy adult cats can develop hyperammonemia and hepatic encephalopathy when fed foods that are devoid of arginine.[4] Arginine levels in food should always be above the minimum dietary allowance for adult maintenance (>1.0% of the diet on a dry matter basis is the daily minimum in cats), and commercial balanced diets contain adequate arginine concentrations.

Vomiting can be a serious complication associated with tube feeding and reintroduction of food. I have recently been using maropitant (Cerenia—Pfizer) in these cats with good success. The drug is metabolized by the liver, so it should be used with caution in animals with hepatic dysfunction. My normal dose for cats is 0.5 mg/kg subcutaneously every 24 hours, and the dose in cats with hepatic lipidosis is halved (0.25 mg/kg subcutaneously every 24 hours). Mertazipine (Remeron—Organon [one-eighth of a 15 mg tablet every three days]) also has antiemetic effects and is an appetite stimulant.

Considerable interest and research is being directed at various nutrient supplements, and at this time many of the recommendations are only speculative or anecdotal. Some suggest arginine (1,000 mg/day), thiamine (100 mg/day), and taurine (500 mg/day) for three to four weeks.[29] Methionine, a reported lipotropic agent, should not be supplemented to cats because it can augment hepatic encephalopathy.[30] Other supplements suggested include zinc, fish oil, and potassium.

New evidence suggests that many—if not all—cats with hepatic lipidosis have a cobalamin deficiency.[14] Deficiency can result in lethargy, anorexia, and weight loss. Anecdotal reports suggest cats improve faster when treated with cobalamin given 250 µg subcutaneously weekly. Serum cobalamin levels can be determined to document the deficiency.

Other therapies suggested include SAMe and other antioxidants.

Summary

It is critical to recognize the complexity of the nutritional needs of patients with liver disease as well as nutrition's importance in their recovery. Practitioners must formulate a diet for their patients that includes appropriate dietary supplements by taking into account their knowledge of the disease being treated and the patient's suspected nutritional needs.

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View this publication and a complete reference list online at www.advanstarvhc.com/c31.

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