Wait, Wait, Don’t Tell Me…
Controversial and Challenging
Feline Cases
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Senior Research Scientist, Nestlé Purina PetCare
Outline of diagnostic approaches that can help practitioners solve three endocrine presentations in cats

Feline IBD: The Good (Diets), the Bad (Bacteria), and the Ugly (Diagnosis)
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The role of intestinal bacteria and diet in the diagnosis and management of IBD in cats

Treatment of Liver Disease:
Medical and Nutritional Aspects
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College of Veterinary Medicine & Biomedical Sciences, Colorado State University, Fort Collins, Colorado
Understanding the major aspects involved in diagnosing and treating canine and feline liver disease

From Problem to Success: A Weight Loss Program That Works, Growing Relationships, Not Girth in Cats
Margie Scherk, DVM, DABVP (Feline),
Vancouver, BC, Canada
Designing a weight loss program that can ensure success—both for the cat and the client
Disorders of the endocrine system are routinely encountered in feline practice. Certain endocrine disorders, such as hyperthyroidism and diabetes mellitus, are relatively simple to diagnose in cats, whereas others, such as hypoadrenocorticism, are more challenging. This article outlines the diagnostic approach for three common endocrine presentations in cats—polydipsia/polyuria (PU/PD), weight gain, and insulin resistance as reflected by clinical cases in the field.

**Evaluation of Polydipsia/Polyuria**

One of the most common presenting complaints for endocrine disorders is PU/PD. The major endocrine diseases that cause PU/PD are, in order of frequency, diabetes mellitus, hyperthyroidism, hyperadrenocorticism, acromegaly or hypersomatropism, hypercalcemia resulting from hyperparathyroidism, hypokalemia associated with hyperaldosteronism, diabetes insipidus, and pheochromocytoma (Table 1).

The diagnostic approach to polydipsia and polyuria is shown in Figure 1. In patients presenting with PU or PD, the clinician must first document whether the patient is indeed drinking or urinating excessively. The most common condition mistaken for PU is pollakiuria (Table 2) resulting from urinary tract disease. When the presence of PU/PD is suspect, the clinician should ask several questions to determine whether the cat is consuming or eliminating excessive water. The presence of large amounts of urine in the litter box as opposed to small, more frequently eliminated amounts of urine points to PU and compensatory PD.

PD may be more difficult to identify than PU. In general, because cats are desert species, it is unusual to witness cats drinking water frequently. In contrast, dogs are often presented for PD when they are, in fact, just “sloppy” drinkers. If the owner can quantitate and measure the amount of water the cat is drinking, any consumption of water in excess of 60 to 70 ml/kg/day would be considered PD.

**Evaluation of Weight Gain**

Endocrine causes of weight gain include, in order of frequency, type 2 diabetes mellitus, hyperadrenocorticism, hypothy
Table 2. Distinguishing PU from Pollakiuria and Incontinence

<table>
<thead>
<tr>
<th>Signs</th>
<th>PU</th>
<th>Pollakiuria</th>
<th>Incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urination</td>
<td>Active</td>
<td>Active</td>
<td>Passive</td>
</tr>
<tr>
<td>Frequency</td>
<td>2–3 times normal</td>
<td>More than 3 times normal</td>
<td>Nocturia</td>
</tr>
<tr>
<td>Urgency</td>
<td>Uncommon</td>
<td>Common</td>
<td>None</td>
</tr>
<tr>
<td>Volume of urine</td>
<td>Increased</td>
<td>Small, multiple</td>
<td>Variable</td>
</tr>
<tr>
<td>Mucus</td>
<td>Rare</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Concentration of urine</td>
<td>Dilute</td>
<td>Concentrated</td>
<td>Either</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
</tr>
</tbody>
</table>

PU = polyuria

Figure 1. Diagnostic Flowchart for PD and PU

ACTH = adrenocorticotropic hormone; ARF = acute renal failure; BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; Cr = creatinine; CRF = chronic renal failure; DDAVP = brand name for desmopressin acetate; DI = diabetes insipidus; DM = diabetes mellitus; fT₄ = free thyroxine; IGF = insulin-like growth factor; K = potassium; LDDS = low-dose dexamethasone suppression; LSA = lymphosarcoma; MDB = minimum database; PD = polydipsia; PSS = portosystemic shunt; PU = polyuria; SCC = squamous cell carcinoma; TT₄ = total thyroxine; U/A = urinalysis; USG = urine-specific gravity
Creating a diagnostic flowchart of common rule outs can help eliminate endocrine disorders as diagnostic differentials (Figure 2).

The dietary history is one of the most important aspects of history taking for weight gain. The examiner should ask what type of diet is being fed—homemade, raw, or commercial. For commercial diets, is the cat primarily fed dry food or a mixture of dry and canned food? If the cat is being fed a commercial food, also ask about the specific brand, and if the diet is homemade, ask for a complete list of ingredients.

Other important questions include:
- How long has the diet been fed?
- When was the diet changed last, and how frequently is it changed?
- How much is the cat eating, and how is the food being measured (weighing vs cups)?
- Is the cat fed ad libitum or restricted? How many times per day is the cat fed?

### Table 3. Causes of Weight Gain

<table>
<thead>
<tr>
<th>Endocrine Causes</th>
<th>Nonendocrine Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperadrenocorticism</td>
<td>Overfeeding</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Feeding treats</td>
</tr>
<tr>
<td>Hypersomatotropism (acromegaly)</td>
<td>Feeding high caloric density food</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Large abdominal tumors</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus—early</td>
<td></td>
</tr>
</tbody>
</table>

(see Nestlé Purina Body Condition System).

The primary differentials for nonendocrine causes of weight gain, which are much more common, feature overfeeding and the feeding of treats. Patient records on the body condition score (BCS) can help determine whether the weight gain is a result of nonendocrine problems.

**Figure 2. Diagnostic Flowchart for Weight Gain**

- **Weight gain**
  - **INCREASED appetite**
    - **Hyperglycemia, increased fructosamine**
    - **Low-carbohydrate diet, insulin, oral hypoglycemics**
      - **RESPONSE**
        - Early type 2 DM
      - **NO RESPONSE**
        - LDDS, IGF
  - **NORMAL appetite**
    - **MDB**
    - **RULE OUT overfeeding**
    - **Normal**
    - **LOW BG**
      - **RULE OUT insulinoma**
      - **NORMAL**
    - **LOW TT₄ and HIGH TSH**
      - **Hypothyroidism**
        - **fT₄ by dialysis**
    - **LOW TT₄ and LOW TSH**
      - **SECONDARY hypothyroidism**
      - **LDDS, IGF**
      - **NORMAL or HIGH fT₄**
      - **Euthyroid sick syndrome**
  - **DECREASED appetite**
    - **MDB, TSH, TT₄**

**Test**
- **Endocrine disorder**

BG = blood glucose; DM = diabetes mellitus; fT₄ = free thyroxine; IGF = insulin-like growth factor; LDDS = low-dose dexamethasone suppression; MDB = minimum database; OM = Purina Veterinary Diets OM Overweight Management Feline Formula; TSH = thyroid-stimulating hormone; TT₄ = total thyroxine
1. Ribs visible on shorthaired cats; no palpable fat; severe abdominal tuck; lumbar vertebrae and wings of ilia easily palpated.

2. Ribs easily visible on shorthaired cats; lumbar vertebrae obvious with minimal muscle mass; pronounced abdominal tuck; no palpable fat.

3. Ribs easily palpable with minimal fat covering; lumbar vertebrae obvious; obvious waist behind ribs; minimal abdominal fat.

4. Ribs palpable with minimal fat covering; noticeable waist behind ribs; slight abdominal tuck; abdominal fat pad absent.

5. Well-proportioned; observe waist behind ribs; ribs palpable with slight fat covering; abdominal fat pad minimal.

6. Ribs palpable with slight excess fat covering; waist and abdominal fat pad distinguishable but not obvious; abdominal tuck absent.

7. Ribs not easily palpated with moderate fat covering; waist poorly discernible; obvious rounding of abdomen; moderate abdominal fat pad.

8. Ribs not palpable with excess fat covering; waist absent; obvious rounding of abdomen with prominent abdominal fat pad; fat deposits present over lumbar area.

9. Ribs not palpable under heavy fat cover; heavy fat deposits over lumbar area, face and limbs; distention of abdomen with no waist; extensive abdominal fat deposits.

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Tips for Investigating Weight Gain

- In cats, always check the underside of the tarsus for evidence of diabetic neuropathy.
- Ask the client to bring photographs of the patient from several years ago for comparison of skull and facial changes.
- Check the patient’s teeth for increased interdental spaces (acromegaly).
- Assign a BCS and record each score in the patient’s medical record. Cats in normal body condition (BCS 4–5 on the Nestlé Purina scale) will have ribs easily palpable and normal abdominal tuck.
- If necessary, perform the knuckle test (quick BCS). Animals in normal body condition have ribs that feel like the tops of the knuckles with the hand extended. Overweight patients have ribs that palpate similar to the palm of the extended hand.

BCS = body condition score

Table 4. Causes of Insulin Resistance

<table>
<thead>
<tr>
<th>Endocrine Causes</th>
<th>Nonendocrine Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>Infection (eg, UTI, pulmonary, skin disease)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Cancer</td>
</tr>
<tr>
<td>Hyperadrenocorticism</td>
<td>Immune disease</td>
</tr>
<tr>
<td>Hypersomatotropism (acromegaly)</td>
<td>Drugs, pancreatitis, liver disease, stress</td>
</tr>
</tbody>
</table>

UTI = urinary tract infection

Evaluation of Insulin Resistance

It is very rare to obtain a perfect glucose curve in a patient. Generally, problems associated with the blood glucose curve can be differentiated by the characteristics of the curve and the insulin dose (dosing interval).

If the patient is receiving less than 2.2 U/kg per dose, the blood glucose curve is usually indicative of one of the following:

- Insufficient insulin dose—Corrective action, increase dose
- Short duration of action of insulin—Corrective action, change to longer-acting insulin or twice-daily dose regimen
- Insulin-induced hypoglycemic hyperglycemia (Somogyi effect)—Corrective action, reduce insulin dose by 25%
- Insulin overlap or prolonged insulin action—Corrective action, change to shorter-duration insulin or insulin mixture (ie, 30% regular, 70% NPH)

If the patient is receiving more than 2.2 U/kg of insulin per dose, insulin resistance should be investigated (Table 4). In cats, the top diagnostic differentials for insulin resistance include hyperthyroidism, hypersomatotropism (acromegaly), and hyperadrenocorticism. 
Feline inflammatory bowel disease (IBD) applies to a number of poorly understood enteropathies characterized by infiltration of inflammatory cells into the gastrointestinal (GI) mucosa. The cellular infiltrate is composed of variable populations of lymphocytes, plasma cells, eosinophils, and neutrophils that can be distributed throughout the GI tract. In severely affected cats, this infiltrate may be accompanied by changes in the mucosal architecture, including villus atrophy, fusion, fibrosis, and lymphangiectasia. Although IBD appears to be a common clinical problem in cats, little is known about the etiopathogenesis or the local and systemic consequences of the disease, including the development of lymphoma and nutritional deficiencies. In addition, the nature of inflammation associated with IBD is just beginning to be characterized beyond the visible changes in gross histopathology that have been described.

This paper reviews what is known about feline IBD, with particular focus on the role of commensal and pathogenic intestinal bacteria as well as diet in the diagnosis and management of the disease.

**Feline IBD: The Good (Diets), the Bad (Bacteria), and the Ugly (Diagnosis)**

**Diagnostic Process**

Feline IBD, a commonly diagnosed condition of adult cats, is characterized by persistent clinical signs consistent with GI disease (eg, vomiting, anorexia, weight loss, diarrhea) that occur concurrently with histologic evidence of mucosal inflammation. The median age of cats presenting with IBD is around 7 years, and most cats present with a history of these signs occurring intermittently for weeks to years. Purebred cats, such as the Siamese and Abyssinian, may be overrepresented, but definitive breed predilections have not been reported. There is no reported predilection based on sex.

**Diagnosis by exclusion**

Because clinical signs of IBD can be associated with various primary GI and extra-GI diseases, it is important to consider broad groupings of differentials and obtain a minimum database (ie, CBC, serum biochemical panel, urinalysis) until sufficient data have been collected to narrow the list of differentials. A number of possible causes of intestinal inflammation must be considered, however, including infectious disease, food sensitivity (allergy) or food intolerance, endocrinopathies (eg, hyperthyroidism), parasitic disease, and neoplastic disease. These differentials should be investigated thoroughly before settling on a diagnosis of idiopathic IBD and instituting a treatment plan.

Food allergy and intolerance can be particularly difficult to distinguish from IBD and other intestinal disorders, especially because of shared clinical signs and identical histopathologic changes in the bowel. Therefore, appropriate food trials are an extremely important component of both reaching a diagnosis and implementing therapy in cats with GI disease or suspected IBD. In addition to food trials, the diagnostic plan for a cat with chronic vomiting or diarrhea should include multiple fecal examinations or therapeutic deworming trials with broad-spectrum agents, such as fenbendazole, assessment of thyroid and
FeLV/FIV status, and assessment of GI function, including measuring cobalamin and folate and conducting trypsin-like immunoreactivity (TLI) and pancreatic lipase immunoreactivity (PLI) tests.

Many cats with IBD have concurrent inflammation of the liver and pancreas—a phenomenon called *triaditis*. Because chronic pancreatitis can cause few distinguishing signs and be difficult to diagnose by laboratory testing alone, a degree of clinical suspicion is necessary to carefully assess cats. Serum cobalamin levels are commonly decreased in cats with severe bowel disease or pancreatitis. Furthermore, in cats with hypocobalaminemia, diarrhea does not resolve until replacement therapy has been instituted.

Imaging and exploratory measures
In addition to laboratory evaluation, radiography and ultrasonography are important aspects of overall assessment of cats with possible IBD. Although abdominal radiographs and ultrasound findings cannot confirm IBD, they are essential for ruling out other GI problems, including intestinal foreign bodies, intussusception, masses, and involvement of other organs, especially the liver and pancreas. Many cats with intestinal inflammation have thickened loops of bowel, changes in bowel layering, or evidence of mesenteric lymphadenopathy. These changes are not indicative of a specific cause but are further confirmation of intestinal disease that requires additional assessment.

Abdominal ultrasonography can reveal important information about the location and severity of lesions, thereby suggesting whether endoscopy or abdominal exploratory surgery might be the appropriate next step. Because intestinal biopsy specimens obtained either endoscopically or during exploratory surgery are essential to confirm the presence of inflammatory infiltrates, either diagnostic measure is an important part of the process. However, a number of problems have been associated with using histopathologic changes or findings to diagnose IBD.

First, problems correlating a pathologist’s interpretation of inflammation found in the GI biopsy specimen with the actual disease have been well documented. The presence of lymphocytes and plasma cells in the wall of the gut does not mean the problem is idiopathic, does not necessarily correlate with the cytokine expression or degree of clinical disease, and does not mean that IBD can be accurately differentiated from lymphoma. As a result, standards for histopathologic interpretation of biopsy specimens have been recommended by pathologists to help improve the utility and consistency of interpreting GI histopathologic findings (see WSAVA Guidelines for GI Histopathology).

Inflammatory response
The basis of the immunologic response in cats with IBD is unknown, and it remains to be determined whether the inflammatory response results from the presence of undefined pathogens or exemplifies an inappropriate response to dietary antigens or intraluminal commensal bacteria. Determining the cytokine and immune cell population in cats with IBD is important from both a

**WSAVA Guidelines for GI Histopathology**

The WSAVA guidelines offer pertinent information about GI histopathology. Small cell (ie, lymphocytic, low-grade) lymphoma can be extremely difficult to distinguish from IBD. Because the disease can be local (only in the jejunum or ileum) or found only in the deeper layers of the intestinal wall (submucosa or muscularis), if during endoscopy, biopsy specimens are not obtained from the appropriate sites or are inadequate in depth, lesions can be missed. If cats are not responding to appropriate therapy or were responding to therapy but are now losing weight or having recurrent diarrhea despite therapy, the possibility of lymphoma should be reconsidered. Several recent reviews on this subject provide more details specific to GI lymphoma and its management.

WSAVA = World Small Animal Veterinary Association
pathologic and therapeutic standpoint, as treatment of IBD in cats is nonspecific and based on dietary modification, administration of antibiotics, and suppression of the immune system.

The Role of Bacteria
In humans and experimental animals, recent studies indicate a strong association between the development of IBD and a breakdown of normal tolerance mechanisms, host susceptibility, and enteric microflora. It is likely that these same factors are important in feline IBD (see Are Bacteria a Key Component?). Modulation of the enteric microenvironment in humans with IBD has been shown to reduce proinflammatory cytokines in the mucosa and, therefore, decrease the inflammatory response. In humans, IBD therapy has included antibiotics with immunomodulating capacity, prebiotics, probiotics, and immunosuppressants as well as other drugs that modify cytokine release.

Unfortunately, studies assessing modulation of enteric flora (using probiotics, prebiotics, or other specific therapy for cytokines) in cats with IBD are only in the early stages. Nevertheless, few studies have shown that intestinal microbiota in cats with IBD are clearly different from those in normal cats and often the difference is a decrease in normal commensals (eg, bifidobacteria, lactobacilli) and an increase in pathogenic species. It is likely that these same factors are important in feline IBD.

One group of investigators is seeking to determine the effect of mucosal bacteria and their relationship to cytokine responses and inflammation in the bowel of cats. Intestinal biopsies were collected from 17 cats undergoing diagnostic investigation of signs of GI disease and from 10 healthy controls. Subjective duodenal histopathology ranged from normal (10) to mild (6) to moderate (8) to severe (3) IBD. The mucosal response was evaluated by objective histopathology and cytokine mRNA levels in duodenal biopsies. The number of mucosa-associated Enterobacteriaceae was higher in cats with signs of GI disease than in healthy cats. These pathogens, including Escherichia coli and Clostridium species, were associated with significant changes in mucosal architecture, principally atrophy and fusion; up-regulation of cytokines, particularly IL-8; and the number of clinical signs exhibited by affected cats.

The study findings indicate that an abnormal mucosa-associated flora is associated with the presence and severity of duodenal inflammation and clinical disease activity in cats. The observations provide a rational basis for future investigations to address the potential causal involvement of mucosa-associated bacteria. They are perhaps most consistent with a model proposed for the mucosal response to gram-negative bacteria, whereby proinflammatory cytokines (eg, IL-1, IL-8, IL-12) produced by epithelial cells in response to such stimuli as gram-negative bacteria are modulated by macrophage production of IL-10. Support for this concept in the canine GI tract is provided by studies of the small intestines of dogs in which expression of IL-10 and IFN-β mRNA by lamina propria cells and the intestinal epithelium was observed in the face of a luminal bacterial flora that was more numerous than that of control dogs.

Additional evidence that bacteria are a key component of IBD in cats has been collaborated by Inness and coworkers, who characterized the gut microflora of both healthy cats and cats with colonic IBD. Cats with IBD were found to have significantly higher populations of Desulfovibrio (a genus of bacteria that produce toxic sulfides) compared with normal cats, which had higher populations of bifidobacteria and bacteroides (normal flora). These authors proposed that modulation of intestinal flora with probiotics and dietary intervention to decrease the production of pathogenic bacteria were likely important in treating cats with IBD.

Finally, another study found that the expression of cytokines in biopsy specimens from the intestines of cats with IBD represented greater transcription of genes encoding IL-6, IL-10, IL-12, TNF-α, and TGF-β than from those of cats with normal intestines. These results also suggested that, in cats with IBD, both proinflammatory and immune dysregulation features were present.

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**Are Bacteria a Key Component?**

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**IBD** = inflammatory bowel disease; **IFN** = interferon; **IL** = interleukin; **TGF** = transforming growth factor; **TNF** = tumor necrosis factor.
mg/kg PO Q 12 H; however, less is known about the effects of tylosin on cats when used long-term.27,28

Finally, data in humans with IBD are increasingly showing that probiotics and antioxidant prebiotic nutraceuticals may be important components of therapy.25 At this time, it is difficult to make specific recommendations concerning the probiotic or nutraceutical therapy with the greatest benefit because of the paucity of studies in cats with IBD and the species-specific nature of probiotics and their effects. However, probiotics that provide an immune-modulating effect or that increase the number of beneficial species while competing against pathogens might be expected to be helpful. In several studies in kittens, probiotics containing Enterococcus faecium (SF68) appeared to improve immune function and had better responses to therapy when exposed to enteric protozoa.29 Furthermore, whereas probiotic therapy alone would not be expected to produce clinical remission, cats undergoing long-term therapy for IBD may benefit from the addition of probiotics to their treatment regimen.

Diets Designed to Promote GI Health
The highly digestible diets from different pet food manufacturers have a variety of formulations—different protein and carbohydrate sources, different levels of fat, and various additives designed to promote intestinal health (eg, fructooligosaccharide [FOS], mannondigosaccharide [MOS], omega-3 fatty acids, antioxidant vitamins, soluble fiber). If one type of highly digestible diet has been fed for at least 2 weeks with minimal response, then it is entirely reasonable to try another diet from a different source or try an entirely different dietary strategy (eg, high-protein/low-carbohydrate, novel antigen, hydrolyzed diet). In addition, diarrhea may be attributed to carbohydrate intolerance or bacterial changes resulting from dietary changes. Thus, the addition of probiotics or prebiotics to help influence microflora is a reasonable therapeutic option, as is the addition of either metronidazole or tylosin.

Treatment of IBD in cats is nonspecific and based on dietary management, antibiotic treatment, and immunosuppression.

The Role of Dietary Management
The use of diet to help manage GI disease is not a new concept, but the type of diet to use has become an increasingly complex issue. In many, if not most, cats with mild IBD, especially those without significant infiltrate of inflammatory cells (mild to moderate infiltrate) or without significant weight loss or other morbidity, the best approach is to feed a highly digestible diet or to change the diet to one with fewer additives, flavorings, or other substances that may be associated with food intolerance. Many cats (nearly two-thirds in one study) with chronic diarrhea have complete resolution of clinical signs when fed a highly digestible diet.30,31

Highly digestible diets are not defined in a regulatory sense but generally indicate a product with protein digestibility of greater than 85% (typical diets are 78% to 81%) and fat digestibility of greater than 90% (typical diets are 77% to 85%). These diets are designed to provide food that is easy to digest because it has moderate to low fat, moderate to increased protein, and moderate to decreased carbohydrates; may have additives to improve intestinal health, such as soluble fibers, omega-3 fatty acids, and increased antioxidant vitamins; and contain no gluten, lactose, food coloring, preservatives, and similar additives. Many different brands fall under the category of “highly digestible,” but they are not all alike. The protein digestibility of a diet is one of the key factors that can determine its success in cats with IBD. In general, meat-source proteins and diets containing meat meals are more digestible than plant-source proteins, and animal proteins are more digestible than meat by-products. In addition, to increase digestibility of foods in cats, the number and amount of carbohydrates in the food are decreased—a single-source carbohydrate food is better than foods with many different sources, and highly digestible carbohydrate sources are better than complex plant-source carbohydrates. Therefore, when one diet from this category is not accepted or seems to make the diarrhea worse, it cannot be assumed that all diets in this category will be ineffective and unaccepted. Diets from different manufac-
turers have various formulations (see Diets Designed to Promote GI Health).

**Novel Antigen or Elimination Diets**

Allergy and intolerance are the most common adverse reactions cats have to food. Food allergy or hypersensitivity is an adverse reaction to a food or food additive with a proven immunologic basis. In contrast, food intolerance is a nonimmunologic abnormal physiologic response to a food or food additive. Food poisoning, food idiosyncrasy, and pharmacologic reactions to foods also fall under the category of food intolerance.

The specific food allergens that cause problems in cats have been poorly documented, with only 10 studies describing the clinical lesions associated with adverse reactions. In these reports, more than 80% of cases were attributed to beef, dairy products, or fish.

The incidence of food allergy in cats remains unknown but is estimated to be only 15% to 20% of all food-related causes of diarrhea. However, food intolerance is believed to contribute to 60% to 65% of feline diarrhea cases. In two separate studies, a majority of cats responded to dietary therapy with a highly digestible diet.

The causes of dietary intolerance that need to be carefully considered in feline diets are primarily protein and carbohydrates—both sources and amounts. The diagnosis of both food allergy and intolerance is based on a dietary elimination trial. The major difference between these two types of adverse food reactions is the length of time on the diet required to achieve a response (cats with food allergy may require 6 to 12 weeks on the elimination diet before an improvement will be seen).

Various commercial and homemade elimination diets, as well as diets formulated with hydrolyzed proteins, may be used in cats with suspected food allergy or intolerance. The key is to select a diet that has a novel protein source based on a careful dietary history and is balanced and nutritionally adequate (commercial diets are best for this); however, a homemade elimination diet may be necessary to find an appropriate test diet. 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. For most cats with food allergy, avoiding the offending food is most effective and can result in complete resolution of signs. However, short-term steroid therapy can decrease the concurrent intestinal inflammation until the appropriate food sources can be identified.

GI disease may decrease the availability of a number of micronutrients, such as vitamins and minerals, thereby having important consequences on the pathogenesis, diagnosis, and treatment of the disease. The diagnostic utility of measuring the serum concentrations of cobalamin and folate in cats with suspected intestinal disease has recently been established. Although the impact of deficiencies in cobalamin and folate is not com-
The incidence of feline IBD is unknown, but food intolerance probably accounts for 60% to 65% of feline diarrhea cases. Allergy and intolerance are the most common adverse reactions cats have to food. The incidence of food allergy in cats is unknown, but food intolerance probably accounts for 60% to 65% of feline diarrhea cases. 

Although other vitamin or mineral deficiencies may occur with longstanding or severe IBD, they are less likely (because of storage of fat-soluble vitamins and some minerals) and supplementation without documentation of a deficiency can be dangerous. Thus, supplementation of fat-soluble vitamins is not generally recommended unless signs of deficiency, such as bleeding from vitamin K deficiency, are occurring or tissue or blood levels of the vitamin are determined.

**Closing Remarks**

In conclusion, much remains to be learned about the complex interplay between GI microflora, dietary antigens, the epithelium, immune effector cells, and soluble mediators in the feline GI tract in health and disease. The development of feline-specific reagents together with the growing realization of the nutritional consequences of IBD have precipitated a shift beyond reliance on qualitative histology, holding promise for improved understanding, therapy, and prevention in the future.

**References**


Few controlled studies are investigating treatments for liver disease in dogs and cats. When recommending specific therapeutic approaches, however, most authors point out the importance of linking adequate nutritional support with specific therapies and general hepatic support. Management of liver-related complications should also be addressed if and when they occur. This article covers the major aspects associated with managing liver disease in small animals and outlines some basic treatment goals (see box).

**Nutritional Management**

The liver is paramount in metabolism and plays a key role in regulating protein, carbohydrates, fat, vitamins, and minerals. Metabolic derangements that occur in dogs and cats with liver disease can lead to malnutrition, impaired hepatic regeneration, and the clinical consequences of hepatic insufficiency (e.g., hepatic encephalopathy [HE], ascites, gastrointestinal [GI] ulceration, coagulopathy, immunosuppression). The liver also has the unique ability to regenerate following injury, a process that occurs through appropriate nutrition.

The overall 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 leads to accumulation of toxic metabolites.

**Basic nutritional concepts**

One of the most important aspects of liver disease therapy is ensuring that the patient has appropriate energy intake to prevent anorexia and weight loss, thereby minimizing catabolism. Adjustments to the diet are required when malnutrition is present. To this end, practitioners must first calculate the patient’s caloric needs.

Calculation of the basal energy requirement (BER) is based on the weight of lean body mass; the weight of fat or ascites is not included (see box). The BER is then multiplied by an illness factor estimated to be 1.0 to 1.4 to achieve daily caloric needs. Although no comprehensive studies have looked at illness factors in dogs or cats with liver disease, studies have shown that humans with cirrhosis have an energy intake comparable with that of normal controls. Energy requirements should be individually adjusted to maintain optimal body weight.

It is important to ensure that poor diet palatability is not the reason a patient refuses to eat. Patients can be offered an ideal diet for a particular condition, but I would rather have

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**How to Calculate BER**

- For animals weighing < 2 kg: 
  \[ 70 \times [\text{kg}^*] \times 0.75 = \text{kcal/day} \]
- For animals weighing > 2 kg: 
  \[ 30 \times [\text{kg}^*] + 70 = \text{kcal/day} \]
- Nutritional requirements for most cats can also be expressed as 50–55 kcal/kg body weight.

*Of lean body mass

BER = basal energy requirement
patients eat almost any diet than nothing at all. When nutritional requirements are not being met by voluntary intake, enteral supplementation should be considered.

Fat
A misconception about dietary fat content and liver disease is prevalent, especially in the nutritional management of feline hepatic lipidosis. In general, dogs and cats with liver disease have a good tolerance for dietary fat. Fat not only improves palatability but provides important energy density to the diet. Therefore, lipid restriction typically is not necessary for dogs or cats with liver disease; this also holds true for cats with idiopathic hepatic lipidosis. However, dietary control is probably the most important aspect of managing a case of hepatic lipidosis.

Carbohydrates
Carbohydrates should make up no more than 35% of the diet’s total calories for cats and 45% for dogs. Adequate carbohydrate intake is important to maintain glucose concentrations, especially in dogs with advanced liver disease or when hypoglycemia is a concern in patients with portosystemic shunts (PSS). Feeding frequent small meals throughout the day may help patients maintain glucose concentrations.

I have observed hypoglycemia in some dogs with cirrhosis and PSS and hyperglycemia in some cats with hepatic lipidosis or cats receiving steroids. In conjunction with liver disease (and sometimes concurrent steroid therapy), cats with glucose intolerance or a tendency to develop hyperglycemia after a meal will require a lower-carbohydrate diet. The best way to prevent hyper- or hypoglycemia is to feed frequent small meals. In general, I prefer to feed an energy-dense, low-fiber diet to patients with liver disease. However, managing dietary fiber plays a role in how it relates to the treatment of hepatic encephalopathy.

Protein
A misconception about protein content and liver disease also exists. 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 approach is not well substantiated, however. Many veterinary nutritionists and gastroenterologists now believe that restricting protein could be detrimental, especially if patients have a negative nitrogen balance.

As a general recommendation, dietary protein should represent 15% to 20% of the digestible kilocalories (kcal) in the diet. Most highly digestible diets (eg, GI diets) are adequate for patients with most liver conditions (see Dietary Protein Intake). Protein restriction should only be instituted in patients with evidence of protein intolerance—most often patients with PSS or signs of HE. In these situations, lower protein content and diets with a milk- or plant-based protein source rather than a meat source are recommended to prevent HE and colonic production of excess nitrogen by-products. Because cats have such a high protein requirement, I rarely—if ever—limit protein intake in cats with liver disease, such as lipidosis, and find HE an uncommon consequence in cats.

Basic Therapeutic Options
Antiinflammatory therapy
Decreasing inflammation should be specifically addressed in dogs with chronic hepatitis and possibly in cats with some types of cholangitis. At Colorado State University, our clinical impression suggests that antiinflammatory therapy is beneficial in some if not all cases of chronic

Dietary Protein Intake

The goals of dietary protein intake are to:

- Adjust quantities and types of nutrients to meet the patient’s nutrient requirements.
- Avoid production of excess nitrogen byproducts that cause hepatic encephalopathy.
- Provide a high-quality, highly digestible protein source. Poor-quality proteins may aggravate hepatic encephalopathy and fail to promote hepatic regeneration.

Protein requirements for patients with liver disease may be greater than those for normal dogs and cats. Most quality commercial and prescription diets are suitable for this purpose.
Getting the Most Out of Antiinflammatory Therapy in Dogs

Azathioprine is an effective immunosuppressant shown to increase survival in humans treated for chronic hepatitis when administered in conjunction with corticosteroids. The therapy may also be beneficial in dogs (do not use azathioprine in cats because of toxicity) by increasing the immunosuppressive response and enabling reduction of both the steroid dose and side effects. Initially, a dose of 2.2 mg/kg/day is suggested, followed by Q 48 H after several weeks. The level of glucocorticoids can frequently be reduced when using azathioprine. Of importance, azathioprine has infrequently been associated with drug-induced hepatic necrosis or acute pancreatitis. If the dog worsens clinically or the alanine aminotransferase (ALT) value increases dramatically, I would stop the medication.

At Colorado State University, we have realized good clinical response when using cyclosporine in some dogs with chronic hepatitis. Our experience using 5 mg/kg Q 12 H or Q 24 H (without steroids) has been encouraging in dogs believed to have immune-mediated chronic hepatitis. The veterinary formulation Atopica (www.atopica.com) is a microemulsified preparation with the same properties and bioavailability as the human product Neoral (www.pharma.us.novartis.com) and its generic counterpart. Generally after several days or longer, I will obtain a blood level at the trough (before the next pill). The ideal range of blood levels is 400–600 ng/mL.

Many dogs develop gingival hyperplasia when higher concentrations of cyclosporine are administered. Azithromycin at 10 mg/kg/day for 4–6 weeks will often decrease gingival hyperplasia. With evidence of clinical response at a dose of 5 mg/kg Q 12 H, I often decrease the frequency to Q 24 H and eventually to alternate-day therapy. Using cyclosporine alone, practitioners can follow the level of liver enzymes and direct therapy based on response without the need for liver biopsy.

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Hepatic copper metabolism

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 because of either a primary genetic defect 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 breed-associated copper hepatotoxicity. With either mechanism of copper accumulation, subcellular damage to hepatocytes can result. Damage from copper apparently results in lipid peroxidation and mitochondrial damage.

If the liver biopsy of a dog with chronic hepatitis indicates significant abnormal hepatic copper accumulation, then dietary copper chelators or zinc therapy should be instituted. Hepatic copper levels of greater than 1,000 mcg/g of dry weight liver (normal < 400 mcg/g liver) require therapy to reduce copper concentrations.

It is first 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 metaboliz-
The Role of Oral Zinc Therapy

oral zinc therapy works by causing an induction of the intestinal copper-binding protein metallothionein. Dietary copper binds to the metallothionein with a high affinity that prevents transfer from the intestine into the blood. When the intestinal cell dies and is sloughed, the metallothionein-bound copper becomes excreted through the stool. 

An initial induction dose of 15 mg/kg Q 12 H (or 50–100 mg Q 12 H) of elemental zinc is suggested. After 1–3 months of induction, the dose can be reduced by approximately half. The goal is to have serum zinc concentrations greater than 200 mcg/dL but less than 500.

Zinc must be administered on an empty stomach and has the frequent side effect of vomiting. Replacement zinc therapy administered at a dose of 2–3 mg/kg/day is given for its antioxidant effects and replacement value in animals with zinc depletion in their liver.
Three case reports of colchicine use in dogs have indicated questionable results.\textsuperscript{19-21} However, based on these reports, a dose of 0.03 mg/kg/day has been suggested. The generic form is inexpensive, with generally only minimal GI side effects noted at high doses.

Recently losartan, an angiotensin-II receptor antagonist used for treating high blood pressure, has shown some effects in preventing hepatic fibrosis by preventing up-regulation of the stellate, or collagen-producing, cells in the liver. Clinical response to losartan has been noted in human studies of hepatitis.\textsuperscript{22}

**Antibiotic therapy**

Antibiotics are indicated in some patients with primary hepatic infections, such as bacterial hepatitis, cholangitis, or leptospirosis. The selection of appropriate antibiotics is based on culture and sensitivity testing. There is, however, evidence that secondary bacterial colonization may take place in a diseased liver.\textsuperscript{23} Kupffer cells, which are fixed hepatic macrophages, function in filtering the portal blood of bacteria and other toxic products. Kupffer cell dysfunction in patients with liver disease could account for a secondary bacterial infection. This is supported by studies that have identified bacteria in many hepatic cultures.\textsuperscript{24} Therefore, it may be prudent to initiate antibiotic therapy for at least a trial of several weeks in patients with significant hepatic disease (ie, chronic hepatitis).

Amoxicillin, amoxicillin–clavulanic acid, cephalosporin, or metronidazole therapy is suggested. Metronidazole may have some immunosuppressive properties as well as anaerobic antibacterial mechanisms. Because of hepatic metabolism of metronidazole, I recommend a dose of 7.5 to 10 mg/kg Q 12 H, which is much lower than that used for other bacterial infections.

**Vitamins and Nutraceuticals for Liver Support**

Although vitamin and nutraceutical adjunct therapies have gained interest in managing certain types of liver disease, few published reports have shown their benefit in clinical disease; much of the information gathered has been generated from in vitro studies. Some current information as well as suggested uses of pertinent vitamins and nutraceuticals are presented here.

**Vitamins**

Because vitamin metabolism, specifically vitamin storage and the conversion of provitamins to a metabolically active state, takes place in hepatocytes of the liver, the vitamin status of patients with liver disease needs to be considered.

Fat-soluble vitamins (ie, A, D, E, K) are prone to be deficient because they require bile salts for absorption. Water-soluble vitamins B and C are generally found in high concentrations in the liver.

Fat-soluble vitamins A, D, E, and K are prone to be deficient because they require bile salts for absorption. Water-soluble vitamins B and C are generally found in high concentrations in the liver.

Vitamin E functions as a cellular membrane-bound antioxidant. Evidence now shows that oxidative damage from free radical generation occurs in patients with liver disease. Because cellular damage is likely multifactorial in these patients, free radicals may play an important role in initiating or perpetuating this damage.\textsuperscript{27,28}

Vitamin E is inexpensive and safe when supplemented at a dose of 10 IU/kg/day: \(\alpha\)-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. d-\(\alpha\)-Tocopherol is also retained in tissues by a 2:1 ratio over the synthetic formulation.\textsuperscript{25} In patients with significant cholestatic liver disease, I suggest a water-soluble formulation.

Vitamin C. Vitamin C (ascorbic acid) 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 transporting fat into mitochondria. Humans with liver disease often have low hepatic vitamin C concentrations, partially because they cannot synthesize vitamin C; however, dogs and cats can synthesize this vitamin.

Although vitamin C supplementation may be beneficial in treating liver disease, supplementation of excessive amounts of vitamin C may be deleterious in patients with increased hepatic copper or iron concentrations because ascorbate is believed to promote oxidative damage caused by these transition metals.26

**Vitamin K.** Vitamin K stores in the liver can become depleted in patients with advanced liver disease and can result in serious coagulopathy. 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-dependent coagulation factors (i.e., factors II, VII, IX, 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, 0.5 to 2.0 mg/kg of parenteral vitamin K1 (phytonadione) SC Q 12 H for two or three doses (or until normalization of prothrombin time) is recommended for dogs and cats with hepatic disease. Vitamin K1 supplementation is recommended for 24 to 36 hours before invasive procedures, such as hepatic biopsy or feeding tube placement.6

**Vitamin B.** 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 B vitamins are water-soluble, they are relatively nontoxic and supplementation using a B-complex formulation is recommended in patients with liver disease.

Cats are particularly prone to vitamin B12 (cobalamin) deficiency. Subnormal concentrations of vitamin B12 have been reported in cats with liver disease, particularly idiopathic hepatic lipodosis.29 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 mcg SC weekly until normal cobalamin concentrations have been maintained. There is not enough vitamin B12 in B-complex formulations to correct its deficiency in cats.

### Nutraceuticals

The North American Veterinary Nutraceutical Council defines 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.”30 Many nutraceuticals used in animals are listed as nutritional supplements. Typical categories include:

- Antioxidants
- Omega fatty acids
- Amino acids
- Chondroprotective agents
- Herbals
- Probiotics

Although some nutraceuticals have shown potential for improving veterinary care, information about their purity, dosage, safety, side effects, and effectiveness remains limited.

*S-Adenosylmethionine.* S-Adenosylmethionine (SAMe), a naturally occurring molecule synthesized in all living cells, is essential in intermediary metabolism and has both hepatoprotective and antioxidant properties.

The liver normally produces abundant SAMe, but evidence also suggests conversion from methionine to SAMe is hindered in patients with liver disease and, therefore, results in the depletion of glutathione concentrations.31 Orally administered SAMe (but not oral glutathione) has been shown to increase intracellular glutathione levels.
in hepatocytes and prevent glutathione depletion when exposed to toxic substances. Therefore, 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. SAMe treatment following acetaminophen administration prevented hepatic glutathione depletion.

Because SAMe is easily oxidized, it is important to use products that have been tested for their stability. In addition, product purity can vary from formulation to formulation, so it is advisable to use products from reputable companies.

**N-Acetylcysteine.** N-Acetylcysteine, the acetylated variant of the amino acid L-cysteine, is an excellent source of the sulphydryl groups. It is converted in the body into metabolites that stimulate glutathione synthesis, thereby promoting detoxification and acting directly as free radical scavengers.

N-Acetylcysteine has historically been used as a mucolytic agent for various respiratory illnesses but apparently also has beneficial effects in conditions characterized by oxidative stress or decreased glutathione concentrations. N-Acetylcysteine is currently the mainstay of treatment for acetaminophen-induced hepatotoxicity. It also appears to have some clinical usefulness as a chelating agent in treating acute metal poisoning, both as an agent protecting the liver and kidney from damage and as an intervention to enhance elimination of metals.

N-Acetylcysteine is available in a drug formulation and as a nutritional supplement. The oral dose recommended for acetaminophen toxicity is 70 mg/kg Q 8 H. The IV loading dose of 140 mg/kg is followed by a dose of 70 mg/kg. N-Acetylcysteine reportedly has extremely low toxicity with few side effects. I use N-acetylcysteine IV when the patient is vomiting or too sick to take oral SAMe, which is my preference as maintenance therapy.

**Phosphatidylcholine.** Phosphatidylcholine is a phospholipid used as a nutritional supplement for its hepatoprotective effects. A building block for cell membranes, phosphatidylcholine is required for normal bile acid transport. It is thought to be hepatoprotective by improving membrane integrity and function.

In vitro studies have shown that phosphatidylcholine increases hepatic collagenase activity and may help prevent fibrosis. Clinical trials have indicated that phosphatidylcholine protects the liver against damage from alcohol, viral hepatitis, and other toxic factors that operate by damaging cell membranes.

Several phosphatidylcholine supplements are available. No major side effects have been reported other than occasional nausea or diarrhea. Phosphatidylcholine is rapidly absorbed, enhances absorption of other compounds, and is included as a carrier in one silybin product.

Given the apparent safety of phosphatidylcholine, animal studies would be worthwhile.

**L-Carnitine.** L-Carnitine is a vitamin-like substance found in most cells. Because it is predominately synthesized in the liver, liver disease can precipitate deficiency. Clinically, carnitine deficiency has been associated with increased ammonia concentrations, hypoglycemia, and fatty livers.

In one study, carnitine given to obese cats undergoing rapid weight loss from caloric restriction was found to protect against hepatic triglyceride accumulation. 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 of study cats than in control cats.

A deficiency of carnitine may lead to impaired mitochondrial function, but studies failed to show carnitine deficiency in cats with hepatic lipidosis. Supplementation with 250 mg/day of carnitine in cats with lipidosis is reportedly associated with better survival rates, but this has not been documented.

**Silymarin.** Silymarin, an active extract of milk thistle, grows wild throughout Europe and has
been used there for more than 2,000 years as a medical remedy for liver disease. In the United States, silymarin is classified as a nutraceutical.

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 using alternative agents for their disease and that milk thistle was the most common nontraditional therapy. 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 suggests that silymarin has a therapeutic effect in humans with acute viral hepatitis, alcoholic liver disease, cirrhosis, and toxin- or drug-induced hepatitis.

To date, limited clinical studies have evaluated the efficacy of silymarin in dogs and cats with liver disease. 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.

The purity and potency of commercial milk thistle products vary by manufacturer, and the therapeutic dose for dogs and cats is unknown, although suggested doses range from 50 to 250 mg/day. Milk thistle reportedly has extremely low toxicity. When the active isomer silybin is complexed with phosphatidylcholine, oral uptake and bioavailability are greater.

I recently conducted a pharmacokinetic study of silybin, specifically evaluating Marin (www.nutramaxlabs.com) in normal cats. There was evidence of some oxidative protection in red blood cells but no outward signs of toxicity at a dose of 5 mg/kg. A new compound Denamarin (www.denamarin.com) contains SAMe and silybin–phosphatidylcholine and is available in a chewable formulation. The combination of compounds apparently has good absorption and is very stable.

**HE and Dietary Protein**

The importance of the dietary protein source has been studied in humans with HE and several experimental studies in dogs with PSS. 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. Foods using soybean meal averted encephalopathic signs in dogs with experimentally created shunts, and Purina Veterinary Diet 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 PSS and chronic hepatic insufficiency. However, the amino acid composition of these protein sources is not significantly different from that of meat sources, suggesting that other food factors (eg, digestibility, levels of soluble carbohydrate, 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. Commercial and homemade foods can be supplemented with various sources of soluble fiber, such as psyllium husk fiber.

**HE = hepatic encephalopathy; PSS = portosystemic shunt**

Secondary complications can develop as liver disease becomes advanced. HE, GI ulceration, and ascites are common in patients with advanced hepatitis or cirrhosis.

**Hepatic encephalopathy**

HE results from either portosystemic shunting of blood (congenital or acquired) or hepatocyte depletion from acute or chronic liver disease. Many factors can cause HE, most of which are derived from nitrogenous products produced in the GI tract. Ammonia is only one of many substances that cause HE 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 HE, whereas higher concentrations of branched-chain amino acids had a more protective effect (see HE and Dietary Protein).

There are three basic therapeutic goals for managing HE (see box on page 22). The first step is using enemas to clean the colon of both bacteria and protein substrates for ammonia production. Slightly acidic enemas can lower the pH of the colon, thereby ionizing ammonia and reducing its absorption. Povidone-iodine can safely be given by

Mounting evidence suggests that milk thistle has medicinal benefits for various types of liver disease as well as protective effects against hepatotoxins.
Intestinal antibiotics can be used to alter bowel flora and suppress urease-producing organisms important in forming factors that cause HE. Antibiotic suggestions include oral ampicillin, aminoglycosides (eg, neomycin, kanamycin, gentamicin), or metronidazole. Metronidazole at a dose of 7 to 10 mg/kg PO Q 12 H has been useful in controlling anaerobic urease-producing bacteria. Practitioners should monitor patients carefully because metronidazole is partially metabolized in the liver; the lower dose range is suggested.

A nondigestible disaccharide lactulose given orally can acidify the colon, convert ammonia to ammonium that is poorly absorbable, and thus trap ammonia in the colon. The fermentation products of lactulose can 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 PO Q 8 H is generally effective, but the dose should be adjusted to cause three or four soft stools a day. Lactulose can also be given by enema when treating severe cases of HE.

Gastrointestinal ulceration

Ulceration in the GI tract, a common occurrence in both advanced acute and chronic liver disease, can cause GI signs, such as vomiting and anorexia. In addition, blood loss into the intestinal tract promotes HE because blood is an excellent protein source of ammonia production. Gastric ulcers should be treated with a histamine-2 (H₂) blocker, such as 2 to 5 mg/kg of ranitidine Q 8 H to Q 12 H and a 1 mg tab/25 kg of oral sucralfate Q 8 H given 1 hour before ranitidine.

Cimetidine should be avoided in patients with liver disease because it is metabolized by the liver and is an enzyme suppressor that can alter hepatic metabolism of other drugs. If blood loss is severe and there is need for transfusion, only fresh blood should be administered because ammonia concentrations can increase in stored blood.

Ascites

In patients with liver disease, ascites occurs when portal hypertension, hypoalbuminemia, and renal sodium and water retention work in concert to cause fluid exudation. The presence of ascites is a poor prognostic indicator.

Diuretics are the major means of managing ascites in small animals. Too rapid removal of ascitic fluid can cause metabolic complications and precipitate HE. The goal of diuretic therapy should be gentle water diuresis.

The two diuretics most commonly used are furosemide and spironolactone. The general consensus at CSU is that spironolactone is more effective with liver disease. The loop diuretic furosemide can, however, cause marked dehydration and loss of potassium, which can precipitate HE. In patients with liver disease, sodium reabsorption at the distal tubule may be great and may counter the effects of furosemide attributable to elevated aldosterone concentrations (reported to occur in some dogs with liver disease). Spironolactone at a dose of 1 to 2 mg/kg/day is consequently the first-line diuretic. Furosemide can be added later if necessary. If an animal has tense ascites, paracentesis should be performed to decrease intraabdominal pressure, relieve compression of the venous circulation, and improve patient comfort.

Summary

It is critical to recognize the complexity of the medical and nutritional needs of patients with liver disease. Practitioners should formulate an individualized therapeutic and dietary plan accordingly. Because there are few good controlled studies evaluating liver disease therapy, it is important to carefully monitor each patient and adjust the treatment, based on clinical response of the patient, laboratory changes, or histologic findings.
References

Obesity is the number one nutritional disorder in pets in the western world. Twenty-five percent of cats seen by veterinarians in the United States and Canada are overweight or obese. In optimal condition, cats should carry 15% to 20% body fat.

In 1998, Donoghue and Scarlett studied diet and obesity in cats. Using multivariate statistical analysis controlled for age, they showed that obesity is a risk factor for:

- Diabetes mellitus
- Skin problems
- Hepatic lipidosis
- Lameness

Other researchers have found that a chronic overweight state, in cats as well as in other species, is associated with an increased risk for:

- Hyperlipidemia
- Insulin resistance
- Glucose intolerance
- Feline lower urinary tract disease
- Anesthetic complications
- Dyspnea and Pickwickian syndrome
- Exercise intolerance
- Heat intolerance
- Impaired immune function
- Exacerbation of degenerative joint disorders
- Dermatologic conditions

Interestingly, mixed-breed cats were found to be at higher risk for becoming overweight than purebred cats were. While this might be genetic, husbandry and awareness of the cat probably play a role. By keeping cats indoors, we eliminate their need to work for food and defend themselves. We leave them without stimulation for much of the day and feed them excessive quantities of palatable, calorie-dense diets.

Neutering has been shown to reduce the energy requirements (resting metabolic rate) of cats by 20% to 25%. A link has been shown between serum leptin levels and weight and fat gains following gonadectomy. Increased leptin levels may contribute to the decreased insulin sensitivity seen in overweight cats.

These tendencies make it important that we counsel our clients to measure the amounts of food being fed and to watch carefully for weight gain and adjust calorie intake accordingly. Ingesting 10 extra pieces of an average maintenance kibble each day above a cat’s energy needs can result in a weight gain of 1 pound of body fat in 1 year. Russell and coworkers showed that the frequency of feeding, along with the quantity fed, makes a significant difference. Feeding small meals more often and limiting the number of treats offered together provide the most appropriate feeding strategy, given innate feline physiology and thus assist with weight loss.

Assessing Body Composition and Condition: Tools
Cats reach their adult weight at about 12
to 15 months of age. This can be used as a guide to determine an individual's ideal size, assuming optimal body condition score (BCS) at that time.

It is easier to prevent weight gain than to lose weight. The prevalence of obesity increases after 2 years of age, plateaus until about 12 years, and then declines thereafter.13 Thus, an approved strategy is to:

1. Record a body weight at every veterinary visit.
2. Calculate the percent weight change to identify trends. This is a valuable tool for detecting weight change patterns and, in my experience, helpful in identifying cats with early chronic illness, including pancreatitis, cholangitis, and bowel malabsorptive conditions (eg, inflammatory bowel disease, intestinal lymphoma, adenocarcinoma). Likewise, a percentage weight change that is increasing gradually helps to identify cats at risk for obesity.

\[
\text{% Weight change} = \frac{\text{Current weight} - \text{Previous weight}}{\text{Previous weight}}
\]

3. Assess the BCS at every visit, categorizing the individual's shape as emaciated, thin, ideal, heavy, or grossly obese on a scale of 1 to 9 (see page 5) or 1 to 5. For a cat in ideal condition, the bony prominences of the body (ie, pelvis, ribs) can be readily palpated but not seen or felt above the skin surfaces. There should be insufficient intraabdominal fat to obscure or interfere with abdominal palpation.

4. Assess muscle condition using a muscle score to help define whether weight is adequately proportioned to lean versus fat.

5. In questionable cases, use radiography and ultrasonography to assess falciform fat deposits, paraumbilic fat, and perirenal fat. In research settings, dual energy x-ray absorptiometry (DEXA) evaluation is used for the most accurate bone density, muscle mass, and fat calculations.

What to Feed

It is not enough to simply feed less of a normal diet. Not only will the patient be unhappy and feel hungry, but all nutrient quantities will be decreased, not just the calories. A diet should be balanced according to energy content. When cats eat enough of the diet to meet energy requirements, then their protein, vitamin, and mineral needs will be met as well.

In cats, exceeding protein needs beyond maintenance requirements helps to induce satiety. When they were fed a diet with 45% of calories from protein, cats lost more fat and less lean mass compared with cats fed a diet with 35% of calories from protein, despite similar total weight loss and rate of weight loss.14

There are a number of approaches to feline weight loss:

1. High protein protects (minimizes loss of) lean mass, stimulates cellular energy metabolism and protein turnover, and may enhance satiety.
2. High moisture can reduce caloric density, which promotes short-term weight loss: It takes a few weeks to a few months for cats to adapt to the lower-caloric density (as fed) in canned foods versus dry foods; however, this only works for some cats.
3. High fiber can reduce caloric density and induce satiety. Some cats will self-restrict calorie intake when fed a dry, high-fiber, low-calorie diet.
4. Low fat will reduce caloric density. High-fat diets are a risk factor for inducing obesity and are generally not considered optimum for a weight loss diet. That said, some cats will lose weight on a high-protein, high-fat, low-carbohydrate diet.

Ultimately, it is the calories ingested versus expended that is required for loss of weight. Given the benefits of achieving lean body mass using the first approach, a goal of at least 40% protein, dry basis, in a low-fat diet (6% to 10% fat) or more protein in a higher-fat diet (12% to 16% fat) is a healthy approach to take.

The energy requirement for an individual is made up of several components: daily energy requirement (DER*), resting energy requirement (RER), exercise energy requirement (EER), thermic effect of food (TEF), and adaptive thermogenesis (AT): 

\[
\text{DER} = \text{RER} + \text{EER} + \text{TEF} + \text{AT}
\]

*Unlike metabolizable energy requirement (MER), DER includes energy required for activity, such as work, gestation, and growth, as well as energy needed for maintaining normal body temperature.
The need for behavior modification
At the initial extended consultation (a 40-minute consultation with the veterinarian), a comprehensive physical examination should be performed to rule out concurrent medical problems. Baseline blood work may be advisable, depending on the age and condition of the cat. A detailed history is needed to become familiar with current feeding habits and routines (see Diet History).

Have the client start a 1- to 2-week feeding journal; all household members who give the cat anything to eat need to record what they have given the cat. The amount as well as exact type (brand) of food and treats should be recorded. Clients can be asked to create this diary before the appointment and bring it along with them. The diet diary provides the material needed to determine the calorie intake that the cat has been receiving and gaining weight on and will be compared with the calorie allowance being recommended. As a rule of thumb, to lose weight a cat needs 60% to 70% of the calories required to maintain his or her ideal weight. In other words:

1. Determine or approximate the cat’s ideal weight.
2. Calculate the calories needed to achieve the ideal weight (wt in kg × 50 kcal/kg/day).
3. Multiply this number by 60% to 70% for the number of calories to feed each day.

Success requires commitment on the part of the client as well as the veterinary team. Clients rely on us to educate them about health and obesity as well as on how to modify their own and their cat’s behavior.

Key Points to Remember
✔ Schedule an initial 40-minute consultation with the veterinarian for a comprehensive physical examination to rule out medical problems.
✔ Have the client keep a feeding diary (minimum 1 week) to be evaluated during the initial visit.
✔ Evaluate current feeding habits and routines.
✔ Calculate current calorie intake.
✔ Calculate recommended calorie intake: 60% to 70% of intake required to maintain goal body weight (may need to use 50% if the cat is very inactive).
✔ Send home a “weight loss pack” with food samples (dry and canned) so the cat has a selection to choose from.
ciently palatable so that a cat eats enthusiastically and the consumer will purchase that food again. Many cat foods are very energy-dense, with the calories coming from fat because fat is palatable for cats and is a relatively inexpensive ingredient. In addition, because it is convenient to feed ad libitum, cats snack all day on high-calorie kibble and commonly eat more than they need rather than 8 to 10 small, 30-kcal (mouse-sized) meals per day as they would in their native state. Domestic cats generally lack exercise when compared with the hunter that they are designed to be.

The TEF is the energy cost of digesting and absorbing food. As mentioned earlier, the TEF is higher when small frequent meals are fed, so feeding multiple small meals is preferable to feeding one or two large meals. One way to incorporate this, as well as give the cat a little challenge (and exercise), is to divide the day’s food amount onto 6 or 7 small saucers and place them throughout the home as if it were a “treasure hunt.” This means that the cat is less likely to gorge, has to look for food, and has a higher TEF cost.

But there is more to obesity than energy in and energy expended. A more holistic approach can provide a greater chance of success. We must also consider why the cat is eating more. Is the cat bored? Is the cat not receiving enjoyable stimuli from other healthier sources and is, therefore, eating too much? What other aspects of normal behavior are not available for the cat to participate in? How is the cat meeting his or her “hedonic budget”? Chronic stress, which may be present in the confined indoor cat, results in neuroendocrine changes that predispose to obesity.15

What drives the client?
In a very interesting study, Kienzle and Bergler16 found that the “positive strokes” received and the behaviors of clients toward their cats differ with the cat’s weight. To quote from the paper itself: "Thirty percent of owners of overweight cats compared with 12% of owners of normal [weight] cats stated that they did not feel very happy prior to acquiring a cat, and the cat was intended to console and encourage them. These results are suggestive of [1] a

An alternative option is to utilize the Veterinary Feeding Guide and Weight Management Program software package from Purina Veterinary Diets. The program would start Fluffy on 316 kcal/day of Purina Veterinary Diet OM, calculated at 40 kcal/kg/day, targeting for a weight loss of 2% of initial body weight per week. When Fluffy returns for a recheck after 2 to 4 weeks, the practice staff enters information about her actual intake and change in body weight over that time. The program can then determine her individual MER and adjust the feeding recommendation if needed. Since the MER is based on average, the initial rate of loss may be more or less than anticipated. The benefit of this approach is that the recommendation is customized to fit the needs and metabolism of the individual patient.

Discuss with the client why cats become overweight. Pet food manufacturers make diets sufficiently palatable so that a cat eats enthusiastically and the consumer will purchase that food again. Many cat foods are very energy-dense, with the calories coming from fat because fat is palatable for cats and is a relatively inexpensive ingredient. In addition, because it is convenient to feed ad libitum, cats snack all day on high-calorie kibble and commonly eat more than they need rather than 8 to 10 small, 30-kcal (mouse-sized) meals per day as they would in their native state. Domestic cats generally lack exercise when compared with the hunter that they are designed to be.

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A closer relationship between overweight cats and their owners than between normal [weight] cats and their owners, (2) more over-humanization of overweight cats than of normal [weight] cats, (3) a potential role of overweight cats as a substitute for human companions.

People with overweight or obese cats tend to underestimate their cat’s BCS and talk about different things to their cats than do people living with cats of normal weight. Not surprisingly, people with overweight cats were more likely to get positive feelings from watching their cats eat, whereas people with cats of normal weight spent more time playing with their cats. While there was “no significant difference between the number of meals and snacks and the type of food received by normal and overweight cats, the overweight cats more often received fresh meat and kitchen scraps or various extra treats added to their regular food,” and cats of normal weight were more likely to get moist food than obese cats were.

Somewhat curiously, people with overweight cats were more interested in their own health than clients with cats of normal weight were, but in reverse, the former group of clients considered preventive care for their cat as less important than the latter group of clients did.

So, in a cat’s weight there is an element of meeting the hedonic budget for people who live with the cat as well. Hence, it is essential that we address the behavior of the people who live with and feed the cat. Encouraging alternative “strokes,” things that make people feel good about their interactions with the cat, such as play and feeling proud of achieving weight loss goals, are not to be taken lightly. Positive feedback from the veterinary team (the outside environment) as well as feedback self-generated by the client are key elements to the success of a weight loss program.

**Giving clients the right tools**

Behavior modifications required to make a weight loss program successful need all key family members to play a role. Are there forms of interaction that the client can have with the cat, other than feeding? Treats are the downfall of many weight control programs. It is best if one

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**Biweekly Weight Loss Record**

- **Weight in pounds**
  - **May 1**: 19
  - **May 15**: 18.5
  - **May 29**: 18
  - **June 12**: 17.5
  - **June 26**: 17

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**Follow-up Is Key!**

- **Assign a technician or nurse as the client’s “buddy” in charge of follow-up**
- **Review program features**
  - Unlimited buddy phone support
  - Program lasts 6 months and is renewable if necessary
- **Week 1—Support phone call**
- **Week 2 and subsequent biweekly appointments:**
  - Schedule a 15-minute visit with the program supervisor and the veterinarian
  - Weigh patient biweekly using the same scale
  - Talk with owners about highlights or problems
  - Update the bar graph and send it home with the client at each biweekly meeting
- **After 6 months a plateau may occur, and new calculations may be needed to promote further safe weight loss.**

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No weight loss program is effective without proper follow-up. Assigning a technician or nurse as a client “buddy” in charge of follow-up helps ensure success.
person handles all of the feeding and others bond through other means (e.g., catnip, combing, playing). Feeding multiple small meals as a treasure hunt is beneficial. Ask clients whether the cat prefers toys that mimic bird movement (flying) or mouse movement (scrambling). Have them develop a new routine of playing with their cat several times a day to add interest and exercise to the cat's life. The cost of the clinic weight loss program might include a bag of catnip and a toy.

Create a bar graph (see Biweekly Weight Loss Record) to be maintained in the computer by staff members and included in the cat’s medical record. Update and send the graph home with clients at every visit as a good reminder of their success.

Follow-up is the key to the success of any weight loss program (see Follow-up Is Key!). A technician or nurse (program supervisor) should become the client’s “buddy” and be in charge of follow-up. No weight loss program is effective without proper follow-up.

References