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Study Grades[†] in Evidence-Based Medicine



Grade I

Well-designed, properly randomized and controlled clinical trial that utilizes patients with naturally occurring disease.

- ▶ Prospective studies



GRADE II

Well-designed and controlled laboratory studies in the target species with naturally occurring disease.



GRADE III

Evidence obtained from one of the following

- ▶ Well-designed nonrandomized clinical trial
- ▶ Cohort- or case-controlled epidemiologic studies
- ▶ Studies using an acceptable disease model
- ▶ Case series
- ▶ Dramatic results from uncontrolled studies



GRADE IV

Evidence obtained from one of the following

- ▶ Bench-top in vivo laboratory studies
- ▶ Opinions based on clinical experience
- ▶ Descriptive studies
- ▶ Studies conducted in another species
- ▶ Pathophysiologic justification
- ▶ Reports of expert committees

[†]Quality of evidence guidelines are adapted from the U.S. Preventive Services Task Force.



How to Make Evidence-Based Decisions in Clinical Practice

Practitioners should know how to counsel owners regarding the available options for medical, surgical, and nutritional care. The prevailing system of veterinary medical education and the practice of continued learning are not based on rigorous assessment of evidence for or against particular management options, including many aspects of clinical nutrition. Journals and textbooks, even those that can be rapidly accessed in the short time required to make clinical decisions, may not be helpful for determining specific risks and benefits of nutritional management. Veterinarians often rely on clinical experience and judgment, perhaps supported by the advice of colleagues or consultants who practice in a similar manner. Evidence-based medicine (EBM) represents a major, but still untested, intellectual advance in clinical decision-making.

Concepts of EBM

The term EBM and its associated concepts were first advanced by a group at McMaster University Health Sciences Centre in Canada, with the first publications in the early 1990s. The underlying concepts, however, are not new. Rooted in clinical epidemiology, EBM reflects a movement to establish clinical medicine as a verifiable scientific activity.

As defined, EBM is the integration of the best research evidence, clinical expertise, and patient values. “Best research evidence” means clinically relevant research, especially from patient-centered clinical studies. “Clinical expertise” refers to the ability to use clinical skills and past experience to rapidly identify each patient’s unique health state, establish a diagnosis, and determine the risks and benefits of potential interventions for that specific patient. “Patient values” originally centered on values of the human patient: unique preferences, concerns, and expectations that they bring to a clinical encounter and that must be integrated into clinical decisions. Integration of these 3 elements is believed to result in clinicians and patients forming a diagnostic and therapeutic alliance that optimizes clinical outcomes and quality of life.

The concepts of EBM also apply to dogs, cats, and other animals. The concept of patient values must be extended to include the unique preferences, concerns, and expectations of each owner as well as those of their animals. Regardless of the definition used, the intent is that use of current best evidence does not replace clinical skills, judgment, or experience; rather, it adds another dimension by incorporating the preferences of the patient and its owner into the decision-making process.

A conceptual model for evidence-based clinical decisions reveals that the best decisions are made when clinical expertise, research evidence, and owner or patient preferences overlap. Clinical expertise is obviously needed to obtain a medical history and to assess a patient’s nutritional and health status. This expertise allows for the individualized care of a specific animal’s needs. Owners have always exercised their preferences for medical care by seeking second opinions, choosing alternative treatments, exercising economic constraints, and adhering (or choosing not to adhere) to recom-

mended therapeutic plans. Moreover, owners currently have greater access to clinical and nutritional information than ever before.

The challenge of integrating clinical expertise with current best evidence from medical and nutritional research is complex. Evidence often represents extrapolations of pathophysiologic principles, studies conducted in other species, and logical conclusions based on data derived from patients in clinical studies. The proliferation of randomized, controlled trials has led to an increase in the quantity and quality of clinically valid evidence. When possible, veterinarians should use information derived from systematic, rigorously controlled clinical studies to make diagnostic and treatment decisions. Evidence-based clinical nutrition or medicine does not always lead to a definitive answer, but it does provide a framework for making decisions and understanding the risk–benefit relationship of various feeding or therapeutic plans. To better understand EBM, an understanding of the rules of evidence is necessary.

The Rules of Evidence

Scientific evidence is the product of appropriately designed and carefully controlled research investigations. A single study does not constitute evidence; rather, it contributes to a body of knowledge that has been derived from multiple studies investigating the same area. Unfortunately, there is neither a central repository for clinical nutrition information nor a single system for establishing quality evidence. Several classification schemes may be useful for establishing rules of evidence for recommendations regarding clinical nutrition.

Traditional sources of evidence include materials such as textbooks, personal journal collections, conference proceedings, and clinical guidelines. Much of this evidence is not based on appropriately conducted clinical studies in the target species. Many clinical and nutritional interventions are used because the basic pathophysiologic rationale made sense despite insufficient data documenting a positive effect. Sources regarded as strong evidence include randomized, controlled trials or systematic reviews of more than 1 study (ie, meta-analyses). (See Study Grades in Evidence-Based Medicine, inside front cover.) These are followed respectively by epidemiologic studies (cohort studies or case–control studies), models of disease, and case series. The hierarchy of evidence is based on the notion of causation and the need to control bias. Guidelines developed by the U.S. Preventive Services Task Force also serve as an excellent example of a rigorous application of an evidence-based appraisal system.

In the future, veterinarians will increasingly need to understand the epidemiologic aspects of disease, apply clinical guidelines to specific patients, and discuss the risk–benefit probability with pet owners. Application of EBM to veterinary medicine clearly offers a new approach for making clinical decisions and managing patient care. Adopting guidelines for veterinary clinical practice that include elements of EBM and adapting them to each patient will likely improve patient outcomes.



Home Care for Prevention of Periodontal Disease in Dogs and Cats

What the owner does at home on a daily basis for plaque control influences long-term oral health as much as professional dental care.

For animals predisposed to or afflicted with periodontal disease, professional treatment is only part of the plan. What the owner does at home on a daily basis for plaque control influences long-term prognosis as much as professional dental care. In order to successfully treat and prevent periodontal disease in pets, a multidimensional approach must be taken. Exacerbating factors should be identified and eliminated, and the animal should receive regular home dental care after examination by a professional. Over the years, many therapeutic and preventive interventions have been advocated for

Case Study

A 7-year-old, 66-lb male Irish Setter is evaluated for severe halitosis and reluctance to eat dry food. Examination of the oral cavity reveals moderate accumulations of plaque and calculus on both dental arcades, periodontitis, exposure of the furcation of tooth roots, and loss of attachment; these findings are most prominent around the caudal mandibular premolars and molars. The remainder of the physical examination is unremarkable. Antibiotics are administered to the dog to help control infection of oral tissues while further diagnostic evaluations are performed. Results of a complete blood count, serum biochemistry analysis, and urinalysis are normal.

After the dog is anesthetized, supragingival scaling, root planning, and subgingival curettage are performed. Severe periodontal disease is found around some left mandibular teeth (fourth premolar and first molar). These teeth are extracted and the extraction sites are closed with sutures. The remaining teeth are polished. Orally administered antibiotics and a canned recovery-type food are dispensed. On follow-up evaluation two weeks later, the extraction sites are healed. The owner comments that the dog is more active. The attending veterinarian considers changes that could be made to the dog's diet to reduce future accumulation of plaque and calculus.





The Owner–Animal–Environment Triad in Managing Periodontal Disease

1. Know the Owner

- ▶ What is the owner's relationship with the pet?
- ▶ Is the pet a well-loved member of the family, or does it have little social contact with the family?
- ▶ Is the person who brought the animal to the hospital the family member who cares most for the animal, and is she likely to take primary responsibility for oral health care decisions?
- ▶ What is the owner's attitude toward dental care in general?
- ▶ Does the owner have anxiety about dental treatment (dental phobia)?
- ▶ What does the owner perceive to be the problem (eg, halitosis, stained teeth, difficulty chewing)?
- ▶ What are the owner's physical capabilities?
- ▶ Will the owner be able to train the animal to enjoy home care and then provide this attention regularly?
- ▶ What does the owner expect from treatment?



2. Know the Animal

- ▶ Is the pet likely to be cooperative with home care?
- ▶ Does the animal have a medical problem that makes one form of treatment preferable to another?
- ▶ Does the pet have any medical or anatomic considerations that make one form of treatment preferable to another?

3. Know the Environment

- ▶ What is the dietary history (commercial foods; "people" food; treats; access to other pet food, such as a dog consuming cat food)?
- ▶ How many other pets are in the household, and what kind are they?

4. Know the Evidence

- ▶ What is the quality and strength of evidence supporting use of a therapeutic or preventive intervention?

Adapted from Hale FA. The owner–animal–environment triad in the treatment of canine periodontal disease. *J Vet Dent* 20:118-122, 2003.

periodontal disease, but evidence of efficacy or effectiveness is highly variable. Several materials accumulate on tooth surfaces and participate in the pathophysiology of periodontal disease. These substances are commonly referred to as tooth-accumulated materials or *dental substrates*. These substrates accumulate in a dynamic process.

Goals and Limits of Dental Home Care

Oral health is achieved through a combination of professional therapy and home care. Dental home care refers to the procedures animal owners use at home to control dental substrate accumulation. The primary goal of dental home care is daily plaque control to maintain oral hygiene and prevent the devel-

opment of gingivitis and periodontal disease. Home care can be harmful to the pet and the owner and can be counterproductive if not approached in the proper manner.

Home care does not routinely remove existing calculus and is not effective for treating established disease, nor is it a substitute for regular professional examinations or treatment. Therefore, dental home care should only be instituted after appropriate professional treatment has established a clean and healthy mouth. It is then used to prevent the situation from deteriorating.

The effectiveness of a dental home care program is linked to the knowledge and commitment of the owner and to cooperation from the pet; therefore careful planning should be employed to achieve optimal results. This dynamic has been termed the *owner–animal–environment triad* for the treatment of periodontal disease. Owners must be involved in the planning process and realize that they play a very important role in the desired clinical outcome.

Evidence-Based Veterinary Dentistry

Veterinarians and veterinary dentists often rely on clinical experience and judgment, perhaps supported by the advice of colleagues who practice similarly. Scientific evidence is the product of appropriately designed and carefully controlled research investigations. A single study does not constitute evidence; rather, it contributes to a body of knowledge that has been derived from multiple studies investigating the same area. Unfortunately, there is neither a central repository for veterinary dentistry information nor a single system for establishing quality evidence. However, the Veterinary Oral Health Council (VOHC) was established in 1997 to provide independent, objective, and credible means of recognizing veterinary dental products that effectively control accumulation of plaque or calculus. The VOHC is run by the American Veterinary Dental College and is endorsed by many international veterinary dental organizations. The VOHC does not conduct dental testing; rather, the council reviews results of tests performed in accordance with VOHC-approved protocols. Those products approved by the council can display the VOHC seal for tartar or plaque control on their packaging and promotional materials.

Foods and Treats that Support Dental Care

Dental Foods

Most dogs and cats eat something every day; therefore, use of foods that provide dental benefits seems appropriate. Conventional wisdom suggests that typical dry, crunchy commercial foods provide a dental benefit to cats and dogs. Although consumption of soft foods may promote plaque accumulation, the general belief that dry foods provide significant oral cleansing should be regarded with skepticism. A moist food may perform similarly to a typical dry food in affecting plaque, calculus, and stain accumulation. In a large epidemiologic survey, dogs consuming dry food alone did not demonstrate improved oral health when compared with dogs eating moist foods.

Several complete and balanced adult pet foods are available that provide substantial oral cleansing compared with typical dry, moist, or snack foods. These foods are distinguished by their enhanced textural characteristics, which provide mechanical cleansing of the teeth. Combining increased fiber content with a size and pattern (texture)

that promote chewing and maximize contact with teeth is critical to obtaining a dental benefit. As a tooth penetrates a typical kibble or biscuit, the initial contact causes the food to shatter and crumble, with contact occurring only at the coronal tip of the tooth surface. Dental foods with specific textural characteristics do not crumble, allowing each piece of food to maintain prolonged contact with the tooth surface, thereby gently removing plaque accumulation. Numerous short-term and long-term (lasting at least 6 months) studies have demonstrated that dental foods with enhanced textural characteristics provide significant plaque, calculus, and stain control in laboratory colony cats and dogs when used after an oral hygiene procedure. **I** **II**

Dental Treats

Treats would include any consumable item that adds to the total calorie intake. No treat has ever been shown to be able to



Most dogs and cats eat something every day; therefore, use of foods that provide dental benefits seems appropriate.

maintain clinically healthy gingiva regardless of the quantity consumed. Treats are only a part of the plaque control program and should be used in addition to (not instead of) brushing.

Several dental treats rely on mechanical abrasion to help reduce dental substrate accumulation. One small study showed that daily addition of an enzyme-containing feline dental hygiene chew to a dry cat food resulted in decreased dental substrate accumulation in client-owned cats. It is unknown if the improvements noted in cats in this study were attributable to abrasive action of the chew, enzyme activity, or a combination of both. **I** **II**

Biscuit Treats

The Association of American Feed Control Officials supports and recommends guidelines developed by the Center for Veterinary Medicine of the U.S. Food and Drug Administration for dental health claims. These guidelines state that food products bearing claims to cleanse, freshen, or whiten teeth by virtue of their abrasive or mechanical action are not objectionable. On the other hand, food products bearing claims for plaque or calculus reduction or prevention or control of breath odor may be misbranded. Enforcement of guidelines is a low priority, and many products that claim to control plaque or calculus offer little or no evidence to document their effectiveness. Hexametaphosphate is a sequestrant that binds salivary calcium, making it less available for precipitation as calculus. Often added to the surface of baked biscuit treats, this agent was shown to significantly reduce calculus accumulation in research colony and client-owned dogs over a 4-week period compared with a regimen of plain, baked biscuits and dry food alone. A separate study demonstrated no significant differences in plaque or calculus accumulation in laboratory colony dogs fed dry food, dry food plus baked biscuits, or dry food plus hexametaphosphate-coated biscuits for 3 weeks. **IV**

Chew Aids

This category includes consumable items that are not considered to be a significant source of calories, such as rawhide strips/bones

Key Points

- ▶ Dental home care should center on daily plaque control to prevent gingivitis and periodontal disease.
- ▶ Home care will be most effective after a veterinarian has established that the animal's mouth is clean and healthy.
- ▶ The VOHC was established to provide independent, objective, and credible means of recognizing veterinary dental products that effectively control accumulation of plaque or calculus.
- ▶ When evaluating the strength and quality of dental research evidence, the distinction between efficacy (results under ideal conditions) and effectiveness (results under home conditions) must be considered.



Some Commercial Foods and Treats Recognized by the VOHC for Effective Plaque and Calculus Control

Product	Type	Claim
Prescription Diet® Canine t/d® Original and Small Bites*	Food	Plaque & Tartar
Prescription Diet® Feline t/d®*	Food	Plaque & Tartar
Science Diet® Oral Care Canine Adult†	Food	Plaque & Tartar
Science Diet® Oral Care Feline Adult*†	Food	Plaque & Tartar
Greenies® Edible Dog Treats‡	Edible Treat	Plaque & Tartar
Hartz® Flavor Infused Oral Chews‡	Rawhide Treat	Plaque & Tartar
Del Monte Tartar Check® Dog Biscuit§	Biscuit Treat	Tartar
Friskies® Cheweez®**	Rawhide Chew Treat	Tartar
Iams® Chunk Dental††	Food	Tartar
Eukanuba® Adult Maintenance Diet for Dogs††	Food	Tartar

*Manufactured by Hill's Pet Nutrition, Inc.
 †Manufactured by S&M NuTec, LLC.
 ‡Manufactured by The Hartz Mountain Corporation.
 §Manufactured by Del Monte Foods Company.
 **Manufactured by Nestlé USA Inc.
 ††Manufactured by The Iams Company.


toothbrush and may have a number of functions. Most veterinary pastes are flavored for the particular taste preferences of dogs and cats, thereby acting as a positive reinforcer that encourages cooperation from the pet. Pastes also often contain some abrasive material, such as ground walnut shells, to improve the mechanical cleaning action of the brush. Massaging the gingiva with a toothbrush produces epithelial thickening and increases keratinization, blood circulation, and mitotic activity in the epithelium and connective tissue. Whether these changes provide substantial protection against microorganisms or are necessary for gingival health is debatable. The plaque removal effect of tooth brushing is likely far more important.

Most veterinarians and veterinary dentists recommend brushing a pet's teeth at least 3 times weekly; however, this regimen may not be often enough, particularly for those with established periodontal disease. Most animal

Dental Products and Procedures Supported by High-Quality Evidence

- ▶ Tooth brushing (cats and dogs)
- ▶ Chlorhexidine (dogs)
- ▶ Textural dental foods (cats and dogs)
- ▶ Zinc ascorbate (cats)
- ▶ Proprietary dental treats (dogs)
- ▶ Short-term use of clindamycin and dental sealants (dogs)

and pig's ears. Any item that a dog may chew into little bits (and possibly swallow) bears some risk of gastrointestinal upset or blockage. Consider each item and its relative risk and choose the safest one available.

Studies suggest that chew aids can be used as an adjunct to other dental home care techniques. Dogs in one survey with access to chewing materials had less calculus accumulation, gingivitis, and periodontitis than those without any enhanced chewing activity. Unfortunately, the study did not measure how often or how long dogs chewed on their respective materials. 

Other Dental Home Care Strategies

Tooth Brushing

Tooth brushing on a regular basis offers one of the best methods for daily plaque control by mechanically disrupting plaque accumulation. After a plaque film has formed, it resists most passive control methods. The use of toothpastes or gels may facilitate removal of dental substrates, but effective brushing can occur without their routine use. Pastes are meant to be used on the

Key Points

- ▶ No treat has ever been shown to be able to maintain clinically healthy gingiva regardless of the quantity consumed.
- ▶ Plain baked dog biscuits have not been shown to significantly reduce plaque and tartar accumulation.
- ▶ One survey showed dogs with access to chewing materials had less calculus accumulation, gingivitis, and periodontitis than those without any enhanced chewing activity.
- ▶ Foods providing the greatest dental benefit have a texture that promotes chewing and maximizes contact with teeth.
- ▶ Most veterinarians recommend brushing a pet's teeth at least 3 times weekly, but this frequency may be insufficient for pets with established periodontal disease.
- ▶ Most chemical agents will reduce or retard plaque accumulation to a degree, but they cannot stop it from forming.

owners do not sustain the level of dedication and motivation required to brush pet's teeth regularly. Although these studies show that tooth brushing is beneficial, the compliance rate with tooth brushing at home by dog and cat owners is approximately 40% to 50% after 6 months. These compliance data, however, were achieved with highly motivated pet owners; there is limited information about long-term compliance rates with tooth brushing by typical pet owners. ▲▲

Chemical Plaque Control

Chemical plaque control agents come in many forms, including toothpastes, gels, rinses, and water treatments. No chemical agent has been shown to be effective in plaque control by itself. Most will reduce or retard plaque accumulation to a degree, but they cannot stop it from forming. Once a plaque film has formed, it will be very resistant to chemical agents that are applied passively.

Conclusions

The concepts of evidence-based medicine can be readily applied to veterinary dentistry, as demonstrated here for evaluating dental

Case Study Revisited

There are several randomized, controlled clinical studies that evaluated the effect of dietary modification for dogs with plaque and tartar accumulation, gingivitis, and oral malodor. The studies were conducted in laboratory settings and involved the use of a nutritional product in dogs with naturally developing oral disease. Results of these studies reveal that dogs that were fed a therapeutic food specially formulated for management of dental conditions had less plaque, tartar, gingivitis, and oral malodor than those fed a typical dry food. This constitutes high quality evidence. The patient is extremely similar to the dogs used in the published studies, and the food is one that is readily available and economically feasible. On the basis of this evidence, use of Hill's® Prescription Diet® Canine t/d® should be strongly recommended for this dog, provided that owner and patient preferences are satisfied.



home care products and programs for management of periodontal disease in cats and dogs. Quality of evidence guidelines previously published in the veterinary literature serve as an excellent example of a rigorous application of an evidence-based appraisal system. Evidence classified as either Grade I or II is most likely to be indicative of outcomes to be expected in clinical practice. In the case of research regarding plaque and gingivitis control, the highest quality of evidence exists for tooth brushing (cats and dogs), chlorhexidine use (dogs), dental foods with textural characteristics (cats and dogs), zinc ascorbate (cats), proprietary dental treats (dogs), and short-

term use of clindamycin or dental sealants (dogs). These are the products and procedures that should be recommended for dental home care programs to control periodontal disease in cats and dogs. With regard to controlling calculus accumulation, the highest quality of evidence exists for tooth brushing (cats and dogs), dental foods with textural characteristics (cats and dogs), dental foods or treats with polyphosphates (cats and dogs), and proprietary rawhide chews (dogs). The effectiveness of other dental home care products and procedures is supported by lower-quality evidence; therefore, these strategies should not be recommended until more published studies are available. 🐕 🐈

This article as well as further information on the topic are available on the Web at www.HillsVet.com/ConferenceProceedings.

Dental Care Agents with Published Evidence

Agent	Classification	Use	Published Evidence
Clindamycin ▲▲	Antibiotic	Postprophylaxis treatment	Controlled studies in dogs showing efficacy
Chlorhexidine ▲▲	Nonspecific antimicrobial agent	Effective in inhibiting plaque accumulation and reducing gingivitis. Used in rawhides chews, dental gels, oral rinses, and bioadhesive tablets	Controlled studies in dogs showing efficacy
Hexametaphosphate and other polyphosphates ▲▲	Mineral chelators and mineralization inhibitors that bind salivary calcium	Used on food, chews, and biscuits	Evidence for and against efficacy (tartar only)
Soluble zinc salts ▲	Mineral salts with antimicrobial activity	Oral cleansing gels, rinses, and dentifrices	Randomized clinical trial in small group of cats; may also help with malodor



Pain Management for Canine Osteoarthritis

Just like humans, dogs with osteoarthritis can benefit from an individualized, multimodal, patient-centered approach to care.

Osteoarthritis (OA), the most common form of arthritis in dogs, is a slowly progressive condition. Articular cartilage degenerates, proteoglycan and collagen are lost, and new bone proliferates. In addition, a variable, low-grade inflammatory response takes place within the synovial membrane. Current estimates of the prevalence of arthritis in older dogs range from 20% to 25%.

Management of Canine Osteoarthritis

Just like humans, dogs with osteoarthritis can benefit from an individualized, patient-centered approach to care. Current treatment modalities used to manage chronic osteoarthritic pain in dogs include nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying osteoarthritis agents (DMOAs), nutraceuticals, exercise and weight management, and therapeutic foods. Most animals will benefit from a combination of the different modalities.

Nonsteroidal Anti-Inflammatory Drugs

Clinical studies have shown that NSAIDs, the most commonly prescribed medications for treatment of OA, effectively relieve inflammation-related clinical signs for at least 60 days; however, the drugs are apparently incapable of slowing the progression of OA. Most NSAIDs act by inhibiting cyclooxygenase (COX)-1 and COX-2, and some also inhibit lipoxygenase. Drug effectiveness and side effects depend on individual response, so treatment should be adapted to each patient. When these agents are prescribed, owners should be advised to watch for possible adverse effects, especially those related to the gastrointestinal, hepatic, renal, and hematopoietic systems. Combining NSAIDs with other therapies can relieve pain and discomfort and improve the quality of life for the patient. Use of NSAIDs in conjunction with therapeutic foods is safe and effective.

Key Objectives for Osteoarthritis Management

- ▶ Control pain and discomfort
- ▶ Reduce clinical signs
- ▶ Slow progression of disease
- ▶ Promote repair of damaged tissue
- ▶ Improve quality of life

NSAIDs Commonly Prescribed for Canine OA

- ▶ Carprofen
- ▶ Deracoxib
- ▶ Etodolac
- ▶ Firocoxib
- ▶ Meloxicam
- ▶ Tepoxalin

Disease-Modifying Osteoarthritis Agents

The DMOAs improve biosynthetic activity in articular cartilage or synovial fluid to slow disease progression. Some of these agents may also reduce inflammation and inhibit cartilage catabolic enzyme activity. Two other DMOAs, glucosamine and chondroitin sulfate, are used either separately or in combination. Glucosamine occurs naturally in the body and is one of the basic sugar components used to synthesize the disaccharide units that compose all the glycosaminoglycan chains attached to proteoglycans. Chondroitin sulfate is a constituent of aggrecan, the aggregating proteoglycan in articular cartilage, and has repeating subunits of glucuronic acid and N-acetyl galactosamine sulfate.

To date, researchers have conducted studies of polysulfated glycosaminoglycan, glucosamine, and chondroitin sulfate in canine models of arthritis and synovitis; however, only PSG has undergone randomized, controlled studies in dogs with spontaneous OA, and those results have been inconsistent. Recent meta-analyses of glucosamine and chondroitin sulfate use in humans have been inconclusive. Glucosamine generally appeared to relieve some clinical signs and to slow the narrowing of joint space; chondroitin sulfate showed similar symptom-relieving effects but its effect on articular cartilage was not confirmed.

Numerous studies in humans and dogs with arthritis suggest that mild to moderate exercise is actually beneficial.

been found to exert some interesting anti-inflammatory effects in certain animal models and *in vitro* assays. A recent trial of a curcuminoid extract in dogs with OA found no treatment effect with force-plate analysis as the primary outcome variable, although veterinary surgeon assessment of response to treatment was positive.

Exercise and Weight Management

In the past, exercise was often restricted or discouraged for patients with arthritis. Numerous studies in humans and dogs with arthritis

Other Nutraceuticals

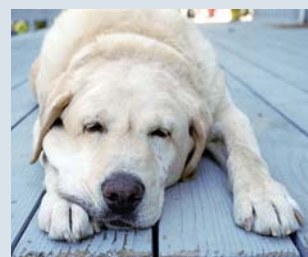
Despite great interest in the discovery of natural compounds, or *nutraceuticals*, to alleviate clinical signs of OA, studies to support existing *in vitro* evidence are lacking. To date, green tea extract and other Asian herbal remedies have not been evaluated in companion animal models or in animals with spontaneous disease. Curcuminoids, types of phytonutrients extracted from turmeric, have

Case Study

A 6-year-old, 75-lb spayed female Labrador retriever is examined for rear lameness resulting from hip dysplasia and degenerative joint disease. According to her owner, the dog has mild to moderate stiffness and difficulty rising from rest. She is reluctant to run, jump, or play, and she occasionally limps. Her clinical signs first began 2 years ago. The dog is fed a low-fat, moderate-fiber, therapeutic food for overweight dogs, but she has access to food provided for the other pets in the house (6 cats and 1 other dog).

Physical examination reveals an overweight dog (BCS=4/5), mild lameness in the left rear limb, mild limitation in range of motion of the affected limb, and mild pain on palpation of the left coxofemoral joint. A complete blood count and results of a serum biochemistry profile and urinalysis are normal. Radiographs reveal changes consistent with bilateral hip dysplasia and degenerative joint disease of the left hip joint.

When the owner learns of his dog's condition, he expresses concern about having to give pills every day. The veterinarian explains that careful dietary monitoring and regular exercise may ease the dog's pain without medication.



suggest that mild to moderate exercise is actually beneficial for reducing pain and discomfort and for improving overall quality of life. Frequent, mild, weight-bearing exercise over an extended period has been shown to increase joint mobility and strengthen supporting muscles. Lower impact forms of exercise in water have often been considered optimal for patients with arthritis, but the specific forms of exercise and physical therapy that are most beneficial to dogs are still being investigated.

Exercise also helps to reduce body weight. Although obese dogs are known to be at increased risk for OA, the exact connection is unclear. Studies of body weight and hip dysplasia in large-breed dogs have confirmed that decreased body weight is beneficial to joints predisposed to OA change. Weight reduction can help to decrease abnormal forces placed on

Key Points

- ▶ OA affects 20% to 25% of older dogs.
- ▶ NSAIDs effectively relieve inflammation-related clinical signs but do not slow progression of disease.
- ▶ Some DMOAs like glucosamine and chondroitin sulfate relieve clinical signs and may slow disease progression by inhibiting cartilage catabolic enzyme activity, but well-designed clinical studies are needed.
- ▶ Most natural compounds (nutraceuticals) are unproven in companion animal models.
- ▶ Proper diet and regular exercise help to maintain a healthy weight, thereby increasing joint mobility and strengthening supportive muscles.



joints and alleviate symptoms. Increasing activity and reducing weight may also help reduce joint inflammation. The improvement in clinical signs has been noted in dogs with only mild to moderate obesity (10% to 20% over ideal weight), emphasizing the importance of weight management. Owners of overweight and obese dogs with OA should take steps to reduce their pets' weights to normal levels.

Therapeutic Foods for Arthritis

Therapeutic foods designed for companion animals with OA need to supply age-appropriate nutrition and nutrients that are critical to their special needs. The right nutrients will reduce inflammation and pain, slow the cartilage degradative process and provide the building blocks for its repair, complement prescribed medications, and provide symptomatic relief. Recent discoveries in fatty-acid nutrition have provided clear evidence that canine OA may be very responsive to dietary additions of specific fatty acids.

Role of Fatty Acids

Both arachidonic acid (AA) and eicosapentaenoic acid (EPA) act as precursors for the synthesis of eicosanoids, an important group of immunoregulatory molecules that function as local hormones and mediators of inflammation. The amounts and types of eicosanoids synthesized are determined by the availability of the polysulfated fatty acid precursor and by the activities of the enzyme system. The eicosanoids produced from AA, the principal precursor under most conditions, appear to be more proinflammatory than those formed from EPA. Ingestion of oils containing omega-3 fatty acids results in a decrease in membrane levels of AA because the omega-3 fatty acids replace AA in the substrate pool and reduce the capacity to synthesize eicosanoids from AA. Inflammatory eicosanoids produced from AA are depressed when dogs consume foods with high levels of omega-3 fatty acids.

Key Findings of *in vitro* Studies of Canine Cartilage Degradation

Canine *in vitro* models have been widely used to study the biological and molecular mechanisms involved in cartilage matrix degradation as degenerative joint disease progresses. Mechanisms of cartilage metabolism in canine OA and the potential role of omega-3 fatty acids to ameliorate the early events in the disease process have recently been investigated. These studies used cartilage tissue explants that were exposed to a variety of cytokines, growth factors, and chemical mediators that activate degradative enzymes and that induce cartilage matrix degradation. Studies were first conducted to determine which catabolic stimulants were best suited for induction of cartilage matrix (proteoglycan) catabolism in a canine model explant culture system.

Researchers then investigated the potential for omega-3 PUFAs to modulate these degenerative processes in canine cartilage metabolism.

These studies identified some similarities and some distinct differences between cartilage from dogs and other species in the response to catabolic agents and omega-3 PUFAs. Stimulated aggrecan loss was associated with increased cleavage by aggrecanases and not by matrix metalloproteinases. Results of these studies indicate that hyaline articular cartilage obtained from various animal species responds very differently to a variety of catabolic stimulants that mimic mechanisms of cartilage degradation in degenerative joint disease. Most important, EPA was the only omega-3 fatty acid able to significantly reduce loss of aggrecan in the canine cartilage *in vitro* model.

Key Findings of *in vitro* Studies

- ▶ Numerous catabolic agents significantly reduce synthesis of canine cartilage proteoglycans.
- ▶ Stimulated aggrecan loss is associated with increased cleavage by aggrecanases, *not* by matrix metalloproteinases.
- ▶ EPA is the only omega-3 fatty acid shown to be able to significantly reduce loss of aggrecan.

Key Findings of Clinical Trials

Spurred by the findings from the aforementioned *in vitro* studies, clinical trials were conducted with a food formula intended to be a therapeutic nutritional aid for dogs with OA. In 4 double-blind, controlled studies, dogs with spontaneous OA were randomized to receive either a control or test food (Hill's® Prescription Diet® Canine j/d®). The test food contained a 39-fold increase in the total omega-3 fatty acid concentration and a 39-fold increase in EPA concentration compared with the control food. For both formulas, owners of the dogs were able to provide either a dry food or a combination of dry plus canned foods. Three of the studies were conducted in U.S. veterinary hospitals; 1 lasted 6 months and 2 prospective studies lasted 3 months. The fourth study was conducted prospectively over 3 months in 2 academic specialty practices in the United States.

In all 4 studies, the OA diagnosis was based on compatible history, clinical signs, and radiographic evidence of arthritis in 1 or more joints on the clinically affected limb. To be eligible for inclusion, dogs also had to be at least 1 year of age, weigh 12.5 kg or more, and consume dry dog food; they were also required to be free of systemic disease as determined by history, physical examination, complete blood count, serum biochemistry analysis, and urinalysis. Exclusion criteria included acute traumatic injuries, complicating disease conditions, preexisting conditions

for which corrective surgery was anticipated during the feeding period, and recent intra-articular injection or arthrocentesis.

Measurements

Change in arthritic condition over time was measured by owner observations and veterinary clinical evaluations. Variables were assessed at the beginning of the study and at set time intervals after onset of feeding the control or test food. In addition, veterinary clinical evaluations were conducted at each time interval. These assessments consisted of an orthopedic examination with a specific emphasis on lameness and pain, limitation in weight-bearing ability, range of motion of the affected joint(s), and willingness to bear weight on the most affected limb when the contralateral limb was elevated.

Clinical Findings

Investigators in the 3 studies conducted in veterinary hospitals reported that physical examinations throughout the studies revealed that the animals receiving the EPA-supplemented test formula improved in several parameters. Veterinarians reported a significant improvement in range of motion and ability to bear

weight. Pain (on palpation of the affected joint) and lameness were also decreased compared to levels recorded at the onset of the studies. In addition, pet owners observed improvements in multiple clinical signs associated with OA: rising from rest, running, walking, and playing.

In the academic specialty practice study, variables were assessed at the beginning of the study and at 45 and 90 days after onset of feeding the control or test food. Gait analyses using a computerized biomechanical force plate were also conducted at the same time intervals. During each test period, 5 valid force-plate trials were obtained for the most

severely affected limb and the ipsilateral limb in each dog.

Orthopedic examinations revealed a greater percentage of dogs with improved clinical signs after consuming the test food compared



Case Study Revisited


The 6-year-old Labrador retriever with degenerative joint disease to whom we were earlier introduced typifies the dog that can benefit from therapeutic foods and increased activity levels. In her case, the veterinarian prescribed Hill's® Prescription Diet® Canine j/d® and encouraged leashed walks. The owner was told to return in 2 months for a prescription for NSAIDs if the dog's condition did not significantly improve.

The owner observed symptomatic improvement within 45 days. A second clinical evaluation after 90 days of nutritional management revealed decreased pain to palpation of the left hip joint. The dog had not lost weight since the first evaluation, but no medications or supplements were necessary to control her clinical signs. The veterinarian suggested that the owner engage in more play sessions with the dog and limit access to other pet food sources in the home so that she could reach optimal body weight and condition. Continued monitoring was recommended.



with those consuming the control food. In addition, more dogs in the test group had a reduction in pain at the end of the 90-day trial when the affected joint was palpated. No significant change in mean peak vertical force was noted for the control group during the 90-day feeding trial, but peak force increased significantly for the test group during the same time interval. The percent mean change in vertical peak force was also significantly different between groups, indicating that weight-bearing capacity of the affected limb increased in the test group over the course of the study.

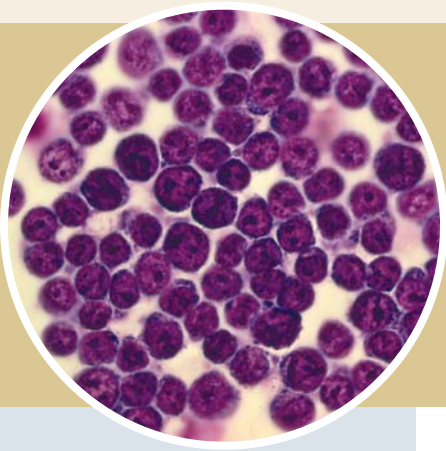
The objective of 1 trial was to determine if the test food influenced the NSAID dose required to manage clinical signs in dogs with OA. In this particular study, carprofen was administered to all dogs to manage clinical signs. At each evaluation period (3, 6, 9, and 12 weeks), the veterinarian considered the results of the orthopedic examination and the pet owner's assessment to determine the feasibility of lowering the carprofen dose. Pet owners reported a decrease in severity of 10 of 15 individual arthritic signs during the first 21 days of feeding the test food. The owners also observed significantly reduced pain in dogs consuming the test food compared with those consuming the control food. For the group consuming the test food, the mean carprofen dose reduction was 25%.

These clinical studies indicate that nutritional management with a therapeutic food containing high levels of total omega-3 fatty acids and EPA (such as Hill's® Prescription Diet® Canine j/d®) may improve clinical signs of canine OA. Furthermore, such food formulas can be used safely and effectively in conjunction with other treatments to better manage osteoarthritis pain. 

This article as well as further information on the topic are available on the Web at www.HillsVet.com/ConferenceProceedings.

Key Findings of Clinical Trials

- ▶ Dogs receiving an EPA-supplemented test food had improved range of motion and weight-bearing capacity as well as decreased pain and lameness.
- ▶ Mean peak vertical force was significantly increased in dogs receiving the test food.
- ▶ Omega-3 fatty acids and EPA supplementation may enable reductions in NSAID doses needed to manage osteoarthritic signs.



Use of Nutraceuticals in Cancer Therapy

Veterinarians and health care teams should approach the owners of pets with cancer in a positive, compassionate, and knowledgeable manner.

Few diseases evoke as much emotion as cancer. Most pet owners will have a personal experience with cancer—in themselves, a family member, or a close personal friend. Furthermore, the popular press is filled with articles about cancer prevention and the promise of therapeutic breakthroughs, including the use of functional foods and nutraceuticals. Because of this heightened awareness of human cancer, pet owners are able to understand the importance of nutrition in animals with cancer and how proper feeding and the use of functional foods or nutraceuticals can enhance the quality and length of life in pets with the disease. Veterinarians and health care teams should approach the owners of pets with cancer in a positive, compassionate, and knowledgeable manner.

Metabolic Alterations in Patients with Cancer ***Alterations in Carbohydrate Metabolism***

Carbohydrate metabolism is dramatically altered in dogs with cancer. Tumors preferentially metabolize glucose (carbohydrates) for energy, forming lactate (lactic acid) as an end product. Dogs with cancer must then expend energy to convert lactate back to glucose, resulting in a net energy gain by the tumor and net loss by the animal. Consequently, dogs with cancer lose energy to the tumor and have elevated blood lactate and insulin levels, indicating altered carbohydrate metabolism. Studies to delineate carbohydrate metabolism in cats with cancer have not been published.

Alterations in Protein Metabolism

Human patients with cancer and weight loss have decreased body muscle mass, decreased skeletal protein synthesis, and altered nitrogen balance. These patients concurrently have increased skeletal muscle protein breakdown, liver protein synthesis, and whole-body protein

Case Study

A 6-year-old sexually intact male Scottish terrier is evaluated because it has been lethargic for several days. The owner also reports that the dog has mild inappetence. Body weight is 20.9 lb (BCS = 3/5). Physical examination reveals enlargement of the spleen and several peripheral lymph nodes. Results of rectal palpation and ocular fundic examination are normal. Analysis of a complete blood count reveals mild normocytic, normochromic, nonregenerative anemia. Results of a serum biochemistry analysis are within reference ranges, except for mild increases in hepatic enzyme activity. Thoracic radiography only reveals sternal lymph node enlargement, but abdominal ultrasonography reveals enlargement of mesenteric lymph nodes and changes consistent with infiltrative disease in the spleen. Cytologic examination of a fine-needle aspirate obtained from a peripheral lymph node reveals a homogenous population of immature lymphoid cells consistent with high-grade lymphoma.

The tentative diagnosis and treatment options are discussed with the owner, who selects the use of chemotherapy for the dog. The owner is interested in knowing whether nutritional therapy or dietary supplements are appropriate for the dog.



synthesis to support tumor growth. The reprioritization of liver protein synthesis is commonly known as the *acute-phase reactant response*. The presence of an acute-phase protein response is strongly associated with reduced survival in human patients with several different forms of cancer. If protein intake does not keep pace with use, an imbalance occurs that alters immune response, gastrointestinal function, and wound healing.

Key Points

- ▶ Dogs have low energy and elevated blood lactate and insulin levels because tumors preferentially metabolize carbohydrates.
- ▶ Reprioritization of liver protein synthesis, known as the acute-phase reactant response, may cause imbalances that alter immune response, gastrointestinal function, and wound healing.
- ▶ Adipose tissue catabolism, a major feature of cachexia in cancer, can deplete fat stores.

Alterations in Fat Metabolism

Adipose tissue catabolism is the second major feature of cachexia in various chronic diseases, including cancer. A decrease in fat synthesis or an increase in lipolysis can deplete fat stores. A lipid-mobilizing factor has been isolated from a cachexia-inducing murine tumor and from the urine of human patients with cancer and weight loss. The lipid-mobilizing factor acts directly on adipose tissue, causing the release of free fatty acids and

glycerol by increasing levels of cyclic adenosine monophosphate in a manner similar to that of the natural lipolytic hormones. Several cytokines alter lipid metabolism.

Functional Foods for Patients with Cancer Soluble Carbohydrate and Fiber

Most dogs and cats do not have a requirement for soluble carbohydrates and fiber in their diet. Pet food manufacturers and homemade recipes use ingredients containing soluble carbohydrates because they are good energy sources and have unique properties that aid in manufacturing and cooking processes. Soluble carbohydrates, however, may be poorly used by animals with cancer and can contribute to increased lactate production. Thus, soluble carbohydrates should comprise less than 25% of the food's dry matter content for animals with cancer.

Arginine

Arginine is an essential amino acid that may have specific therapeutic value in animals with cancer. Adding arginine to parenteral solutions has been

shown to decrease tumor growth and metastatic rates in rodent cancer models. Increased dietary arginine, in conjunction with increased dietary omega-3 fatty acid intake, has been shown to improve clinical signs, quality of life, and survival time in dogs treated for cancer. The exact mechanisms whereby arginine benefits patients with cancer are unknown, but they may include modulating the immune system or altering neuroendocrine responses. The minimum effective level of dietary arginine for animals with cancer has not been determined, but the positive correlation between plasma arginine concentrations and survival in dogs with lymphoma receiving chemotherapy suggests that it is appropriate to provide more than 2.5% arginine on a dry matter basis. Cats should receive foods with similar levels until research discloses a more effective level.

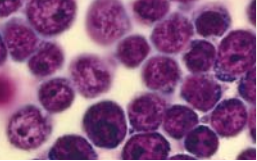
Fat and Omega-3 Fatty Acids

Some tumor cells have difficulty using lipids as a fuel source, while host tissues continue to oxidize lipids for energy. This finding led to

Dietary Recommendations for Animals with Cancer*

Dogs	Cats
Soluble carbohydrates: < 25%	Soluble carbohydrates: < 25%
Protein: 30% to 45%	Protein: 40% to 50%
Fat: 30% to 45%	Fat: 25% to 35%

*Percentages reflect composition of food dry matter.



Dietary Essentials: Omega-3 Fatty Acids and Arginine

Clinical studies in humans have shown that fish oil, a good source of omega-3 fatty acids, modulates the immune response and prolongs survival of human patients with solid tumors. Supplementation with EPA has also been linked to improved cell-mediated immune function in human patients with esophageal cancer. Omega-3 fatty acid levels are higher in adipose tissue of women responding to chemotherapy for breast cancer.

In a group of dogs receiving chemotherapy for lymphoma, consumption of food supplemented with arginine and omega-3 fatty acids helped to raise plasma arginine and fatty acid concentrations. Plasma levels of arginine and omega-3 fatty acids positively correlated with survival time. Another group of dogs that were undergoing radiation therapy for nasal tumors were fed food supplemented with arginine and omega-3 fatty acids. Again, their elevated plasma levels of arginine and omega-3 fatty acids positively correlated with quality of life and negatively correlated with inflammatory mediators and mucositis in irradiated areas. More research may disclose similar findings in cats.

the hypothesis that foods relatively high in fat may benefit animals with cancer compared with foods relatively high in carbohydrates. Pets in North America receive most of their nutrient intake from commercial dry pet foods. These foods are usually high in soluble carbohydrate (25% to 60%) and relatively low in fat (7% to 25%). These characteristics make most commercial dry foods inappropriate for nutritional management of animals with cancer.

Omega-3 fatty acids, especially those found in certain types of fish and fish oil (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]), are probably the most important nutraceuticals to consider for animals with cancer. Several human epidemiologic studies have suggested that consumption of fish or higher levels of omega-3 fatty acids is beneficial. Fish consumption is believed to protect against colorectal cancer in women and prostate cancer in men. Higher omega-3 fatty acid concentrations in adipose tissue are associated with a reduced risk of breast cancer in women. The recommendation for feeding high levels of omega-3 fatty acids like EPA and DHA to pets with cancer derives from many sources of research, including *in vitro* cell culture studies; extensive studies in rodent models involving several different types of cancer; clinical trials in human patients with severe forms of cancer; and clinical trials in dogs treated for lymphoma, nasal tumors, hemangiosarcoma, and osteosarcoma.

Fish oil and EPA/DHA supplementation inhibit lipolysis and the muscle protein degradation associated with cachexia in various animal models. Studies in rodent models of cancer have shown that EPA significantly reduces protein degradation and tumor-induced lipolysis, therefore playing a key role in the reversal of tumor-induced catabolic effects.

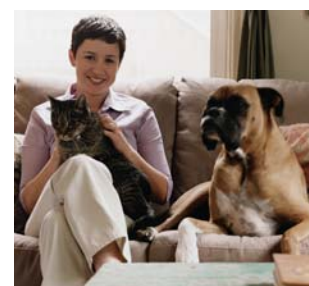
The matrix metalloproteinase (MMP) family of zinc-dependent enzymes plays a key role in degrading basement membrane components and extracellular matrix. These enzymes exhibit activity that is detectable in canine and feline neoplastic tissue and in serum of tumor-bearing animals. This activity is higher in tumor tissue than in unaffected stromal tissue, indicating that MMP may be involved in the pathogenesis of tumor growth and metastasis. Omega-3 fatty acids can modulate MMP activity and may influence tumor growth and metastasis via this mechanism.

Clinical Studies Using Omega-3 Fatty Acids in Patients with Cancer

Human clinical trials with fish oil or EPA/DHA supplementation have focused on patients with severe forms of cancer that carry a poor prognosis and have significant morbidity associated with pronounced cachexia. Fish oil or EPA/DHA supplementation in human patients with unresectable pancreatic cancer has been shown to reverse weight loss, normalize energy expenditure, reduce cytokine production, decrease production of catabolic mediators, and reduce (or stabilize) production of acute-phase proteins. The strong association between acute-phase protein response and reduced survival in patients with cancer may explain the positive response to omega-3 fatty acid supplementation.

To date, clinical studies have demonstrated that a high-fat, low-carbohydrate food supplemented with arginine and high levels of omega-3 fatty acids offers the following benefits:

- Increased survival time of dogs undergoing single-agent cancer chemotherapy by more than 50% compared with the survival time of historic controls
- Increased survival time of dogs undergoing single-agent cancer chemotherapy by more than 30% compared with the survival time of similar dogs consuming an unsupplemented food
- Increased survival time of dogs undergoing single-agent cancer chemotherapy compared with that achieved with aggressive multi-drug chemotherapy protocols
- Reduced pain with radiation therapy, thereby improving the quality of life



Arginine is an essential amino acid that may have specific therapeutic value in animals with cancer.

Characteristics of Hill's® Prescription Diet® Canine n/d®

- ▶ High caloric content
- ▶ High in protein
- ▶ High in fat
- ▶ Low in carbohydrates
- ▶ High in omega-3 fatty acids
- ▶ High in arginine

- Suppressed clinical signs of cancer for longer intervals (ie, longer periods of remission)
- Counteraction against the persistent metabolic changes found in canine cancer patients

Although clinical trials with functional foods have been performed for only a limited number of cancer types, the underlying metabolic abnormalities caused by cancer have been documented in dogs with many different types of tumors. To achieve the levels of omega-3 fatty acids found in Hill's® Prescription Diet® Canine n/d®, typical pet foods need to be supplemented with 12 to 20 fish oil capsules per day for a dog weighing 10 kg. Use of an appropriate therapeutic food is more economical and less stressful than administering multiple daily supplements, increasing the likelihood that the owner will heed the recommendations of the clinician.

Other Nutraceuticals for Patients with Cancer

Antioxidant Vitamins

At present, two opposing hypotheses exist regarding use of antioxidant nutrients for patients with cancer. One hypothesis suggests that supplementation with high doses of multiple micronutrients, including high-dose dietary antioxidants (eg, vitamins C and E, carotenoids, selenium), may improve the efficacy of cancer therapy. Some investigators believe that these nutrients improve immune function, increase tumor response to radiation or chemotherapy, decrease toxicity to normal cells, and help to reverse the metabolic changes that contribute to cachexia. The other hypothesis suggests that dietary antioxidants should not be used because they may protect cancer cells against damage by chemotherapy or radiation therapy. The second hypothesis is based on evidence that dietary fish oil inhibits tumor growth by increasing lipid peroxidation within cancer cells, and the beneficial effects of fish oil supplementation can be blocked by concurrent administration of vitamin E. Additional studies are needed to determine optimal antioxidant nutrient intake for pets with cancer.

Trace Minerals

Serum zinc, chromium, and iron concentrations are lower in dogs with lymphoma and osteosarcoma than in normal dogs. The clinical significance of these abnormalities is unknown, particularly because serum levels may or may not correlate with tissue levels of trace minerals. At the present time, trace mineral supplementation

does not appear to be necessary if the animal is fed a complete and balanced commercial food; however, trace mineral supplementation is essential if the owner feeds a home-prepared food.

Glutamine

Glutamine levels in plasma and skeletal muscle are decreased in tumor-bearing animals. Glutamine has many important biochemical roles and is a preferred energy fuel for cells with rapid turnover such as lymphocytes, enterocytes, and malignant cells. Studies have shown that glutamine supplementation stabilizes weight loss and improves protein metabolism, systemic immune response, and gut-barrier function (less bacterial translocation) during radiation treatments and chemotherapy. Glutamine is best supplied by high-quality, high-protein pet foods.

Randomized Clinical Trial Findings: Functional Food

Trial 1: Dogs receiving doxorubicin for stages IIIa and IVa lymphoma and consuming Hill's® Prescription Diet® Canine n/d®

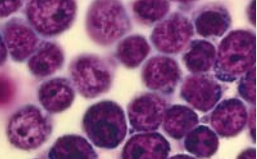
- ▶ Higher serum concentrations of EPA, DHA, and arginine
- ▶ Lower serum glucose, lactate, and insulin levels after intravenous glucose and food tolerance tests
- ▶ Normal serum interleukin-6 and acute-phase protein concentrations

Trials 2 and 3: Dogs with histologically confirmed, high-grade (stage IIIa or IVa) lymphoblastic lymphoma and consuming Prescription Diet® Canine n/d®

- ▶ Higher serum levels of omega-3 fatty acids and arginine compared with levels in dogs fed the unsupplemented control food
- ▶ Increased omega-3 fatty acid levels for dogs fed the supplemented food; significantly associated with a longer disease-free interval, longer survival time, and improved quality of life
- ▶ Median survival times for dogs with lymphoma treated with Prescription Diet® Canine n/d® and single-agent chemotherapy approached median survival times achieved with aggressive multi-drug chemotherapy

Trial 4: Dogs receiving radiation therapy for nasal tumors and consuming Prescription Diet® Canine n/d®

- ▶ Higher serum concentrations of EPA, DHA, and arginine compared with those of controls
- ▶ Lower tissue concentrations of inflammatory mediators, improved performance scores, and a lesser degree of histologic damage to normal tissues from radiation therapy



Key Points

- ▶ Animals with cancer may benefit from a food that is lower in soluble carbohydrates and higher in digestible fat and protein than that which is appropriate for healthy animals.
- ▶ Increased dietary arginine and omega-3 fatty acid intake has been shown to improve clinical signs, quality of life, and survival time in dogs treated for cancer.
- ▶ Antioxidants may improve immune function and increase tumor response to therapy, but vitamin E may counteract the benefits offered by fish oil supplementation.
- ▶ Trace mineral supplementation does not appear to be necessary if the animal consumes a well-balanced commercial food.
- ▶ Glutamine supplementation stabilizes weight loss and improves protein metabolism and systemic immune response.
- ▶ More research is needed to determine the usefulness of tea polyphenols for cancer management in animals.
- ▶ Although garlic appears to produce an anticarcinogenic effect, its use in animals is discouraged because of the risk for toxicity.

Case Study Revisited

There are 2 separate, randomized, controlled clinical studies in which clinicians used single-agent chemotherapy (ie, doxorubicin) and a therapeutic food in dogs with lymphosarcoma. One of these studies was published in a peer-reviewed journal, whereas the other was a research abstract at a major veterinary meeting. Results of both studies indicate that dogs with lymphosarcoma that consumed a therapeutic food supplemented with fish oil and arginine while being treated with doxorubicin have a significantly longer disease-free interval, longer survival time, and improved quality of life, compared with dogs eating a standard food while receiving similar chemotherapy. Based on these clinical studies, this dog was gradually transitioned to Hill's® Prescription Diet® Canine n/d®.

There are no published clinical studies in which nutritional supplements were effective in dogs with multicentric lymphosarcoma. Any recommendations for use of supplements would be made on the basis of expert opinions, clinical experience, studies in other species, or pathophysiologic justification. These are grade IV evidence, which is the weakest form of evidence for making a therapeutic recommendation.



Garlic

Animal and *in vitro* studies suggest that active ingredients in garlic, onions, leeks, and chives (genus *Allium*) have an anticarcinogenic effect. The positive effect appears to be related to the presence of oil-soluble and water-soluble organo-sulfur compounds, primarily allyl derivatives like allicin. The exact cancer-preventive mechanisms and effects are not clear. Routine use of garlic extracts in pets with cancer is discouraged because of the potential for toxicity (hemolysis, Heinz-body anemia) and the lack of clear evidence of efficacy.

Tea Polyphenols

Several animal studies have demonstrated an anticarcinogenic effect of polyphenols, including flavones, flavonols, isoflavones, and catechins. Extracts derived from the tea plant (*Camellia sinensis*) contain many polyphenolic compounds. Polyphenols isolated from green tea or water extract of green tea afford protection against chemically induced carcinogenesis in several different organ systems in animal models. In addition, green tea modulates and increases the efficacy of cancer chemotherapeutic drugs in some animal models. Green tea extracts are found in a few commercial pet foods and are available as supplements, but no controlled clinical trials with tea polyphenols are yet available in animals with cancer. 🐕

This article as well as further information on the topic are available on the Web at www.HillsVet.com/ConferenceProceedings.



Adverse Reactions to Food: How to Better Manage Your Patients

Dogs and cats may develop food allergies after prolonged exposure to one brand or one form of food.

An adverse reaction to food is any abnormal response to an ingested food or food additive. Food *intolerance* refers to a large category of adverse food reactions caused by nonimmunologic mechanisms. Although the terms *allergy* and *hypersensitivity* should be reserved for those reactions that have an immunologic basis, these terms have been used to describe all adverse reactions to food in dogs and cats—including reactions that are truly food intolerances. Dogs and cats may develop food allergies after prolonged exposure to one brand or one form of food. In contrast, reactions resulting from food intolerance may occur after a single exposure to a food ingredient because immune amplification is not necessary.

The fact that food-related reactions appear relatively infrequently is testimony to the effectiveness of the gastrointestinal (GI) mucosal barrier and oral tolerance. Carefully controlled prevalence studies of adverse food reactions in dogs and cats have not been performed. Prevalence is hard to establish because adverse food reactions mimic other diseases, especially pruritic dermatoses, and they often coexist with other allergic conditions. Food allergy is probably the third most common hypersensitivity skin disease in dogs and cats after arthropod (flea) hypersensitivity and atopic dermatitis.

Lymphocytic–plasmacytic enteritis and eosinophilic enteritis, the most common forms of inflammatory bowel disease (IBD) identified in dogs and cats, are the most common cause of chronic vomiting and diarrhea in these two species. Although no obvious cause for IBD can usually be identified, food sensitivity seems to be a possible culprit. Clinical responses to modified feeding plans suggest that hypersensitivity to food antigens plays a role in dogs with chronic colitis. Chronic colitis or other forms of IBD are not known to be direct manifestations of an adverse food reaction; modifying the feeding plan may merely be palliative in some animals.



Clinical Signs of Possible Adverse Food Reaction

Dermatologic Responses

Dogs

Adverse food reactions have been reported in dogs ranging in age from four months to 14 years. Up to one third of canine cases, however, may occur in dogs less than one year of age. Because many adverse food reactions occur in young dogs, the index of suspicion for food allergy may rise above that for atopic dermatitis when pruritic dermatoses occur in dogs younger than six months of age. No gender predisposition has been noted.

Adverse food reactions in dogs produce no set of pathognomonic cutaneous signs and typically occur as nonseasonal pruritic dermatitis, occasionally accompanied by GI signs. Reactions often mimic other common canine skin disorders. Up to half of dogs with suspected adverse food reactions may have concurrent allergic disease, such as flea-allergic dermatitis or atopic dermatitis.

One fourth of dogs with adverse food reactions have lesions only in the region of the ears. This finding suggests that adverse food reactions should always be suspected in dogs with otitis externa, even if accompanied by secondary bacterial or *Malassezia*

GI Barriers to Ingested Food Antigens

Break down ingested antigens (physiologic)

- ▶ Gastric acid and pepsin
- ▶ Pancreatic enzymes
- ▶ Intestinal enzymes
- ▶ Intestinal epithelial cell lysozyme activity

Block penetration of ingested antigens (physiologic)

- ▶ Unstirred water layer
- ▶ Intestinal mucus coat (glycocalyx)
- ▶ Intestinal microvillus membrane composition
- ▶ Intestinal peristalsis

Block penetration of ingested antigens (immunologic)

- ▶ Antigen-specific secretory IgA in gut lumen
- ▶ Clear antigens penetrating GI barrier
- ▶ Monocyte-macrophage system
- ▶ Serum antigen-specific IgA and IgG

Case Study

A 7-year-old, 45-lb intact female golden retriever is examined for chronic conjunctivitis and facial pruritus that have persisted since the dog was two years of age. Intermittent soft feces have also been noted. Atopic dermatitis was diagnosed at four years of age. Hyposensitization to house dust-mite extract has been performed for the last two years, but her owner has not noticed any obvious improvement. Oral glucocorticoids have provided some relief. The dog is fed various commercial dog foods and has access to cat food in the same household.

Physical examination reveals bilateral conjunctivitis, mucoid ocular discharge, periocular erythroderma, swollen eyelids, and reddened skin and alopecia around the mouth. The ears are normal, and there is no evidence of ectoparasite infestation. Results of skin impression smears and fecal examination are normal. A fungal culture shows no growth. The attending veterinarian suspects a food allergy and considers an elimination food trial to determine the best possible treatment protocol.



Picture courtesy of Dr. Kenichi Masuda, Dept. of Veterinary Internal Medicine, Tokyo University, Tokyo, Japan

infections. Atypical dermatologic adverse food reactions in dogs include erythema multiforme, claw disease, and generalized erythematous wheals (urticarial vasculitis).

Cats

Adverse reactions to food may affect cats from six months to 12 years of age. In one study, disease developed in almost half of the cats by two years of age. Siamese or Siamese cross-breed cats accounted for nearly one third of cases in two studies, suggesting a potential increased risk. In addition to severe, generalized dermatologic signs, one study reported that angioedema, urticaria, or conjunctivitis occurred in one third of cats with adverse food reactions. Concurrent flea-allergy dermatitis or atopic dermatitis may occur in up to 30% of cats with suspected adverse food reactions. Moderate to marked peripheral lymphadenopathy is found in up to one third of cats with dermatologic manifestations of food allergy. Absolute peripheral eosinophilia occurs in 20% to 50% of feline cases. Other clinical signs are listed in the sidebar.

GI Responses

Gastrointestinal disturbances occur in up to half of dogs and cats with cutaneous manifestations of food sensitivity. An adverse food reaction is more likely to be the explanation for a dog's pruritus if the animal is having more than three bowel movements per day. There are no well-documented breed predispositions to food allergies, but Chinese Shar-Pei and German shepherd dogs are commonly affected. Furthermore, gluten-sensitive enteropathy has been well documented in Irish setters.

Clinical Signs of Possible Adverse Food Reaction

Dogs

- ▶ Nonseasonal pruritic dermatitis
- ▶ Otitis externa
- ▶ Recurrent pyoderma, seborrhea, or folliculitis
- ▶ Gastric and small bowel dysfunction
- ▶ Colitis
- ▶ Vomiting
- ▶ Intermittent diarrhea
- ▶ Weight loss
- ▶ Excessive flatulence
- ▶ Soft feces
- ▶ Increased frequency of defecation

Cats

- ▶ Severe, generalized pruritus without lesions
- ▶ Miliary dermatitis
- ▶ Pruritus with self-trauma around the head, neck, and ears
- ▶ Self-inflicted alopecia
- ▶ Moist dermatitis
- ▶ Scaling dermatoses
- ▶ Angioedema
- ▶ Urticaria
- ▶ Conjunctivitis
- ▶ Eosinophilic plaques
- ▶ Indolent ulcers of the lips
- ▶ Peripheral lymphadenopathy
- ▶ Absolute peripheral eosinophilia
- ▶ Gastric and small bowel dysfunction
- ▶ Colitis
- ▶ Vomiting
- ▶ Intermittent diarrhea
- ▶ Weight loss
- ▶ Flatulence
- ▶ Soft feces
- ▶ Increased frequency of defecation

Dogs and cats of almost any age can be affected, including those as young as weaning age.

Every level of the GI tract can be damaged by food allergies. Clinical signs usually relate to gastric and small bowel dysfunction, but colitis can also occur. Vomiting and intermittent diarrhea are prominent features. Weight loss, flatulence, and soft feces are also seen. The increased frequency of defecation will normalize with use of an appropriate elimination food.

The role of food allergy in canine and feline IBD is unknown. Hypersensitivity to food is probably involved in the pathogenesis of this syndrome; food protein-induced enterocolitis may be a more appropriate diagnosis for some animals. Irritable bowel syndrome, another disease affecting dogs, is characterized by chronic recurrent abdominal pain against a variety of antigens. Feeding changes will often alleviate the signs of irritable bowel disease, implying that food sensitivity plays a role in this syndrome.

Immunologic Reactions to Food

Food Allergens

The specific food allergens or ingredients that cause problems in animals have been poorly documented. The major food allergens that have been identified in humans are generally water-soluble glycoproteins that have molecular weights ranging from 10,000 to 70,000 daltons. Most are stable to treatment with heat, acid, and proteases. Other physiochemical properties that account for their unique allergenicity are poorly understood.

Pathophysiologic Mechanisms

Unlike food allergies in humans, the pathogenesis of adverse food

reactions in dogs and cats has not been fully elucidated. In addition to documented IgE-mediated food hypersensitivity in canine models, spontaneous IgE-mediated food allergy has been reported. However, other studies have been unable to detect antigen-specific IgE antibodies in dogs with known adverse food reactions. These findings would suggest that adverse food reactions in at least a subset of dogs may be attributable to IgE-mediated food allergy. Type 2 (cytotoxic), type 3 (immune complex), and type 4 (cell-mediated) hypersensitivity reactions have been implicated in food allergy disorders in people and other animals, but the specific involvement has not been clearly established.

Nonimmunologic Reactions to Food

Nonimmunologic, abnormal physiologic reactions to food include food intolerance and dietary indiscretion. Like the terms food allergy and food hypersensitivity, the term *food intolerance* has been applied inappropriately to any and all adverse reactions to food. Food intolerance mimics food allergy except that it can occur on the first exposure to a food or food additive because nonimmunologic mechanisms are involved. The incidence of food intolerance versus food hypersensitivity or food allergy is unknown.

Commonly Reported Food Allergens

Dogs (15 studies, 278 dogs)	Cats (10 studies, 56 cats)
▶ Beef	▶ Beef
▶ Dairy products	▶ Dairy products
▶ Wheat	▶ Fish

Reactions to Food Additives

Although food additives are frequently incriminated as causing problems in dogs and cats, few data confirm this perception. Some veterinary dermatologists have linked food colorants and other food additives to erythema multiforme and other skin eruptions. Further studies are needed to document the occurrence of adverse reactions to pet food additives and the responsible pathogenic mechanisms.

Reactions to Vasoactive Amines in Food

Another cause of intolerance is pharmacologic reaction to substances found in food, such as vasoactive or biogenic amines.



Examples of Nonimmunologic Reactions to Food

- ▶ Hematologic abnormalities in cats caused by propylene glycol
- ▶ Oxidative damage to hemoglobin from onion disulfides
- ▶ Erythema multiforme
- ▶ GI clinical signs in response to ingested scombroid fish
- ▶ Osmotic diarrhea after excessive consumption of lactose
- ▶ Vomiting and diarrhea after such dietary indiscretions as gluttony, pica, and garbage ingestion

The role of histamine and other vasoactive amines in food intolerance in animals is unknown. Adverse reactions to ingested scombroid fish (such as tuna, mackerel, skipjack, and bonito) have been observed in cats and dogs. Surveys to detect histamine in pet foods found the highest levels of histamine in moist fish-based cat foods and cat foods containing soluble fish products.

Carbohydrate Intolerance

The diarrhea, bloating, and abdominal discomfort that occur when lactose-intolerant animals ingest milk are relatively common metabolic adverse reactions. Puppies and kittens normally have adequate levels of intestinal lactase to permit digestion of lactose in the dam's milk. Often, brush-border disaccharidase activity decreases after weaning to a fraction of the activity found in young animals. Osmotic diarrhea will frequently occur when excessive lactose is consumed. Puppies, kittens, or adult animals may develop diarrhea when given cow's or goat's milk because these milk sources contain more lactose than either bitch's or queen's milk. Disaccharide intolerance commonly develops after episodes of enteritis or rapid food changes. Loss of intestinal brush-border disaccharidase activity contributes to the diarrhea associated with enteritis. Inadequate intestinal disaccharidase activity is also one of the factors responsible for diarrhea subsequent to rapid food changes. Several days are required for intestinal disaccharidase activity to adapt to changes in food carbohydrate sources.

Key Nutritional Factors

Because most food allergens are thought to be glycoproteins, protein in food is the nutrient of most concern in patients with suspected adverse food reactions. The variety of proteins in the food, their sources, the amounts, and the digestibility of the proteins are all important factors; whether the patient has been previously exposed to the proteins is also a consideration.

Assessment of the Food and Feeding Method The Ideal Elimination Food

Dietary elimination trials are the main diagnostic method used

in dogs and cats with suspected adverse food reactions. At the present time, intradermal skin testing, radioallergosorbent tests, and enzyme-linked immunosorbent assays for food hypersensitivity are considered unreliable in animals with dermatologic disease.

The ideal elimination food should provide a limited number of protein sources, preferably a protein hydrolysate or one to two different types of intact protein to which the animal has not been previously exposed (novel protein). This recommendation often includes a commercial or homemade food with one animal protein source and one vegetable protein source. Excess protein levels should be avoided to reduce the amount of potential allergens to which the dermatologic patient is exposed. A higher protein level may be necessary to counteract protein losses from the GI tract or in cases of impaired absorption because of severe GI disease.

Protein digestibility is also an important factor when assessing an elimination food. Complete digestion of food protein results in free amino acids and small peptides that are poor antigens. Consequently, an incompletely digested food protein has the potential to incite an allergic response because of residual antigenic proteins and large polypeptides. A protein digestibility of at least 87% is recommended for such foods. An alternative strategy is to use a food containing protein hydrolysates. Protein hydrolysates have molecular weights below levels that commonly elicit an allergic response.

Although specific pet food additives have not been documented to cause adverse food reactions, food additives generally should be avoided in elimination foods. The ideal elimination food should avoid such ingredients as certain kinds of fish that are known to contain higher levels of vasoactive amines than those found in other pet food ingredients.

Finally, although elimination trials are only performed for several weeks to months, the food used in the trial should be nutritionally complete and balanced for the intended species, age, and lifestyle of the animal. Elimination trials are often performed with young animals in which nutritionally inadequate foods are more likely to cause problems.

Characteristics of an Ideal Elimination Food

- ▶ Low to moderate levels of dietary protein
- ▶ Low levels of vasoactive amines
- ▶ Absence of food additives
- ▶ High protein digestibility (at least 87%)
- ▶ Limited sources of protein
- ▶ Composition dominated by protein hydrolysate or novel protein sources
- ▶ Nutritional adequacy for the intended species, age, and lifestyle of the animal

Commercial Elimination Foods

Several companies manufacture foods with limited and different protein sources. These commercial products are attractive because they are convenient, often contain protein hydrolysates or novel protein sources, and are nutritionally complete and balanced for either dogs or cats. Unfortunately, few of these commercial foods have been adequately tested in dogs and cats with known adverse food reactions; only some (approximately 16 of over 60 commercial elimination foods) have undergone the scrutiny of clinical trials involving patients with dermatologic or GI disease. In published clinical trials, usually two thirds to three fourths of patients with suspected adverse food reactions showed significant improvement in clinical signs when fed commercial elimination-type foods.

Therapeutic Foods Containing Protein Hydrolysates

The newest concept for managing veterinary patients with suspected adverse food reactions is to use foods containing hydrolyzed protein ingredients. Veterinary therapeutic foods containing protein hydrolysates offer several hypothetical advantages to traditional commercial or homemade elimination foods. Protein hydrolysates of appropriate molecular weight (greater than 10,000 daltons) will not elicit an immune-mediated response and may be regarded as truly hypoallergenic. Foods containing protein hydrolysates may also benefit patients that have increased GI permeability (such as those with inflammatory bowel disease), in which enhanced protein absorption contributes to the pathogenesis of the disease. Protein hydrolysates have been used for many years in human infant formulas and for human patients with various GI diseases.

Numerous veterinary products contain protein hydrolysates as major ingredients. Some of these products contain only hydrolyzed protein sources, whereas others contain hydrolyzed and intact protein sources. Novel or unique protein sources are less important with protein hydrolysates. Total protein content, average molecular weight of the hydrolyzed protein, and digestibility of nutrients vary among these products. Protein hydrolysates in some commercial veterinary therapeutic foods have markedly lower immunogenicity than the parent proteins, making them excellent ingredients for elimination foods.

Several published clinical studies document use of foods containing protein hydrolysates in veterinary patients. These studies showed that over 90% of dogs with confirmed adverse food reactions remained free of clinical signs when consuming a commercial protein hydrolysate food. One study also showed positive responses in a few dogs with inflammatory bowel disease. Clinical trials with protein hydrolysate foods have been conducted in patients seen in private and specialty practices with dermatological and GI

disease. These studies showed that two thirds of dogs have complete or partial improvement in clinical signs when fed a food containing protein hydrolysates. So far, no clinical studies with protein hydrolysate foods have been conducted in cats.

Protein Ingredients

Commercial foods containing novel protein ingredients have been available for over 40 years for use in animals with suspected adverse food reactions. Novel protein ingredients are not inherently hypoallergenic; simply, they are protein-containing ingredients that are not found in the pet's normal diet and are not usually associated with adverse food reactions. These can include (but are not limited to) such ingredients as lamb, venison, rabbit, duck, egg, various types of fish (dog food only), potato, sweet potato, and tapioca. In a recent clinical study, novel protein foods with enhanced levels of omega-3 fatty acids and antioxidants were useful aids for managing dogs with chronic, nonseasonal, pruritic dermatitis. These findings suggest that foods like those used in the study should also be considered in overall management of animals with suspected allergic dermatitis.

Homemade Elimination Foods

Homemade foods are often recommended as the initial test food for dogs and cats with suspected food allergy. Homemade test foods usually include a single protein source or a combination of a single protein source and a single carbohydrate source. Many homemade foods are nutritionally inadequate for growth or adult maintenance because of their minimal ingredients. In general, homemade foods lack a source of calcium, essential fatty acids, and certain vitamins and other micronutrients; they also contain excessive levels of protein, which are contraindicated in food allergy cases. Feeding nutritionally inadequate homemade foods to young dogs and cats for more than three weeks may result in clinical problems. Homemade recipes should be formulated by or evaluated by a veterinary nutritionist.



The ideal elimination food should avoid such ingredients as certain kinds of fish that are known to contain higher levels of vasoactive amines than those found in other pet food ingredients.

Case Study Revisited

Although grade I and II studies are not available for this condition (because of ethical concerns regarding the management of patients with food allergies), a recent grade III study used a protein-hydrolysate food in dogs similar to this patient. Sixty-five percent of the dogs had improvement in clinical skin disease, and all dogs with concurrent gastrointestinal signs showed clinical improvement. The commercial therapeutic food used in the study is readily available and economically feasible for the client. On the basis of this evidence, the veterinarian strongly recommends the study food as part of an elimination food trial for this dog. Improvement was noted after feeding Hill's® Prescription Diet® Canine z/d ULTRA®. Clinical signs were seen again when the dog ate the cat's food, but the owners were able to eliminate this problem by feeding the cat in an area inaccessible by the dog.



Undertaking the Elimination Trial

Performing a Trial in Patients with Dermatologic Disease

Before an elimination trial is initiated, the client should feed the dog or cat its usual food for several days. During this time, the client should record the type and amount of food ingested, any other ingested food items (such as table foods, treats, and snacks), and the occurrence and character of adverse reactions. The patient should then be fed a controlled elimination food for four to 12 weeks. No substances other than the prescribed food should be ingested, including treats, supplements, and chew toys. Chewable flavored medications, such as heartworm prophylactics, have been shown to cause adverse reactions in dogs and should be changed or eliminated in animals with suspected food allergy or food intolerance. During the elimination trial, the pet owner should document the type and amount of food ingested daily and the occurrence and character of adverse reactions. A daily food diary helps to document progression of clinical signs during the elimination trial and whether a strict elimination trial was performed in the home environment. The diary will often reveal different findings than those noted during the follow-up examination. A tentative diagnosis of an adverse food reaction is made in patients with dermatologic signs if the level of pruritus markedly decreases. This improvement may be gradual and may take four to 12 weeks to become evident. Dogs with chronic, recurrent otitis externa may require 6 months or longer for improvement.

Confirmation of Diagnosis

A diagnosis of an adverse food reaction is confirmed if clinical signs reappear within 10 to 14 days after the animal's former food and

other ingested substances are offered as a challenge. Reinstating the elimination food should resolve the clinical signs induced by the food challenge. *Provocation* involves introducing single ingredients until as many positive reactions as possible can be documented. Clients and veterinarians are often reluctant to pursue challenge and provocation once clinical signs have improved or been eliminated. Provocation may also be difficult to perform in many dogs and cats because commercial pet foods contain large numbers of ingredients and feeding the same ingredients often cannot be duplicated in challenge studies.

Elimination trials are often difficult to interpret because of concurrent allergic skin disease affecting up to half of dogs and cats with adverse food reactions. These patients may only partially respond to an elimination trial. Flea-allergy dermatitis and atopic dermatitis are the most common canine and feline allergies and should be eliminated through other diagnostic testing.

Performing a Trial in Patients with GI Disease

Elimination-challenge trial designs for patients with GI disease are similar to those for patients with dermatologic problems, but shorter elimination periods (two to four weeks) are usually satisfactory. One study in cats with GI sensitivity showed that vomiting stopped almost immediately in all affected cats and diarrhea resolved within two or three days. In chronic relapsing conditions, the elimination period chosen must be longer than the patient's usual symptom-free period to allow reliable assessment of how food sensitivity contributes to the patient's signs.

As with skin disease, the degree of clinical improvement during the elimination trial will be 100% only if food sensitivity is the sole cause of the patient's problems. For example, resolution of allergies acquired as a result of GI disease will not eliminate the clinical signs associated with the primary GI disease process. Recrudescence of GI signs after challenge of a food-sensitive patient with the responsible allergen will usually


A diagnosis of an adverse food reaction is confirmed if clinical signs appear within 10 to 14 days after the animal's former food is offered as a challenge.

occur within the first three days but may take as long as seven days, particularly if the responsible allergen was removed from the food for longer than one month.

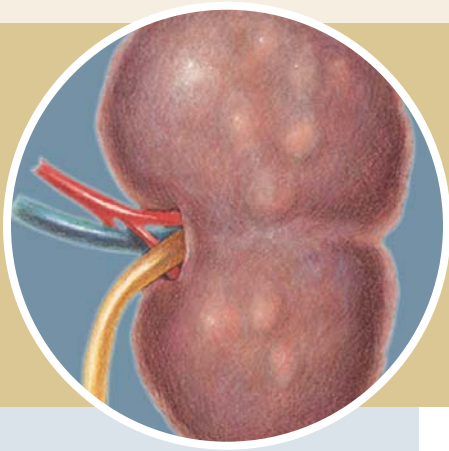
Reassessment

For most adverse food reactions, avoiding the offending foods or food additives is the most effective treatment. How selective or meticulous an avoidance diet must be depends on the individual animal's sensitivity. Some dogs and cats may suffer adverse reactions to even trace quantities of an offending food or food additive, whereas others may have a higher tolerance level. Concurrent allergies will influence the threshold level of clinical signs in some

animals. Symptomatic therapy for pruritic animals may also include corticosteroids and antihistamines. Corticosteroid therapy is often prescribed with feeding changes for cats with IBD.

Both homemade and commercial foods can be used for long-term maintenance of patients with suspected food allergy, but homemade recipes must be nutritionally adequate. An attempt should always be made to find an acceptable commercial food that will increase owner compliance with the feeding change and to ensure a nutritionally adequate ration. 

This article as well as further information on the topic are available on the Web at www.HillsVet.com/ConferenceProceedings.



Treating Feline Chronic Kidney Disease: An Evidence-Based Approach

Routine clinical practice is never “blind,” so clinicians and pet owners both know when active treatment is being received.

In planning therapy for cats with chronic kidney disease (CKD), veterinarians should ideally base their recommendations on results of randomized, controlled clinical trials. Unfortunately, the safety and efficacy of many therapies recommended for cats with CKD have never been examined systematically in cats with spontaneous disease. Often, treatments are recommended on the basis of less convincing evidence, such as clinical experience, expert opinion, pathophysiologic rationale, or studies performed in other species or in cats with artificial disease. Evidence from the recalled experiences of clinicians, however, tends to overestimate the efficacy of these interventions. Routine clinical practice is never “blind,” so clinicians and pet owners both know when active treatment is being received. The desire of pet owners and clinicians for success, together with the placebo effect, can cause both parties to overestimate efficacy.

In examining evidence that supports or refutes a therapeutic claim, veterinarians should consider whether the evidence is clinically relevant. Treatments are indicated when they provide important clinical benefits, but studies often focus on outcomes that may or may not have any clinical relevance to pets and their owners. For example, a study linking calcitriol therapy to corrected hyperparathyroidism does not necessarily provide sufficient reason for recommending such ther-

Key Points

- ▶ Clinicians should consider the quality of data supporting a recommendation to use (or not use) a given form of therapy.
- ▶ The safety and efficacy of many therapies recommended for feline CKD have never been examined systematically in cats with spontaneous disease.
- ▶ Clinically useful studies demonstrate that nutritional management will positively influence outcomes that are important to pets and their owners.

Case Study

A 14-year-old neutered male domestic shorthair cat is examined for weight loss. The owners also report a recent increase in water consumption and frequency of urination (the litter pan must be cleaned more often than in the past). The cat weighs 7 lb (BCS=2/5). The left kidney is small and irregular; the right kidney cannot be palpated. There is no evidence of thyroid nodules. Results of hemography reveal mild nonregenerative anemia (packed cell volume is 34%). Azotemia is detected; blood urea nitrogen is 45 mg/dl (reference range, 10–30 mg/dl) and serum creatinine level is 2.5 mg/dl (reference range, 0.4–1.8 mg/dl). Results of other laboratory studies, including serum thyroxine (T₄) level, are within reference ranges. The tentative diagnosis is naturally developing stage 2 chronic kidney disease.



apy. Laboratory measurements, such as serum parathyroid hormone levels, are often used as “substitute end points” in studies because they are easily obtained. Such results only provide a pathophysiologic rationale for applying the treatment to patients. More clinically useful studies demonstrate that the treatment will positively influence outcomes that are important to pets and their owners, such as increased activity or appetite, decreased vomiting, decreased incidence of uremic crises, or prolonged good-quality lifespan.

Because of the very nature of cats, overtreatment can be just as deleterious as undertreatment in sustaining an acceptable quality of life.

Because of the very nature of cats, overtreatment can be just as deleterious as undertreatment in sustaining an acceptable quality of life. When considering their options, clinicians should consider the quality of data supporting a recommendation to use (or not use) a given form of therapy. Of course, not all recommendations can or will be based on randomized,

controlled studies. Nonetheless, it is important to recognize the inherent limitations of recommendations based on less secure forms of evidence.

Therapeutic Options for the Cat with CKD

Dietary Management

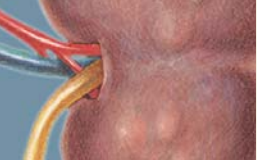
Although dietary management is probably the most commonly prescribed treatment for cats with CKD, clinicians are often challenged by the notoriously finicky feline appetite. They must weigh the decision to recommend a therapeutic renal food or to

allow the cat to continue its current food rather than risking reduced food intake. Two recent clinical trials support dietary management for feline CKD. In the first study, which was neither blinded nor randomized, a striking enhancement of survival time was associated with feeding a renal food compared with a regular food. The control group in this study was composed of cats that refused to eat the renal food. Although cats electing not to consume the renal food may have an intrinsically worse prognosis unrelated to their diet (the principal criticism of this study), the size of the difference in outcome suggests that the clinical benefit of feeding the renal food was likely real: median survival time was increased nearly 2.5 times when the renal food was fed.

We performed a randomized, controlled trial to assess the effect of dietary management in reducing mortality in cats with stages 2 and 3 CKD (serum creatinine values ranging from 2.0 to 3.5 mg/dl) that

Scoring the Quality of Research Recommendations

- Grade I: Highest quality; evidence obtained from at least one properly randomized, controlled clinical trial
- Grade II: Well-designed and controlled laboratory studies in the target species with naturally occurring disease
- Grade III: Average quality; data obtained from one of the following:
 - ▶ At least one well-designed clinical trial without randomization
 - ▶ Cohort or case-controlled analytic studies
 - ▶ Study using acceptable laboratory models or simulations in the target species (preferably from more than one center)
 - ▶ Multiple time series
 - ▶ Uncontrolled experiments that produced dramatic results
- Grade IV: Weakest quality; data obtained from one of the following:
 - ▶ Opinions of respected authorities on the basis of clinical experience
 - ▶ Descriptive studies
 - ▶ Studies in other species
 - ▶ Pathophysiological justification
 - ▶ Reports of expert committees



IRIS Staging System for Feline CKD

The International Renal Interest Society (IRIS) (www.iris-kidney.com) identifies the stage of CKD on the basis of two or more serial determinations of serum creatinine concentration (obtained while the patient is well hydrated) and further delineation of the stage according to the patient's magnitude of proteinuria and blood pressure. Each category is qualified by stating if there is clinical evidence of end-organ damage.

Primary Categorization: Serial Serum Creatinine Determinations

Stage	Serum Creatinine, mg/dl	Interpretation
1	< 1.6	Nonazotemic: Some other renal abnormality is present (eg, inadequate concentrating ability or presence of irregularity on palpation)
2	1.6–2.8	Mildly azotemic: Clinical signs usually mild (eg, polyuria or polydipsia) or absent
3	2.9–5.0	Moderately azotemic: Many extrarenal clinical signs may be present
4	> 5.0	Severely azotemic: Difficult to manage without invasive life-support methods

Secondary Categorization: Urine Protein-to-Creatinine Ratio

Urine Protein-to-Creatinine Ratio	Interpretation
< 0.2	Nonproteinuric
0.2–0.4	Borderline proteinuric
> 0.4	Proteinuric

Secondary Categorization: Blood Pressure

Systolic Blood Pressure, mm Hg	Diastolic Blood Pressure, mm Hg	Risk Level
< 150	< 95	Minimal
150–159	95–99	Low
160–179	100–119	Moderate
≥ 180	≥ 120	High

were fed a control food or Hill's® Prescription Diet® Feline k/d®. This study confirmed the significant benefit of nutritional management in reducing renal mortality. Significant adverse effects of feeding the therapeutic renal food were not detected in these studies. Seemingly, the greatest problem with advocating therapeutic renal foods for cats with CKD has been acceptance of the foods by cats. Food acceptance can usually be achieved by correcting the metabolic complications of CKD and by introducing the food gradually.

Phosphate-Binding Agents

Phosphorus is retained in CKD, eventually resulting in hyperphosphatemia. Hyperphosphatemia has been reported to be a reliable

clinical index of hyperparathyroidism in cats with CKD. Detected in approximately 60% of cats with CKD, hyperphosphatemia becomes more prevalent as renal function declines. In one study, the prevalence of renal secondary hyperparathyroidism in cats with CKD was reported to be 84%. In this study, all cats with end-stage CKD, 87% of cats with some clinical signs of CKD, and 47% of clinically normal cats with only biochemical evidence of CKD were found to have hyperparathyroidism. This condition was even detected in nine cats with CKD that had normal serum calcium and phosphorus concentrations.

In many cats, dietary management alone appears to normalize hyperparathyroidism. Phosphate-binding agents may be useful in further reducing phosphate retention and hyperparathyroidism, but the efficacy of such therapy has yet to be established in cats. Clinical reports and clinical impressions suggest that phosphate-binding agents are useful in reducing serum phosphate concentrations, but some cats may poorly tolerate these agents. Researchers have reached the consensus that phosphate retention and hyperparathyroidism promote progression in CKD. No conclusive data confirm this association in cats, however, and mechanisms responsible for this effect remain unresolved. **IV**

Calcitriol Therapy

The kidneys are responsible for converting 25-hydroxycholecalciferol to its most active metabolite, 1,25-dihydroxycholecalciferol, or calcitriol. Calcitriol is the major renal hormone responsible for calcium metabolism. Among its important functions is modulation of parathyroid hormone activity at the transcriptional level. Because CKD may impair produc-

tion of calcitriol, calcitriol deficiency may be one factor promoting renal secondary hyperparathyroidism. Calcitriol supplementation has been advocated as a means of normalizing hyperparathyroidism. We performed a randomized, controlled clinical trial examining the effect of low-dose calcitriol therapy on progression of CKD and clinical signs. Calcitriol was ineffective in altering renal mortality or improving appetite, activity, or quality of life. These findings fail to support a recommendation for calcitriol therapy for cats with CKD.

Antihypertensive Therapy

Hypertension is a well-recognized complication of CKD in cats, possibly affecting as many as 20% of cats with the disease. The

most profound clinical effect of hypertension in cats seems to be hypertensive retinopathy with retinal detachment, hemorrhage, and blindness, but cats with such severe ocular manifestations reflect only a small percentage of those with CKD and hypertension. More subtle ocular lesions of hypertension are much more common.

Although cats with hypertension and hypertensive retinopathy are likely to benefit from intervention with antihypertensive drug therapy, its renoprotective benefit in cats is largely extrapolated from observations in humans and experimental studies in animals. The potential benefits of intervention might include prolonging survival in cats with CKD and reducing the incidence of hypertensive retinopathy and hypertensive encephalopathy.

The calcium-channel blocker amlodipine currently appears to be the drug of choice for managing hypertension in cats. At least one clinical trial has shown the drug to be effective for lowering blood pressure. Another experimental study demonstrated that amlodipine was effective in preventing ocular manifestations of hypertension. The observations are consistent with uncontrolled clinical observations in cats with spontaneous renal disease. ▲▲

Key Points

- ▶ Introduction of dietary management has been shown to significantly reduce renal mortality.
- ▶ Observational studies have shown that phosphate-binding agents help reduce serum phosphate levels, but some cats may not tolerate these agents.
- ▶ A randomized, controlled trial of calcitriol therapy demonstrated no benefit for altering renal mortality or improving appetite, activity, or quality of life in cats with CKD.
- ▶ The calcium-channel blocker amlodipine has been shown to be more effective than ACE inhibitors for managing hypertension in cats.
- ▶ The benefits of potassium supplementation have only been demonstrated in cats with overt signs of hypokalemic myopathy.
- ▶ Human recombinant erythropoietin has been shown to correct anemia of CKD in cats but autoantibody reactions have limited its usefulness.
- ▶ Acidosis presents an unnecessary metabolic risk that can be easily corrected by administration of potassium citrate or sodium bicarbonate.

Case Study Revisited

The attending veterinarian wanted to answer the following question: For cats with early chronic kidney disease, does dietary management delay the onset of uremic crises, reduce the risk of future uremic crises, or delay death? A literature search revealed two recent clinical trials that support dietary management of CKD. One of them was a study with good evidence that feeding food with reduced protein and phosphorus levels produced tangible benefits. This cat was transitioned to Hill's® Prescription Diet® Feline k/d® and did well for three years until he was lost to follow-up. He had no uremic crises and minimal proteinuria during this time frame.



Angiotensin-Converting Enzyme Inhibitor Therapy

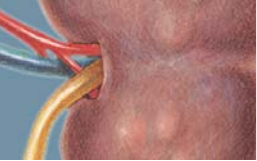
Angiotensin-converting enzyme (ACE) inhibitors appear to be of value in limiting progression of CKD in various forms of human renal diseases, but proteinuric patients may be the only ones to see a significant clinical benefit. The ACE inhibitor benazepril has been licensed in several countries for use in managing cats with CKD. Two studies examined the physiological effects of benazepril in cats with induced renal disease. Systemic arterial and glomerular capillary pressures were shown to be reduced and glomerular filtration rates were increased by such therapy. However, the magnitude of reduction in systemic blood pressure was small and a beneficial effect of reducing proteinuria was not evident. These initial studies failed to detect any evidence that administering benazepril resulted in long-term structural or functional renal protection.

Preliminary data have been reported from a randomized, controlled clinical trial that investigated the effectiveness of benazepril in cats with spontaneous CKD. In this study, benazepril reduced proteinuria, increased appetite, and improved survival time and quality of life, particularly in older Persian cats with marked proteinuria. In a separate study, treatment with enalapril and benazepril did not change plasma renin activity, aldosterone concentration, or indirect systolic arterial blood pressure in cats with hypertension associated with CKD. However, another study showed that benazepril is well tolerated when administered with amlodipine in hypertensive cats and may assist in managing cats with poorly controlled blood pressure. ▲▲▲

The calcium-channel blocker amlodipine currently appears to be the drug of choice for managing hypertension in cats.

Potassium Supplementation

On the basis of Grade III evidence, it is generally accepted that



potassium supplementation is warranted for cats with chronic kidney failure and hypokalemia, even in absence of overt clinical signs. Grade IV evidence suggests that all cats with kidney failure should be given potassium supplements to limit total body potassium depletion and to prevent hypokalemia, hypertension, and progressive renal injury. Because today's feline therapeutic renal foods generally contain high levels of potassium, additional randomized, controlled clinical trials are necessary to determine if further supplementation is necessary or beneficial. Hypokalemia is often a symptom of acidosis, therefore the underlying condition should be treated early in addition to correcting the secondary potassium deficits. ▲IV

Erythropoietin Therapy

Administration of human recombinant erythropoietin has been shown to be effective in correcting anemia of CKD in cats. Clinical trials that used patients as their own controls revealed substantial improvement in appetite and quality of life with the initiation of erythropoietin therapy. Unfortunately, the development of antibodies directed against the drug has limited the usefulness of this therapy in a substantial number of cats. Consequently, clinicians should carefully select cases that are most likely to benefit from erythropoietin. ▲III

Alkalization Therapy

Alkalization therapy is indicated for cats with moderate to severe metabolic acidosis associated with CKD on pathophysiologic grounds and extrapolation from findings in other species. The rationale for alkalization therapy has been that acidosis: 1) can impair protein nutrition, 2) may promote progression of renal disease, and 3) can induce clinical signs similar to uremia. However, unpublished data from our laboratory indicate that mild acidosis (such as that which results from feeding a typical

commercial acidifying diet) does not appear to promote progressive renal injury or impair nutrition. Nonetheless, acidosis *does* appear to impose an unnecessary metabolic risk that can easily be corrected in cats by administration of potassium citrate or sodium bicarbonate. ▲IV

Conclusion

The concepts of evidence-based medicine can be readily applied to management of feline CKD. Quality-of-evidence guidelines previously published in the human and veterinary literature serve as an excellent example of a rigorous application of an evidence-based appraisal system. By using this system, clinicians can assume that grade I and II evidence will be the most reliable predictors of results they can expect in clinical practice. High-quality evidence exists for use of specific therapeutic renal foods and ACE inhibitors in animals with significant proteinuria; consequently, these therapeutic interventions should be recommended routinely for management of CKD in cats. Moderate quality evidence exists for the use of antihypertensive agents in animals with hypertension associated with chronic kidney disease, ACE inhibitors for renal disease other than glomerulopathies, and hormone replacement therapy for animals with anemia. At present, the lowest quality of evidence exists for use of subcutaneous fluid therapy, calcitriol, alkalizing agents and intestinal phosphate binders, assisted feeding, and renal hemodialysis. Randomized, controlled clinical trials are needed to validate the benefits and risks of many treatments recommended for feline CKD and to better identify those animals who would benefit most from these forms of management. 🐾

This article as well as further information on the topic are available on the Web at www.HillsVet.com/ConferenceProceedings.



Treating Canine Chronic Kidney Disease: An Evidence-Based Approach

The veterinarian who is planning therapy for a dog with chronic kidney disease (CKD) should ideally look for recommendations that are based on results of randomized, controlled clinical trials.

The veterinarian who is planning therapy for a dog with chronic kidney disease (CKD) should ideally look for recommendations that are based on results of randomized, controlled clinical trials. Such research is often hard to find, unfortunately, because many therapies have never been examined in an appropriate and systematic fashion in dogs with spontaneous disease. Instead, treatments may be recommended on the basis of clinical experience, expert opinion, pathophysiologic rationale, or studies performed in other species or in dogs with artificial disease. Evidence culled from such sources tends to encourage overestimation of therapeutic efficacy, so clinicians must recognize the inherent limitations of recommendations that are based on less secure forms of evidence.

Scoring the Evidence

One means for accommodating these limitations is to assign a score to define the strength and quality of the recommendation. Grade I evidence, the highest quality evidence, is obtained from at least one properly randomized, controlled clinical trial. Grade II evidence is data collected from controlled clinical studies in the target species in a laboratory setting. Grade III evidence may be data obtained from 1) at least one well-designed clinical trial without randomization; 2) case-controlled analytic studies; 3) studies utilizing acceptable laboratory models or simulations in the target species, preferably from more than one center; 4) multiple time series; or 5) uncontrolled experiments that produced dramatic results. Grade IV evidence, the weakest form of evidence, is derived from 1) opinions of respected authorities formulated on the basis of clinical experience, 2) descriptive studies, 3) studies in other species, 4) pathophysiological justification, or 5) reports of expert committees. This scoring system recognizes that the quality of the evidence supporting a recommendation is an important consideration when making therapeutic decisions.

Case Study

A 10-year-old neutered male Shih Tzu is presented for a routine health evaluation. Body weight is 16.5 lb (BCS=3/5.) The owners report a recent increase in water consumption and frequency of urination. Results of physical examination are unremarkable, except for mild periodontal disease. Laboratory tests are performed, including a hemogram, urinalysis, and serum biochemical analysis. Azotemia is detected, with an increase in serum creatinine concentration (2.5 mg/dl [reference range, 0.4 to 1.8 mg/dl]) and urine specific gravity of 1.018. Results of other laboratory tests are normal. Subsequent microbial culture of a urine sample reveals no growth. The tentative diagnosis is naturally developing stage 2 chronic kidney disease. The attending veterinarian must consider whether dietary management will reduce the risk for future uremic crises and prolong the animal's life.



Quality-of-Life Outcomes

Most important, treatments are indicated when they provide valuable clinical benefits. Although studies often focus on outcomes that may not have any clinical relevance, veterinarians should look

for evidence demonstrating that the treatment will improve appetite, increase activity levels, or reduce the incidence of uremic crises. Research end points that relate to quality of life (one of the most important considerations for dog owners) are particularly useful to note.

Therapeutic Options for the Dog with CKD Dietary Management

Dietary management is probably the most commonly prescribed therapy for dogs with CKD, but dogs with selective appetites present a big dilemma to clinicians: Is it in the dog's best interest to switch to a therapeutic renal food if the unwanted food change will result in drastically reduced caloric intake? We recently completed a randomized, controlled clinical trial designed to determine if clin-

ically important benefits were consistently gained when a typical canine maintenance food was changed to a therapeutic renal food in dogs with spontaneously occurring CKD. Other than being randomly assigned to either the renal food or the maintenance food, the dogs were managed in an identical manner with respect to other treatment interventions.

We found that feeding a manufactured renal food results in a better quality of life and a substantially longer life in dogs with stage 3 disease. Compared with dogs fed the maintenance food, dogs that consumed the renal food (Hill's® Prescription Diet® Canine k/d®) experienced fewer uremic crises and lower renal-related mortality. Feeding the renal food reduced the relative

risk of a dog having a uremic crisis by over 70%. In fact, dogs fed the renal food remained free of uremic signs almost 2.5 times longer than dogs fed the maintenance food. In addition, dogs fed the renal food had a median survival time that was more than 3 times longer than dogs fed the maintenance food. Renal-related death was the primary cause for the higher rate of premature mortality among dogs fed the maintenance food. The longer survival times observed in the renal food group appeared to be attributed to much slower declines in renal function. ▲

Dietary Phosphorus Restriction and Phosphate-Binding Agents

Phosphate retention and hyperparathyroidism are major causes of kidney disease progression in many species. Research in humans receiving hemodialysis therapy for CKD revealed that the adjusted relative risk of mortality was stable in patients with serum phosphorus concentrations below 6.5 mg/dl, but mortality increased significantly with higher serum phosphorus levels. The overall mortality risk associated with hyperphosphatemia was 1.06 per serum phosphorus elevation of 1 mg/dl. On the basis of these types of findings, researchers sought to determine whether dietary phosphorus restriction might also be beneficial for dogs.

In a model of induced CKD in dogs, combined dietary phosphorus and protein restriction were shown to slow progression of kidney disease and to improve survival. Mechanisms respon-

We found that feeding a manufactured renal food results in a better quality of life and a substantially longer life in dogs with stage 3 CKD.

Key Points

- ▶ Clinicians should look for recommendations that are based on results of randomized, controlled clinical trials.
- ▶ Evidence from sources other than randomized trials may overestimate therapeutic efficacy.
- ▶ Research evidence is graded on a 4-point scale, with grade I being the highest quality (obtained from randomized trials) and grade IV being the weakest (obtained from sources like observational studies or research in other species).
- ▶ Studies are particularly useful when they demonstrate that the treatment will influence outcomes like appetite, activity levels, and overall quality of life—factors that are important to pets and their owners.

IRIS Staging System for Canine CKD

The International Renal Interest Society (IRIS) (www.iris-kidney.com) identifies the stage of CKD on the basis of two or more serial determinations of serum creatinine concentration (obtained while the patient is well hydrated) and further delineation of the stage according to the patient's magnitude of proteinuria and blood pressure. Each category is qualified by stating if there is clinical evidence of end-organ damage.

Primary Categorization: Serial Serum Creatinine Determinations

Stage	Serum Creatinine, mg/dl	Interpretation
1	< 1.4	Nonazotemic: Some other renal abnormality is present (eg, inadequate concentrating ability or presence of irregularity on palpation)
2	1.4–2.0	Mildly azotemic: Clinical signs usually mild (eg, polyuria or polydipsia) or absent
3	2.1–5.0	Moderately azotemic: Many extrarenal clinical signs may be present
4	> 5.0	Severely azotemic: Difficult to manage without invasive life-support methods

Secondary Categorization: Urine Protein-to-Creatinine Ratio

Urine Protein-to-Creatinine Ratio	Interpretation
< 0.2	Nonproteinuric
0.2–0.5	Borderline proteinuric
> 0.5	Proteinuric

Secondary Categorization: Blood Pressure

Systolic Blood Pressure, mm Hg	Diastolic Blood Pressure, mm Hg	Risk Level
< 150	< 95	Minimal
150–159	95–99	Low
160–179	100–119	Moderate
≥ 180	≥ 120	High

sible for the effect of hyperphosphatemia on mortality remain unresolved. Clinical or experimental studies establishing the value of adding phosphate-binding agents to dietary phosphate restriction in dogs have not been reported. **II**

Calcitriol Therapy

The kidneys are responsible for converting 25-hydroxycholecalciferol to calcitriol, its most active metabolite. The renal hormone primarily responsible for calcium metabolism, calcitriol modulates parathyroid hormone activity at the transcriptional level. Because CKD may impair production of calcitriol, calcitriol deficiency may be one factor promoting renal secondary

Key Points

- ▶ A study showed that dogs with CKD that consumed a manufactured renal food experienced fewer uremic crises and lower renal-related mortality.
- ▶ Combined dietary phosphorus and protein restriction have been shown to slow the progression of CKD in dogs.
- ▶ A randomized, controlled trial demonstrated that calcitriol therapy reduced renal mortality but did not appear to influence appetite, activity, or quality of life in dogs with CKD.
- ▶ No well-controlled clinical trials of ACE inhibitors in dogs with CKD have been reported, but enalapril may produce a modest reduction in blood pressure.
- ▶ Enalapril has also been shown to reduce proteinuria; therefore it may slow the progression of CKD in dogs.
- ▶ The use of human recombinant erythropoietin in dogs has been shown to correct anemia associated with CKD, but the agent should be prescribed cautiously because of the risk for adverse reactions.

hyperparathyroidism. Calcitriol supplementation has been advocated as a means of normalizing hyperparathyroidism. Parathyroid hormone may act as a uremic toxin; therefore, calcitriol supplementation may also ameliorate a variety of supposed toxic effects of the hormone in CKD. We performed a randomized, controlled clinical trial examining the effect of low-dose calcitriol therapy on progression of CKD and clinical signs. Calcitriol was effective for reducing renal mortality but did not appear to influence appetite, activity, or quality of life. **I**

Antihypertensive Therapy

Hypertension is a well-recognized complication of CKD, often leading to hypertensive retinopathy with retinal detachment, hemorrhage, and blindness. Hypertension-related disorders of the central nervous system have also been observed, including seizures, loss of balance, abrupt changes in personality, and confusion. Studies in our laboratory have suggested that hypertension is also a risk factor for shortened survival times in dogs with kidney disease. The justification for treating hypertension in dogs is largely extrapolated from observations in humans and experimental animals. The likely benefits of



Case Study Revisited

The veterinarian found a randomized, controlled study (grade I, the highest quality) that demonstrated that dogs with mild to moderate naturally developing chronic renal failure that were fed a therapeutic food had fewer uremic crises, slower renal decline, decreased mortality rate, and improved quality of life than those dogs fed an adult maintenance food. The study also reported that feeding the therapeutically formulated diet to dogs with a lesser degree of azotemia (serum creatinine concentration, 2.0 to 3.1 mg/dl) delayed the onset of uremic crises for approximately five months.

The patient is extremely similar to dogs enrolled in the published clinical study, and the therapeutic food used in the study is readily available and economically feasible. Lower-quality evidence (grades III and IV) also exists for use of dietary modification of single nutrients in dogs with experimentally induced renal failure. On the basis of this evidence and other tenets of conservative medical management, use of Hill's® Prescription Diet® Canine n/d® should be strongly recommended for this patient, provided that owner and patient preferences are satisfied.



intervention might include retarding the progression of kidney disease and reduced incidences of hypertensive retinopathy and hypertensive encephalopathy. Well-controlled clinical trials investigating the effectiveness of antihypertensive agents in hypertensive dogs with CKD have not been reported; however, one study did demonstrate that enalapril, up to 0.5 mg/kg daily, can produce a modest reduction in blood pressure. **IV**

Angiotensin-Converting Enzyme Inhibitor Therapy


Research in humans has shown that angiotensin-converting enzyme (ACE) inhibitors limit the progression of kidney disease in proteinuric patients. A prospective clinical trial performed in dogs with spontaneous idiopathic glomerulonephritis recently confirmed that enalapril reduced proteinuria and may have helped to stabilize the progression of kidney disease. Although ACE inhibitors are commonly prescribed for humans with CKD, more research is needed to determine whether ACE inhibitors should be regularly recommended for dogs that do not have proteinuria. **I III**

Erythropoietin Therapy

Administration of human recombinant erythropoietin has been shown to be effective in dogs for correcting anemia secondary to CKD. Uncontrolled clinical trials have also indicated a substantial improvement in appetite and quality of life associated

with this treatment. Unfortunately, development of antibodies directed against the drug has limited the usefulness of this therapy in a substantial number of dogs. Consequently, clinicians should carefully select those patients that are most likely to benefit from erythropoietin for treatment. Dogs with CKD-related anemia may also benefit from earlier intervention, but this interesting concept has not received adequate examination. **III** The efficacy and safety of recombinant canine erythropoietin therapy was recently evaluated in dogs with anemia of chronic kidney disease and those with chronic kidney disease and red cell aplasia induced by human recombinant erythropoietin therapy. Although this drug showed promising results, the product is not commercially available.

Conclusion

The concepts of evidence-based medicine can be readily applied to management of canine CKD. Quality-of-evidence guidelines previously published in the human and veterinary literature serve as an excellent example of a rigorous application of an evidence-based appraisal system. By using this system, clinicians can assume that grade I and II evidence will be the most reliable predictors of results they might expect in clinical practice. High-quality evidence exists for use of specific therapeutic renal foods, calcitriol, and ACE inhibitors in animals with significant proteinuria; consequently, these therapeutic interventions should be recommended routinely for management of CKD in dogs. Moderate-quality evidence exists for the use of antihypertensive agents in animals with hypertension associated with CKD, ACE inhibitors for renal disease other than glomerulopathies, hormone replacement therapy in animals with anemia, and hemodialysis. At present, the lowest quality of evidence exists for use of subcutaneous fluid therapy, alkalinizing agents, and intestinal phosphate binders. Randomized, controlled clinical trials are needed to validate the benefits and risks of many treatments recommended and used in patients with CKD and to better identify those animals who would benefit most from these forms of management. 

This article as well as further information on the topic are available on the Web at www.HillsVet.com/ConferenceProceedings.