In an AVMA sponsored conference on euthanasia, slaughter and depopulation called “Humane Endings” in October, 2014, the keynote speaker described the change in public perception of the importance of animals of all kinds. He described the increasingly pervasive public perception of animals as connected to humans and the associated increased public aversion to animal deaths and killing. He concluded that animal death and killing will become more emotional and more contentious. While his remarks were directed at all the participants, the implications for the experience clients have of euthanasia are clear. Our obligation to provide a painless death for the beloved animal and an acceptable experience for owners of companion animals is becoming more complex.

With the decreasing nuclear family, an outcome of the decline of agricultural community, the rise of industrialization, climbing divorce rates and prolonged life spans, comes the increase in isolation from family, neighbors and community. Yet people need love, companionship and emotional support. This has given rise to the redefinition of pets as family members. About 90% of respondents in one study of 100,000 US households rated a pet as important or extremely important to the family. About 90% of respondents in one study of 100,000 US households rated a pet as important or extremely important to the family. For many complex reasons, the emotional attachments which many humans develop for their pets not only equals but frequently transcends the emotional attachment which they form with humans and can be a source of unconditional love, support, comfort, safety, security and stability.

When highly attached owners recognize that a moment has arisen in the clinical management of a life-limiting medical condition when a cure is not an attainable goal, it is normal for them to experience strong emotions, generally termed anticipatory grief. Anticipatory grief is the psyche’s way of preparing for impending loss. This is often the beginning of a period of powerful emotional states which can blur judgment at a time when clear thinking and planning may be key to resolution of grief and ending the suffering of a beloved pet.

Pet owners often trust veterinarians and/or see them as authority figures. During loss, clients may look to the veterinarian to provide strength, guidance, leadership. Given clients expectations and the impact of end-of-life conversations on pet owner and the veterinary team, compassionate communication should be considered both a core clinical skill and an ethical obligation for veterinarians.

One core belief that must be developed in clients is that preserving quality of life takes precedence over measures to prolong life. With the sophistication of veterinary medicine and technology comes the ability to prolong suffering by engaging in many more forms of therapy than were previously unavailable for beloved pets. Veterinarians now have to advocate for the animal interest to end a life when further intervention will cause or exacerbate suffering. This life-prolonging technology has rendered the term “natural death” progressively meaningless, giving rise to complex ethical struggles with medical futility and who decides when to pull the plug and why.

The owner becomes the animal’s proxy and will decide if and when euthanasia is a better option than life for an animal that is suffering despite receiving the best comfort care available. The strongest desire of highly attached pet owners facing the loss of a beloved pet is to do what is best for the animal. It is an elusive goal and one which requires the owner’s interpretation of the animal’s state.

A veterinarian can help by educating an owner in how to assess quality of life, attributing relative weight to specific experiences like the presence or absence of joy, pain, or frustration. In the general practitioners’ relationships with clients there is very often a long more intimate connection than there is with specialists to whom the animal may have been referred for care. Therefore, the generalist should stay involved after a referral and advocate for what is right for the pet. This is also important for the emotional state of the owner. Powerful emotions can ensue when decisions are second-guessed. Decisions made too early may cause profound guilt. A decision thought to be made too late may be interpreted as causing suffering for a beloved family member. The uncertainty that is a natural part of being a proxy for another’s best interest is always present.

In the best possible situation, before the anticipatory grief has begun, Quality of Life considerations are best made, once a trusting relationship is built between a client and the veterinarian. A journal kept from the time a potentially life-threatening condition has been recognized can be helpful in recognizing the balance between levels of happiness and distress based upon the behavior of the pet. Since there are no generally acceptable lines between what is acceptable and not acceptable Quality of Life, the individual observations can help reduce the burden on the client. We must build the client’s confidence that they can comprehend their pet’s condition and “walk in his shoes”. By trusting the ability of persons most closely bonded to feel in their gut what the animal is experiencing, we encourage good choices.

The skills of educating, supporting, guiding and facilitating are key to assisting the client. More importantly, the veterinarian must not try to solve the owner’s problems by making decisions for them, by giving them advice on what course they should take, rationalizing their choices or rescuing them. Presenting options gives families control over the process leading to inevitable loss by
helping them find their own view of what constitutes the best way to care for their animal. A sense of control – even if limited – has been shown to correlate with healthy grieving and emotional healing. The manner in which a veterinarian provides care for a client whose pet has died has the potential to alleviate or aggravate grief, influence client and veterinarian satisfaction and create or destroy long-lasting relationships.

It is essential to listen to what is most important to the family under the circumstances, what their concerns are, how they want to spend their time as options become limited and what kind of tradeoffs they are willing to make. The sense of control should extend to the physical and social environment surrounding a beloved pet during the last moments. Planning in advance, before powerful emotions hold sway over decisions, will allow the family to think clearly through their plan. As emotional states become more ascendant, remind the owners of their decisions. They may choose the form of death, natural or euthanasia, who should be present, the tenor of the ritual and whether children should be involved. If euthanasia is elected, the mechanics of the process should be discussed. If the client is comfortable with placement of an IV catheter or not, how to administer a sedative if one is needed and so on. The location may be of concern as well, whether outdoors, in the owner’s lap, at home, on the floor. Conventional rituals that support and comfort people at the time of the loss of a human loved one, funerals, calling hours, or celebrations of life, have not evolved around pet loss. This one event may be all the ritual possible for a highly attached client whose family may not perceive the death as a loss of a loved one.

References
AVMA Guidelines for Euthanasia; 2013 Edition
There is no question of the “growing problem” of obesity among adult cats around the world. In a study of 12 owner-owned cats in the United Kingdom, even referral to a weight loss center did not insure rapid weight loss. Many factors were found to be significant in this study, owner compliance with directions was considered one of the most significant. All cats lost weight, but more slowly than predicted. Exercise may not have been encouraged or treats may have been added. In the end, we humans are the most important reason for this dangerous trend. Of particular interest in this study was the lost of lean body mass during weight loss. While fat loss was the most significant, the loss of lean body mass meant that muscle and basal metabolic rate declined. In another study of cats on a weight loss plan, the owners of the cats who did not lose weight consistently under-estimated the body condition score of their cat. The perception of normal on the part of the individual responsible for feeding had an impact on weight management.

Because obesity is a world wide trend in both adults and children, there may be some instructive value in examining the characteristics of successful weight loss and management in humans. Those who lost weight and successfully maintained their target weight were far more likely to plan meals, measure food, track calories, plan exercise, exercise for at least 30 minutes a day and weigh themselves every day. The use of over the counter weight loss supplements was negatively correlated to weight loss. While several of these strategies may not be relevant to cats as we shall explore, the idea of tight control appears to be the most significant concept that can be derived from human research on weight loss.

Cats are obligate carnivores and as such have specific nutrient requirements that reflect their evolutionary background. The natural diet of the cat is high protein, low carbohydrate diet derived from the prey they consume in the wild. As obligate carnivores cats differ from dogs and other omnivores in their nutritional requirements and physiologic adaptations. Cats have not developed many of the metabolic pathways for processing higher carbohydrate diets that omnivorous have and because of the lack of these pathways have different requirements in their diet than dogs and other omnivores.

Commercial dry cat foods are convenient to give to cats, many cats enjoy or even prefer them and they are tolerated well by many in cats in most situations. However, because of the inherent differences in metabolism feeding high carbohydrate diets to cats may predispose them to obesity and may also have untoward effects during times of illness malnutrition. Higher protein, low carbohydrate diets may also be more effective in managing certain diseases such as hepatic lipidosis, diabetes mellitus and obesity.

Weight reduction requirements differ between omnivores and cats and reflect the cat's inability to store excess starch as glycogen. Glucose exceeding energy requirements is stored as fat.

Feeding high fiber, low fat diets to obese cats does result in weight loss but at the expense of lean body mass. The basal metabolism of the cat may be lowered, predisposing the animal to regaining of the weight. In several studies Cats fed a high protein; low carbohydrate diet lost weight but maintained their lean body mass in comparison to cats fed a high carbohydrate low fat diet. The amount of food available to cats on such a diet should be regulated.

When feeding cats a high protein low carbohydrate diet for obesity management canned foods provide the optimal amounts of protein and carbohydrate and canned kitten food provides the closest approximation to the cat's natural diet.

Unlike dogs, 'domestic' cats are not evolved to scavenge. They have a small liver and a simple digestive system that is not able to cope with toxic or bacterial contamination. Their feeding is therefore restricted to live, healthy prey. Whilst dogs hunt cooperatively and are able to bring down prey that is much bigger than themselves, the cat, being a solitary hunter, is only able to catch relatively small prey. It also does not have pressure to share its prey with other members of its roup, because it does not depend upon them to help catch it.

The wild and feral cousins of the domestic cat spend 6–8 hours per day hunting. Of the 100–150 hunting attempts per day perhaps 10% will be successful. With a failure rate as high as this a cat may expect to have periods during which the amount of prey captured barely meets energy expenditure. On successful days the cat may catch a surfeit of food.

The result is that in the cat, hunting activity is not related to hunger or satiation. The cat would soon die if it took a break for several hours after every meal, because this would mean it would miss the best hunting opportunities. Hunting is also not related to the pleasurable taste of the prey. Small mammals and birds do not come in a variety of appetizing flavors, and in any case the cat's perception of flavor is geared to detect spoilage, not to enable it to be a gastronome.

Given the tightly regulated activity and feeding pattern of cats, and the lack of social significance of feeding, it would be expected that obesity would be unlikely in this species.

However, obesity is an increasing issue, and relates to feeding patterns that fail to take into account the natural behavior of the cat, and which are designed to satisfy human attitudes to the value of offering food as an attempt to show care.
A typical domestic cat expends very much less energy on finding and consuming food than its feral counterpart. Meals are presented in a bowl and may be consumed in seconds. No elements of the hunting strategy are activated.

In the domestic environment cats may have few opportunities to climb or explore three-dimensional space so their energy expenditure is typically very low compared to wild cats. This tips energy utilization in favor of increased storage, and hence obesity.

Cats do not go shopping, so the food we give them is designed to appeal to human shoppers and not to cats. Humans are social eaters and expect to enjoy shared meals and social interaction. Many owners expect that a happy cat is one that shows appreciation for the food we give by clearing the food bowl in the way that a person or a dog might.

Food and feeding regimes are therefore designed to reinforce these human misconceptions. Owners feed highly appetizing foods that are likely to encourage the cat to eat more than it might otherwise choose. This is much the same as the effect of intense flavor on overwhelming satiation in man. We also know that feeding multiple flavor variations of foods will increase a cat's total food intake.

Without reeducation, owners will constantly seek to 'improve' the food they give their cats so that they begin to eat in the same way as people. A meal that is not immediately consumed is taken as an indication that the cat is dissatisfied with its food.

The consumption of larger than normal quantities of food at each meal is likely to distend the cat's stomach and create the same false perception of hunger that is seen in man, the satiation of which is further reinforced by the extremely appetizing nature of the food. Most cats will approach their owners for attention or play many times during the day. Sociable cats have quite a high demand for interaction of this kind. Many of the cat's resources are focused in the kitchen area; food, latrines, cat door, etc. Cats will therefore approach their owners in the kitchen or will entice their owners there.

Unfortunately this is misinterpreted as an indication that the cat wishes to have more food. Owners will often replace old food with fresh. Given that the owner has offered no other interaction this may be attractive to the cat, which is unwilling to eat spoiled or old food. When the cat begins to eat the owner reinforces this by showing attention, or by playing a game after the cat has eaten.

In this way the cat may eat as a substitute for other activities, or may learn to eat in order to get the attention and play that it actually wanted. The cat therefore eats more than it might normally choose to, because its demands for other kind of interaction are not met, or are conditional on eating.

In addition, recent evidence indicates that owners of overweight cats interpret the needs of their pets differently from owners of cats of normal weight. Obese-cat owners do understand that when a cat vocalizes or approaches that this is for attention and social interaction. In this respect they are no different from owners of normal cats. However, they are more likely to perceive hunger in the vocalizations of cats, which drives them to offer food. This is quite similar to the way that humans interact with each other; if we have a visitor we don't assume that this person has come round to get food but we still offer it as a sign of hospitality. This is because one of the primary methods of showing care toward another person is to identify and satisfy their undeclared needs.

This appears to be at the root of the reason for why owners of obese cats find it hard to stick to diet programs. Cats may evoke a greater emotional response from some people due to the type and pitch of their vocalizations, which are more like those of a human infant. In some cases owners of obese cats can become quite distressed as a result of the emotional conflict they experience when balancing the need to diet the cat for health reasons, and the stress they experience when deliberately not meeting the animal's apparent physical need for food.

Cats do not eat as a social group, and find it uncomfortable and stressful to feed close to one another. If food is restricted to two meals per day, fed by the owner, then a group of cats will be forced to eat in close proximity to one another. This not only increases anxiety and aggression because food cannot be consumed in private, but also pressures the individual cat to eat an uncomfortably large amount of food at one sitting, because that food will otherwise be rapidly eaten by the other cats. Cats therefore eat beyond natural satiation due to the stress of reduced food availability.

References
Svetkey, L. et al. Comparison of Strategies for Sustaining Weight Loss The Weight Loss Maintenance Randomized Controlled Trial. JAMA, March 12, 2008—Vol 299, No. 10
Varaday, K. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss?obesity reviews (2011) 12, e593–e601
Lower urinary tract signs (LUTS) – dysuria, peruria, pollakiuria and stranguria – are a common reason pet cats are brought to veterinary practices. When presented with a cat with these signs clinicians need to know whether this is the first episode or whether it is a chronic, recurrent disease as well as what other health problems the cat may have. Armed with this information an appropriate diagnostic plan can be made.

Cats may have multiple reasons for their clinical signs as well as other medical conditions and environmental requirements that need to be addressed. For example, Buffington et al. have presented evidence that some cats with severe, chronic LUTS seem to have a functional rather than a structural lower urinary tract disorder and that peruria can occur in apparently healthy cats exposed to stressful circumstances. There is significant overlap at the present time among treatment recommendations for some LUT disorders particularly with regard to ensuring that the patient’s environmental needs are met.

Severe chronic idiopathic LUTS has been described as a naturally occurring model of interstitial cystitis in women. Interstitial cystitis (IC) has been defined as a disease of chronic irritative voiding signs, sterile and cytologically negative urine and cystoscopic observation of submucosal petechial hemorrhages. The same description in which cystoscopy was not performed in cats but in which other appropriate diagnostic procedures did not identify a cause became defined as Feline Interstitial Cystitis (FIC)

In addition to epithelial abnormalities identified in the bladder of cats with FIC, investigators found significant alterations in components of acetylcholine synthesis and release in the esophageal mucosa from cats with FIC. This suggested that changes in the nonneuronal cholinergic system may contribute to alterations in cell-to-cell contacts and possibly communication with underlying cells that may, in turn, contribute to changes in sensory function and visceral hyperalgesia. Differences in sensory neuron anatomy and physiology also are present in cats with FIC suggesting a more widespread abnormality of sensory neuron function. The acoustic startle response is a reflex motor protective response to a perceived threat. It is a brainstem reflex response to unexpected auditory stimuli and is increased in cats with FIC.

Differences in sympathetic nervous system function have also been identified in cats with FIC. Among them are changes in the brain stem in the region associated with the most important source of norepinephrine in cats and humans. It is involved in such brain functions as vigilance, arousal and analgesia and mediates the visceral response to stress. Other changes in brainstem help to explain the waxing and waning course of symptoms and the aggravation of signs by environment stressors.

Some cats with FIC appear to have abnormalities in the hypothalamic-pituitary-adrenal axis such that there is a decrease in serum cortisol secretion compared with healthy cats. Adrenal glands in these cats were grossly smaller in cats with FIC when compared to healthy cats.

Cats with FIC often have variable combinations of comorbid disorders such as behavioral, endocrine, cardiovascular and GI problems. External stressors appear to exacerbate clinical signs of these disorders. Many human beings with IC suffer from variable combinations of comorbid disorders as well. These appear to have no consistent pattern of onset and so cannot be attributed to LUTS but rather may be some common disorder affecting more than one organ which then responds in its own way.

Ongoing research in both humans and cats with chronic LUTS has begun to include a more comprehensive evaluation of the entire patient. Nosology is defined as the classification of diseases. Until a better understanding of the larger picture of cats presenting with LUTS, naming this constellation of symptoms and organs systems involved should remain vague and not reflect only LUTS. Dr. Buffington has suggested “Pandora’s Syndrome” He and his colleagues, Drs. Westropp and Chew propose tentative criteria for diagnosis of Pandora syndrome:

1. Presence of clinical signs referable to other organ systems in addition to chronic idiopathic signs for which the patient is being evaluated
2. Evidence of early adverse experience (e.g abandonment, orphaning) and which may differ by individual
3. Waxing and waning of severity of clinical signs with events that (presumably) activate the central stress response system
4. Resolution of signs with effective multimodal environmental modification

Whatever the eventual name, restricting the description of these patients to their LUTS does not capture all of the currently recognized features of the syndrome. A more comprehensive evaluation of cats with these and other chronic idiopathic signs may result in a more complete diagnosis and lead to additional treatment approaches that may improve outcomes. For example, the relationship between the environment and health is quadratic rather than linear, with both deficient and threatening environment increasing the risk of poor health outcomes.

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Individual patients presenting with chronic LUTS benefit by a more comprehensive evaluation to elucidate the effect on risk for Pandora syndrome. Included in this history should be:

- Where the cat was obtained
- Any other health or behavior problems that may be present
- Structure of the cat’s environment – amount of time indoors, activity level, availability and management of resources, other cats in the home, people living with the cat.
- Presences of signs referable to other organ systems
- Perceived allergic responses to skin, lung or GI tract
- Any unusual or problematic behaviors

The physical exam should be performed with evaluation of the lower urinary tract last to avoid being distracted and missing other abnormalities such as over-grooming, obesity, acne, cardiac abnormalities or GI tract issues.

For an initial episode in an apparently healthy, young unobstructed patient, the most likely explanation is either a sickness behavior in an otherwise healthy cat or acute idiopathic LUTS. After ruling out other causes of LUTS, the client should be counseled regarding individually tailored multimodal environmental modification (MEMO) to make sure the cat’s environmental needs are being met. The client can also be taught to look for other signs of sickness behaviors and to evaluate response to MEMO for adequacy of accommodation.

Table 1
Forms used as part of the evaluation of cats presented the Ohio State University Veterinary Medical Center for evaluation of chronic lower urinary tract signs. These forms have not been formally validated beyond their face validity for cases in the authors’ practice area. They are offered as an example of an instrument that could be developed and validated for broader use

Cat and client history form
Cat’s name____________________ Owner name_____________________ Date______________
Contact information: Telephone: ☐__________ E-mail: ☐____________
☐ Please check preferred method of contact

Cat Information: Breed___________ Color_______ Date of Birth_______ Weight ☐ lb ☐ kg
Owned for? _____ years _____ months; ☐ M ☐ F ☐ Neutered? If yes, date: ________
☐ Declawed? ☐ N ☐ Y If yes, Front only ☐ All four paws ☐

Body Condition (please check box that looks most like your cat):
☐Skinny ☐Lean ☐Moderate ☐Stout ☐Obese

Please check the boxes that best apply to your cat:

Diet: (please be as specific as you can, eg, Buckeye Best (company) Adult Chicken and Rice (flavor)
Wet food: name____________________ ☐None ☐25% ☐50% ☐75% ☐100%
Dry food: name____________________ ☐None ☐25% ☐50% ☐75% ☐100%

How many hours each day, on average: does your cat spend indoors?
☐Indoor only ☐18-24 ☐12-18 ☐6-12
☐0-6 Is time outside supervised? ☐Yes ☐No

If you have more than one cat, what is their relationship? ☐Not related
☐Littermate ☐Sibling ☐Parent-Offspring ☐Other (____________________)
Where did you obtain your cat (source)?
- Shelter
- Offspring from a pet I already own(ed)
- Purchased from a friend
- Gift
- Purchased from a breeder
- Purchased from a pet shop
- Stray/orphan
- Other ____________________________

Does your cat frequently (please check all that apply):
- Try to escape
- Pace at outside doors
- Cry at outside doors
- Hide
- Act fearful
- Act friendly
- Follow owners around the home
- Destroy things when left alone
- Act ‘depressed’ (little interest in feeding, grooming, environment, etc.)

Housing (______):
- Apartment: □ studio □ 1-2 bedrooms □ 3 or more bedrooms,
- Zip Code
- House: □ attached/twin duplex □ attached, 3 or more units, □ single
□ other

Total Cats _____ Total Dogs _____ Other Pets ____________

Other People ____________

Please help us understand what your cat does around the house by placing a check (√) in the box next to each behavior that best describes how commonly your cat does each of the behaviors described below

<table>
<thead>
<tr>
<th>Does your cat:</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good Bit of the Time</th>
<th>Some of the time</th>
<th>A little bit of the time</th>
<th>None of the Time</th>
<th>Does Not apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leave household articles (furniture, drapes, clothing, plants, etc) alone</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Eat small amounts calmly at intervals throughout the day</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Drink small amounts calmly at intervals throughout the day</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Use the litterbox</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Get along with people in the home</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Get along with other pets in the home</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Remain calm when left alone</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Stay relaxed during normal, everyday handling (grooming, petting)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Calm down quickly if startled or excited</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>React calmly to everyday events (telephone or doorbell ringing)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Play well with people</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Play well with other family cats</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Show affection without acting clingy or annoying</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Tolerate confinement in a carrier (including travel)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Groom entire body calmly</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<td>□</td>
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<tr>
<td>Use scratching posts</td>
<td>□</td>
<td>□</td>
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<td>□</td>
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<tr>
<td>Play with toys</td>
<td>□</td>
<td>□</td>
<td>□</td>
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</table>

Comments; anything else your cat regularly does or does not do that you think might be helpful for us to know about?
Health history
The cat’s condition today is ____________________________________________________________
Previous illnesses or surgeries _______________________________________________________
Current medications ________________________________________________________________

Directions: For items below, please use the following choices to describe how many times you have seen your pet experience the symptom, adding comments/explanation as appropriate.

Score =
0 = I have NEVER seen it
1 = I have seen it at least ONCE
2 = I see it at least ONCE per YEAR
3 = I see it at least ONCE per MONTH
4 = I see it at least ONCE per WEEK
5 = I see it DAILY

<table>
<thead>
<tr>
<th>Score</th>
<th>How often does your cat:</th>
<th>Comments/explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cough</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sneeze</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have difficulty breathing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stop eating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomit □food □hair □bile □other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have hairballs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have constipation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Defecate outside the litter box</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strain to urinate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have frequent attempts to urinate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinate outside the litter box</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have blood in the urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spray urine</td>
<td></td>
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<tr>
<td></td>
<td>Groom more than cats usually do</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shed more than cats usually do</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scratch him/herself more than cats usually do</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have discharge from eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seem fearful</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seem to need a great deal of contact or attention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Destroy things when left alone</td>
<td></td>
</tr>
</tbody>
</table>

Please check any of the following diseases your cat has been diagnosed with:

- □ Periodontal (dental) disease
- □ Asthma
- □ Inflammatory bowel disease
- □ Skin disease
- □ Allergies
- □ Diabetes mellitus
- □ Cardiomyopathy (heart problems)
- □ Obesity
- □ Other

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Household resource checklist

The following questions ask about your cat’s resources so we can learn more about the environment your cat(s) live in. Please ✔ DK if you don’t know, NA if it does not apply, or Yes or No after each question. If you have more than one cat, please answer for all cats. Resources (food, water, litter and resting areas) for each cat are assumed to be out of (cat) sight of each other, such as around a corner or in another room. If they are in sight of each other, please answer No.

### Space

<table>
<thead>
<tr>
<th></th>
<th>DK</th>
<th>NA</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Each cat has its own resting area in a convenient location that provides some privacy</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2</td>
<td>Resting areas are located such that another animal cannot sneak up on the cat while it rests</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3</td>
<td>Resting areas are located away from appliances or air ducts that could come on unexpectedly (machinery) while the cat rests</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4</td>
<td>Perches are provided so each cat can look down on its surroundings</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5</td>
<td>Each cat can move about freely, explore, climb, stretch, and play if it chooses to</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>6</td>
<td>Each cat has the opportunity to move to a warmer or cooler area if it chooses to</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>7</td>
<td>A radio or TV is left playing when the cat is home alone</td>
<td>☐</td>
<td>☐</td>
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</tr>
</tbody>
</table>

### Food and water

<table>
<thead>
<tr>
<th></th>
<th>DK</th>
<th>NA</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Each cat has its own food bowl</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>9</td>
<td>Each cat has its own water bowl</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>10</td>
<td>Bowls are located in a convenient location to provide privacy while the cat eats or drinks</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>11</td>
<td>Bowls are located such that other animals cannot sneak up on the cat while it eats or drinks</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>12</td>
<td>Bowls are washed regularly (at least weekly) with a mild detergent</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>13</td>
<td>Bowls are located away from machinery</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

### Litter boxes

<table>
<thead>
<tr>
<th></th>
<th>DK</th>
<th>NA</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Each cat has its own box (one box per cat, plus one)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>15</td>
<td>Boxes are located in convenient, well-ventilated locations that still give each cat some privacy while using it</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>16</td>
<td>Boxes are located on more than one level in multi-level houses</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>17</td>
<td>Boxes are located so another animal cannot sneak up on the cat during use</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>18</td>
<td>Boxes are located away from machinery that could come on unexpectedly during use</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>19</td>
<td>The litter is scooped daily</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>20</td>
<td>The litter is completely replaced weekly</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>21</td>
<td>Boxes are washed regularly (at least monthly) with a mild detergent (like dishwashing liquid), rather than strongly scented cleaners</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

### Litter boxes (continued)

<table>
<thead>
<tr>
<th></th>
<th>DK</th>
<th>NA</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>Unscented clumping litter is used</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>23</td>
<td>A different brand or type of litter is purchased infrequently (less than monthly)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>24</td>
<td>If a different type of litter is provided, it is put in a separate box so the cat can choose to use it (or not) if it wants to</td>
<td>☐</td>
<td>☐</td>
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</tbody>
</table>

### Social contact

<table>
<thead>
<tr>
<th></th>
<th>DK</th>
<th>NA</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Each cat has the opportunity to play with other animals or the owner if it chooses to on a daily basis</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>26</td>
<td>Each cat has the option to disengage from other animals or people in the household at all times</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>27</td>
<td>Do any cats interact with outdoor cats through windows?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

### Body care and activity

<table>
<thead>
<tr>
<th></th>
<th>DK</th>
<th>NA</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>Horizontal scratching posts are provided</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>29</td>
<td>Vertical scratching posts are provided</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>30</td>
<td>Chew items (eg, cat-safe grasses) are provided</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>31</td>
<td>Toys to chase that mimic quickly moving prey are provided</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>32</td>
<td>Toys that can be picked up, carried, and tossed in the air are provided</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>33</td>
<td>Toys are rotated on a regular basis (at least weekly) to provide novelty</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

If you have additional comments on any of the questions, please write them below, including the question #.

By submitting this form, you agree that anonymous information from it may be used for cat health-related research.
The interrelationship between calcium, phosphorus, parathyroid hormone, activated vitamin D and fibroblast growth factor has a profound impact on the progression of chronic kidney disease (CKD) in dogs and cats. Beneficial effects of calcitriol treatment during CKD have traditionally been attributed to regulation of parathyroid hormone (PTH). New analysis of information emphasize direct renoprotective actions independent of PTH and calcium. It is now apparent that calcitriol exerts an important effect on renal tubular Vitamin D which may be important in maintaining adequate circulating Vitamin D. This in turn may be vital for important actions of Vitamin D on peripheral tissue. Limited information is available reporting the benefit of calcitriol treatment in dogs and cats with CKD. However, a survival benefit has been shown in dogs with CKD treated with calcitriol compared to placebo. The concentrations of circulating Vitamin D have recently been shown to be low in people and dogs with CKD and are related to survival in people. In 2015, there will be compelling data regarding the benefit of calcitriol use in cats with CKD.

Rather than focus on the dearth of evidence for several forms of intervention, this talk will focus on a historic review of the use of dietary therapy, phosphorus binding agents and calcitriol over a ten year period. These are all client-owner cats. Therefore, these are not randomized, blinded, controlled studies. Rather, these cases are a demonstration of practical interventions that have prolonged good quality of life in cats who may not have agreed to all of the recommendations made in the literature.

In assessing renal disease in cats, the most sensitive indicator is the loss of urine concentrating ability. The use of an early morning urine sample to assess urine specific gravity (USG) may help to counter effects of diet or drugs on a tested sample. Using the International Renal Interest Society (IRIS) values for classification of renal disease can be helpful in planning therapy. In some classifications IRIS 2 is divided in to 2a (Cr. 1.6-2.4 mg/dl) and 2b (2.5-2.8 mg/dl). In our practices the classification of 2a with USG less than 1.030 eating a mostly dry diet formula, for example, are started on treatment for chronic progressive renal disease (CPRD). Early intervention prolongs quality of life, good body condition score and wellbeing in a number of key ways. We use ultrasound guided cystocentesis in every cat from whom urine is obtained. This allows a quick early morning visit by the owner, a sterile sample for culture if indicated, a full assessment of the appearance of the urinary bladder and observation of complications such as uroliths.

One of the most frustrating aspects of treating this and any condition requiring lifelong therapy in cats is the difficulty clients have complying with our recommendations. Cats resist contact or intervention they haven’t agreed to and clients want to preserve the relationship they have with their cat, often at the expense of appropriate therapy. It is essential then to choose the most effective forms of therapy, to provide options when resistance is experienced and to communicate a willingness to the client to assist in preserving the relationship they have with their beloved cat.

While it has been shown that dietary modification has the most positive long-term effect on outcome, the relationship between survival and protein restriction or the attendant restriction of phosphorus has yet to be illuminated fully. Strong evidence, however, supports dietary phosphorus restriction in animals with kidney disease. Serum phosphorus is an independent predictor of disease in cats with chronic kidney disease. Cats with induced renal disease fed phosphorus –restricted diets had less severe histological renal changes than cats fed normal diets.

Phosphate retention and hyperphosphatemia are primarily due to impaired renal phosphate excretion. If renal function is normal, clinically significant hyperphosphatemia seldom develops. In the early stages of CPRD increased levels of PTH can keep serum phosphorus within the reference range by decreasing expression of the sodium-phosphate transport system in the proximal tubule resulting in increased urine phosphate excretion. This allows for normalization of serum phosphorus at the expense of hyperparathyroidism.

As cats are quite specific about preferences in taste, texture and flavor, the use of renal formulated diets may not always be possible. Alternatives may not have been thoroughly tested to the extent that prescription diets are but the truth of the statement “It is more important THAT he eats than WHAT he eats” is undeniable. Treatment goals of dietary modification start with maintaining body weight and a normal body condition score. If renal diets are not tolerated, warm canned diets diluted with some form of flavored moisture are a good choice. Other alternatives include adding other forms of moisture to food to increase fluid intake, providing flavored waters to encourage moisture consumption, water fountains and multiple drinking places throughout the house.

If a renal diet is not fed, most cats will tolerate low doses of aluminum hydroxide in food to act as a phosphorus binder, before serum phosphorus levels leave the normal range. Serum phosphorus should remain in the 4-5 mg/dl range, especially if calcitriol is considered. Low body condition scores and malnutrition are negative prognostic indicators in dogs and the same is likely to be true in cats. If adequate caloric intake and preservation of lean body mass does not occur, quality of life will decline.

Studies done to confirm preservation of lean body mass in cats fed a low protein diet, about 28% on an as-fed basis, were, as one would anticipate, time restricted to around 4 months. With the advent of a better plan for managing renal patients, they are living for...
The effects of uremia on appetite are well known, particularly in human renal patients. The use of H2 blockers for uremic gastritis can be helpful in encouraging consumption of adequate calories. The use of mirtazapine as an appetite stimulant is helpful in those cats who can tolerate it. We use 1/8 of a 15 mg tablet every day to every third day depending upon response to therapy. Many cats with CPRD are underweight and dosing of ¼ of a tablet as has been recommended is often followed by restlessness, anxiety and vocalizing in cats who are sensitive to it. Clients can be quite upset by this and may be less inclined to follow other treatment recommendations. Both of these forms of therapy imply being able to accomplish giving fragments of a pill to a cat on a regular basis and over a prolonged period of time. Strategies for this should be included in client education including the use of “sticky” high value food like cheese in a can, cream cheese or pill pockets and other soft treats.

Calcitriol has long been reported to provide benefits to the human uremic patient by lowering parathyroid hormone concentration. This has also been reported in dogs and cats. Oral calcitriol has been shown to increase survival in human patients with CPRD including those treated prior to dialysis. The antiproteinuria effects of Vitamin D analogs are of crucial significance because proteinuria is a major risk factor for the progressive decline of renal function in both dogs and cats. Podocytes are critically important in overall glomerular function and structure. Injury to podocytes commonly leads to proteinuria and glomerulosclerosis. A marker for podocyte injury, desmin, was lowered by calcitriol in one model of CPRD in rats. Fibrosis as either glomerulosclerosis or tubulointerstitial fibrosis is a common sequelae in CPRD. Calcitriol in physiologic doses interfered with glomerular proliferation and growth, lessening glomerulosclerosis in a rat model. Calcitriol treatment of an experimental glomerulonephritis model in rats inhibited medullary cell proliferation, glomerulosclerosis and albuminuria.

The renin-angiotensin-aldosterone system (RAAS) is a major mediator of progressive renal injury in CPRD. The RAAS system is present entirely within the kidney and is present in most renal cells including tubular epithelia.

Calcitriol is a negative endocrine regulator of RAAS. Calcitriol suppresses renin biosynthesis and has a protective role against hyperglycemia-induced renal injury in diabetic human patients. Through its effect to inhibit RAAS, calcitriol decreases production of Angiotensin II and thus lessens these fibrogenic consequences as well as other harmful renal effects.

A glomerular mesangial or interstitial inflammatory reaction with marked involvement of macrophages and lymphocytes attends all forms of renal disease. Together with control of RAAS, the ability of calcitriol to control inflammation are hallmarks of renoprotective actions.

In our practices, early diagnosis of CPRD at the IRIS 2a or b level is the key to successful management. A cat with or without proteinuria, with or without hypertension with a USG less than 1.030 and normal Calcium and Phosphorus will be started on Calcitriol at a dose of 2.5-3.5 ng/Kg per day. This is compounded into a chicken or fish flavored oil base by a compounding pharmacy licensed to produce compounded pharmaceuticals for the human market. Calcium, Phosphorus and their product will be measured in 2 weeks.

While the literature is clear that iCA is a far more accurate measure of total body calcium, it is an expensive test. Our protocol calls for frequent testing of renal values including calcium and phosphorus. We would be treating a fraction of the cats we can help if this costly test were included. Instead we use a protocol advocated by Larry Nagode and Dennis Chew, Pathology and Urology professors respectively at the Ohio State University Veterinary College.

One of the benefits of the preservation of renal tissue using this protocol is the preservation of erythropoietin production and the consequent preservation of normal hematocrits. Cats with IRIS Stage 3-4 CPRD are still feeling better, more active and eating better with adequate circulating red cells. Anemia is a quality of life issue.

Hepcidin excess prevents iron absorption from the diet and blocks iron release from body stores by binding to and inducing the degradation of the iron export protein ferroportin. A mechanism for the EPO sparing effects of vitamin D is suggested by recent data demonstrating a hepcidin lowering effect of vitamin D. In vitro treatment with vitamin D of monocytes isolated from hemodialysis patients downregulated hepcidin transcription. Furthermore, oral administration of vitamin D in healthy volunteers lowered serum levels of hepcidin by 50% compared to baseline levels within 24 hr and persisted for 72 hr. Supplementation with vitamin D has also been reported to have beneficial effects on increasing erythropoiesis and decreasing inflammation. These initial results are promising, and a randomized controlled study is warranted to determine whether correction of vitamin D deficiency can ameliorate ACD.

References
Journal of Veterinary Emergency and Critical Care, Calcitrol, Calcidiol, Parathyroid hormone and fibroblast growth factor-23 interactions in chronic kidney disease. Volume 23 (2) 2013, pp 134-162.
Pancreatitis is an inflammatory disease of the exocrine pancreas. It can be divided into acute and chronic types based upon histological findings. Two main forms have been described. Neutrophilic inflammation and varying amounts of pancreatic acinar cell and peripancreatic fat necrosis characterize acute pancreatitis. Chronic pancreatitis is characterized by lymphocytic inflammation, fibrosis and acinar atrophy. While the cell types involved differ in this description, they appear to represent, in some studies, different points on a continuum of disease.

Diagnosis of both forms is difficult. There may be comorbidities that complicate signs. Clinical signs may be vague or mild. The diagnostic tools like imaging or clinical tests can lack sensitivity and specificity. Biopsy samples may be difficult to interpret or unavailable for many reasons.

There appears to be a strong association in several studies between pancreatitis, inflammatory bowel disease (IBD) and cholangitis, giving rise to the term “triaditis”. This may be partially explained by the proximity of the common bile duct and major pancreatic duct in the duodenal papilla. Enteric bacteria were found in >1/3 of cases supporting the suspicion of a relationship between pancreatitis and the translocation of bacteria from the gut. Vomiting, a common sign in cats with IBD or cholangitis may also raise intraluminal pressure and further increase the risk of pancreaticobiliary reflux. The relationship between cholangitis and pancreatitis has recently been challenged however, though its relationship with IBD has not.

Ischemia is another recognized cause of acute pancreatitis. Inadvertent compression or ligature and hypotension during surgery can cause ischemia of the pancreas. Careful surgical technique and anesthetic monitoring prevent these events from occurring. The pancreas can be the cause of ischemia if fibrosis, edema or inflammation compromise pancreatic blood flow. Other causes like infectious agents, hypercalcemia, drug reactions and nutritional imbalances have been reported but are rare. Most commonly pancreatitis is considered idiopathic as no obvious cause can be found.

Serum feline pancreatic lipase immunoreactivity (fPLI) is the most recent addition to laboratory tests seeking a useful diagnostic ante-mortem test for feline pancreatitis. There are two tests, developed by the same laboratory. SpecfPLI is a quantitative test for which concentrations > 5.3 are consistent with pancreatitis. A grey zone is found from 3.5-5.3ug/l and is notable on the Spec test and on the Snap fPLI test, which is a semi-quantitative test. A positive Snap fPLI includes the grey zone when it is positive so results should be confirmed by Spec fPLI. The sensitivity of the Spec fPLI is still without adequate data. Moderate to severe pancreatitis was 100% sensitive in one study but much lower, 54%, for mild pancreatitis based upon histopathology. However, the number of patients was small and there was some bias evident on patient selection for histopathology. More studies are needed to properly evaluate sensitivity and specificity of SpecfPLI. Snap fPLI has not been independently validated. Importantly, fibrosis or atrophy from long-standing chronic pancreatitis would not be expected to increase fPLI.

Other abnormal laboratory findings have been observed but are not diagnostic as well. From 26-55% of cats have a normocytic, normochromic nonregenerative or regenerative anemia. Less than half have a leukocytosis. Leukopenia may be present and has a poorer prognosis. Other hematological findings are non-specific and cannot distinguish between acute, chronic or supplicative pancreatitis. Biochemistry abnormal values are often present but are not specific for pancreatitis and may represent comorbid conditions with pancreatitis.

Abdominal radiographs are may be suggestive of cranial loss of serosal detail or a mass effect but are largely useful to rule out concomitant conditions like intestinal obstruction. Ultrasound is relatively specific in differentiating pancreatitis from other GI disease but cannot differentiate between acute and chronic forms. Hypoechoic pancreas, hyperechoic peripancreatic adipose or abdominal effusion is relatively specific for pancreatitis in cats. Mild forms of pancreatitis are more difficult to discern than moderate to severe forms on ultrasound. In some cats, the pancreas is more difficult to detect and is dependent on operator experience.

The use of endosonography may improve the general visualization but did not alter the diagnosis of pancreatitis in one study. Ultrasound is still recommended for diagnosis of pancreatitis and will reveal other abnormal findings such as pancreatic masses, cysts or stones. Computed tomography has not been helpful and is not recommended for diagnosis. Magnetic resonance imaging is the modality of choice in humans and may be helpful in cats.

Histopathology remains the gold standard for ante-mortem diagnosis though there are limitations to this as well. Cats with severe pancreatitis are poor candidates for anesthesia. Even for those patients stable enough, the results may not alter treatment planning and patient management. Patients undergoing laparotomy or laparoscopy for other reasons should have the pancreas biopsied. Focal lesions may be visible as well as more generalized changes that will guide sample collection. Multiple samples are recommended as lesions can be geographically distributed or very mild and difficult to discern. Mild changes may not explain the patient’s clinical signs as well.
Despite the challenges of diagnosis, pancreatitis is an important condition. Anorexia and weight loss found with pancreatitis can cause concurrent hepatic lipidosis. Several studies have shown the relationship between Diabetes Mellitus (DM) and pancreatitis. Other concurrent diseases can be complicated by the presence of pancreatic inflammation most notably IBD. End-stage CP can result in exocrine pancreatic insufficiency.

Management of pancreatitis is comprised of three main aspects: nutrition and antiemetic therapy, fluid and electrolyte correction and analgesia. A high protein, low carbohydrate, moderate fat diet is the recommended formulation. While fasting is not recommended, gradual reintroduction of food should be instituted to avoid the electrolyte and other disturbances that occur with refeeding syndrome. Though nausea may be difficult to discern, it should be treated to insure adequate intake of food. NK-1 receptor antagonist maropitant and 5HT3 antagonists are beneficial. Maropitant may also relieve some of the pain associated with pancreatitis. Cobalamin deficiency is common in cats and should be addressed with B12 injections weekly for 6 weeks and every 1-2 months thereafter. Appetite improvements with the use of cobalamin supplementation have been reported.

If voluntary food intake is not rapidly restored a nasoesophageal tube for short-term use or an esophagostomy or gastrostomy tube may be required. The goal of a nasoesophageal tube is for stabilization until anesthetic risk is lowered adequately to permit a more lasting tube to be placed. In the case of severe malnutrition and persistent anorexia, partial parental nutrition along with some enteral nutrition has been shown to maintain gut wall barrier function in humans.

Vomiting, anorexia and diarrhea can lead to severe dehydration and electrolyte disturbances. Hypokalemia and hypocalcemia are no uncommon. Aggressive fluid therapy is required to correct pancreatic hypoperfusion.

Pain is a common feature of pancreatitis though difficult to evaluate in cats. Buprenorphine, oxymorphone or fentanyl may be good choices.

Comorbidities must be treated at the same time, insulin for DM, therapy for diabetic ketoacidosis, cholangitis or inflammatory bowel disease. Plasma (20ml/kg i.v.) or colloids (10-20ml/kg/day i.v.). may be indicated in the presence of hypoproteinemia or shock. Colloids such as dextran 70 and hetastarch may also have antithrombotic effects that help maintain the microcirculation.

Prophylactic broad-spectrum antibiotics (e.g. amoxicillin ± enrofloxacin depending on severity) may be warranted in patients with shock, fever, diabetes mellitus or evidence of breakdown of the GI barrier. Bacterial translocation has been demonstrated in experimental feline pancreatitis using distinct E. coli placed in the colon, and other sites e.g. bile, and colonization was prevented with cefotaxime (50mg/kg TID). A recent study revealed that bacterial infection is present in the pancreas of 35% (11/31) of cats with moderate to severe pancreatitis. The high frequency of infection (71%, 5/7) in acute necrotizing and suppurative pancreatitis may be linked to the poor prognosis associated with this form of pancreatitis. These localization and type of intrapancreatic bacteria suggests translocation of enteric bacteria is a likely source of infection.

Coagulation abnormalities should be pursued and treatment with parenteral vitamin K can be assessed. Where a coagulopathy e.g. DIC, or hypoproteinemia are present, or the patient with pancreatitis is deteriorating, fresh frozen plasma (10-20 ml/kg) may be beneficial in alleviating the coagulopathy, hypoproteinemia and restoring a more normal protease-antiprotease balance. The administration of heparin (75-150 IU/kg TID) may be potentially useful in ameliorating DIC, promoting adequate microcirculation in the pancreas and clearing lipemic serum. In experimental pancreatitis isovolemic rehydration with dextran has also been shown to promote pancreatic microcirculation in dogs. A dopamine infusion (5μg/kg/min) had a protective effect when administered to cats within 12 hrs. of induction of experimental pancreatitis. H1 and H2- antagonists blocked the progression of edematous to hemorrhagic pancreatitis in experimental cats and may be beneficial in patients.

Oral pancreatic enzyme extracts have been reported to reduce pain in humans with chronic pancreatitis, though this is controversial. The presence of a protease mediated negative feedback system has not been described in cats.
Many drugs are available to treat the clinical signs associated with GI diseases or to treat the disease process itself. A thorough knowledge of these drugs, including several of the newer developments, is necessary for the practitioner to effectively treat dogs and cats with GI diseases.

**Antiemetics**

Antiemetics are effective in reducing the frequency of vomiting or in some cases completely eliminating it. In the outpatient it relieves a very objectionable clinical sign for the owner. In the hospitalized patient it reduces the severity of dehydration and electrolyte changes and allows the animal to rest. Antiemetics should be used cautiously, as continued vomiting is an important sign that the underlying condition may be progressing or that an incorrect diagnosis has been made. Masking this important parameter may give the clinician a false sense of security that the animal is improving, when actually heightened surveillance and therapy is indicated. The author is most comfortable prescribing antiemetics when a definitive diagnosis has been reached or when used for only a brief period in animals with self-limiting vomiting.

**Metoclopramide**

Metoclopramide (Reglan) is a highly effective antiemetic with both central and peripheral effects. Metoclopramide is a dopamine antagonist that very effectively blocks the CRTZ and raises the threshold of the vomiting center. Peripherally it augments acetylcholine release from postganglionic nerves and increases the tone and amplitude of gastric contractions and increases gastroesophageal sphincter pressure. These actions oppose some of the physical events necessary for the vomiting reflex to occur. Short term side effects are uncommon and include depression, nervousness, and restlessness. Metoclopramide is contraindicated in intestinal obstructions. Dosages of 0.2-0.4 mg/kg TID SQ are often effective. Because it has a short half life it may need to be administered by constant infusion 1.0-2.0 mg/kg/day IV.

Metoclopramide can also be used to treat esophagitis. Increasing tone of the GES helps to reduce the reflux of acid which would impede healing of the esophageal mucosa. Increasing gastric motility and emptying will help to move acid and ingesta out of the stomach into the duodenum, reducing the amount available to reflux into the esophagus. Metoclopramide's prokinetic effects are useful in treating gastric motility disorders, a group of under diagnosed conditions causing chronic vomiting (see article on gastric motility disorders.

**Ondansetron**

Ondansetron (Zofran) is a serotonergic antagonist that is very effective in blocking the nausea and vomiting associated with chemotherapy. It is effective in blocking neural transmission in both the chemoreceptor trigger zone and in vagal afferent pathways. Dosages of 0.5-1.0 mg/kg PO can be given 30 minutes prior to administration of chemotherapy. It can also be used to reduce vomiting associated with GI disorders at 0.1-0.15 mg/kg slow IV BID-QID. The author has not found it necessary to use the drug in this manner, although others have found it very effective. Presently, the drug is very expensive.

**Maropitant – cerenia™**

Maropitant is a neurokinin receptor antagonist that blocks the actions of substance P in the central nervous system. It was released in the summer of 2007. It is approved for the prevention and or treatment of acute vomiting (dogs and cats) and motion sickness (dogs) > 8 weeks of age. Dosage for motion sickness is 8 mg/kg PO q 24H. Dosage for acute vomiting is 1 mg/kg SC q 24 H for up to 5 days. The drug is metabolized via hepatic P450 enzymes. It is considered a safe drug and side effects were similar to placebo. It was more effective than metoclopramide in a European clinical study in reducing vomiting in a large number of dogs with a variety of common causes for acute vomiting. It has also been shown to reduce vomiting associated with cisplatin administration in dogs with neoplasia.

**Erosion and ulcer therapy**

Erosion and ulceration of the gastric and duodenal mucosa commonly occur in chronic gastritis and gastric-duodenal ulcer disease. Back-diffusion of acid across a damaged mucosa leads to further damage and retards healing processes. Reduction of gastric acid secretion, protection of ulcerated mucosa, or augmentation of cytoprotection promotes healing of erosions and ulcers.

**H-2 receptor blockade**

Drugs such as cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepsid), and nizatidine (Axid) block the H-2 receptor on the gastric parietal cell and dramatically decrease acid production. Cimetidine (5-10 mg/kg QID) and ranitidine (2 mg/kg BID-TID) have been used most commonly in veterinary medicine. Both can be given orally or parenterally and have not been commonly associated with adverse effects. Cimetidine can inhibit hepatic cytochrome P-450 enzymes, potentially interfering with the metabolism of other
drugs. Famotidine, 0.5 mg/kg SID-BID, and nizatidine, 5 mg/kg SID (this dosage has not been well established), have not been used as frequently in veterinary medicine, but are also effective. All four of these drugs are now available over the counter in smaller dosage forms than prescription strength, making treatment of cats and small dogs easier. Elixirs are available for cimetidine, ranitidine, and famotidine.

Sucralfate
Sucralfate (Carafate) is a sulfated disaccharide that forms an adherent gel and binds to an ulcer crater, protecting it from acid and pepsin. It also stimulates the synthesis of prostaglandin, increases mucosal cytoprotection, and binds epithelial growth factor at the ulcer, where it stimulates cellular proliferation. It has been shown to be as effective as H-2 receptor blockers in healing ulcers in humans. Because sucralfate can bind other drugs, medications should be given 1-2 hours prior to sucralfate administration. The recommended dose is 1 gm/25 kg TID-QID in dogs and 0.25 gm TID in cats. Because absorption is minimal, toxicity is uncommon. Long-term use may lead to constipation because of its aluminum content. There is no evidence to support that combination therapy with an H-2 receptor antagonist provides added benefit compared to therapy with either sucralfate or an H-2 blocker alone.

Sucralfate is also effective to treat esophagitis because of its ability to coat ulcerated mucosa. The suspension form is necessary for this indication.

Proton pump inhibitors (PPI’s)
PPI’s inhibit the action of the proton pump at the apical portion of the parietal cell that exchanges H+ for luminal K+, thus preventing secretion of acid. As a weak base they accumulate in the acid compartment of the parietal cell, necessitating only SID administration. Omeprazole (Prilosec) is the most commonly used PPI in veterinary medicine. The recommended dose is 1.0 mg/kg SID. The enteric-coated granules (20 mg) are packaged in gelatin capsules to resist degradation by gastric acid. If less than one capsule is to be administered (20 mg), the granules should be repackaged in gelatin capsules. Zegerid is an omeprazole powder that is mixed with bicarbonate to protect the drug from gastric acid. It can be divided into smaller doses. Another PPI, lansoprazole (Prevacid) granules can be mixed in an acid juice, such as apple juice and administered. Other PPI’s such as pantoprazole (Protonix), rabeprazole (Aciphex), esomeprazole (Nexium) must be reformulated into a form that protects the drug from gastric acid damage. Omeprazole also inhibits hepatic p-450 enzymes. Several recent studies have shown that PPI’s in dogs are better at inhibiting acid secretion than H2 blockers. In humans H2 blockers begin to suppress acid faster than PPI’s. Many clinicians will concurrently use an H2 blocker for 2-3 days when starting PPI therapy. Also in humans, PPI’s result in faster ulcer healing and relieve clinical signs sooner than H2 blockers. These effects are not proven in dogs or cats.

Probiotics
Probiotics are live bacteria that confer a health benefit to the host. Common bacteria include lactobacilli, bifidobacteria, and enterococci. In humans a daily dose is often 5-10 million. To be effective viability must be maintained throughout production, storage, distribution, passage through the upper GI tract into the colon. Many commercially available products do not survive transit into the colon and are not as effective as “advertised”. The bacteria should be able to be cultured from the feces during treatment, but will usually disappear once oral administration ends. The bacteria must be nonpathogenic and not transmit antibiotic resistance. Probiotic bacteria have been reported to have many beneficial effects on the host including conditioning the immune system, synthesizing B vitamins, producing digestive enzymes, producing antibacterial factors, competing with pathogens for adhesion sites and nutrients, enhancing epithelial repair, increasing mucus production, decreasing luminal pH, and protecting tight junctions. However, all probiotics do not do all of the above. In humans some probiotics have been shown to be beneficial in acute infectious diarrhea, prevention of antibiotic associated diarrhea, pockitis, cow’s milk allergy, IBD, and irritable bowel syndrome. Currently there is accumulating but weak evidence demonstrating benefits of probiotics in dogs and cats with diarrhea.

References
Gastrointestinal endoscopy is commonly performed in cats and is useful in the diagnosis of many (GI) gastrointestinal disorders. Many GI diseases require mucosal biopsy for diagnosis and endoscopy is a minimally invasive technique, with less morbidity when compared to surgical exploratory and full-thickness biopsy. Gastrointestinal endoscopy also has therapeutic value as foreign bodies can be removed, esophageal strictures dilated, and percutaneous endoscopic gastrostomy tubes placed. Endoscopic skills can easily be developed by practitioners that 1) acquire knowledge of the normal endoscopic anatomy, 2) become familiar with the appearance of common lesions, 3) receive appropriate hands-on instruction, and 4) devote the time and effort required to learn proper technique.

Although rigid endoscopic equipment can be useful in diagnosing some esophageal and colonic disorders, the author routinely performs flexible endoscopy in cats. Flexible endoscopes provide better mucosal visualization and allow the tip to be advanced around flexures and through many sphincters of the gastrointestinal tract. Endoscopes to be used in cats should have four-way tip deflection, automatic air-water insufflation, a large biopsy channel, a diameter less than 10 mm and a working length of at least 100 cm. Available accessories should include biopsy forceps, cytology brushes, and a variety of foreign-body retrieval forceps.

It is the author's opinion that endoscopic capability should be available to the average private practice. Endoscopy encourages the practice of high-quality medicine by providing a minimally invasive, highly useful, diagnostic and therapeutic procedure.

**Indications**

There are numerous indications to perform gastrointestinal endoscopy in cats (Table 1). Some of the disorders that can be diagnosed via endoscopy are included in Table 2. Endoscopic examination of the esophagus will provide valuable diagnostic information in cats examined for regurgitation. Esophagoscopy should be performed if barium contrast radiographs demonstrate an intraluminal mass, mucosal irregularity or ulcer, a narrowed lumen or a motility disorder associated with normal luminal diameter. Esophagoscopy is also indicated if survey thoracic and barium contrast radiographic examinations are normal. Foreign bodies (string, fish hooks, pins, needles, bones, and hair balls) observed on radiographs can be removed endoscopically with less morbidity than thoracotomy. Strictures can be dilated via balloon catheters passed through the endoscope biopsy channel.

Gastroduodenoscopy is a very important diagnostic procedure in cats that chronically vomit. The author performs endoscopy, rather than upper GI barium studies, because endoscopy offers the following advantages: 1) direct mucosal inspection; 2) directed mucosal biopsy; 3) ability to remove foreign bodies; 4) ability to visualize subtle mucosal lesions; 5) assessment of respectability of neoplastic masses; and, 6) is rapid to perform. Some potential disadvantages of endoscopy include: 1) necessity of general anesthesia; 2) inability to examine the entire small intestine; 3) inability to detect lesions in the muscularis and serosa; and, 4) inability to evaluate gastric motility and emptying. Gastric and small intestinal mucosal samples can be collected via endoscopy with less morbidity than exploratory celiotomy with gastrotomy and enterotomy. Therapeutically, gastroduodenoscopy is indicated if foreign bodies are visualized on radiographs or if an owner has observed or suspects foreign-body ingestion. In cases of suspected foreign body ingestion radiographic studies should always confirm the presence of a foreign body prior to endoscopy. Endoscopic retrieval of gastric foreign bodies is readily accomplished in most cases. Foreign bodies in the small intestine are very difficult to remove endoscopically and exploratory surgery is indicated in most cases. A final indication for gastroduodenoscopy is placement of percutaneous endoscopic gastrostomy tubes (PEG). This rapid and simple procedure provides a convenient avenue for nonstressful enteral nutritional support in cats with prolonged anorexia or oral, pharyngeal, or esophageal disorders.

Duodenoscopy is a valuable diagnostic procedure in cats with chronic small intestinal diarrhea. If laboratory evaluation does not establish a diagnosis, small intestinal biopsy is indicated. Endoscopy can provide small intestinal mucosal samples for histopathologic evaluation. In most cats, samples can be obtained from the duodenum and sometimes the jejunum. It is difficult and often dangerous to enter the ileum in cats via colonoscopy. However, biopsy forceps can be gently passed through the ileocolic sphincter and tissue samples obtained. After instillation of saline, a fluid aspirate can also be collected from the small bowel which can aid in the diagnosis of *Giardia*. Because the common histologic causes of chronic small bowel diarrhea usually diffusely involve the small intestine, a diagnosis can often be reached with endoscopic biopsy.

The major indication for performing colonoscopy is obtaining mucosal biopsy samples in cats with chronic large-bowel diarrhea. Some cats with acute, large-bowel diarrhea associated with moderate-to-severe hematochezia rapidly require a definitive diagnosis. Colonoscopy can often provide an answer in a minimally invasive fashion.
Unique characteristics of endoscopy in cats
The principles and techniques of performing fiberoptic endoscopy in cats are very similar to those employed in dogs. However, there are some important differences encountered when performing endoscopy in cats (Table 3). The most important species difference is the small diameter and length of cats' gastrointestinal tracts. This is most critical in the antrum, pylorus, duodenum, and ileum where the diameter limits endoscopic maneuverability, making mucosal examination and advancement of the endoscope more difficult. However, this difficulty can be overcome by patience, proper technique, and endoscopic experience.

Small diameter (pediatric) endoscopes (7.8mm) can be maneuvered through these difficult areas in cats easier than larger endoscopes (9.8mm). However, the major disadvantage of pediatric endoscopes is that they have smaller biopsy channels (2.0 vs 2.8mm) which result in smaller biopsy samples that may be more difficult for the pathologist to interpret. In addition, the variety and size of foreign-body retrieval forceps is limited for pediatric endoscopes. With experience, larger endoscopes (9.8mm) can be successfully maneuvered through a cat's gastrointestinal tract. However, an all-feline practice might benefit from purchasing and using a smaller pediatric endoscope.

The feline esophagus differs anatomically from the canine esophagus, which is composed of striated muscle. The caudal one-third of the esophagus in cats contains smooth muscle which results in a series of transverse folds. Additionally, submucosal blood vessels can be commonly seen.

The relatively small feline stomach can easily and quickly become over-distended by insufflation of air during gastroscopy. Gastric distention can cause respiratory compromise and may activate vagal reflexes that produce bradycardia. The endoscopist should constantly monitor the amount of air within the stomach and apply suction when necessary to maintain a minimally distended stomach.

The antral portion of the stomach is small and is attached at a more acute angle to the gastric body than in dogs. Endoscopic manipulation in this area is limited by the small luminal diameter, and the endoscopist may have difficulty advancing the endoscope into the antrum. Often the endoscope will retroflex into the gastric body instead of entering the antrum. The small antrum also makes it difficult to obtain a direct frontal view of the angularis incisura, an important endoscopic landmark, which is easily visualized in dogs. The pyloric sphincter is often open in cats.

Cats have a single duodenal papilla, that transports bile and pancreatic secretions, that is located in close proximity to the pylorus and can be difficult to visualize in many cats. The relatively short esophagus and stomach is an advantage in cats because more endoscope length is available for advancement into the small intestine. In many cats it is possible to advance the endoscope through the duodenum into the jejunum, allowing a greater area of mucosa to be observed and sampled.

The feline colon also differs from the canine colon in several respects. The rectal area of cats usually has less mucosal folding than dogs, resulting in easier and quicker endoscope passage through the descending colon. The feline cecum is extremely short (approximately 1cm in length) and it can be entirely viewed from the ascending colon. The cecocolic sphincter is often open.

Patient preparation
Proper preparation for esophagogastroduodenoscopy requires withholding food for 12 hours prior to the procedure. Endoscopy is performed with the cat under general anesthesia and positioned in left lateral recumbency. This will position the antrum “away” from the table-top and will help facilitate endoscopic intubation of the duodenum. Various pre-anesthetic agents have been shown to not affect the endoscopist’s ability to pass through the gastroesophageal and pyloric sphincters.

Colonoscopy requires a feces-free colon and a clear ileal effluent. Food should be withheld for 24 hours prior to the procedure. The author routinely uses an iso-osmotic GI lavage solution of polyethylene glycol and electrolytes, that is not absorbed as it moves through the gastrointestinal tract, GoLYTELY®, to prepare cats for colonoscopy. Antiemetics should be administered 15-30 minutes prior to GI lavage solutions to minimize vomiting due to gastric distention. Metoclopramide 0.2-0.4 mg/kg SC or maropitant 1 mg/kg SC can be utilized. Using nasogastric installation, two doses (30ml/kg) of GoLYTELY® two hours apart, the afternoon prior to endoscopy, are administered. This large volume of fluid flushes feces from the colon. Sedation is not used during GI lavage solution administration as aspiration of these solutions can be fatal. Warm water enemas (20ml/kg) are given after each dose and prior to anesthesia induction. Sodium phosphate enemas should never be used to prepare cats for colonoscopy because they can lead to fatal hyperphosphotemia. Some experts do not use GI lavage solutions, administering multiples enemas instead. To perform colonoscopy, the cat should be placed under general anesthesia and positioned in left lateral recumbency. This will position the descending colon “away” from the table and facilitate advancement of the endoscope into the orad colon.

This seminar has reviewed the indications for performing GI endoscopy in cats, listed the common diseases encountered, and has emphasized the unique features of performing endoscopy in cats. It is the author's hope that practitioners without endoscopic capability will seriously consider purchasing equipment and receiving endoscopic instruction. The practice of feline medicine can be improved by frequently using this minimally invasive procedure to obtain diagnostic biopsy samples, remove foreign bodies, or place a percutaneous endoscopic gastrostomy tube.
Table 1 - Indications for gastrointestinal endoscopy

**Esophagoscopy**
- Foreign Body Retrieval
- Intraluminal Mass
- Irregular Mucosa or Ulcer
- Stricture Dilation
  - Regurgitation with Normal Survey and Barium Radiographs
- Motility Disorder with Normal Luminal Diameter

**Gastroduodenoscopy**
- Chronic Vomiting
- Foreign Body Retrieval
- Placement of Percutaneous Gastrostomy Tube
- Acute Vomiting with Hematemesis
- Chronic Small Bowel Diarrhea

**Colonoscopy**
- Chronic Large Bowel Diarrhea
- Acute Large Bowel Diarrhea with Hematochezia
- Ileal Biopsy with Chronic Small Bowel Diarrhea
- Demonstrated on Survey or Barium Contrast Radiographs

Table 2 - Disorders diagnosed by endoscopy

**Esophagus**
- Foreign Body
- Esophagitis
- Stricture
- Neoplasia

**Stomach**
- Gastritis
- Gastric Ulcer
- Foreign Body
- Neoplasia

**Small intestine**
- Inflammatory Bowel Disease
- Neoplasia
- Foreign Body
- Duodenal Ulcer

**Large intestine**
- Inflammatory Bowel Disease
- Neoplasia

Table 3 - Unique features of endoscopy in cats vs dogs

- Small diameter of gastrointestinal tract
- Short length of GI tract
- Transverse folds in caudal esophagus
- Visible submucosal esophageal blood vessels
- Ease of achieving gastric over-distention
- Acute angle of gastric antrum
- Single duodenal papilla
- Jejunum often accessible
- Fewer rectal mucosal folds
- Short cecum with cecocolic sphincter usually open

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References
Acute Pancreatitis in Dogs:
An Update
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Acute vomiting – diagnostic approach

The first step in the approach to the acutely vomiting dog is to determine that vomiting and not regurgitation is present. Vomiting is associated with signs of nausea (depression, salivation, and frequent swallowing,) that is followed by abdominal contractions prior to the expulsion of material. Regurgitation is associated with esophageal disorders and occurs passively, usually associated with increased intrathoracic pressure that may be caused by excitement, activity, or changes in body position.

Once you have determined the dog is vomiting rather than regurgitating, the next step is to determine if a self-limiting or life threatening problem is present. This assessment is crucial and must be based on a thorough history, careful physical examination, clinical experience and judgment, and a sound understanding of the differential diagnosis of acute vomiting. Dogs with acute pancreatitis can present with both types of vomiting. Animals should be considered to have a potential life-threatening problem if some of the following are present: Moderate or severe abdominal pain, lethargy, dehydration or pyrexia, enlarged distended bowel, frequent and severe diarrhea, hematemesis, frequent vomiting or increasing frequency of vomiting, signs of systemic disease, or puppies with an incomplete vaccination history. If a clear distinction cannot be reached, it is better to error on the cautious side and consider a potential life-threatening problem.

Dogs with a self-limiting problem require minimal diagnostic testing and symptomatic treatment, and often cease vomiting within 12-24 hours of initial presentation. A minimum data base for animals with self-limiting vomiting should include determination of packed cell volume and total solids, zinc sulfate fecal flotation, and digital rectal examination. Some common causes include acute gastritis or enteritis, dietary indiscretion, drug administration, toxin ingestion, foreign body ingestion, parasites, and coronavirus. Reclassification to life-threatening status may be indicated if an animal initially assessed as having self-limiting acute vomiting continues to vomit despite appropriate symptomatic therapy.

Life-threatening cases of acute vomiting require an in-depth diagnostic evaluation, vigorous symptomatic management, and often specific therapy directed at the underlying cause. The initial minimum data base for life-threatening acute vomiting includes a complete blood count, biochemical profile with amylase and lipase, urinalysis, zinc sulfate fecal flotation, and survey abdominal radiographs. After the initial evaluation, additional diagnostic studies may be indicated in some instances, such as upper GI endoscopy, upper GI barium series, abdominal ultrasonography, ACTH response testing, or surgical exploration of the abdomen. Some common causes include acute gastritis, dietary indiscretion, hookworms, foreign body obstruction, intussusception, parvovirus, distemper, HGE, acute renal failure, acute liver failure, hypoadrenalcorticism, diabetes mellitus, and pyometra.

Acute pancreatitis

Acute pancreatitis commonly occurs in the middle-aged, obese female dog. Clinical signs include vomiting, diarrhea, abdominal pain, and fever. Historical association may be made with ingestion of a fatty meal or corticosteroid administration. Acute pancreatitis rapidly leads to severe dehydration (dry mucous membranes, loss of skin turgor, prolonged capillary refill time, or enophthalmos) and may progress to hypovolemic shock (tachycardia and weak peripheral pulses). In a recent necropsy study, 64% had pancreatic inflammation, many with chronic changes. Most of these dogs had another primary necropsy diagnosis, suggesting that chronic subclinical inflammation with lymphocytes may be an age related change. These findings question the utility of pancreatic biopsy as a gold standard for diagnosis.

The pathogenesis of AP is complex. It is a self-perpetuating auto-digestive process. As auto-digestion of the pancreas occurs, potent digestive enzymes are released into the parenchyma of the pancreas, blood vessels, and to the adjacent abdominal cavity. This causes severe hemodynamic alterations, localized inflammation, and can trigger disseminated intravascular coagulation. Depletion of circulating and tissue anti-proteases occurs. Vascular collapse develops due to a combination of the following: fluid loss from vomiting and diarrhea, release of vasoactive substances, release of cardiodepressant substances, or fluid sequestration within the abdominal cavity. Progression of the disorder may depend on preservation of pancreatic microcirculation, which can be maintained by fluid therapy.

Cases of AP can have inconsistent laboratory parameters. Diagnosis should not be based on any single test. Common changes include: leukocytosis with a left shift, elevated hematocrit, total protein, and prerenal azotemia (dehydration), elevated ALT and ALP, hypercholesterolemia, hyperglycemia, hypocalcemia, and lipemia. Classically, serum amylase, lipase, and trypsin-like immunoreactivity (TLI) should be elevated. However, elevations are not definitive for pancreatitis as amylase is contained in many tissues and lipase has recently been identified in the stomach. Amylase, lipase, and TLI depend on the kidney for elimination, thus prerenal azotemia due to dehydration from any cause of vomiting results in mild elevations. Some cases of AP have normal or only
slightly elevated serum amylase, lipase, and TLI. In experimental AP, serum trypsin-like immunoreactivity (TLI) increases prior to amylase and lipase. Based on preliminary results, a new serum test is showing promise in diagnosing pancreatitis in dogs. The test, serum canine pancreatic lipase immunoreactivity (cPLI), was developed by Texas A&M researchers and immunologically measures lipase from the pancreas. The test showed a sensitivity of 82% in the diagnosis of acute pancreatitis; these results are from a low number of cases (11), but are promising. A modification of this test using a monoclonal antibody and a recombinant antigen for calibration has been marketed by IDEXX as the Spec cPL. This test compares favorably with the cPLI and because of plate stability can be run daily with results rapidly reported. In a recent study of necropsied dogs with macroscopic evidence of pancreatitis the cPLI and SPEC cPL correlated and their overall sensitivity was 64%. IDEXX has also developed an in-house screening test (SNAP cPL) that has been shown to correlate with the Spec cPL. More data are needed, but these tests may be the most accurate serum tests for diagnosing acute pancreatitis in dogs.

Radiographic signs of AP are nonspecific and don't often contribute to diagnosis except by eliminating the presence of intestinal obstruction. Ultrasonographic evaluation of the abdomen can be very helpful and may identify a pancreatic mass or an enlarged hypoechoic pancreas that may surrounded by a hyperechoic rim. Pancreatic abscesses and cysts can also be identified.

**Treatment**

The therapeutic plan should prevent pancreatic secretion and manage hypovolemia while supporting pancreatic circulation. In severe cases, the dog should be maintained NPO and vigorous fluid therapy administered. Lactated ringers is an appropriate fluid to use at a volume necessary to correct dehydration, provide maintenance (44-66 ml/kg/day), and to replace losses due to vomiting and diarrhea. Potassium supplementation, 20 mEq/l KCl, is necessary to replace losses in diarrhea, vomitus, and urine and supplement the lack of food intake. Potassium supplementation should be based on measurement of serum potassium levels. Plasma transfusion (6-12 ml/kg) has been recommended to provide a fresh source of protease inhibitors. Mildly affected dogs may be held NPO and given fluids subcutaneously until the vomiting ceases for 12 hours. Vigorous pain control should be utilized, as pain may be one trigger for continued vomiting. Enteral nutrition should be administered as soon as reasonably possible.

Treatment should continue until parameters used to make a diagnosis return to normal, often 3-5 days in moderately affected dogs. Gradual oral alimentation can be initiated. Initially, ice cubes or small amounts of water are frequently offered. If vomiting does not occur, small amounts of a bland diet can be frequently offered. This diet should be soft and low in fiber, highly digestible, high in carbohydrates, low in fat, and low in protein. Boiled rice, rice with chicken, low fat cottage cheese, or prescription diets such as i/d® (Hills Pet Products), EN® (Ralston Purina), or Low Residue (Iams) are effective. The size of the meals should be slowly increased and the frequency of feeding decreased if vomiting does not recur. If the dog does not vomit for 3 days, the normal diet can be slowly added. Low fat diets have been recommended to prevent relapse.

If vomiting is severe, antiemetics can be used. Usually maropitant 1mg/kg q 24h is used. However, a phenothiazine, chlorpromazine 0.5 mg/kg q 4-6h, or metoclopramide, 0.2-0.4 mg/kg q 8h can be used. Because phenothiazines cause vasodilation they cannot be started until the dog has been rehydrated. Metoclopramide is contraindicated in cases with GI obstruction so obstruction should be eliminated prior to its use. If prolonged fluid therapy is necessary (7-10 days) total parenteral nutrition should be considered.

The prognosis for cases of AP is variable. Self-limiting cases respond to minimal therapy. Life-threatening cases warrant a guarded prognosis. Response to therapy in 3-5 days is a favorable prognostic sign. Dogs requiring intensive therapy for longer than 7 days carry a guarded prognosis. Because the etiology is unclear, recurrent bouts can occur.

Because the diagnosis of AP is difficult to prove, a thorough evaluation of other causes of acute vomiting, acute diarrhea, and abdominal pain should be performed. Classic findings of AP include: 1) acute vomiting, 2) cranial abdominal pain, 3) pyrexia, 4) leukocytosis with a left shift, 5) elevated serum amylase, lipase, cPLI, and SNAP cPLI and 6) ultrasonographic findings of an enlarged hypoechoic pancreas. Supportive findings include: 1) signalment 2) recent fatty meal, 3)corticosteroid administration, 4) lipemia, 5) hypocalcemia, 6) elevated ALT, ALP, and bilirubin, and 7) hypercholesterolemia.

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Chronic Vomiting in Dogs and Cats: The Roles of Ultrasonography in Diagnosis and Helicobacter in Treatment

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Chronic vomiting (intermittently or continuously for at least 7 days) in dogs and cats is a common and frustrating problem for clients and veterinarians. Because many diseases cause chronic vomiting, a thorough evaluation must be performed to arrive at an accurate diagnosis. Definitive diagnosis of many diseases requires mucosal biopsy. In the past, exploratory celiotomy was necessary to obtain biopsy specimens. However, the increased availability of flexible fiberoptic endoscopy in veterinary medicine has allowed less invasive tissue biopsy.

The first step in the approach to the chronically vomiting patient is to determine that vomiting and not regurgitation is present. Vomiting is associated with signs of nausea (depression, salivation, frequent swallowing, and vocalization in some cats) that is followed by abdominal contractions prior to the expulsion of material. Regurgitation is associated with esophageal disorders and occurs passively, usually associated with increased intrathoracic pressure that may be caused by excitement, activity, or changes in body position.

Once you have determined vomiting is present the history and physical examination can contain many clues to the etiology. A thorough dietary history should be obtained. In some cases, correcting dietary indiscretion or instituting a highly digestible diet for 3-4 weeks will resolve the vomiting. Dietary indiscretion can be due to a recent diet change, feeding of table scraps, free-roaming behavior allowing ingestion of garbage, ingestion of foreign objects, exposure to toxins (including house plants), excessive ingestion of hair, or feeding a low quality poorly digestible diet. The history may identify the use of drugs, such as NSAIDs, that can cause vomiting due to gastritis or ulceration. The presence of diarrhea or signs of systemic disease may help to rank the rule-out list.

Physical examination may be normal or only demonstrate signs of weight loss. An abdominal mass or dilated loop of small bowel may be identified as a cause of high partial small bowel obstruction. If vomiting has recently become more frequent, signs of dehydration may be present (delayed capillary refill time, enophthalmos, decreased skin turgor, tachycardia, pale mucous membranes, and cold extremities). Signs suggesting systemic disease include: polyuria / polydipsia, polyphagia, hepatomegaly, cataract formation, icterus, encephalopathy, ascites, pyrexia, bradycardia, tachycardia, small irregular kidneys, oral ulceration, pale mucous membranes, splenomegaly, or an abdominal mass.

Table 1 lists some causes of chronic vomiting in dogs and cats. Systemic diseases can usually be ruled out by a thorough history, careful physical examination and routine laboratory tests (complete blood count, biochemical profile, urinalysis, amylase, lipase, and cPLI, heartworm antibody test, and T4). Correction of dietary indiscretion or a 3-4 week trial with a highly digestible diet should be performed before more invasive testing. Gastrointestinal causes of chronic vomiting may involve either the stomach or orad small intestine. An efficient plan to evaluate gastrointestinal causes includes fecal examination for parasites, survey abdominal radiography, and endoscopic examination with mucosal biopsy. If endoscopy is not available, a barium contrast upper GI series and exploratory laparotomy can be used (Table 2). Although helpful in some cases, the diagnostic utility of abdominal ultrasound has not yet been fully determined. Abnormalities that can be detected include thickened stomach or small bowel, gastric, small bowel or pancreatic masses, enlarged regional lymph nodes, enlarged hypoechoic pancreas, dilated small bowel, abnormal gastric or small bowel motility, or evidence of an intraluminal foreign body.

Survey abdominal radiographs rarely establish a cause for chronic vomiting (unless a radiodense foreign body is seen) and a barium upper GI series is usually indicated. Advantages of contrast radiography versus endoscopy and laparotomy include the following: 1) available in all practices, 2) noninvasive, 3) does not require general anesthesia, 4) always visualizes the duodenum, 5) evaluates gastric size and position, 6) provides a qualitative description of gastric motility and emptying of liquids, and 7) detects extraluminal and submucosal / muscular masses. A barium series is time consuming to perform, costly to the client, and is a source of radiation exposure to the hospital staff. If lesions are identified, tissue biopsy is needed to confirm a diagnosis. If a foreign body is detected, it must be removed via endoscopy or exploratory laparotomy. The upper GI series is insensitive for mucosal lesions.

Abdominal ultrasonography has recently been added to the diagnostic plan for many dogs and cats with chronic vomiting or chronic diarrhea. Ultrasound has been shown to be very helpful in animals with a mass lesion, especially neoplasia. An ultrasound guided fine needle aspirate or tru-cut biopsy can be performed. Ultrasound has also been shown to helpful in cases with chronic pancreatitis. Other advantages of ultrasound include: being noninvasive, imaging of the liver and biliary system, imaging of the small and large bowel and mesenteric lymph nodes, and assessment of the layers of the GI tract and its motility. Disadvantages include the need for expensive equipment and specialized training, interference by gas within the GI tract, and difficulty in imaging the pancreas.

A recent study has been performed in which the diagnostic utility of abdominal ultrasound in dogs with chronic vomiting has been evaluated. A single radiologist performed each abdominal ultrasound. Two interns, who did not directly participate in case
management, reviewed each medical record. In each case, the contribution the ultrasound made towards the final diagnosis was assessed and scored from 1-5, based on the following scale:

1. Diagnosis was obtained via ultrasonography (including ultrasound-guided aspirate or biopsy). Additional biopsy via endoscopy or exploratory celiotomy was not necessary.
2. Ultrasonography provided data that suggested endoscopy was not indicated and exploratory celiotomy should be performed to obtain a diagnosis. Ultrasonography suggested how to obtain a tissue biopsy, making it very important for diagnosis.
3. Ultrasonography provided important diagnostic information that helped assess other data, including endoscopic findings. Ultrasonography was important in arriving at a diagnosis.
4. Ultrasonography provided descriptive information that did not affect assessment of other data obtained via endoscopy or exploratory celiotomy. The same diagnosis would have been reached without performing ultrasonography.
5. Ultrasonography provided conflicting information that did not support, or may have hindered obtaining the final diagnosis.

In the group of dogs with chronic vomiting, the following factors were associated with a higher diagnostic utility of abdominal ultrasound: presence of weight loss, higher percentage of body weight lost, increasing age, increasing duration of vomiting, an increased frequency of vomiting/week, and a final diagnosis of GI lymphoma or gastric adenocarcinoma. Based on diagnostic utility scores, abdominal ultrasonography was vital or beneficial to obtaining a diagnosis in 22.5% of cases, not helpful in 68.5%, and of marginal value in 9%. Considering all contributions to case management (including factors unrelated to the vomiting problem), abdominal ultrasound was considered helpful in 27% of dogs with chronic vomiting.

Exploratory celiotomy can be performed in veterinary hospitals and allows visual inspection of serosal surfaces, palpation of the stomach and small intestine, and limited mucosal visualization. It also allows for exploration and biopsy of the pancreas, mesenteric lymph nodes, and the entire small and large intestines. Directed large full-thickness biopsies can be obtained from the stomach and small intestine. Definitive treatment for some conditions (foreign bodies and tumors) can be accomplished. A duodenal aspirate for Giardia can be collected. Disadvantages include the need for general anesthesia, the surgical risk to the patient, post-operative morbidity and the risk for complications, and expense to the client.

Endoscopic examination lacks some of the disadvantages of the upper GI series and exploratory laparotomy. Advantages include the following: 1) visual mucosal inspection of the entire stomach and some of the duodenum, 2) directed tissue biopsy, 3) few false-negative procedures (related to the endoscopist's skill), 4) less invasive than laparotomy, 5) quick to perform, 6) the ability to remove foreign bodies, 7) assessment of the feasibility of surgical resection of tumors, and 8) ability to obtain a duodenal aspiration sample for Giardia. Disadvantages include the cost of equipment, the clinical skills necessary to perform endoscopy, the small size of biopsy samples, biopsy of mucosa only, the inability to resect masses, failure to enter the duodenum, evaluation of the orad small bowel only, and the necessity of general anesthesia. Because of the usefulness of endoscopy in cases with chronic vomiting, the author routinely performs endoscopy (and reaches a diagnosis) instead of performing a barium upper GI series or exploratory laparotomy.

Thorough endoscopic examination of the stomach and duodenum of the dog and cat can be performed with a flexible fiberoptic gastroscope with an outside tip diameter of <10 mm or less. Four-way control of the tip of the endoscope is necessary. Biopsy channels of 2.8 mm in diameter or greater will provide adequate biopsy samples for histologic evaluation and accept a wide range of foreign body forceps.

The endoscopic examination is performed after an overnight fast with the animal under general anesthesia and placed in left lateral recumbency. The endoscope should only be advanced if the gastrointestinal lumen is clearly visible, reducing the possibility of tissue perforation. The endoscope is passed through the lower esophageal sphincter into the cardiac region of the stomach. Initial assessment of the rugal folds should be made before insufflation and gastric distention. Gastric mucosa appears pinker than esophageal mucosa. It is smooth, glistening, and tough. The endoscope is advanced along the greater curvature until the angularis incisura is located. Deflection of the endoscope tip towards the antrum (control knob down) will allow visualization of the antral and pyloric region. Movement of the tip towards the cardia (control knob up) will provide a retroflexed view of the gastric body, fundus and cardia. To enter the duodenum, the scope should be advanced towards the pylorus and gently pushed through. If difficulty is encountered, rolling the animal into dorsal recumbency may allow successful passage. The duodenal mucosa has a more granular appearance than the stomach and is slightly paler. A duodenal aspirate for Giardia should be performed.

If abnormalities are found, multiple biopsies of lesions should be taken. If gross abnormalities are not present, biopsies of standard regions should be obtained (cardia, greater curvature, angularis incisura, antrum, pylorus, and duodenum). A biopsy sample should be placed in a rapid urease test to detect the presence of Helicobacter spp. Multiple samples can be placed into the test media, although the author routinely places a single biopsy from the angularis into a CLO test (Tri-Med Specialties Inc. 9531 Arden, Lenexa, KS 66215, 800 874 6331). Foreign bodies can be removed with grasping forceps. In addition, brush cytology of lesions may allow rapid diagnosis.

By following the diagnostic plan outlined above, most cases with chronic vomiting can be efficiently diagnosed, allowing for development of an appropriate therapeutic plan. Systemic diseases should be thoroughly evaluated before more invasive and expensive tests are performed. Correction of dietary indiscretion or institution of a highly digestible diet may eliminate clinical signs.
The use of endoscopy allows a less invasive, more efficient and accurate diagnosis of gastrointestinal causes of chronic vomiting to be reached. Serious complications such as perforation of the stomach are very uncommon and can be avoided with careful endoscopic technique.

**Helicobacter gastritis in dogs**

*Helicobacter pylori* infection is the most common cause of chronic gastritis and peptic ulceration in humans. It is also associated with an increased risk of gastric lymphoma and adenocarcinoma. Spiral bacteria were described in 1896 in humans and several animal species. They were “rediscovered” in 1983 when they were reported to cause of peptic ulceration in humans. *Helicobacter pylori* is a microaerophilic curved spiral gram negative organism with 4 flagella. The bacterium lives in gastric mucus, can attach to epithelial cells, and may penetrate intercellular junctions. High bacterial urease concentration cleaves urea to produce ammonia, which helps to neutralize the acid environment surrounding the bacterium. The immune system does not result in removal of the organisms; without treatment infection is life-long. Some studies have shown as many as 90% of people are infected with *H. pylori*. Luckily, most infections are not associated with clinical signs. Diagnosis can be made with serology, cytology of gastric mucus, culture of biopsies, histopathology of biopsies with H&E or silver stains, C-13 or C-14 labeled urea breath tests, or rapid urease tests. Many treatments have been studied, but the gold standard to which they are all compared to is omeprazole, ampicillin or tetracycline, metronidazole, and bismuth for 2 weeks.

Many species of spiral bacteria have been identified in dogs and cats: *H. felis, H. pylori, and H. Heilmannii* (formerly called *Gastrospirillum hominis*), *H. Salomonis*, and *H. bizzozeronii* are the most common. Experimentally, infection has been established in both dogs and cats and lymphoid follicular gastritis developed. However, in these experimental studies, clinical signs were absent or very mild. Several surveys of laboratory, shelter, and pet populations (with and without GI signs) have shown a very high prevalence rate in dogs and cats, nearing 100% in some studies. Peptic ulceration is very rare in dogs and cats, demonstrating the pathophysiologic difference between *H. pylori* and the spiral bacteria commonly found in dogs and cats. Little is known about the effects of treatment of dogs and cats with chronic vomiting and *Helicobacter spp.* infection. At the present time there are many unanswered questions regarding *Helicobacter in dogs and cats.* Some questions include: 1) What is the relationship between *Helicobacter* and dogs and cats with chronic gastritis and vomiting? 2) What is the optimal treatment to eradicate the organism? 3) After treatment, is reinfection or recrudescence a common occurrence in dogs and cats? 4) What factors can help predict if a dog or cat with chronic gastritis and *Helicobacter* would benefit from treatment for *Helicobacter?* 5) Does *Helicobacter* have a role in other diseases such as gastric cancer and inflammatory bowel disease?

Because of the potential pathophysiologic relationship between *Helicobacter spp.* in dogs and cats and chronic gastritis and vomiting, the author has treated clinical cases for *Helicobacter*. In some cases, treatment has resulted in resolution or improvement in clinical signs. Until additional studies about *Helicobacter* in dogs and cats are available, it seems prudent to at least determine if spiral bacteria are present in dogs and cats with chronic vomiting, during gastroscopic examination or exploratory celiotomy. Spiral bacteria can be identified in gastric biopsy or brush cytology specimens, or indirectly identified by rapid urease testing of gastric mucosal samples. Obtaining results from histologic evaluation of biopsy samples requires 24-72 hours. Results of rapid urease tests and gastric brush cytology are available much sooner.

I have completed a clinical study comparing 2 treatments for *Helicobacter* in dogs. Dogs with chronic vomiting for at least 2 weeks, with *Helicobacter spp.* identified in gastric biopsy samples and gastritis, with or without inflammatory bowel disease, were entered into the study. The diagnostic workup included a CBC, biochemical profile, UA, fecal examination, abdominal ultrasonography, gastroduodenoscopy with mucosal biopsy, gastric cytology, and CLO test. Dogs with systemic diseases, gastric foreign bodies, gastric / duodenal neoplasia, pyloric hypertrophy, or *Physaloptera* infection were not eligible for the study. Dogs were randomly assigned to receive either triple therapy (amoxicillin 15 mg/kg, metronidazole 10 mg/kg, and Pepto Bismol tablets [(<5 kg; 0.25 tablet, 5-9.9 kg; 0.5 tablet, 10-24.9 kg; 1.0 tablet, and >25 kg; 2.0 tablets]) or quadruple therapy (triple therapy plus famotidine 0.5 mg/kg). All drugs were given BID for 2 weeks. Owners kept a daily diary of clinical signs and endoscopy was repeated 4 weeks and 6 months after treatment was completed. Results of the study have not yet been published but have been reported in abstract form. Six months after completing either therapy, approximately 40% of dogs had gastric biopsy specimens that were negative for *Helicobacter*. There was no difference between the 2 treatments in the percentage of dogs that remained negative. Both treatments reduced the frequency of vomiting by approximately 85%. Dogs that were negative for *Helicobacter* had a greater reduction in vomiting frequency than those that were positive and almost 80% of this group had at least a 90% reduction in vomiting frequency.

Because of the high rate of treatment failure in this study after 6 months, I have been investigating the use of clarithromycin based protocols; clarithromycin (7.5 mg/kg BID), in combination with amoxicillin (15 mg/kg BID) or omeprazole (0.7 mg/kg SID). Unfortunately, preliminary data 4 weeks and 6 months after completion of therapy appears to be similar to triple or quadruple therapy. Overall reduction in vomiting was about 80%, but only about 40% of dogs negative for *Helicobacter* had at least a 90% reduction in vomiting frequency. Additionally a recent study treated a small number of dogs and cats for 3 weeks using triple therapy. Eradication results were encouraging.
It will take many controlled clinical studies before we can understand the potential role of *Helicobacter* in dogs and cats with chronic gastritis, and can answer many of the questions I have proposed. Although treatment of *Helicobacter* offers another, and very different, therapeutic route for animals with chronic gastritis, we must remember that a direct cause and effect relationship between *Helicobacter* and chronic gastritis has not yet been established in dogs or cats. Failure of a patient to rapidly respond to antimicrobial treatment suggests that something besides *Helicobacter* is causing the chronic gastritis and vomiting. Presently, based on current evidence, I recommend 3 weeks of therapy with clarithromycin, amoxicillin, and omeprazole.

**Table 1 - Some causes of chronic vomiting**

**Systemic**
- Diabetes mellitus
- Chronic renal failure
- Hepatobiliary diseases
- Chronic pancreatitis
- Feline hyperthyroidism
- Hypoadrenocorticism
- Lead poisoning
- Feline heartworm disease
- Systemic mastocytosis
- Drug therapy: NSAID

**Gastrointestinal - stomach**
- Chronic gastritis
  - Dietary indiscretion
  - Hair-induced
  - Plasmacytic lymphocytic
  - Eosinophilic
  - *Helicobacter*
- Foreign body
- Ulcer
- Neoplasia
- Pyloric hypertrophy
- *Physaloptera*
- Gastric motility disorder

**Gastrointestinal - small intestine**
- Inflammatory bowel disease
  - Plasmacytic-lymphocytic
  - Eosinophilic
- Partial obstruction-stagnant loop syndrome
  - Neoplasia
  - Foreign body
  - Intussusception
  - Extra-luminal obstruction
- Diffuse mucosal lymphosarcoma
- Histoplasmosis
- Ulcer
Table 2: Comparison of diagnostic modalities

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Chronic vomiting case 1

Signalment

Himalayan, 3.5 years, NM

History
- Chronic intermittent vomiting for 1 year
- Food followed by mucus
- Several hours after eating
- Frequency: 2 x / week, progressed to once every day
- Vomiting associated with abdominal contractions and retching
- No weight loss, good appetite, no diarrhea
- Diet: c/d and table scraps

Physical examination
Normal

Regurgitation or vomiting (circle one)

Differential diagnosis
- Systemic Heartworm disease
- Liver diseases
- Hyperthyroidism
- GI - Dietary indiscretion
- Hair-induced gastritis / duodenitis
- Chronic gastritis
- IBD
- Gastric foreign body

Diagnostic plan
- CBC, biochemical profile, UA, heartworm antibody, T4, fecal
- +/- abdominal radiograph
- +/- abdominal ultrasound
- Endoscopy
- Upper GI barium series
- Exploratory laparotomy

Diagnostic results/diagnosis
- MDB - normal
- HW antibody - neg
- T4 - 2.4 (1-2.5)
- Fecal - neg x2, large amount of hair
- Endoscopy - granular / friable duodenum, duodenal aspirate neg for *Giardia*, CLO – neg
- Histopathology - normal stomach, mild IBD in SI

Diagnosis
- Dietary indiscretion?
- Hair-induced gastritis / duodenitis?
- IBD?

Therapy
- Hypoallergenic diet - d/d, frequent grooming, no table scraps
- FU 4 weeks - rare vomiting, challenge with c/d - no vomiting
• FU 1.5 yrs - vomiting associated with table scraps

Chronic vomiting case 2

Signalment
6 year old, MN, Shetland sheepdog

History
• Vomiting 1x / q48H for 2 years
• Yellow foam, twigs
• Vomiting associated with abdominal contractions
• Normal appetite, no diarrhea
• Present diet: Purina EN, fruits and vegetables
• HW: Filarabits plus

Physical examination
Normal

Regurgitation or vomiting (circle one)

Differential diagnosis
• Systemic  No likely rule outs
• GI  Dietary indiscretion
• Chronic gastritis
• Inflammatory bowel disease
• Physaloptera
• Gastric foreign body

Diagnostic plan
• CBC, biochemical profile, UA (anesthesia workup)
• Fecal
• +/- abdominal ultrasound
• +/- abdominal radiograph
• Endoscopy
• +/- upper GI barium series
• exploratory laparotomy

Diagnostic results/diagnosis
• CBC, biochemical profile, UA - normal
• Endoscopy - mucosal follicles, superficial erosions, granular duodenum, CLO pos
• Histopathology - gastritis, IBD, spiral bacteria

Therapy
• Triple therapy- amoxicillin, metronidazole, Pepto Bismol BID x 14 days
• Continue EN, avoid table food
• FU 6 weeks - vomited 3x, normal endoscopy, normal histopathology, CLO neg, silver stain neg
• FU 6 months - Vomited 4 times, added fruits, cheese, dog treats, and hot dog!
• Endoscopy - stomach contained grass and bird seed, CLO neg, histopathology normal

References


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Icterus in Dogs and Cats: A Practical Diagnostic Approach
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Blacksburg, VA

Icterus, or jaundice, is defined as yellowish discoloration of the serum, skin, and mucous membranes. It is caused by excessive amounts of bilirubin, which occurs when the rate of production exceeds the rate of elimination. Bilirubin is a waste product of red blood cell metabolism without benefit to the body, but has major diagnostic implications in disease. Serum bilirubin must be approximately 2.5-3.0 mg/dl or greater to produce clinically detectable icterus.

Pathophysiology
Bilirubin is a waste product of red blood cell metabolism that has important diagnostic implications in animals with hepatobiliary diseases. Most bilirubin is derived from the normal breakdown process of hemoglobin from senescent RBCs. Hemoglobin is phagocytosed by the reticuloendothelial system and converted into bilirubin. It is bound to albumin and transported to the liver, where it is taken up by the hepatocyte, conjugated with glucuronic acid, and secreted into bile canaliculi by active transport, which is the rate limiting step. Bile is stored within the gallbladder until feeding, when it enters the duodenum. Bacterial metabolism occurs in the small intestine producing several urobilins. One of these, urobilinogen, is reabsorbed within the small intestine, but most of it is removed from the portal blood by the liver and excreted back into bile. Urobilinogen which remains in circulation is removed by the kidney. In dogs, the renal tubules can convert hemoglobin to bilirubin, conjugate it, and excrete it into the urine. Urobilinogen remaining within the bowel may be passed in the feces or metabolized to stercobilins which impart color to the feces. Cats differ from dogs in that their renal threshold is considerably higher, and bilirubinuria does not occur in normal cats.

Elevated serum bilirubin is commonly found in hemolytic diseases, intrahepatic or extrahepatic cholestasis, or less commonly due to rupture of the biliary system, which is usually associated with trauma. The liver has a tremendous ability to metabolize excessive bilirubin, thus prehepatic, or hemolytic icterus, only results when moderate or severe red blood cell destruction is present. In general, higher levels are found in cases with extrahepatic cholestasis vs. intrahepatic cholestasis. However, it is possible to have normal serum bilirubin in a variety of hepatobiliary disorders. In cholestatic disorders, elevated serum AP occurs prior to any changes in bilirubin metabolism in both dogs and cats. As the cholestatic process progresses, bilirubinuria precedes hyperbilirubinemia in dogs, but hyperbilirubinemia precedes bilirubinuria in cats due to their higher renal threshold. Icteric plasma can usually be detected when bilirubin reaches 1.5-2.0 mg/dl. Serum bilirubin level must be >2.5-3.0 mg/dl to detect clinical icterus. Although it is possible to measure conjugated levels (as thus determine unconjugated levels) with the Van den Bergh test, the author has found little clinical significance for utilizing this test.

Obstruction of bile flow within the liver or during its extrahepatic transport, results in regurgitation of conjugated bilirubin from hepatocytes back into the sinusoids and into systemic circulation. Hepatocellular swelling, inflammation, necrosis, or fibrosis, especially in the perportal area, can obstruct bile flow. Hepatocyte dysfunction may interfere with the uptake, conjugation, or excretion of bilirubin and cause icterus. Thus, most hepatic disorders can cause intrahepatic icterus.

Several surveys of icteric cats have shown that the most common causes of icterus include: lipidosis, cholangitis, feline infectious peritonitis, toxic hepatopathy, hepatic neoplasia, sepsis, and hemolytic anemia. Post-hepatic disorders that obstruct bile flow occur more commonly in dogs than cats; examples include: gallbladder mucocoele, cholecystitis, cholelithiasis, pancreatitis, biliary carcinoma, pancreatic adenocarcinoma, and duodenal neoplasia. Trauma to the biliary system (gallbladder, common bile duct, cystic duct, or intrahepatic bile ducts) can result in leakage of bile into the abdomen, bile peritonitis, resorption of the bilirubin into plasma, and icterus.

Bile retained within the liver is toxic and leads to hepatocellular degeneration. Thus, prolonged extrahepatic cholestasis can lead to hepatic disease and complicate the distinction between hepatic and post-hepatic icterus.

Clinical signs
Owners may notice icterus or it may be identified during physical examination. It is easiest to detect icterus in the sclera, conjunctiva, gingiva, hard palate, vulva or penis. It is more difficult to detect discoloration of the skin, but it can be noticed on the inside surfaces of the ears or on the caudoventral abdomen. The history may reveal exposure to potentially hepatotoxic drugs or chemicals. Abdominal trauma, often 5-10 days previously, may have occurred and resulted in leakage of bile.

Other clinical signs are dependent on the cause of icterus. Prehepatic, or hemolytic cases, are often weak, lethargic, and tachypneic, and may have dark discolored urine, a systolic heart murmur, not previously detected, or hepatosplenomegaly. Animals with hepatic or post-hepatic disorders may have some of the following signs: anorexia, weight loss, pyrexia, vomiting, diarrhea, abdominal distention, encephalopathy, polyuria / polydipsia, or bruising or bleeding tendencies. Abdominal distention due to hepatomegaly or ascites or cranial abdominal pain may be detected during physical examination.

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Diagnostic plan
The most important initial diagnostic step with the icteric patient is to evaluate the hematocrit to determine if prehepatic, or hemolytic icterus, is present. Moderate or severe anemia with a normal total protein suggests hemolysis. The presence of hemolysis is also supported by hemoglobinuria or autoagglutination, although neither must be present. Further evaluation of hemolysis should include a review of red blood cell morphology for spherocytosis, hemoproteozoa, determination of the reticulocyte count, a Coombs test, and a FeLV ELISA test in cats.

If the hematocrit is normal or if mild anemia is present, the icterus is due to either hepatic or post-hepatic causes. The distinction between hepatic and post-hepatic disease is very important because hepatic disease can be diagnosed with a minimally invasive liver biopsy (often with the assistance of ultrasonography), while post-hepatic disorders often need more invasive exploratory surgery to diagnose and potentially relieve the obstruction. To obtain a liver biopsy via exploratory celiotomy, when less invasive methods are available, is not in the animal's best interests. The best method to distinguish hepatic from post-hepatic disorders is abdominal ultrasonography. Post hepatic disorders are associated with a distended gall bladder, and enlarged and tortuous cystic, bile, or intrahepatic bile ducts. A potentially neoplastic mass of the biliary system or pancreas, signs of pancreatitis (an enlarged hypoechoic pancreas with a hyperechoic rim and potentially plication of the duodenum), gallbladder mucocoele (immobile bile with fine striations) an echogenic choledolith, or a thickened gallbladder wall may be found. With intrahepatic disorders the liver may be enlarged and diffusely hyper or hypoechoic or contain focal or multifocal abnormalities.

Without ultrasonographic assistance the distinction between hepatic and post-hepatic disorders is much more difficult. If the animal is relatively bright and alert, post-hepatic disease is more likely present. Elevated resting or post-tolerance serum ammonia levels support hepatic disease. A serum AP increased 3 or more times more than an elevated serum ALT suggests post-hepatic cholestasis. Finally, very high serum bilirubin levels (>10-15 mg/dl) are most often associated with post-hepatic disorders. Finally, hypoalbuminemia and a low BUN support hepatic icteris. None of these criteria are absolutely reliable, but they do provide some assistance in making the decision to perform closed liver biopsy vs. exploratory surgery.

The complete diagnostic evaluation of a case of hepatic icterus should include a CBC, biochemical profile, urinalysis, FeLV / FIV ELISA in cats, abdominocentesis and fluid analysis (if ascites is suspected), coagulation profile, hepatic ultrasound, and a liver biopsy utilizing the least invasive method available. If examination of the ascitic fluid suggests bile peritonitis, diagnosis and treatment requires exploratory celiotomy. The pivotal step in evaluation of a suspected case of post-hepatic disease is ultrasonography. A laboratory minimum data base should be collected to evaluate concurrent disease as well as the metabolic effects of the primary disorder. Additional diagnostic tests depend on sonographic findings but may include thoracic radiographs to look for metastasis, and exploratory celiotomy for definitive diagnosis and relief of the obstructing process.

Icterus case 1
Signalment
Welch corgi, MN, 8 year old

History
- Icterus
  - Acute hemorrhagic diarrhea RX with metronidazole 500 mg BIDx7
  - Diarrhea returned and RX again
  - Anorexia on day 8, icterus day 11
  - RX IV fluids and enrofloxacin
  - Previous HX – acute pancreatitis 3 months ago, increased water consumption since then 2x
  - Vaccinations current, monthly milbemycin

Physical examination
Icterus
Trifurcate icterus
- Prehepatic – hemolytic
- Hepatic
- Posthepatic

Initial diagnostic plan
- PCV – rule out hemolysis
- CBC, biochemical profile, UA
- Abdominal ultrasound
Diagnostic results

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<td>Urine bilirubin</td>
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</table>

Abdominal ultrasound – liver slightly small, normal hepatic parenchyma, normal gall bladder and biliary system

**Differential diagnosis – hepatic icterus**

- Drug-induced hepatotoxicity
- Chronic hepatitis
- Cholangitis
- Toxic hepatopathy
- Hepatic neoplasia - lymphoma
- Cirrhosis

**Diagnostic plan**

- Coagulogram – PT and PTT
- Parenteral vitamin K
- Liver biopsy

**Diagnostic results**

- PT 7.3, PTT 9.3
- Laparoscopy – yellow liver, swollen rounded edges, lobular surface pattern
- Hepatic culture – negative aerobic / anaerobic
- Histopathology – suppurative hepatitis, lymphoplasmacellular cholangiohepatitis, hepatocyte vacuolation
- Hepatic copper 258 ppm (120-400)

**Therapy**

- Hills K/d
- Cefadroxil – 4 weeks
- Ursodeoxycholic acid 15 mg/kg/day
- SAMe, milk thistle, vitamin E

**Case follow-up**

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- 2 weeks – eating chicken, rice, cottage cheese, more active
- 4 weeks – eating well most days, active, vomits q 2-3 days
  - Prednisone 2 mg/kg/day
- 10 weeks – eating well, active, gaining weight
- 20 weeks – eating well active, gained 3 kg, intermittent diarrhea – resolved following withdrawal of prednisone, continuing ursodeoxycholic acid, SAMe, vitamin E
- 2 years – clinically normal, normal biochemical profile, ursodeoxycholic acid, SAMe, vitamin E discontinued after 7 months

**References**


Dietary Management of Diarrhea

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Dietary management is a vital component of successful treatment of many Gastrointestinal (GI) diseases that cause diarrhea. Some conditions can be managed with diet alone, while others require concurrent medical management. In these cases, dietary management may facilitate the use of lower medication dosages, reducing the potential for side-effects. This seminar will provide an overview of “GI” diets and will briefly review the principles of dietary management of selected diarrheal disorders of the dog and cat.

“GI” diets

The traditional GI diet should be highly digestible, low in fat, low in fiber, and contain high quality nutrients. Some diets are lactose and gluten free, although the necessity of omitting these substances has not been proven. Decreasing fat content often reduces palatability, so many of the commercially available GI diets contain low-moderate fat levels compared to maintenance diets. Although many home-made recipes are available, most veterinarians utilize commercially available diets “GI” diets for client practicality and ease and consistency of treatment. Each of the major prescription pet food companies markets a “GI” diet. These diets adhere to the nutritional profile discussed above and are more similar to each other than different. Each company has components of their diet that they feel make it superior to their competitors, however published results proving benefits of these diets or direct comparisons between these diets in spontaneous canine and feline diseases are lacking.

Hills markets dry and canned i/d which can be fed to puppies and kittens and adult dogs and cats. The diet contains a low level of soy fiber, which has properties of both insoluble and soluble fibers. Nestle Purina markets EN in both dry and canned formulations for dogs and as a pouch for cats. In the canine diet approximately 30% of the fat is supplied as medium chain triglycerides, which are easier to assimilate than long chain triglycerides and are absorbed directly into the portal system. EN can also be fed to puppies. The feline product contains added soluble fiber. Both diets contain a ratio of omega-3 and omega-6 fatty acids which may be beneficial in managing inflammation. The Iam’s product is low-residue, available as a dry formulation for puppies, and dry and canned for adult dogs and cats. These products contain beet pulp fiber, which is insoluble, but highly fermentable. They also contain fructooligosaccharides, which are metabolized by enteric bacteria and promote a healthy gut flora. They also are enhanced with omega-3 fatty acids. Waltham diets are marketed by their recent merger partner Royal Canin. Their low fat diet is available as a dry and canned product which is suitable for puppies and adult dogs. It contains the lowest level of fat of any of the prescription products. Innovative Veterinary Diets markets canine sensitive for adult dogs in a dry and canned formulation and a dry formulation for adult cats. The canine diet contains fructooligosaccharides and is supplemented with amylase, lipase, and protease. The feline product has enhanced levels of omega-3 fatty acids.

Acute vomiting and/or diarrhea

There are many causes of acute vomiting/diarrhea. Most cases are mild and self-limiting and can be easily managed. Dietary indiscretion is a very common cause of acute vomiting and/or diarrhea. For most vomiting cases, withholding food and water (NPO) and maintaining hydration with subcutaneous fluids is important. The animal should be held NPO until vomiting does not occur for 12-24 hours. Initially water should be offered in small amounts. If vomiting does not occur a “GI” diet or a homemade equivalent should be fed in small frequent meals. If vomiting does not occur the amount fed is gradually increased to meet maintenance requirements. The “GI” diet should be fed for 3-5 days after vomiting ceases and the animal’s original diet slowly reintroduced over 3-5 days. Causes of dietary indiscretion should be corrected.

In cases of diarrhea, holding animals NPO is somewhat controversial. I usually without food for 12 hours and then initiate feeding a “GI” as described for acute vomiting. Digestibility of the diet is extremely important when treating diarrhea as malabsorbed nutrients can lead to worsening of diarrhea due to osmotic forces and potentially bacterial overgrowth. In addition, low fat content is important because malabsorbed fats can be acted on by intraluminal bacteria and form hydroxy fatty acids, which can worsen diarrhea by decreasing mucosal absorption, increasing secretion, altering mucosal permeability, and altering intestinal motility.

Lymphangiectasia

Dilation of small intestinal lymphatics and rupture into the lumen leads to protein losing enteropathy and low serum proteins in dogs. Cases may be idiopathic, or secondary to chronic inflammatory conditions of the small intestine. The aim of dietary management is to decrease lymphatic flow by supplying a very low fat diet. Reduced fat diets used for weight control, such as Hills r/d, Purina OM, Iams reduced calorie dry, or Royal Canin calorie control dry can be effective. Caloric supplementation with medium chain triglyceride oil (MCT) may be necessary. Medium chain triglycerides are absorbed into the venous system, not via lymphatics, and do not stimulate lymphatic flow. Ultra-low fat home made diets consisting of low fat cottage cheese, rice and potatoes can be very effective.
Plasmacytic lymphocytic enteroocolitis – Inflammatory bowel disease

Inflammatory bowel disease is a common idiopathic condition in dogs and cats that causes vomiting and/or diarrhea of small and/or large bowel origin. Diagnosis requires histologic demonstration of intestinal inflammation in the absence of known causes of intestinal disease. Increased mucosal permeability leads to penetration of the mucosa by food antigens and initiation of hypersensitivity, that worsens the inflammatory process. It is also possible that dietary hypersensitivity may play a role in the initiation of mucosal damage.

Because of the potential role of dietary antigens as either a primary or secondary factor in the pathogenesis of IBD, hypoallergenic diets have been recommended as the initial treatment. A hypoallergenic diet must contain protein and carbohydrate sources novel to the patient. A thorough dietary history should be obtained to determine which ingredients the animal has not been previously exposed to. Many hypoallergenic diets are commercially available and utilize lamb, egg, rabbit, venison, duck, fish, or kangaroo as a protein source (Table 1). A homemade diet can also be formulated using these protein sources, or others such as cottage cheese or tofu with rice or potatoes as a carbohydrate source. Homemade diets can be deficient in vitamins and minerals. They can be safely fed for trial periods, but must be completely balanced for long term use. Vitamin and mineral supplements must be carefully selected because many contain extracts and flavorings.

The hypoallergenic diet should be fed for four weeks and must be the only nutrient source that the dog or cat receives. Other household pet's food, table scraps, treats, and flavored vitamin, heartworm, and flea products must be avoided. Free roaming animals must be strictly supervised to avoid the potential for dietary indiscretion. If the clinical signs resolve when the hypoallergenic diet is fed, the animal should be challenged with its original diet. Clinical signs should rapidly return if dietary hypersensitivity is a component of IBD.

Although hypersensitivity can occur to any dietary constituent, common offending allergens include beef, cows milk, eggs, fish, wheat, soybeans, oats, or corn. There is some clinical evidence the animal can subsequently develop hypersensitivity to other antigens. Some have advocated rotating diets to prevent this from occurring. In addition, use of a "sacrificial" hypoallergenic diet along with anti-inflammatory medications, until the mucosal barrier is repaired, and then switching to a different hypoallergenic diet has been suggested. Poorly digestible novel proteins may induce hypersensitivity in patients with increased mucosal permeability because protein digestion usually renders it non-allergenic. Cooked eggs and cottage cheese are assimilated more readily than many meats and may be more hypoallergenic to intestinal mucosa than meat-based diets.

Recently, hydrolyzed protein diets have been developed in which protein size has been reduced and are no longer antigenic. Hills z/d ultra (dogs) and z/d low allergen (cats) contains hydrolyzed chicken liver and muscle. Purina HA (dogs) and royal Canin Hypoallergenic HP (dogs and cats) contain hydrolyzed soy protein. These products are available as dry formulations only. The diets meet many of the criteria for “GI” diets also, as they are relatively low in fat, low in fiber, and highly digestible.

A recent study in cats with chronic GI signs emphasizes the importance of hypoallergenic diets in the treatment of IBD. Out of 55 cats with idiopathic IBD treated with an elimination diet, based on dietary history, 16 were confirmed to have dietary sensitivity and 11 others responded to the hypoallergenic diet. These 11 cats did not have their clinical signs return when challenged with their original diet. The most common offending substances were beef, wheat, corn, gluten.

Probiotics

Probiotics are live bacteria that confer a health benefit to the host. Common bacteria include lactobacilli, bifidobacteria, and enterococci. In humans a daily dose is often 5-10 million. To be effective viability must be maintained throughout production, storage, distribution, passage through the upper GI tract into the colon. Many commercially available products do not survive transit into the colon and are not as effective as “advertised”. The bacteria should be able to be cultured from the feces during treatment, but will usually disappear once oral administration ends. The bacteria must be nonpathogenic and not transmit antibiotic resistance.

Probiotic bacteria have been reported to have many beneficial effects on the host including conditioning the immune system, synthesizing B vitamins, producing digestive enzymes, producing antibacterial factors, competing with pathogens for adhesion sites and nutrients, enhancing epithelial repair, increasing mucus production, decreasing luminal pH, and protecting tight junctions. However, all probiotics do not do all of the above. In humans some probiotics have been shown to be beneficial in acute infectious diarrhea, prevention of antibiotic associated diarrhea, pouchitis, cow’s milk allergy, IBD, and irritable bowel syndrome. Currently there is accumulating but weak evidence demonstrating benefits of probiotics in dogs and cats with diarrhea.

Chronic idiopathic large bowel diarrhea

I routinely add soluble fiber to a highly digestible diet in dogs with chronic idiopathic large bowel diarrhea, even if irritable bowel syndrome has been diagnosed. In cases of fiber-responsive large bowel diarrhea (FRLBD), chronic intermittent or continuous large bowel diarrhea is usually accompanied by hematochezia, excess fecal mucus, and tenesmus. Abdominal pain and vomiting can occur in some dogs. Nervousness, abnormal personality factors, and stressors have been identified in approximately 40% of cases. However, in some of these cases, a temporal relationship to the diarrhea could not be established.

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Soluble fiber, psyllium hydrophilic mucilloid (Metamucil®, Procter & Gamble), added to a highly digestible diet (i/d® Hills), has resulted in excellent or very good results in approximately 80% of dogs with chronic idiopathic large bowel diarrhea. In the authors’ cases, the median amount of Metamucil® added to the diet was two TBSP / day which was approximately 1.3 g psyllium / kg / day. I have not been able to identify any clinical findings that help to predict whether a dog will respond to fiber supplementation. In some dogs, the amount of fiber added to the diet can be reduced or withdrawn entirely, while in others the highly digestible diet can be replaced with a grocery store brand of food after the diarrhea resolves.

Dietary fiber is a collective term for a wide variety of plant polysaccharides and lignins that are resistant to mammalian digestive enzymes. There are many types of dietary fiber, each with diverse chemical, physical, and physiologic properties. Water soluble fibers include pectin, gums, mucilages, and some hemicellulloses. They are found in the parenchymatous portions of fruit and vegetables, and in the seeds of leguminous plants. Water insoluble fibers includes cellulose, lignin, and some hemicelluloses. They are found in cereal grains and seed coats.

There are several potential mechanisms by which dietary fiber supplementation may result in clinical improvement in dogs with FRLBD. Soluble fiber adsorbs a large quantity of water, improving fecal consistency. Colonic bacteria, which make up approximately 40-55% of the dry stool mass, ferment soluble fiber, which results in a vast increase in the numbers (but not types) of colonic bacteria and quantity of bacterial byproducts. Bacterial fermentation of fiber leads to the production of short chain fatty acids, of which butyrate serves as an energy source for colonocytes. Insoluble fiber greatly adds to fecal volume. Thus, dietary fiber can increase fecal bulk which increases colonic distention, the major stimulus for normal colonic motility. With increased colonic distention, an improved motility pattern in dogs with FRLBD may result in resolution of clinical signs.

Psyllium comes from the seeds or husks of the plant ispaghul and consists of approximately 90% soluble fiber. Although there are no other reported studies evaluating the use soluble fibers in dogs with diarrhea, there are in human beings. Treatment with psyllium has been shown to be beneficial in children with nonspecific chronic diarrhea of childhood, adults with chronic idiopathic diarrhea, patients with ulcerative colitis in remission, and some with irritable bowel syndrome. Psyllium has also been shown to improve diarrhea in human burn patients receiving enteral nutrition and in another group of tube-fed patients. Psyllium also improved fecal consistency in humans with experimentally induced secretory diarrhea and also reduced the acceleration of colonic transport in those with lactulose-induced diarrhea.

### Table 1. Some limited antigen foods

<table>
<thead>
<tr>
<th>Company</th>
<th>Food name</th>
<th>Major ingredients</th>
<th>dog or cat</th>
<th>dry or canned</th>
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<tr>
<td>Hills</td>
<td>d/d</td>
<td>Egg, rice</td>
<td>dog</td>
<td>dry</td>
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<tr>
<td>Hills</td>
<td>d/d</td>
<td>Duck, rice</td>
<td>dog</td>
<td>dry</td>
</tr>
<tr>
<td>Hills</td>
<td>d/d</td>
<td>Salmon, rice</td>
<td>dog</td>
<td>dry</td>
</tr>
<tr>
<td>Hills</td>
<td>d/d</td>
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<td>dog / cat</td>
<td>canned</td>
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<td>Purina</td>
<td>LA</td>
<td>Salmon, trout, rice</td>
<td>dog</td>
<td>dry</td>
</tr>
<tr>
<td>Iams</td>
<td>Response FP</td>
<td>Catfish, potato</td>
<td>dog</td>
<td>dry, canned</td>
</tr>
<tr>
<td>Iams</td>
<td>Response KO</td>
<td>Kangaroo, oats</td>
<td>dog</td>
<td>dry</td>
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<tr>
<td>Innovative Veterinary Diets</td>
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<td>Lamb, potato</td>
<td>dog, cat</td>
<td>dry, canned</td>
</tr>
<tr>
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<td>Limited ingredient diet</td>
<td>Venison, potato</td>
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<td>dry, canned</td>
</tr>
<tr>
<td>Innovative Veterinary Diets</td>
<td>Limited ingredient diet</td>
<td>Duck, potato</td>
<td>dog, cat</td>
<td>dry, canned (dog only)</td>
</tr>
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<td>Limited ingredient diet</td>
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<td>dry, canned</td>
</tr>
<tr>
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<td>Limited ingredient diet</td>
<td>Whitefish, potato</td>
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<td>dry, canned</td>
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<td>Sensitivity RC, LR</td>
<td>Catfish, rice</td>
<td>dog</td>
<td>dry (RC), canned (LR)</td>
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<tr>
<td>Royal Canin</td>
<td>Sensitivity RD, VR</td>
<td>Duck, rice</td>
<td>cat</td>
<td>dry (RD), canned (VR)</td>
</tr>
<tr>
<td>Wysong</td>
<td>Anergen</td>
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<tr>
<td>Nature’s Recipe</td>
<td>Allergy</td>
<td>Venison rice</td>
<td>dog</td>
<td>dry, canned</td>
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<tr>
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<td>Lamaderm</td>
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<tr>
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<td>dry</td>
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References
Giardia and Trichomonas Foetus: An Update
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Giardia

*Giardia* is a flagellate protozoan parasite commonly encountered in small animal veterinary practice. The most common clinical syndrome associated with *Giardia* is acute small bowel diarrhea, but in some cases acute large bowel diarrhea, chronic small or large bowel diarrhea, or rarely acute or chronic vomiting may occur. Studies throughout the world have found infection rates ranging from 1%-39% in pet and shelter dogs and cats. Recently a study utilizing PCR found 80% of cats in Perth Australia to be positive. Many of the *Giardia* infected animals did not have diarrhea. Younger animals had a higher rate of infection.

It appears that various strains possess differing degrees of pathogenicity. Clinical signs may be self-limiting in some patients. Severe disease may occur in puppies or kittens, animals with other gastrointestinal parasites or diseases, or debilitated animals, but also can occur in otherwise healthy patients. *Giardia* cysts are not routinely identified by commonly used fecal flotation solutions because cysts become shrunken and cannot be identified. In addition, the numbers of cysts shed in the feces fluctuate over time. Many commonly used anthelmintics are not effective against *Giardia*. Although the issue is presently unresolved, some strains of *Giardia* are a zoonotic threat. This paper will review the important clinical aspects of giardiasis and will present a practical diagnostic plan and differential diagnosis.

Infection is acquired by ingestion of cysts, only a small number are necessary. Most dogs and cats infected with *Giardia* remain asymptomatic. When clinical signs occur, acute small bowel diarrhea is most common. Small bowel diarrhea has the following characteristics: liquid to semi-formed feces, moderately increased frequency of defecation, and normal to increased quantity of feces per defecation. The presence of melena (digested blood) is uncommon in cases of giardiasis. Diarrhea usually is self-limiting in animals that develop clinical signs, and has been described as pale, malodorous, and fatty. Severe diarrhea may be accompanied by dehydration, lethargy, and anorexia. However, most affected patients remain bright and alert, afebrile, and maintain a normal appetite. Occasionally acute vomiting may accompany diarrhea. The author has endoscopically observed severe erosion of the duodenum in some cases that resolved following successful treatment for *Giardia*. A mild eosinophilia has been demonstrated.

Chronic small bowel diarrhea with weight loss, poor body condition, and intermittent vomiting may also occur. In addition, the author occasionally has identified *Giardia* in cases of chronic vomiting. *Giardia* may be found in dogs and cats that have other gastrointestinal diseases, especially inflammatory bowel disease. In these cases, the clinical signs and laboratory findings reflect the underlying disease. In humans, *Giardia* may mimic inflammatory bowel disease.

Acute or chronic large bowel diarrhea with hematochezia, excess fecal mucus, and tenesmus may occur on occasion. In cases of large bowel diarrhea, the frequency of defecation is moderately to greatly increased and quantity of feces per defecation in reduced. Excess fecal mucus is often seen in infected cats.

Differential diagnosis and diagnostic plan

There are many causes of diarrhea in dogs and cats. Common causes for acute diarrhea include the following: *Giardia*, hookworms, roundworms, coccidia, dietary indiscretion, foreign body, toxins, drugs, hemorrhagic gastroenteritis (HGE), coronavirus, parvovirus, and intussusception. A thorough and logical diagnostic plan should be followed to facilitate reaching an accurate diagnosis, minimizing stress to the patient and expense for the owner.

The initial step in evaluation of cases with acute diarrhea is to distinguish between self-limiting and life-threatening causes. Most cases are self-limiting and can be diagnosed with a thorough history, careful physical examination, and fecal examination. Life-threatening cases may be associated with some of the following findings: frequent diarrhea, moderate to severe dehydration or abdominal pain, frequent vomiting, or systemic signs such as fever, icterus, lymphadenopathy, coughing, nasal discharge, or dyspnea. Puppies and kittens with severe clinical signs, especially if unvaccinated, should be suspected of having an infectious disease.

A recent dietary change, dietary indiscretion, or administration of medication may be identified in the history and suspected as the cause of self-limiting diarrhea. If the history does not identify an underlying problem, a fecal examination should be performed to identify *Giardia* or other parasites. Appropriate therapy for GI parasites, correction of dietary indiscretion, discontinuing suspect medications, or feeding a low-fat, highly digestible diet will often resolve clinical signs. Animals that are mildly dehydrated may require subcutaneous fluid therapy while those with very frequent diarrhea may benefit from motility modification with narcotics. Failure of the diarrhea to resolve indicates that a more thorough diagnostic approach should be followed.

Animals suspected of having a potentially life-threatening problem should receive: fecal examinations for parasites, complete blood count, biochemical profile, urinalysis, and survey abdominal radiographs. Additional procedures may be necessary to confirm specific disorders.
*Giardia* can be identified in animals with either self-limiting or life-threatening acute diarrhea. Because fecal examination should be the initial diagnostic test ordered, a diagnosis can often be reached without performing many unnecessary and expensive diagnostic tests.

Diagnosis of *Giardia* can usually be made by appropriate fecal examination techniques. If giardiasis is suspected, but cannot be confirmed, a therapeutic trial may be indicated. However, cessation of diarrhea after treatment does not confirm a definitive diagnosis of giardiasis.

Microscopic examination of a drop of fresh feces mixed with a drop of normal saline may allow identification of motile trophozoites. Trophozoites can be identified by their rapid "falling leaf" motion and concave ventral surface. Trophozoites may be associated with mucus and the only motility visible may be the flagella. Trichomonads are the only other motile organism similar in size (11x7um) to *Giardia*. They may be differentiated from *Giardia* by an undulating membrane along the entire length of the body, rolling rapidly progressive and erratic motility, lack of a concave surface and a single nucleus. Trophozoites are not often found in semi-formed or firm feces. One study in dogs showed that examination of fresh feces on 3 separate days identified approximately 40% of dogs infected with *Giardia*. In that study, approximately 90% of infected dogs were identified with three zinc sulfate fecal examinations.

Examination of feces by zinc sulfate flotation is considered to be the most accurate, practical, rapid, and inexpensive, diagnostic test available. In addition to identifying *Giardia* cysts, eggs of common parasites can also be seen. Approximately 2 gm of feces are mixed with 15 ml of a 33% solution of zinc sulfate, strained, the tube filled with additional zinc sulfate, and centrifuged for 3-5 minutes at 1500 rpm. If a free-swinging head centrifuge is available, additional zinc sulfate is added to create a meniscus and the tube covered with a coverslip. The coverslip can be transferred to a microscope slide for examination after centrifugation. If a fixed-head centrifuge is used, the surface layer of fluid can be transferred to a microscope slide with the bottom of a small glass tube or bacteriologic loop. The microscope slide or coverslip can be examined for cysts. Lugol's iodine may be added to the centrifuge tube to stain cysts and make identification easier. However, with experience, cysts can be identified without staining. Yeast can sometimes be confused with *Giardia*. Most yeast are approximately half as large as *Giardia* cysts and don't contain internal structures. Barium sulfate, several proprietary antidiarrheals, and enemas administered prior to collection of feces may interfere with *Giardia* detection. A recent study clearly demonstrated the importance of centrifugation of zinc sulfate fecal flotations. In fecal samples in which the solution was not centrifuged, 1/50 samples was positive for *Giardia* cysts. When the samples were centrifuged, 11/50 samples were positive for *Giardia* cysts and an additional 8 cases of whipworms were also identified.

Duodenal aspiration of fluid with examination of the sediment for motile trophozoites was at one time considered the gold standard for diagnosis of *Giardia* in dogs. Unfortunately this requires either endoscopy or exploratory laparotomy. Ten ml of saline can be infused into the duodenum, through a polyethylene tube passed through the biopsy channel of an endoscope or with a needle and syringe during exploratory laparotomy. The fluid should be aspirated, centrifuged, and immediately examined microscopically for motile trophozoites. A study published in 1983 comparing duodenal aspiration and zinc sulfate flotation found that duodenal aspiration was positive in 89% of cases while a single zinc sulfate flotation was positive in only 39% of cases. Two more recent studies performed in the author's institution have contradicted these findings. In a group of research dogs carefully monitored for parasites during a 17 month period, a single zinc sulfate examination identified 77% of infected dogs while a duodenal aspirate identified 67%. More recent investigation found that 3 zinc sulfate examinations identified 96% of infected dogs versus 88% with duodenal aspiration. These recent studies support the validity of zinc sulfate flotation as the diagnostic test of choice for *Giardia* in dogs. A recent review of clinical cases in which duodenal aspiration was performed during upper GI endoscopy, found very few positive tests for *Giardia*. The reasons why so few *Giardia* infections were identified were thought to be due to the frequent treatment with metronidazole and the use of zinc sulfate fecal flotation prior to endoscopy. Thus, cases with *Giardia* were either identified or responded to treatment, avoiding the necessity of endoscopic examination. The authors recommended that duodenal aspiration be performed in cases undergoing upper GI endoscopy if treatment for *Giardia* has not administered or if zinc sulfate flotation was not performed.

Several fecal ELISA tests have been marketed for human use. These tests identify *Giardia* specific antigens from trophozoites. Use of one of these tests (Prospect T/Giardia™, Alexon Inc., Mountain View, CA) yielded similar results to zinc sulfate flotation in 84% of examinations in dog feces. However, in 15% of examinations, the ELISA was positive when a single zinc sulfate examination was negative. *Giardia* was subsequently identified in approximately half of these cases when two additional zinc sulfate flotations were examined. In 1% of fecal samples, the ELISA was negative while the fecal examination was positive. Another report found that a fecal ELISA test was falsely negative in 14% of zinc sulfate positive samples from dogs. This study also found a positive ELISA in 10% of zinc sulfate negative samples. These studies point out that falsely negative ELISA tests occur, and suggest that a negative fecal ELISA does not eliminate the possibility of *Giardia* infection. In addition, it is possible that the fecal ELISA may be a more sensitive test and identify some cases of *Giardia* missed with zinc sulfate examination. Because of the expense of the fecal ELISA tests, the time required to perform the assay, the lack of identification of other parasite eggs, and the lack of data from cats, the author recommends using zinc sulfate flotation as the test of choice in identifying animals infected with *Giardia*. The Prospect/Giardia assay
has been modified and is available as a rapid in-office test. In one study of natural infection in research dogs, in 31.6% of fecal samples cysts were identified by zinc sulfate flotation, but the rapid ELISA was negative. In 4.3% of fecal samples cysts were not seen with zinc sulfate but the ELISA was positive. Recently, a rapid in-office ELISA has been marketed for veterinarians (IDEXX SNAP® Giardia). Preliminary sensitivity and specificity data look promising.

**Treatment**

The author recommends using either metronidazole or fenbendazole for treating giardiasis in dogs and cats. The dosage of metronidazole should be 50 mg/kg SID for 5 days. It has been previously suggested to split the dosage and administer it BID. In one study it was effective in 67% of infected dogs at 22 mg/kg BID for 5 days. In a different study in a group of research cats, 25mg/kg BID of metronidazole benzoate suspension resulted in negative fecal samples 15 days after treatment. Tablets should not be divided as the medication is bitter and unpalatable. Compounding with tasty flavors, such as tuna or sardine juice, will increase palatability for cats and small dogs that receive less than one tablet. Some authors have found that a lower dosage, 10 mg/kg BID, is effective in cats. Severe neurologic side effects, including seizures and coma, have been reported in dogs receiving higher dosages or prolonged treatment. However, neurologic signs can occur with lower dosages, but are usually reversible if the drug is discontinued.

Metronidazole is a potential mutagen and carcinogen, so treatment of pregnant animals should be avoided. Metronidazole enters the parasite by passive diffusion. Under anaerobic conditions, the compound is reduced, forming toxic derivatives that bind to DNA, RNA, and other proteins, leading to denaturation and strand breakage. In humans, metronidazole is metabolized in the liver. Sixty to eighty percent of the metabolites and parent compound is eliminated by the kidney. Approximately 15% is eliminated in the feces. Drug interactions are uncommon, but phenobarbital and prednisone may increase hepatic metabolism while cimetidine may decrease it.

Fenbendazole, a drug that has been utilized for many years in dogs without toxicity, has been shown to be very effective in treating research dogs with *Giardia* at a dosage of 50 mg/kg SID for three days. Fenbendazole has the advantage of being effective against hookworms, roundworms, whipworms, and some tapeworms. It is poorly soluble in water and rapidly passes through the gastrointestinal tract. It mechanism of action is believed to be binding with the parasite tubulin and inhibiting microtubule assembly. It is safe to administer to pregnant animals. Fenbendazole has been shown to be safe in cats at up to 250 mg/kg SD for 9 days. Fenbendazole, 50 mg/kg SID for 5 days, resulted in negative fecal samples 23 days after treatment in 4 of 8 research cats that were co-infected with *Cryptosporidium parvum*.Febental, which is metabolized to fenbendazole, combined with praziquantel and pyrantel was effective in research dogs naturally infected when treated for either 3 or 5 days. In this research setting bathing the dogs after treatment and moving to a clean environment was very important. The large animal anthelmintic, albendazole (Valbazen® Suspension, SmithKline Beecham) was reported to be safe and effective in treating dogs with *Giardia* at a dosage of 25 mg/kg bid for 2 days. However, recent clinical data has demonstrated bone marrow depression can develop in dogs and cats. The author does not currently recommend the use of albendazole.

Furazolidone (Furoxone® Suspension, SmithKline Beecham) is available as a suspension and is convenient to administer to cats and small dogs (4 mg/kg BID for 7 days). It has been shown to be effective in cats. Quinacrine has been shown to be 100% effective in dogs at 6.6 mg/kg BID For 5 days. Approximately half of the dogs treated developed minor and reversible anorexia, fever, or lethargy. Quinacrine has been shown to improve clinical signs in cats but not to eliminate infection. Unfortunately, quinacrine is not currently available in the United States.

Persistent clinical signs or shedding of cysts after treatment may suggest treatment failure, lack of client compliance, reinfection (can be from the animal’s hair coat), misdiagnosis, or underlying gastrointestinal disease. Confirming the diagnosis by a different diagnostic test or having a fecal sample evaluated by a commercial laboratory, evaluating client compliance, treating for 10 days, using a different medication, changing the animal's environment, or further diagnostic testing to identify a primary gastrointestinal disorder is indicated.

**Zoonosis**

Estimates of the number of human infections within the United States in 2002 ranged from 424,000 to 2.1 million. Human infection is acquired via consumption of contaminated food or water, or person to person or animal to person transmission (the Centers for Disease Control and Prevention consider *Giardia* to be a potentially zoonotic disease). Direct animal to person transmission may be responsible for only a small percentage of human cases. However, the contribution of animals to contamination of water is unknown. Some *Giardia* strains are capable of infecting humans and dogs and cats. In the past, studies evaluating zoonosis have yielded contradictory results. The genetic diversity and population structure of *Giardia* has not been fully understood until recently. Molecular genetic studies have recently found that most strains that infect humans are different from most strains that infect dogs and cats. However, it is prudent to consider zoonotic transmission from dogs and cats possible, so adequate precautions should always be taken when contacting feces or infected animals.
Large numbers of cysts can be intermittently shed for long periods of time. Cysts are very susceptible to drying and many common disinfectants. Quaternary ammonium compounds inactivated cysts more rapidly and at lower concentrations than phenolic or a group of miscellaneous compounds. Phenolic compounds were effective but required longer application times. Many of the miscellaneous disinfectants were effective only at higher temperatures. Dog and cat feces should be disposed of promptly and hands washed immediately after contact with feces or infected pets. If the hair coat is soiled with feces, the pet should be shampooed to remove fecal material. Children and immunocompromised adults should avoid contact with feces or infected pets.

**Trichomoniasis**

*Tritrichomonas foetus* is an anaerobic protozoa with an undulating membrane and 3-5 flagella. It varies in length from 10-25 um and 3-15 um in width. It has been described as causing chronic large bowel diarrhea and fecal incontinence, especially in purebred cats from catteries. Clinical signs often develop around 1 year of age. Greatly increased frequency of defeation and hematochezia are typical. Diarrhea often spontaneously resolves after approximately 1 year, although it may take up to 2 years in some cats. In one study, approximately 50% of cats were found to be positive by PCR despite resolution of diarrhea for almost 3 years! In a study from a cat show, approximately 30% of catteries were found to have a positive cat and about 30% of all cats tested were positive. Recently the organism was found to be a separate species from that found in cattle and renamed *Tritrichomonas blagburni*.

Diagnosis can be made by examination a fresh fecal / saline smear, InPouch TF culture, or PCR of feces. On a saline smear the organisms move in a jerky erratic and rapid manner. Movement can be observed on the following websites:

www.vetmed.auburn.edu/~blagbbl/blagburn.mpg

www2.ncsu.edu/unity/lockers/project/cvmaprhome/gookin_jody.htm

 Examination of a fecal smear may be positive in only about 15% of cases. The BioMed Feline InPouch™ contains antibiotics to limit bacterial growth. Approximately 0.05 g of fresh feces is incubated at 25°C and examined under 400x every 48H. This method may detect approximately 55% of positive cats. PCR evaluation of feces has been shown to detect approximately 95% of infected cats.

Treatment of cats is difficult. The best currently available treatment is ronidazole 30mg/kg SID-BID for 10 days. Many cats will develop reversible neurologic toxicity 3-9 days into treatment. Clinical signs include anorexia, lethargy, trembling, agitation, instability, and a blank stare. In many cats, signs of toxicity will resolve 6-10 days after stopping the treatment. Feces often become

References


Medication-induced esophageal strictures in cats

Doxycycline is commonly used in cats to treat many potentially infectious diseases. The drug is acidic and can be caustic to esophageal epithelial cells. It may accumulate within epithelial cells, where it can decrease protein synthesis and potentially decrease mucosal repair. Esophagitis can progress to stricture formation after doxycycline administration in cats. These strictures result in dramatic reduction of the esophageal lumen and severe regurgitation and dysphagia. Clinical signs usually develop within 7-10 days of administration of doxycycline. Treatment requires repeated endoscopic balloon dilation, with is an expensive and invasive procedure. Doxycycline induced esophageal strictures in cats usually occur in the proximal esophagus. Stricture diameter is often very small (often 1-5 mm) at initial diagnosis, smaller than strictures associated with anesthesia and gastroesophageal reflux. Usually re-stricturing is a major problem and affected cats often require more frequent dilations than cats with strictures due to other causes.

Intralesional corticosteroid injection may reduce the frequency of repeated dilations. Post-dilation treatments often include and H2 blocker, metoclopramide, sucralfate, prednisone, and in some cats placement of a PEG tube. Oral feeding with a liquid or blenderized diet is often necessary after dilation.

Two recent studies in normal cats have clearly demonstrated that transport of capsules and tablets through the esophagus after “dry” swallows was very delayed. This delay is thought to be responsible for the development of esophagitis and subsequent esophageal stricture formation. As many sick cats are anorectic and potentially dehydrated, it is possible that esophageal transport of tablets and capsules may actually be slower than demonstrated experimentally. To aid transport of tablets and capsules and avoid stricture formation, a 6 ml water flush or a small amount of food should always follow doxycycline administration in cats. Doxycycline should be discontinued at the first signs of regurgitation or dysphagia. Recently esophagitis and strictures have also been seen with clindamycin.

The diagnostic utility of abdominal ultrasound in dogs with chronic vomiting and with chronic diarrhea

Abdominal ultrasonography has recently been added to the diagnostic plan for many dogs and cats with chronic vomiting or chronic diarrhea. Ultrasound has been shown to be very helpful in animals with a mass lesion, especially neoplasia. An ultrasound guided fine needle aspirate or tru-cut biopsy can be performed. Ultrasound has also been shown to helpful in cases with chronic pancreatitis. Other advantages of ultrasound include: being noninvasive, imaging of the liver and biliary system, imaging of the small and large bowel and mesenteric lymph nodes, and assessment of the layers of the GI tract and its motility. Disadvantages include the need for expensive equipment and specialized training, interference by gas within the GI tract, and difficulty in imaging the pancreas.

Two studies have been performed in which the diagnostic utility of abdominal ultrasound in dogs with chronic vomiting or chronic diarrhea has been evaluated. A single radiologist performed each abdominal ultrasound. Two internists, who did not directly participate in case management, reviewed each medical record. In each case, the contribution the ultrasound made towards the final diagnosis was assessed and scored from 1-5, based on the following scale:

1. Diagnosis was obtained via ultrasonography (including ultrasound-guided aspirate or biopsy). Additional biopsy via endoscopy or exploratory celiotomy was not necessary.
2. Ultrasonography provided data that suggested endoscopy was not indicated and exploratory celiotomy should be performed to obtain a diagnosis. Ultrasonography suggested how to obtain a tissue biopsy, making it very important for diagnosis.
3. Ultrasonography provided important diagnostic information that helped assess other data, including endoscopic findings. Ultrasonography was important in arriving at a diagnosis.
4. Ultrasonography provided descriptive information that did not affect assessment of other data obtained via endoscopy or exploratory celiotomy. The same diagnosis would have been reached without performing ultrasonography.
5. Ultrasonography provided conflicting information that did not support, or may have hindered obtaining the final diagnosis.

In the group of dogs with chronic vomiting, the following factors were associated with a higher diagnostic utility of abdominal ultrasound: presence of weight loss, higher percentage of body weight lost, increasing age, increasing duration of vomiting, an increased frequency of vomiting/week, and a final diagnosis of GI lymphoma or gastric adenocarcinoma. Based on diagnostic utility scores, abdominal ultrasonography was vital or beneficial to obtaining a diagnosis in 22.5% of cases, not helpful in 68.5%, and of marginal value in 9%. Considering all contributions to case management (including factors unrelated to the vomiting problem), abdominal ultrasound was considered helpful in 27% of dogs with chronic vomiting.

In the group of dogs with chronic diarrhea the following factors were associated with a higher diagnostic utility of abdominal ultrasound: the presence of weight loss, palpation of an abdominal or rectal mass on initial physical examination, localization of
diarrhea to mixed bowel (vs. large bowel), diseases that commonly have mass lesions that should be visible on ultrasound examination, and a clinical diagnosis of GI neoplasia.

**New treatments for IBD**

**Budesonide**
Can be used when corticosteroid side effects are present although clinical signs have improved with prednisone. Budesonide is a corticosteroid related to 16-α-hydroxyprednisolone. Rapid hepatic metabolism (90% first pass) to compounds with minimal biologic activity occur. It has strong affinity for corticosteroid receptors within GI mucosa. It is formulated in 3 mg coated capsule that dissolve at pH>5.5 and deliver medication to distal ileum and proximal colon. Less systemic effects than prednisone but does suppress the pituitary adrenal axis in dogs. Dosage is empirical, but 1-3 mg/day has been suggested. Anecdotal evidence supports its efficacy in IBD.

**Cyclosporine**
Diminishes cytokine production and exerts antiproliferative effect on T-lymphocytes. It prevents production of IL-2, IFN-gamma, TNF-alpha, granulocyte-macrophage colony stimulating factor, and IL-4. It is metabolized in the liver via P450 enzymes. Drugs such as ketoconazole, that inhibit hepatic cytochrome P450, increase blood levels of cyclosporine. Toxicity in dogs includes vomiting, diarrhea, anorexia, gingival hyperplasia, papillomatosis, hypertrichosis, alopecia and excessive shedding. Seizures may develop in cats. Dosages 5mg/kg/day. Blood levels can be monitored. It has been shown to be effective in dogs with IBD that were nonresponsive to prednisone. Pharmacokinetics in dogs with IBD have been shown to be similar to healthy dogs.

**Chlorambucil**
Chlorambucil is an alkylating agent with cytotoxic effects similar to cyclophosphamide. It alkylates DNA in proliferating cells, with greater effects on B cells than T cells. Myelosuppression is less severe than cyclophosphamide. It has been utilized in cats with GI small cell lymphoma. Recently it was reported to have success in a group of dogs with IBD and protein losing enteropathy. When used with prednisolone it was more effective compared to a group treated with prednisolone and azathioprine. Serum albumin and body weight improved and survival was lengthened. Starting dosage was 4-6 mg/m² q 24 H for 7-21 days and then reduced to q 48H.

**Helicobacter gastritis in dogs**

*Helicobacter pylori* infection is the most common cause of chronic gastritis and peptic ulceration in humans. It is also associated with an increased risk of gastric lymphoma and adenocarcinoma. Spiral bacteria were described in 1896 in humans and several animal species. They were “rediscovered” in 1983 when they were reported to cause of peptic ulceration in humans. *Helicobacter pylori* is a microaerophilic curved spiral gram negative organism with 4 flagella. The bacterium lives in gastric mucus, can attach to epithelial cells, and may penetrate intercellular junctions. High bacterial urease concentration cleaves urea to produce ammonia, which helps to neutralize the acid environment surrounding the bacterium. The immune system does not result in removal of the organisms; without treatment infection is life-long. Some studies have shown as many as 90% of people are infected with *H. pylori*. Luckily, most infections are not associated with clinical signs. Diagnosis can be made with serology, cytology of gastric mucus, culture of biopsies, histopathology of biopsies with H&E or silver stains, C-13 or C-14 labeled urea breath tests, or rapid urease tests. Many treatments have been studied, but the gold standard to which they are all compared to is omeprazole, ampicillin or tetracycline, metronidazole, in IBD.

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Many species of spiral bacteria have been identified in dogs and cats: *H. felis, H. pylori, and H Heilmannii* (formerly called *Gastrospirillum hominis*), *H. Salomonis* and *H. bizzozeronii* are the most common. Experimentally, infection has been established in both dogs and cats and lymphoid follicular gastritis developed. However, in these experimental studies, clinical signs were absent or very mild. Several surveys of laboratory, shelter, and pet populations (with and without GI signs) have shown a very high prevalence rate in dogs and cats, nearing 100% in some studies. Peptic ulceration is very rare in dogs and cats, demonstrating the pathophysiologic difference between *H. pylori* and the spiral bacteria commonly found in dogs and cats. Little is known about the effects of treatment of dogs and cats with chronic vomiting and *Helicobacter spp*. infection. At the present time there are many unanswered questions regarding *Helicobacter* in dogs and cats. Some questions include: 1) What is the relationship between *Helicobacter* and dogs and cats with chronic gastritis and vomiting? 2) What is the optimal treatment to eradicate the organism? 3) After treatment, is reinfection or recrudescence a common occurrence in dogs and cats? 4) What factors can help predict if a dog or cat with chronic gastritis and *Helicobacter* would benefit from treatment for *Helicobacter?* 5) Does *Helicobacter* have a role in other diseases such as gastric cancer and inflammatory bowel disease?

Because of the potential pathophysiologic relationship between *Helicobacter spp.* in dogs and cats and chronic gastritis and vomiting, the author has treated clinical cases for *Helicobacter*. In some cases, treatment has resulted in resolution or improvement in clinical signs. Until additional studies about *Helicobacter* in dogs and cats are available, it seems prudent to at least determine if spiral bacteria are present in dogs and cats with chronic vomiting, during gastroscopic examination or exploratory celiotomy. Spiral bacteria can be identified in gastric biopsy or brush cytology specimens, or indirectly identified by rapid urease testing of gastric mucosal samples. Obtaining results from histologic evaluation of biopsy samples requires 24-72 hours. Results of rapid urease tests and gastric brush cytology are available much sooner.
The least expensive and most practical diagnostic method of the 3 commonly used tests, that also has the quickest turnaround time, is gastric brush cytology. After completion of the endoscopic examination and collection of biopsy samples from the duodenum and stomach, a brush cytologic specimen can be collected. A guarded cytology brush is passed through the endoscope's biopsy channel into the gastric body along the greater curvature. The cytology brush is extended from the sheath, and gently rubbed along the mucosa from the antrum towards the fundus, along the greater curvature. Hemorrhagic areas associated with previous biopsy sites should be avoided. The brush is retracted into the protective sheath and withdrawn from the endoscope. The brush is extended from the sheath, gently rubbed across several glass microscope slides, which are air dried, and stained with a rapid Wright stain. The slide is examined under 100x oil immersion. Areas with numerous epithelial cells and large amounts of mucus are initially viewed. If present, the spiral bacteria are easily seen. They are usually at least as long as the diameter of a red blood cell and their classic spiral shape is obvious. The author examines at least 10 oil immersion fields on 2 slides before the specimen is considered negative. Unlike diagnostic tests that involve using a single (or several) small biopsy samples, brush cytology gathers surface mucus and epithelial cells from a much larger area, increasing the chances for identification of bacteria. Brush cytology was found to be more sensitive than urease testing or histopathological examination of gastric tissues in identifying Helicobacter organisms in dogs and cats.

The rapid urease test detects the presence of bacterial urease, produced by the Helicobacter spp., in a gastric biopsy sample. A commercially available test, the CLOtest®, is utilized in the author’s clinic. Individual tests cost approximately $6.00. The test consists of an agar gel with urea and a pH indicator, phenol red, placed within a small plastic well. The tests should be kept refrigerated prior to use. A biopsy sample obtained from the angularis incisura of the stomach is pushed into the gel. The test is maintained at room temperature and examined frequently for a 24-hour period. If bacterial urease is present, urea will be hydrolyzed to ammonia, which will change the pH of the gel. The color of the gel will turn from yellow to magenta. The rate at which the gel changes color is proportional to the number of Helicobacter spp. present. When large numbers of bacteria are present in the biopsy sample, the rapid urease test quickly changes color, often within 15-30 minutes. If the color of the gel has not changed within 24 hours, the test is interpreted as negative. Because of false positives and negatives, the cost of the tests, the turn around time for test results (especially if negative), and the ease and reliability of brush cytology, the author feels that the rapid urease test is the least valuable of the 3 commonly utilized methods of diagnosis in my clinic.

Histopathologic identification of Helicobacter spp. within gastric biopsy samples, utilizing hematoxylin and eosin (H&E) or special stains, has a specificity of 100% and a sensitivity of greater than 90% in studies in humans. Because of the patchy distribution of organisms within the stomach, examination of samples from multiple gastric locations will increase sensitivity. In my clinic, samples from the pylorus, angularis incisura, gastric body along the greater curvature, and the cardia are routinely examined. Spiral bacteria can be seen within the mucus covering the surface epithelium, within the gastric pits, glandular lumen, and the parietal cells. In cats, bacteria have been identified submucosally within gastric lymphoid follicles. Spiral bacteria associated with the mucosal surface or within gastric pits are relatively easy to detect with routine H&E staining of tissues. However, if the distribution of bacteria favors gastric glands and glandular epithelial cells, bacteria are much more readily detected with a silver technique. Therefore, if bacteria are not identified with H&E staining, a modified Steiner's Silver stain is used. Because of similarities in morphologic characteristics it is not possible to identify specific species using routine histologic staining techniques. Besides the identification of Helicobacter, histopathologic evaluation of biopsy samples allows assessment of underlying inflammation or neoplasia, which may be the cause of the animal's clinical signs.

I have completed recently a clinical study comparing 2 treatments for Helicobacter in dogs. Dogs with chronic vomiting for at least 2 weeks, with Helicobacter spp. identified in gastric biopsy samples and gastritis, with or without inflammatory bowel disease, were entered into the study. The diagnostic workup included a CBC, biochemical profile, UA, fecal examination, abdominal ultrasonography, gastroduodenoscopy with mucosal biopsy, gastric cytology, and CLO test. Dogs with systemic diseases, gastric foreign bodies, gastric/duodenal neoplasia, pyloric hypertrophy, or Physaloptera infection were not eligible for the study. Dogs were randomly assigned to receive either triple therapy (amoxicillin 15 mg/kg, metronidazole 10 mg/kg, and Pepto Bismol tablets [<5 kg: 0.25 tablet, 5-9.9 kg: 0.5 tablet, 10-24.9 kg: 1.0 tablet, and >25 kg: 2.0 tablets]) or quadruple therapy (triple therapy plus famotidine 0.5 mg/kg). All drugs were given BID for 2 weeks. Owners kept a daily diary of clinical signs and endoscopy was repeated 4 weeks and 6 months after treatment was completed. Results of the study have not yet been published but have been reported in abstract form. Six months after completing either therapy, approximately 40% of dogs had gastric biopsy specimens that were negative for Helicobacter. There was no difference between the 2 treatments in the percentage of dogs that remained negative. Both treatments reduced the frequency of vomiting by approximately 85%. Dogs that were negative for Helicobacter had a greater reduction in vomiting frequency that those that were positive.

Because of the high rate of treatment failure in this study after 6 months, I have been investigating the use of clarithromycin based protocols; clarithromycin (7.5 mg/kg BID), in combination with amoxicillin (15 mg/kg BID) or omeprazole (0.7 mg/kg SID). This study is ongoing, but preliminary data 4 weeks after completion of therapy appears to be similar to triple or quadruple therapy. A recent study treated a small number of dogs and cats for 3 weeks using triple therapy. Eradication results were encouraging.
It will take many controlled clinical studies before we can understand the potential role of *Helicobacter* in dogs and cats with chronic gastritis, and can answer many of the questions I have proposed. Although treatment of *Helicobacter* offers another, and very different, therapeutic route for animals with chronic gastritis, we must remember that a direct cause and effect relationship between *Helicobacter* and chronic gastritis has not yet been established in dogs or cats. Failure of a patient to rapidly respond to antimicrobial treatment suggests that something besides *Helicobacter* is causing the chronic gastritis and vomiting.

**Giardiasis and zoonosis**

Estimates of the number of human infections within the United States in 2002 ranged from 424,000 to 2.1 million. Human infection is acquired via consumption of contaminated food or water, or person to person or animal to person transmission (the Centers for Disease Control and Prevention consider *Giardia* to be a potentially zoonotic disease). Direct animal to person transmission may be responsible for only a small percentage of human cases. However, the contribution of animals to contamination of water is unknown. Some *Giardia* strains are capable of infecting humans and dogs and cats. In the past, studies evaluating zoonosis have yielded contradictory results. The genetic diversity and population structure of *Giardia* has not been fully understood until recently. Molecular genetic studies have recently found that most strains that infect humans are different from most strains that infect dogs and cats. However, it is prudent to consider zoonotic transmission from dogs and cats possible, so adequate precautions should always be taken when contacting feces or infected animals.

**References**


Gastrointestinal Laboratory Testing: What Does it Mean?
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Routine laboratory testing
Performing a biochemistry panel allows the patient to be evaluated for complications of gastrointestinal (GI) disease, such as dehydration, electrolyte abnormalities, or hypoproteinemia. Dogs with hypoadrenocorticism often but not always have hypernatremia, hypokalemia, and low serum sodium to potassium concentration ratios. Dogs with protein-losing enteropathies often have severe hypoalbuminemia (<2 g/dL) and this is sometimes but not always accompanied by hypoglobulinemia. Additionally, in dogs with chronic enteropathy, hypoalbuminemia is a negative prognostic indicator. Metabolic diseases/abnormalities such as hepatic disease, renal disease, or hypercalcemia can also be ruled out with a serum chemistry panel. Whenever a serum chemistry panel is performed it is justifiable to perform urinalysis also. Urinalysis helps rule out certain metabolic diseases such as renal insufficiency and urinary tract infections. Pertinent changes on a complete blood count include the presence of neutrophilia with a left shift indicating an inflammatory response, eosinophilia, which is consistent with eosinophilic gastroenteritis, mast cell neoplasia, hypoadrenocorticism, or lymphoma, and lymphocytosis, which could indicate chronic antigenic stimulation or lymphoid neoplasia. Dogs that are sick with GI disease are expected to have a stress leukogram and the absence of this in a sick dog is suspicious for hypoadrenocorticism.

Certain endocrinopathies can also cause GI signs and consequently endocrine testing is sometimes indicated. When hypoadrenocorticism is suspected it should be ruled out by measuring the baseline cortisol concentration or by performing an ACTH stimulation test. A baseline serum cortisol concentration >2 mg/dL effectively rules out hypoadrenocorticism. An ACTH stimulation test should be performed to definitively diagnose or rule out hypoadrenocorticism in dogs with a baseline cortisol ≤2 mg/dL. However, an ACTH stimulation test should be performed initially if hypoadrenocorticism is highly suspected in order to reach a diagnosis more expeditiously. Hyperthyroid cats often have gastrointestinal signs and in cats with vomiting and diarrhea that are greater than 7 years of age, total serum thyroxine (T4) concentrations should be measured. If these are towards the upper limit of the reference interval in a cat in which hyperthyroidism is suspected, free T4 concentrations should be measured as this test is more sensitive (although it is less specific). Hypothyroidism can lead to reduced intestinal motility in dogs and theoretically this could lead to diarrhea. Dogs with clinical signs and clinicopathological findings consistent with hypothyroidism should be screened by measuring their serum total T4 concentration. If this is below the lower limit of the reference interval the dog should be further evaluated for hypothyroidism by measuring serum free T4 and endogenous TSH concentrations.

Tests for selected infectious diseases
Giardia duodenalis can cause chronic small bowel diarrhea in dogs and chronic small or large bowel diarrhea in cats. While Giardia cysts can be detected by fecal floatation and Giardia trophozoites can be detected direct examination of fecal samples, these techniques do not have optimal sensitivity. Direct immunofluorescence assays (IFA) are considered to be the gold standard for diagnosing Giardia infection in dogs and cats. These tests can also detect Cryptosporidium spp. A patient-side SNAP test is also available and this is useful for in-house screening of patients for Giardia.

Cryptosporidium spp. can cause subclinical or mild clinical signs in healthy dogs and cats and more severe signs in immunocompromised individuals. The aforementioned fecal Giardia/Cryptosporidium IFA was previously considered to be the gold standard for diagnosing infection but recent studies have shown that the fecal enzyme immunoassay and fecal PCR assays are more sensitive.

Tritrichomonas foetus is a protozoal parasite that has recently been recognized as an important cause of diarrhea in cats. This organism can be diagnosed observing motile trophozoites during examination of a fresh fecal smear. However, the sensitivity of this technique was reported to be very low. These organisms can also be cultured from the feces of infected cats using the InPouch culture system. This technique is simple to perform and is usually run as an in-house assay. However, the sensitivity of this technique is poor to moderate. The optimal way to diagnose Tritrichomonas foetus infection in cats is by fecal PCR. The sensitivity of this test is very good.

Tests for pancreatic disease
Serum lipase and amylase activities may be increased in dogs and cats with pancreatitis. However, other tissues such as the GI tract or the kidneys also produce both these enzymes and consequently they lack tissue specificity for pancreatitis. For example, serum lipase activity has been shown to increase after dexamethasone administration or with non-pancreatic disease. Some practitioners use a cutoff of greater than three-times the upper limit of the reference interval in an attempt to improve specificity. Unfortunately, these assays also lack sensitivity, indeed in most studies over half of dogs with acute pancreatitis have serum amylase and lipase activities
within the reference interval. These characteristics limit the utility of serum amylase and lipase activities assays for diagnosing pancreatitis in dogs.

Assays to measure serum pancreas-specific lipase concentrations have been developed. Pancreas-specific lipase can be measured by either the Spec cPL test or the SNAP cPL test in the dog and Spec fPL and SNAP fPL in cats. Because the lipase that is measured is specific to the pancreas these assays are more accurate than conventional serum lipase activity assays. These assays have been shown to perform better than other currently available blood tests for diagnosing pancreatitis. For the Spec cPL test values <200 μg/L are considered to be within the reference interval. Values between 200 μg/L and 400 μg/L and are considered to be equivocal for pancreatitis, other differential diagnoses and retesting in two weeks should be considered. Values >400 μg/L are suggestive of pancreatitis. The SNAP cPL test is an in-house test that gives a result rapidly. The results of this test can be positive or negative. Positive results correspond to a Spec cPL concentration of ≥200 μg/L. Consequently, the specificity of this test is lower than that of the Spec cPL test when using a cutoff of 400 μg/L but the sensitivity is equivalent to using a cutoff of 200 μg/L. The SNAP cPL is therefore a useful test to screen for pancreatitis. If the result is negative, acute pancreatitis is unlikely and if the result is positive a Spec cPL test should be performed to confirm the result. In a study looking at clinical cases of acute pancreatitis the sensitivity of the Spec cPL test using a cutoff of 200 μg/L was reported to be 87−94% and the specificity was reported to be 81−88% when using a cutoff of 400 μg/L. For the SNAP cPL test the sensitivity was reported to be 92−94% and the specificity was reported to be 71−78%. The reported sensitivities of the Spec cPL test for diagnosing clinically apparent acute pancreatitis range from 82−94%. In dogs diagnosed with pancreatitis on necropsy, that did not necessarily have clinical signs of pancreatitis, the reported sensitivities for diagnosing histologically mild pancreatitis and moderate pancreatitis with a cutoff of 400 μg/L were 21% and 71%, respectively. These findings suggest that this test is more sensitive for diagnosing symptomatic acute pancreatitis than chronic pancreatitis or subclinical pancreatitis. The reported specificity for diagnosing mild and moderate pancreatitis with a cutoff of 400 μg/L in this study was 100%.

Spec fPL values <3.6 μg/L are considered to be within the reference interval. Values between 3.6 μg/L and 5.3 μg/L are equivocal, so other potential causes of the cat’s clinical signs should be considered, as should repeated testing in two to three weeks. Values >5.3 μg/L are consistent with pancreatitis. The SNAP fPL test gives a positive or negative result. A negative SNAP fPL test corresponds to a Spec fPL <3.6 μg/L, which means that pancreatitis is unlikely. A positive fPL test translates to a Spec fPL ≥3.6 μg/L, which could be equivocal or indicative of pancreatitis. Therefore the SNAP fPL test is best used a screening test and cats with positive results should be tested with the Spec fPL to confirm a value >5.3 μg/L. In cats the sensitivity of the pancreas specific lipase test was reported to be 54% for histologically mild pancreatitis and 100% for histologically moderate to severe pancreatitis with a reported overall specificity of 84%.

Although, the pancreas is the only organ that produces pancreas specific lipase it is possible for pancreatitis to occur secondary to other abdominal disorders such as peritonitis. For example, a recent study showed that some dogs with upper GI foreign bodies had increased Spec cPL concentrations. When diagnosing pancreatitis in dogs and cats it is very important not to overly rely on one test. The diagnosis of pancreatitis should be made based on a combination of consistent clinical signs, ruling out other causes of the clinical signs, pancreas specific lipase measurement, and where available abdominal ultrasound findings.

Species-specific trypsin-like immunoreactivity (TLI) are the diagnostic test of choice for diagnosing exocrine pancreatic insufficiency (EPI) in dogs and cats. Canine trypsin-like immunoreactivity (cTLI) measured using widely available chemiluminescent assay or a radioimmunoassay kits. The canine radioimmunoassay kit that is run by many laboratories will be phased out shortly. Feline trypsin-like immunoreactivity is measure using a radioimmunoassay that is only performed at the Texas A&M University Gastrointestinal Laboratory. The canine assay is reported to have excellent sensitivity and specificity for diagnosing exocrine pancreatic insufficiency. The diagnostic accuracy of the canine assay has not been as well studied but is also likely to be very good. Samples for TLI measurement should be collected after food has been withheld for 12 hours to avoid lipemia. As TLI assays are species specific they are not affected if the dog or cat is receiving pancreatic enzymes supplements. In dogs values between 5.7 μg/L and 45.2 μg/L are considered to be within the normal range. Values <2.5 μg/L are considered to be diagnostic for EPI in dogs. Values between 2.5 μg/L and 5.6 μg/L are considered to be equivocal for EPI and can be seen in dogs with small intestinal disease or in those that are in the process of developing EPI. In cats TLI (fTLI) concentrations between 12.0 μg/L and 82.0 μg/L are considered to be within the normal range and values <8.0 μg/L are diagnostic for EPI. It is possible that a dog or cat that is developing EPI due to chronic pancreatitis could have falsely normal TLI concentration due to a flare up of inflammation in the residual exocrine pancreatic tissue. Serum samples for TLI measurement where possible should be collected from patients with chronic pancreatitis when they are do not have clinical signs consistent with pancreatitis.

**Tests for intestinal disease**

Cobalamin (vitamin B₁₂) is a water-soluble vitamin that is abundant in commercial pet foods. Cobalamin has a complex mechanism of absorption from the intestinal tract and is of diagnostic and therapeutic importance. Dietary cobalamin is bound to animal proteins and once in the stomach these proteins are partially digested releasing the cobalamin, which immediately binds the R binder protein. Upon
reaching the small intestine the R binder protein is digested and the cobalamin binds to intrinsic factor, which in dogs and cats is mainly produced by the pancreas. The cobalamin-intrinsic factor complexes bind to specific receptors located in the ileal wall and the cobalamin is absorbed. The process can be disturbed in a variety of ways. Eventually the body’s cobalamin reserves are depleted leading to decreased serum cobalamin concentrations. Diffuse severe chronic ileal disease can impede the absorption of cobalamin and therefore can lead to hypocobalaminemia. Exocrine pancreatic insufficiency can also lead to hypocobalaminemia because loss of the exocrine pancreatic mass is associated with decreased production of intrinsic factor and pancreatic proteases, which cleave cobalamin from R binder protein. Because of this serum TLI concentrations are often measured at the same time as cobalamin to rule out EPI. Cobalamin-intrinsic factor complexes can be absorbed by anaerobic intestinal bacteria. When numbers of these bacteria increase, which may occur in primary or secondary small intestinal dysbiosis, cobalamin absorption is decreased. Eventually, this leads to hypocobalaminemia. There are several commercially available immunoassays that can measure canine and feline serum cobalamin concentrations. Many dogs and cats with gastrointestinal disease will have decreased serum cobalamin concentrations, but it is important to realize that a normal serum cobalamin concentration does not rule out ileal disease. Hypocobalaminemia has been associated with increased metabolic derangements such as increased serum methylmalonic acid concentrations and altered amino acid metabolism in cats and increased serum methylmalonic acid concentrations in dogs. Additionally, hypocobalaminemia has been associated with a poorer prognosis in dogs with small intestinal disease and reduced weight gain in cats. Because of this the author recommends supplementing cobalamin in dogs with a serum cobalamin concentrations below 380 ng/L and cats with a concentration below 400 ng/L.

Folate (vitamin B9) is another water-soluble vitamin that is abundant in commercial pet foods. Most of the dietary folate is in the form of folate polyglutamate, which is poorly absorbed. Folate conjugase is a jejunal brush border enzyme that hydrolyses folate polyglutamate to folate monoglutamate, which is subsequently absorbed by folate transporters in the proximal small intestine. Folate absorption can be decreased in patients with diffuse proximal small intestinal disease because of reduced intestinal folate conjugase activity and loss of mucosal folate transporters. When the patient’s folate reserves are depleted folate deficiency and hypofolatemia can occur. Therefore, folate concentrations below the lower limit of the reference interval suggest proximal small intestinal disease. However, small intestinal disease should not be ruled out in dogs and cats with normal serum folate concentrations. Folic acid supplementation should be considered in patients with low serum folate concentrations. The author gives a dose of 200 μg by mouth for small dogs and cats and 400 μg for medium and larger dogs, once a day for four weeks. Many bacterial species including some that are part of the small intestinal microbiota can synthesize folate, which can then be absorbed by the host. Therefore, some patients with small intestinal dysbiosis can have increased serum folate concentrations. However, serum folate concentrations are not a sensitive diagnostic test for small intestinal dysbiosis. Therefore, dysbiosis should not be ruled out in dogs with serum folate concentrations within the reference interval. The relationship between small intestinal dysbiosis and serum folate concentrations has not been studied in cats and antibiotics responsive enteropathy is not as well characterized in this species as in dogs. However, the possibility of dysbiosis should still be considered in cats with increased serum folate concentrations.

There are four potential causes of severe hypoalbuminemia (<2.0 g/dL) in dogs and cats: severe exudative dermatological disease, protein-losing enteropathy, hepatic insufficiency, and protein-losing nephropathy. Most of the time it is possible to diagnose protein-losing enteropathy (PLE) by ruling out the three other causes, especially if the patients has clinical signs consistent with GI disease. However, some patients with PLE do not have clinical signs of GI disease and some patients may have a hepatic insufficiency or a protein-losing nephropathy in addition to a PLE. A good example of this situation would be a Soft Coated Wheaton Terrier with protein losing nephropathy and PLE. In such patients it can be beneficial to document fecal protein loss prior to performing intestinal biopsy. Alpha-1 protease inhibitor is a protein that is a similar size to albumin. Therefore when albumin is lost through the intestinal wall, so is alpha-1 protease inhibitor. Albumin is digested in the intestinal tract by digestive and bacterial proteinases, so albumin measurement of fecal albumin concentration cannot be used to diagnose PLE. However, alpha-1 protease inhibitor is not broken down in the intestinal tract and so the fecal concentration of this protein can used to diagnose PLE. In theory this assay could be used to diagnose PLE before the patient’s serum albumin concentration decreased. This assay is commercially available for use in adult dogs and is performed by the Gastrointestinal Laboratory at Texas A&M University. Naturally passed fecal samples from the patient should be collected over three consecutive days and placed in pre-weighed tubes, which are available from our laboratory on request. Approximately, 1 g of feces is needed for each tube. Each sample should be frozen after collection and the samples should be shipped overnight on ice. In dogs mean three-day α1-PI concentration ≥13.9 μg/g feces or a α1-PI of one individual sample of ≥21.0 μg/g feces is considered to be abnormal. Dogs <1 year of age have higher fecal alpha-1 PI concentrations than adult dogs and the assay has not been validated for use in puppies.
Increased Liver Enzyme Activities in Dogs: When Do You Biopsy?
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Increased serum liver enzyme activities, especially increased serum alkaline phosphatase (ALP) activities are commonly identified in dogs. They often represent a diagnostic challenge to clinicians for a number of reasons. Firstly, sometimes increased serum liver enzymes activities can occur due to primary hepatobiliary disease and other times they can occur secondary to extra-hepatic disease. This may be because that enzyme is also produced by tissues other than the liver. Additionally, the liver plays a major role in the metabolism and the excretion of drugs, xenobiotics, as well as endogenous toxins. The liver is perfused by the portal circulation, whereby a large proportion of its blood supply comes from the splanchnic circulation via the portal vein. Consequently, the liver is susceptible to injury caused by a variety of toxins, diseases in other parts of the body, and ischemia. Thirdly, sometimes increased liver enzyme activities can occur due to benign processes, such as, hepatic nodular hyperplasia or can be due to conditions that are progressive and require early intervention to have an optimal outcome, such as, chronic hepatitis. This can make it difficult for clinicians to know how aggressive to be when working up these dogs. Extensive diagnostic evaluation, including invasive tests such as liver biopsy, are costly and are not be indicated in all cases. Sometimes in depth evaluation of dogs with increased serum liver enzyme activities is not required. For example, when there are mild increases in ALP activity. On the other hand with some diseases, such as chronic hepatitis, increased serum liver enzyme activities occur before the development of clinical signs. Therefore hepatic biopsy and treatment at an early stage is essential to optimize the patient’s outcome.

Hepatic enzymology
Alanine aminotransferase (ALT) is found primarily in the cytosol of hepatocytes. ALT is released when the cell membrane permeability of the hepatocytes increases or if there is hepatocyte necrosis. Although this enzyme is found in a variety of tissues, increased serum ALT activities are considered to be relatively liver specific. The exception to this is that rarely ALT activity can increase in patients with severe muscle injury. Alanine aminotransferase is considered to be a sensitive marker of liver injury. Aspartate aminotransferase (AST) is found in the mitochondria and cytosol of hepatocytes. The cytosolic fraction is released when the cell membrane permeability of the hepatocytes increases or if there is hepatocyte necrosis, whereas the mitochondrial fraction is only released when there is necrosis. Increases in AST generally parallel those in ALT but muscle disease can cause an increase in serum AST activity. Because of this, AST is considered less liver specific than ALT.

The hepatic, bone, and steroid induced ALP isoenzymes can all contribute to serum ALP activity. In the liver this enzymes is bound to the membranes of the hepatocytes that form the bile canaliculi and the sinusoidal membranes. When there is cholestasis, this membrane bound ALP is released into the circulation and the synthesis of this enzyme is induced. Alkaline phosphatase is therefore considered to be a sensitive marker of cholestasis in dogs. Because of the two non-hepatic isoenzymes ALP is not liver specific. Serum ALP activities can be increased when there is increased osteoblast activity e.g. growing dogs or dogs with osteolytic disease. Synthesis of the steroid induced ALP isoenzyme is induced by both exogenous and endogenous glucocorticoids. It is also important to note that increased serum ALP activities have been reported in a family of apparently healthy Siberian Huskies and also in some apparently healthy Scottish Terriers, vacuolar hepatopathy due to excess adrenal production of androgens is suspected to be the cause in this breed. Gamma-glutamyltransferase (GGT) is an enzyme that is found bound to the hepatocytes that comprise the bile canaliculi and bile ducts. Increases in serum GGT activity generally parallel those in ALP as both are considered to be relatively sensitive markers of cholestasis. In general increases in GGT are considered to be less sensitive but more specific for the presence of hepatobiliary disease than those of ALP.

Causes of increased serum ALT activities

Primary hepatopathies

<table>
<thead>
<tr>
<th>Cause</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory</td>
<td>Acute hepatitis, chronic hepatitis, lobular dissecting hepatitis, copper associated hepatopathy, cholecystitis</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Primary, metastatic</td>
</tr>
<tr>
<td>Infectious</td>
<td>Leptospirosis, infectious canine hepatitis, toxoplasmosis, schistosomiasis, histoplasmosis, leishmaniasis, bartonellosis</td>
</tr>
<tr>
<td>Trauma</td>
<td>Contusions, herniation, torsion</td>
</tr>
<tr>
<td>Hyperplastic nodules</td>
<td>Portosystemic shunts, primary hypoplasia of the portal vein, intrahepatic arteriovenous fistulas</td>
</tr>
</tbody>
</table>

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Secondary hepatopathies

Endocrine disease  Diabetes mellitus, hyperadrenocorticism, adrenal hyperplasia, hyperthyroidism
Inflammatory  Enteritis, pancreatitis, peritonitis, systemic inflammatory response syndrome, sepsis
Hypoxia  Anemia, thromboembolic disease, congestive heart failure, anaphylaxis, circulatory shock
Metabolic  Storage diseases
Xenobiotic related causes
Drug toxicity  Barbiturates, carprofen, antimicrobials, azathioprine, glucocorticoids, griseofulvin, or ketoconazole
Toxic  Heavy metals, copper, carbon tetrachloride, petrochemicals, mycotoxins, blue green algae, or cycads

Extrahepatic sources of ALT

Severe muscle injury (uncommon)

Causes of increased serum ALP activities

Liver isoenzyme
Hepatocellular disease  Nodular hyperplasia, vacuolar hepatopathy, , toxic hepatitis, chronic hepatitis, hepatic neoplasia, infectious disease
Biliary tract disease  Cholangitis, cholecystitis, cholelithiasis, neoplasia, gall bladder mucocele, extrahepatic bile duct obstruction
Extrahepatic disease  Endocrine (diabetes mellitus, hypothyroidism), inflammatory (pancreatitis, enteritis, sepsis), right sided heart failure
Idiopathic (Scottish Terriers)
Bone isoenzyme
Growth (young dogs)
Osteolytic disease  Neoplasia, osteomyelitis
Fracture repair
Hyperparathyroidism  Primary or secondary
Idiopathic (Huskies)
Hyperthyroidism

Glucocorticoid induced isoenzyme

Endocrine  Hyperadrenocorticism, adrenal hyperplasia
Drugs  Corticosteroids, phenobarbital, primidone

Initial patient evaluation

There are many causes of increased liver enzymes activities, so it very important for clinicians to go from a list of all the possible causes to a list of all the causes that are probable for that patient. Information collected during history taking and physical examination are often very helpful when doing this. The patient’s signalment can help refine the differential list. For example, very young dogs are more likely to suffer from congenital conditions such as congenital portosystemic shunts (CPSS) or certain infectious diseases, such as, canine infectious hepatitis than neoplasia or inflammatory conditions, such as, chronic hepatitis. Some breeds, such as, Bedlington Terriers, Skye Terriers, West Highland White Terriers, Dalmations, and Labradors are predisposed to copper associated hepatitis. Doberman Pinchers and Cocker Spaniels, especially females are predisposed to chronic hepatitis. The breeds of dog predisposed to CPSS include the Maltese Terrier, Yorkshire Terrier, Havanese Terrier, Pug, and Miniature Schnauzer. Increased serum liver enzyme activities are more concerning in these breeds. When taking a history it is very important to ask specifically about exposure to hepatotoxins such as cycads, blue green algae, amanita mushrooms, aflatoxins, heavy metals, xylitol, or chlorinated compounds. A variety of drugs can also be hepatotoxic, these include: ketoconazole, various antibiotics, azathioprine, carprofen, lomustine, acetaminophen, ketoconazole, mitotane, and phenobarbital. It is important to specifically ask about any herbal remedies that the dog is receiving as many of these have been reported to be hepatotoxic, including: herbal teas, pennisroyal oil, and comfrey. Ascertain the dog’s vaccination history is also worthwhile as leptospirosis and canine adenovirus 1 can cause hepatic injury. The clinical signs seen in dogs with liver disease are often fairly non-specific and include: vomiting, diarrhea, weight-loss, polyuria/polydipsia, and hyporexia. When these signs are present, they warrant further investigation in an attempt to determine their cause. Certain historical findings may be relevant because they are suggestive of an extra-hepatic disease that can cause increased liver enzyme activities. For example, polyphagia is consistent with diabetes mellitus or hyperadrenocorticism. Physical examination findings consistent with hepatobiliary disease include: icterus, ascites, poor body condition, stunted growth, hepatomegaly, or signs of hepatic encephalopathy. It is important to remember that dogs with hepatobiliary disease do not always display clinical signs and may have no significant abnormalities on examination. Physical examination may also reveal findings that are suggestive of extra-hepatic disease. For example, bilateral symmetrical alopecia is consistent with hypothyroidism or hyperadrenocorticism.
Routine laboratory testing
Other changes on a serum biochemistry panel can provide important clues as to the cause of increased serum liver enzyme activities. When serum concentrations of albumin, cholesterol, glucose, and urea are below the lower limit of the reference interval or towards the low limit of the reference interval and/or when the serum bilirubin concentration is above the higher limit of the reference interval, this is consistent with decreased hepatic function. It is important to remember that these changes are not specific for hepatobiliary disease. For example, the serum bilirubin concentration may also be increased when there is hemolysis. Additionally, due to the hepatic functional reserve capacity, liver disease must be severe before these changes are seen. Patterns of serum liver enzymes activities can be suggestive of certain pathologies. For example, during cholestasis the serum activity of ALP is dramatically increased and is higher relative to that of ALT. There may also be evidence of extra-hepatic diseases. Analysis of a complete blood count can suggest inflammatory conditions, rule out hemolysis, and if microcytosis is present be suggestive of CPSS. Urine specific gravity can be decreased in patients with hepatic insufficiency or portosystemic shunts. Excessive bilirubinuria in dogs implies hemolytic or hepatobiliary disease. Because dogs have a relatively low renal threshold for bilirubin, bilirubinuria is often detected before bilirubinemia or jaundice. Urate urolithiasis seems to be more common in patients with PSS than those with other types of hepatic dysfunction. However, it should be noted that urate crystalluria is not specific for hepatobiliary disease.

When do you recommend further diagnostic testing?
Once basic diagnostic evaluation of the dog has taken place the decision whether or not to pursue further diagnostic testing should be made. Every case is different so it is difficult to make universal recommendations. However, I can offer the following general guidance.

- If there are clinical findings or other laboratory test results that are suggestive of primary hepatobiliary disease, further diagnostic testing should be pursued.
- If there are clinical findings or laboratory tests results that suggest the extra-hepatic diseases that can lead to increased liver enzyme activities further diagnostic evaluation is needed.
- If serum liver enzymes activities (ALP or ALT) are severely (three times greater the upper limit of the reference interval) or persistently increased (greater than twice the upper limit of the reference for more than 3 to 4 weeks) further diagnostic evaluation is needed.
- As ALT is more liver specific than ALP, increases in serum ALT activity are more concerning than increases in ALP
- If none of these conditions apply then it is reasonable to wait and recheck the serum liver enzymes at a later date.

Further diagnostic testing
The utility of plain abdominal radiographs for diagnosing hepatobiliary disease is limited and they rarely lead to a definitive diagnosis. However, they can be used to assess the hepatic size and to rule out certain extrahepatic diseases. Abdominal ultrasound is more useful than radiology for evaluating the hepatic parenchyma and the biliary tract. It is also sometimes possible to diagnose portosystemic shunts using this modality. However, unless a disease is characterized by architectural changes of the hepatobiliary system, often a definitive diagnosis cannot be made with ultrasound examination. It is also important to remember that dogs with severe liver disease may not have any changes on abdominal ultrasound examination. Despite this limitation, when primary hepatic disease is suspected, abdominal ultrasound is usually performed prior to liver biopsy.

Measurement of plasma ammonia and paired preprandial and postprandial bile acids are sensitive tests for portosystemic shunting and one of these tests should be performed when this is suspected. However, because of the hepatic functional reserve capacity, these tests are not as sensitive for detecting hepatic insufficiency and normal results do not rule out severe liver disease. Therefore, performing these tests does not always alter the decision whether or not to perform hepatic biopsy.

In selected cases hepatic cytology is useful as it can lead to a definitive diagnosis of certain diseases and can be highly suggestive for the presence of others. Indications for performing hepatic cytology are a suspicion that a round cell tumor is present, when infectious agents such as Histoplasma capsulatum are suspected, and when hepatic masses are observed on abdominal ultrasound.

To make a definitive diagnosis of primary hepatic disease liver biopsy is often required. As discussed previously there are different biopsy techniques and each has advantages and disadvantages. No matter which technique is chosen, it is important to collect multiple biopsies as well as to save one to be sent for copper quantification and another for bacterial culture. Although, supportive treatment such as the hepatoprotectant agents discussed in the next lecture are important in the management of patients with hepatic disease they are not a replacement for the specific treatments, such a copper chelating agents, that may be indicated once a histological diagnosis has been made. When in doubt, if there is a suspicion of primary hepatic disease, such as chronic hepatitis, it is better to biopsy rather than to delay biopsy until the dog is in end-stage liver failure, at which point treatment is unlikely to be effective.
When should I biopsy the liver?

Again it is hard to make universal rules as every case is different but I can offer the following general guidelines:

- Hepatic biopsy is indicated when a hepatic mass has been diagnosed and a diagnosis was not been made based on cytology.
- Hepatic biopsy is indicated when the serum ALT activity has been greater than twice the upper limit of the reference interval for more than 3 to 4 weeks and extrahepatic disease is unlikely to be the cause.
- Hepatic biopsy should be considered when there are multiple acquired portosystemic shunts. Acquired shunts suggest that there is hepatic parenchymal disease e.g. chronic hepatitis, which requires biopsy to be definitively diagnosed. However, acquired portosystemic shunts occur late in the course of disease and are irreversible. Consequently, the prognosis for these dogs is poorer so some clients may not wish to proceed.
Defining the cat’s problems
The first step in working up a cat with chronic diarrhea is to make an accurate list of the cat’s problems. Trying to determine if the diarrhea is small bowel, large bowel, or mixed in nature seems very obvious but clinicians often skip this step. Determining this helps when it comes to writing a list of differential diagnoses and in formulating a diagnostic plan. Having said this, sometimes it is over simplistic to say the diarrhea is from either the large or small bowel as occasionally both are affected. Aside from helping to localize the site of disease the character of the cat’s stool can give other important diagnostic clues. For example, steatorrhea is consistent with exocrine pancreatic insufficiency, and especially foul smelling large bowel diarrhea with Tritrichomonas foetus infection. It is important to take note of non-gastrointestinal clinical signs as they can indicate metabolic causes of diarrhea. For example, polyuria/polydipsia would be consistent with hyperthyroidism, hypercalcemia, or renal disease.

Formulating a differential diagnosis list
The next step when working up a cat with chronic diarrhea is to formulate a list of relevant differential diagnoses. Again this may seem obvious but it can be very tempting to skip this step and try to reach a diagnosis by pattern recognition alone, or just to think of a list of the diagnostic tests that you will perform. The problem-oriented approach is especially useful for more complicated or atypical cases and for less experienced clinicians. It is important to recognize which of these diseases are more or less likely based on the patient’s signalment. For example, in cats less than two years old infectious and dietary responsive causes of diarrhea are common whereas in older cats inflammatory bowel disease and intestinal lymphoma are more likely. This helps the clinician go from a list of all the possible causes of the clinical signs to a list of the probable causes for that patient.

Causes of feline chronic diarrhea
Extra-intestinal disease
Hyperthyroidism*, hepatobiliary disease, pancreatitis, exocrine pancreatic insufficiency, hypercalcemia, renal disease, peritonitis, toxemia/septicemia
Infectious agents
Helminths, protozoa (Tritrichomonas foetus*, Giardia**, Cryptosporidium), viral (Feline corona virus/feline infectious peritonitis, FeLV, FIV), bacterial (Salmonella, Campylobacter, Clostridium), fungal (Histoplasma)
Inflammatory disease
Inflammatory bowel disease (IBD)**
Dietary responsive enteropathy
Dietary allergy*,**, dietary intolerance*,**
Neoplasia
Intestinal lymphoma*, mast cell tumor, carcinoma, gastrinoma (rare)
Drugs
Non-steroidal anti-inflammatory drugs, antimicrobials, cancer chemotherapeutic agents
Other
Dysbiosis (it is controversial if dysbiosis is a primary cause of diarrhea in cats)
* - a common cause of chronic small intestinal diarrhea
** - a common cause of chronic large intestinal diarrhea

Staged diagnostic approach
Probably the most important thing when approaching a cat (or dog) with chronic diarrhea is to have a logical staged approach to performing diagnostic testing. Initially, cheaper less invasive tests are performed in order to rule out metabolic and infectious diseases. As there are no reliable diagnostic tests for dietary allergy/intolerance or dysbiosis, diagnostic trials are an important part of this process. Ideally therapeutic trials are performed sequentially rather than in parallel, so if there is a positive response the clinician knows what it was due to. If there is no response to these therapeutic trials and no diagnosis is made after performing the initial diagnostic tests, more expensive and invasive tests are performed. In some cases intestinal biopsy is indicated later in the diagnostic process. Every case is different but general guidelines for this staged approach are detailed below:
Stage 1: initial evaluation
a. Perform a fecal direct smear and floatation to rule out helminth infection
b. Consider administering a broad spectrum anthelmintic, such as fenbendazole at a dose of 50 mg/kg by mouth once daily for three days, regardless of the fecal analysis results.
c. Perform a diet trial with a highly digestible intestinal diet.

**Stage 2: non-invasive testing**

a. Rule out metabolic/systemic disease by performing a complete blood count, serum chemistry panel, urinalysis, and thyroid function testing. Evaluation of a serum chemistry panel can also be helpful to determine if there are systemic complications of gastrointestinal disease or if there are any concurrent diseases.
b. Perform further infectious disease testing
   1. Giardia/Cryptosporidium antigen testing should be sent to a commercial laboratory
   2. Tritrichomonas fetus fecal PCR. This parasite is an important cause of diarrhea in cats, especially in cats <12 months old that have come from a shelter or a pedigree breeding colony
c. FeLV/FIV testing
   1. If indicated evaluate the cat for FIP
d. Perform non-invasive tests for gastrointestinal disease in cats with small intestinal diarrhea or cats with large intestinal diarrhea in which concurrent small intestinal disease is suspected
   1. Serum pancreatic lipase immunoreactivity (fPLI) to screen for pancreatitis
   2. Serum trypsin-like immunoreactivity (fTLI) to diagnose exocrine pancreatic insufficiency
   3. Serum cobalamin and folate to screen for small intestinal malabsorption. It is possibly for a cat with small intestinal disease to have serum cobalamin and folate concentrations within the reference interval. Increased serum folate concentrations may indicate small intestinal dysbiosis or may occur in cats fed diets with high folate content.
e. Abdominal ultrasound examination seldom leads to a definitive diagnosis but can be helpful in directing further diagnostic testing. If intestinal thickening is present this is consistent with intestinal lymphoma (especially if the muscularis layer is thickened) or inflammatory bowel disease. This may prompt the decision to recommend intestinal biopsy. Ultrasound examination may also help determine if there is concurrent pancreatitis and/or hepatobiliary disease.

**Stage 3: therapeutic trials**

a. The cat should be supplement with parenteral cobalamin if indicated. I supplement cats with serum cobalamin concentrations less than 400 ng/L.
b. The only reliable way to diagnose dietary intolerance/allergy is to perform a dietary trial. If the cat has failed to respond to a trial with an “intestinal” diet the next step is to feed a novel protein or hydrolyzed antigen diet. If the cat will eat one of these diets they should be fed exclusively. Gastrointestinal disease usually responds more quickly to a successful dietary trial than dermatological disease but the trial should last for a minimum of three weeks. Another option that can be helpful in some cats with diarrhea is to feed a higher protein lower carbohydrate diet.
c. Consider a therapeutic trial with tylosin or metronidazole for dysbiosis. Cats with chronic enteropathies have been shown to have a different intestinal microbiota than healthy cats. However, it is controversial if dysbiosis in cats is a primary disease or if it occurs secondary to another disease process. I routinely perform a tylosin trial in dogs with chronic diarrhea but I do not do so with cats. However, I have seen some cats with chronic diarrhea that respond to tylosin but not to other medications including prednisolone. Other cats have responded well to probiotics but not to other medications.

**Stage 4: intestinal biopsy**

If a diagnosis has not been reached or the cat has not responded to any intervention, the next step is to recommend intestinal biopsy. This can be performed endoscopically or surgically during a laparotomy. Each technique has advantages and disadvantages. Obviously endoscopy is less invasive and the mucosal surface of the gastrointestinal tract can be evaluated. Where I practice, endoscopy is considerably cheaper and faster than laparotomy. The disadvantages of endoscopy are the need for specialized equipment and training to use it optimally, the relatively small size of the biopsy specimens that are collected, and the inability to reach the middle section of the small intestine using conventional techniques. If endoscopic biopsy is selected it is very important to collect multiple biopsies from the stomach, duodenum, ileum, and colon. Where possible both the duodenum and the ileum should be intubated during biopsy collection rather than collecting biopsies blindly. Good technique helps ensure that the full thickness of the mucosa is biopsied. It is also imperative that the specimens are examined at the time of collection to make sure they are adequate, that they are handled correctly by spreading them out on damp sponge mucosal side up.

The advantages of surgical biopsy collection are that the biopsies are of full thickness and that any part of the small intestine can be evaluated. Additionally, some cats with intestinal disease have concurrent hepatobiliary and/or pancreatic disease and laparotomy allows samples of these organs to also be collected. Surgical biopsy is more invasive than endoscopic biopsy and dehiscence of the enterotomy site is a serious potential complication. The suspected site of disease must be considered when choosing a biopsy.
technique. If the cat is suspected to have large intestinal disease without small intestinal involvement endoscopic biopsy is preferred as surgical colonic biopsies are rarely performed. Whereas surgical biopsy would be a better choice than endoscopy if abdominal ultrasound examination demonstrates segmental thickening of the jejunum. Laparoscopic biopsy collection when available may offer the best of both worlds.

**Stage 5: further treatment based on histological findings**

Further treatments are selected based on the histomorphological diagnosis. The most common inflammatory infiltrates are lymphocytes and plasma cells. Lymphoplasmacytic infiltrates (or other types of infiltrate) are not diagnostic for IBD as they can occur due to other conditions such as dietary intolerance or allergies. Therefore, IBD should only be diagnosed when other causes of inflammation have been ruled. Mild lymphoplasmacytic enteritis can be seen in healthy animals and even when standardized criteria are used there is considerable disagreement between pathologists evaluating gastrointestinal biopsy specimens. This can make it difficult for clinicians to make treatment decisions based on histology reports. Additionally, it can be difficult to differentiate between severe lymphoplasmacytic inflammation in cats with IBD and small cell intestinal lymphoma, especially when evaluating endoscopically collected biopsy specimens. The use of immunophenotyping to determine if the cells comprising the infiltrate are T-cells, B-cells, or a mixture and PCR for antigen receptor rearrangements to determine lymphocyte clonality can be helpful in making this distinction. These tests should be used in conjunction with histological evaluation of biopsy specimens.

Some clients will decline intestinal biopsy procedures for financial or other reasons and some cats may not be stable enough to tolerate anesthesia and biopsy. If this is the case, once parasitism, other infectious diseases, extra-intestinal disease, and diet responsive diseases have been ruled out, the two most common differential diagnoses that remain are IBD and small cell lymphoma. Therefore, it is reasonable to perform a prednisolone trial treatment. Cats with IBD or small cell lymphoma often have a positive response to this medication so it is important to counsel clients about both these two possible diagnoses.

**When to be more aggressive**

Obviously this staged approach is time consuming and for some cats it best to pursue diagnostic testing more aggressively. This often means performing gastrointestinal biopsy before doing therapeutic trials. Indications for this more aggressive approach include but are not limited to: severe weight loss, anorexia, the presence of an intestinal mass, melena, and protein losing enteropathy.

**Concurrent pancreatic and/or hepatobiliary disease?**

It is important to remember that many cats with diarrhea will have pancreatic and or hepatobiliary disease in addition to intestinal disease. When cats have concurrent IBD and pancreatitis, the pancreatitis should be treated symptomatically and prednisolone should be used to treat the IBD. Often the pancreatitis resolves when the IBD is treated and the prednisolone does not seem to make the pancreatitis worse. The exception to this is when the cat also has concurrent acute neutrophilic cholangitis with a positive bacterial culture (bile or liver). If this is the case the cat should be treated with antimicrobials and possibly ursodeoxycholic acid before treating with prednisolone.

**Nutritional support**

Some cats with chronic diarrhea are hyporexic or anorexic. These cats may also have reduced absorption of nutrients from the food that they do consume and increased metabolic requirements. This can predispose them to malnutrition and possibly even to hepatic lipidosis. Therefore, it is essential to provide adequate nutrition to these patients. Placement of a feeding tube is therefore often indicated. Feeding tubes can also make it easier for owners to medicate sick cats. Esophageal feeding tubes are easy to place, rarely have serious complications, and can be removed when they are no longer needed. The need for a feeding tube should be considered in cats undergoing anesthesia for intestinal biopsy. Appetite stimulants such as mirtazapine can also used as a short-term measure to get cats to eat. Forced syringe feeding of cats should be avoided as it can lead to food aversion.

It is important to treat cobalamin deficient cats with cobalamin as well as treating their underlying disease process. Cobalamin deficient cats provided supplementation might be less likely to respond to treatment for their underlying disease. Cyanocobalamin is given at a dose of 250 μg per cat SQ once weekly for 6 weeks, then once monthly. Cobalamin also seems to act as an appetite stimulant and may also be administered for this reason.

**Treatment tips**

In cats with idiopathic inflammatory bowel disease, if the response to prednisolone alone is not optimal, chlorambucil can be used as an adjunctive treatment. There are several dosing protocols that have been reported. For cats with that are relatively easy to pill a dose of 2 mg per cat PO three times a week can be used. In smaller cats or cats that don’t tolerate chlorambucil well the dose frequency can be reduced to twice weekly. For cats that are harder to pill, pulse dosing can be used. This entails giving a dose of 20 mg/m² once every 2 weeks. Generally this drug is very well tolerated in cats but it may cause myelosuppression so complete blood counts should be monitored periodically.
Some cats with IBD or lymphoma also have comorbid conditions, such as diabetes, that mean the use of prednisolone is contraindicated. Budesonide is a corticosteroid, which is extensively metabolized on its first pass through the liver. This means it causes fewer systemic side effects than prednisolone. In these cases budesonide can be used instead of prednisolone. However, there may still be some systemic side effects associated with this drug. A dose of 1 mg per cat PO q24 hours has been recommended.
Hepatic enzymology

Hepatic enzymes can be divided into markers of hepatocellular damage and markers of cholestasis. Serum alanine aminotransferase (ALT) and aspartate transaminase (AST) activities are the two most commonly measured markers of hepatocellular leakage while serum alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) activities are the two most commonly measured markers of cholestasis. Although increased serum hepatic enzyme activities are considered to be sensitive, they are not specific for primary liver disease. This is because these enzymes are also produced by extrahepatic tissues. The relative importance of these extrahepatic isoenzymes varies but their release can lead to increased serum activities. Also, the production of some hepatic enzymes can be induced by certain hormones and drugs leading to an increase in their serum activities in patients without hepatic disease. Furthermore, serum hepatic enzyme activities can be increased due to secondary hepatopathies. The magnitude of hepatic enzyme activity increases may aid in the assessment of the severity or the extent of hepatic injury but should not be considered to be prognostic. The liver has a large capacity for regeneration, so even in cases of severe hepatic injury, with dramatically raised hepatic enzyme activities, a full recovery is possible. Conversely, in cases of chronic end-stage liver disease, such as cirrhosis, serum hepatic enzyme activities may not be severely increased, or may even be within the reference interval due to the replacement of hepatocytes with fibrous tissue. Consequently, serial evaluation of serum hepatic enzyme activities is more useful for assessing prognosis than measurement at a single point in time.

Alanine aminotransferase is an enzyme found primarily in the cytosol of hepatocytes. ALT is released into the serum when hepatocyte membrane permeability is increased, or if there is hepatocellular necrosis. ALT is considered to be the most liver specific enzyme. Although uncommonly, severe muscle injury can result in an increased serum ALT activity. Aspartate aminotransferase is another aminotransferase enzyme that is used as a marker of hepatocellular leakage. AST is found in skeletal muscle, the brain, liver, kidney, cardiac muscle, and to a lesser extent within other tissues. The extrahepatic isoenzymes of AST are relatively more important than they are for ALT. Muscle disease can cause an increase in serum AST activity. Because of this, AST is considered less liver specific than ALT.

Alkaline phosphatase is an enzyme bound to the membranes of the hepatocytes that comprise the bile canaliculi and the sinusoidal membranes. It is considered a sensitive marker for cholestasis, especially in the dog, but is not liver specific. Cholestasis, canalicular cell necrosis, and increased hepatic synthesis may lead to the release of this enzyme into the circulation. Synthesis of this enzyme can be induced by certain drugs, most notably corticosteroids. The possibility that an increase in serum ALP activity could be due to extrahepatic disease such as osteolytic disease, or could be induced by glucocorticoids in the dog, can make the interpretation of this finding challenging. Gamma-glutamyltransferase is an enzyme that is bound to the membranes of those hepatocytes that form the bile canaliculi and bile ducts and also periportal hepatocytes. In comparison to ALP its distribution includes more distal areas of the biliary tree, but measurement of serum GGT activity is not useful to distinguish between intrahepatic and extrahepatic cholestasis. GGT is also produced by a number of extrahepatic tissues. Most of the GGT activity in serum is thought to be due to the hepatic isoenzyme.

Markers of liver function on a biochemistry panel

Measurement of serum bilirubin concentration can be used to assess liver function. Hyperbilirubinemia can be the result of hepatobiliary or extrahepatic disease. Hyperbilirubinemia is classified as being pre-hepatic, hepatic, or post-hepatic in origin. Pre-hepatic hyperbilirubinemia is caused by increased production of bilirubin due to hemolysis and distinguished from other causes of hyperbilirubinemia by the presence of severe anemia. Hepatic hyperbilirubinemia is due to a decreased rate of hepatocyte bilirubin uptake, conjugation, or excretion (due to intrahepatic cholestasis). Usually, hepatocyte dysfunction and intrahepatic cholestasis occur concurrently. Because of the hepatic reserve capacity, hepatic disease must be severe in order to cause hyperbilirubinemia. Other markers of hepatic insufficiency, when present, provide support for the presence of hepatic hyperbilirubinemia. Post-hepatic hyperbilirubinemia is due to extrahepatic bile duct obstruction. This is often due to pancreatic inflammation or, much less commonly, neoplasia. The main diagnostic tool for documenting extrahepatic bile duct obstruction is abdominal ultrasound. Typically, extrahepatic bile duct obstruction leads to dramatic increases in serum cholestatic enzyme activities relative to increased in hepatocellular leakage enzyme activities and hypercholesterolemia.

Albumin is a very important plasma protein that is produced exclusively by the liver. In order for a decrease in serum albumin concentration to occur, the rate of albumin loss must exceed the rate of hepatic synthesis. Mild decreases in serum albumin concentration can occur due to a variety of conditions. However, the differential diagnoses for severe hypoalbuminemia (≤2.0 g/dL) are limited to hepatic insufficiency, severe exudative skin disease, protein losing enteropathy, and protein losing nephropathy. It is possible to determine the cause of severe hypoalbuminemia from a combination of clinical findings, measurement of the serum
globulin concentration, urinalysis (including a urine protein creatinine ratio), tests of gastrointestinal protein loss, and tests of liver function. Hypoalbuminemia is a relatively insensitive marker for hepatic insufficiency and is only likely to be seen in patients with advanced chronic liver disease or portosystemic shunts (PSS).

Urea is produced from ammonia in the liver and is released into the bloodstream and subsequently excreted by the kidneys. Blood urea nitrogen concentration (BUN) may be close to or below the lower limit of the reference interval in patients with hepatic insufficiency, PSS, or urea cycle enzyme deficiencies. However, blood urea nitrogen concentration may also be decreased due to medullary solute washout caused by diuresis, malnutrition, a protein restricted diet, and is a normal finding in neonates.

Serum cholesterol concentrations may be increased, normal, or decreased in patients with liver disease. Increased or decreased fasting serum cholesterol concentrations are not sensitive or specific for hepatobiliary disease in dogs or cats. In patients with severe hepatic insufficiency or PSS serum cholesterol concentration may be decreased due to impaired hepatic synthesis. Hypocholesterolemia might also occur due to inadequate dietary intake, maldigestion, malabsorption, or hypoadrenocorticism. The serum cholesterol concentration of patients with hepatobiliary disease may be within the reference interval. Patients with cholestatic disease can become hypercholesterolemic. Serum triglycerides concentrations may be increased or normal in patients with liver disease. A mild increase in serum triglyceride concentration may develop in patients with cholestasis and there is some evidence that hypertriglyceridermia is associated with gall bladder mucocele formation.

The liver has a large reserve capacity for glucose production. Consequently, hepatic insufficiency must be severe in order for hypoglycemia to occur. Hypoglycemia also occurs in a proportion of patients with congenital PSS. Hepatic neoplasia can also lead to hypoglycemia. This is caused by release of insulin like substances. A variety of extrahepatic conditions can also lead to hypoglycemia.

Tests of hepatic function
Ammonia is produced in small intestinal enterocytes from the catabolism of glutamine and in the colon due to bacterial breakdown of protein and other nitrogenous substances. The ammonia is transported in the blood from the intestines through the hepatic portal circulation to the liver. The extraction of ammonia from the portal circulation is highly efficient. Endogenous ammonia is produced from the breakdown of nitrogenous substances in the body, especially glutamine. In the liver the ammonium is converted to urea by the enzymes of the urea cycle, or is used during the conversion of glutamate to glutamine. Urea enters the circulation and is excreted by the kidneys. Ammonium that is not removed by the liver enters the systemic circulation. The liver has a large reserve capacity for the conversion of ammonia into urea. Because of this, plasma ammonia measurement is a relatively insensitive marker for hepatic insufficiency. However, measurement of blood ammonia concentration is a sensitive test for congenital PSS and acquired portosystemic collaterals. This is because when portosystemic shunting occurs, the ammonia absorbed from the intestines bypasses the liver and reaches the systemic circulation directly. Generally, hyperammonemia is considered specific for hepatic insufficiency or PSS. However, although they are uncommon, urea cycle enzyme deficiencies may also cause an increased blood ammonia concentration.

Serum bile acids (SBA) measurement is a useful test of liver function in dogs and cats. Nearly all of the bile acids that are produced by the hepatocytes are conjugated to an amino acid. In both dogs and cats conjugation is primarily to taurine, but dogs may also convert to a conjugation with glycine. In contrast, even taurine depleted cats conjugate their bile acids almost exclusively to taurine. The conjugated bile acids produced by the liver are called primary bile acids. These are secreted in the bile, and then stored in the gall bladder. Cholecystokinin is released from endocrine cells in the small intestine. This hormone stimulates gall bladder contraction and the flow of bile into the duodenum. When the gall bladder contracts the bile acids are released into the intestines. Spontaneous gall bladder contraction also occurs during the interdigestive phase. A process known as enterohepatic circulation recycles bile acids. Primary bile acids are lipid insoluble and thus are only absorbed from the intestines when they bind to specific high affinity ileal mucosal receptors. This ileal reabsorption is very efficient. The reabsorbed bile acids enter the portal circulation and upon reaching the liver they are efficiently extracted from the plasma and subsequently re-excreted. Due to the increased release of stored bile acids during the postprandial period, small increases in total SBA concentration occur in animals with normal hepatic function. Hepatobiliary disease can cause increased SBA concentrations by interfering with hepatocellular function, by causing decreased bile flow, or by altering the hepatopetal blood flow.

The main clinical use of SBA measurement is to assess hepatic function in patients suspected to have hepatic disease, with serum bilirubin concentrations that are within the reference interval. Collecting paired preprandial and two-hour postprandial samples can increase sensitivity. Numerous studies have shown that SBA measurement is a useful test for diagnosing hepatobiliary disease, including PSS in dogs and cats. Measurements of SBA concentrations have several limitations. Firstly, this test does not allow differentiation between various types of hepatobiliary disease. Also, measurement of serum bile acids in a patient with proven cholestasis is of no clinical benefit. Additionally, there is limited utility in measuring SBAs concentrations in patients with hyperbilirubinemia. It should also be noted that the magnitude of increases of SBA concentration are not correlated with prognosis or disease severity. It is important to note that fasting SBA concentrations may be higher than the upper limit of the reference interval or higher than the postprandial value due to spontaneous contraction of the gall bladder in the fasting state, or due to delayed gastric
emptying. This could result in an increased fasting SBA concentration in the absence of hepatobiliary disease. Increased fasting and postprandial serum bile acids concentrations can be the result of increased bacterial deconjugation of primary bile acids into secondary bile acids. False negative results may occur if enterohepatic circulation of bile acids does not occur due to lack of gall bladder contraction. This could be a problem if a patient is anorectic, does not eat enough food, consumes a diet with insufficient protein or fat, vomits the test meal, or has delayed gastric emptying.

**Hepatic cytology**

Cytological evaluation of hepatic fine needle aspirates can aid in making a diagnosis of liver disease. Suppurative, mixed inflammatory, lymphocytic and, more rarely, eosinophilic patterns of inflammation can be appreciated cytologically. Each pattern of inflammation suggests a group of possible diagnoses. The finding of dark green or black bile casts suggests cholestasis. Infectious diseases such as histoplasmosis can be definitively diagnosed based on the cytology. Hepatocellular vacuolation can be classified as being caused by lipid or not. Lipid vacuolation of hepatocytes is characterized by colorless cytoplasmic vacuoles. Severe lipid vacuolation is suggestive of hepatic lipidosis in cats. However, feline hepatic lipidosis often occurs secondary to another disease process. Non-lipid vacuolation is characterized by generalized hepatocyte swelling and lacy vacuolation. Metastatic tumors and round cell tumors, such as lymphoma, affecting the liver can often be diagnosed cytologically. Additionally, cytological evaluation can aid in distinguishing liver nodules due to extramedullary hematopoiesis from those due to neoplasia. However, it is not possible to distinguish hepatic nodular hyperplasia from hepatic adenoma or well-differentiated carcinoma cytologically. Some cases of hepatocellular carcinoma can be diagnosed cytologically if criteria for malignancy are present.

Cytological evaluation of bile can also be useful for the diagnosis of biliary disorders, particularly in cats. The finding of neutrophils and bacteria on bile cytology supports a diagnosis of feline neutrophilic cholangitis. Cytology is essential for the diagnosis of this disease, as cats with neutrophilic cholangitis may not have typical hepatic histopathological changes and it can be difficult to distinguish these cats from those with lymphocytic cholangitis. Bile should also be submitted for aerobic and anaerobic bacteriological culture.

**Hepatic histopathology**

Histopathological evaluation of the liver allows a morphological and sometimes an etiological diagnosis to be made. To optimize the value of histopathological evaluation of the liver, particular attention should be paid to specimen collection, specimen handling, and communication between the clinician and the pathologist. Liver biopsies can be collected in a number of ways. Each method has advantages and disadvantages, and there is controversy in the veterinary literature as to which technique is optimal. Laparotomy allows collection of relatively large wedge biopsies, with direct visualization. This technique does not require specialized equipment or training, and excessive bleeding can be readily identified. However, laparotomy requires general anesthesia and is the most invasive biopsy technique. Percutaneous needle biopsy techniques have been described. These techniques may be possible under heavy sedation and are the least invasive method for collecting liver biopsies. Ultrasound guidance is often used, allowing biopsy of focal lesions. It is also possible to biopsy tissue that is deeper within the hepatic parenchyma than is possible with other techniques. However, the specimens that are collected are relatively small and may be inadequate for accurate assessment in some patients. Excessive hemorrhage after biopsy may not be identified immediately. Laparoscopy allows collection of biopsies using forceps with laparoscopic guidance. This technique requires general anesthesia, but is less invasive than laparotomy. The biopsies collected are larger than needle biopsies and excessive bleeding can be visualized. However, laparoscopy requires specialized equipment and training. The use of biopsy forceps may result in crushing artifact and the tissue collected may be too superficial to identify lesions that lie deeper within the hepatic parenchyma. Regardless of the technique used, a tiny proportion of the organ is sampled and, because liver disease can affect the hepatic parenchyma in a heterogeneous manner, sampling error is possible. To reduce the effect of sampling error, several biopsies from different areas of the liver should be collected and focal lesions should be specifically biopsied.

Quantification of hepatic metal concentrations requires submission of tissue for flame atomic absorption spectroscopy. While zinc has a role as an antioxidant, hepatic copper and iron accumulation can lead to oxidative liver injury. Copper is the most frequently measured of these metals and quantification is essential for the diagnosis of hepatic copper accumulation. These measurements are usually performed on freeze-dried pieces of liver. Specimens for metal measurement should not be stored in saline and should be kept in metal free containers.
Prokinetic agents

There are several prokinetic agents that are currently used in small animal practice. However, randomized placebo controlled clinical trials to assess the efficacy of these agents for treating delayed gastric emptying and intestinal hypomotility in dogs and cats have not been performed. Because of this it is difficult to make definitive recommendations regarding their use.

Cisapride is a serotonergic drug that acts principally on 5-HT₄ receptors. Its sites of action include the lower esophageal sphincter, pyloric antrum, small intestine, and colon. This drug can be given orally at a dose of 0.1−0.5 mg/kg q8–12 hours in dogs and cats. In humans cisapride has been withdrawn from the market as it cross-reacts with serotonergic receptors in the myocardium and can result in fatal cardiac arrhythmias, such as, Torsades des pointes. However, generic cisapride is still available from compounding pharmacies for veterinary use in the United States. As cisapride is given orally it may be impractical to give it to a patient with intractable vomiting. Mosapride and prucolopride are newer specific 5-HT₄ receptors agonists that are used in humans with gastrointestinal motility disorders. These agents were developed to avoid the serious cardiac side effects that can occur in humans treated with cisapride. Preliminary data suggests that they may be efficacious in dogs and cats but neither drug is currently available in the United States.

Erythromycin is a macrolide drug, that when used at sub-antimicrobial doses, stimulates motilin receptors in the gastrointestinal tract. Erythromycin thus stimulates phase III migrating myoelectric complexes that empty non-digestible solids from the stomach between meals. This increases the rate of gastric emptying but may allow incompletely processed larger food particles to be passed into the duodenum. Erythromycin also has a prokinetic effect on the small intestine and colon. The prokinetic dose of erythromycin is 0.5−1.0 mg/kg q8 hours PO or IV.

The prokinetic effects of metoclopramide are due to its serotonergic effect on 5-HT₄ receptors. The sites of action of this drug are the pyloric antrum and possibly the duodenum. This drug also has an antiemetic effect because it is a dopamine receptor antagonist. Metoclopramide can be given orally or subcutaneously at a dose of 0.2–0.5 mg/kg q8 hours. Alternatively, this drug can be given as an intravenous constant rate infusion at a dose of 1−2 mg/kg/hour. In the author’s experience the prokinetic effects of metoclopramide are not as strong as those of cisapride or erythromycin. However this drug may be useful in patients that need an antiemetic as well as a prokinetic agent.

Ranitidine is an acetyl-cholinesterase inhibitor and therefore increases the concentration of acetylcholine in synaptic spaces. This means this drug has should have a prokinetic effect on the pyloric antrum and possibly the small intestine and colon. Additionally, ranitidine is a histamine-2 receptor antagonist and therefore decreases gastric acid production. However, ranitidine appears to be less effective at suppressing acid production than famotidine. Ranitidine is given orally or when diluted as a slow intravenous injection at a dose of 1–2 mg/kg q12 hours. In the author’s experience the prokinetic effects of this drug are weak.

Delayed gastric emptying

Three functions of gastric motility have been recognized: i) accommodation is the active process by which the fundus of the stomach relax to allow expansion in the presence of a meal. ii) tituration is the process by which food is propelled by muscular gastric antrum against a closed pylorus. This breaks down food into smaller particles. iii) propulsion is the process by which particles of food <2 mm in size are forced from the gastric antrum through the pylorus into the duodenum. After a meal liquids are first emptied from the stomach followed by digestible solids Once the meal has been emptied from the stomach powerful interdigestive phase III migrating myoelectricaly complexes empty the remaining contents of the stomach including larger indigestible solids. The control of gastric emptying is complex and involves local and central neuronal pathways, paracrine factors, and endocrine mediators. The characteristics of a meal, such as, size, texture, fat content, and protein content can all affect the rate of gastric emptying. The rate of gastric emptying decreases when dry foods and foods with a high protein or high fat content are consumed.

Delayed gastric emptying is common in dogs and cats with a variety of medical conditions. Typical clinical signs include vomiting, gastric distension, anorexia, and abdominal pain. Delayed gastric emptying can have severe clinical consequences such as aspiration, malnutrition, and compromise of the intestinal barrier function.

Delayed gastric emptying can be caused by mechanical obstruction of the gastric outflow tract and this can be intraluminal, for example a foreign body; mural, for example hypertrophic gastropathy; or extra-gastric, for example due to a massive hepatocellular carcinoma. The treatment of mechanical obstruction is often surgical and so these conditions will not be discussed here. The other cause of delayed gastric emptying is functional obstruction where there is decreased gastric smooth muscle motility. This can be caused by gastric diseases such as gastroduodenal ulcers, gastric dilation/gastric dilation and volvulus, infections, post surgery,
gastritis, neoplasia, or may be idiopathic. Extra-gastric causes include: stress, conditions resulting in abdominal inflammation, such as pancreatitis, electrolyte disorders, and metabolic disorders. Additionally, medications such as opioids, anticholinergics, and beta-adrenergic agents can lead to delayed gastric emptying.

In a research setting there are several ways to assess gastric emptying time in dogs and cats. Scintigraphic assessment is considered to be the gold standard but requires specialized equipment and the use of a radioisotope. Radiographic studies using liquid barium given on its own or mixed with food are not representative of solid-phase gastric emptying. However, these studies can be useful for diagnosing gastric outflow tract obstruction. Wireless motility capsules have recently been used for the assessment of gastric emptying in dogs. This technique is convenient but specialized equipment is needed and the disposable capsules are expensive. Abdominal ultrasound has been used to assess gastric and the measurements correlate with scintigraphy in humans. The time taken for the antral cross-sectional area to contract to 50% of its maximum is calculated. This technique is relatively straightforward to perform and the necessary equipment is available in many practices. The only practical limitation of this technique is that it is time consuming. Due to the limitations discussed above, in a clinical setting the diagnosis of delayed gastric emptying is usually made based on the presence of consistent clinical findings. Delayed gastric emptying should be suspected in patients with intractable vomiting or anorexia, especially if they have an underlying disease that can reduce gastric motility, such as pancreatitis. The presence of gastric distension noted on abdominal palpation, abdominal radiographs, or abdominal ultrasound examination in a patient that has not eaten recently is also suggestive of this syndrome. Additionally, if the patient has a gastric feeding tube in place, measurement of the residual volume of food in the stomach can be very helpful. Mechanical obstruction should be ruled out and this is usually done by a combination of plain abdominal radiographs and ultrasound examination. As previously mentioned contrast radiographs may also be helpful. If functional reduced gastric motility is diagnosed the patient should be evaluated in an attempt to determine the underlying causes such as causes electrolyte abnormalities, and peritonitis. Typical diagnostic evaluation would include a complete blood counts, serum, biochemistry panel, urinalysis, abdominal ultrasound, and radiographs.

Aside from treating the underlying cause where possible the main forms of treatment for delayed gastric emptying are dietary management and administration of prokinetic agents. Feeding small frequent meals can be helpful as can warming the patient’s food. Canned foods are generally preferred over dry food and it can be helpful to liquidize the food using a food processor. Hospitalized patients with feeding tubes can be fed liquid diets as a constant rate infusion using a syringe pump rather than feeding meals. If this is not possible syringe feeding should take place of over at least 15 minutes. Restriction of dietary fat content is also helpful. The author uses erythromycin or cisapride to treat delayed gastric emptying in patients that can tolerate oral medications. In patients who cannot tolerate oral medications intravenous erythromycin possibly in combination an intravenous constant rate infusion of metoclopramide can be used.

Small intestinal hypomotility
Small intestinal motility serves three purposes: i) mixing of ingesta with digestive enzymes and other secretions ii) circulation of the intestinal contents to facilitate contact with the intestinal mucosa iii) net aborad movement of the intestinal contents. Four patterns of motility are recognized: i) segmentation, whereby circular smooth muscle contractions divide the bowel into segments, locally mixing and circulating the intestinal contents. ii) peristalsis, whereby longitudinal smooth muscle propels a bolus of food in an aborad direction iii) intestinointestinal inhibition, whereby if a section of bowel is over distended contractile activity in the rest of the bowel is inhibited, preventing movement of ingesta into the distended section. iv) migrating myoelectric complexes move indigestible material, mucus, and secretions from the stomach to colon in between meals. Cats have migrating spike complexes, which are less forceful than the migrating myoelectric complexes that occur in dogs and humans.

Ileus is the functional inhibition of propulsive bowel activity. This is often associated with clinical signs such as decreased food intake, vomiting, and diarrhea. Small bowel ileus can be caused by primary intestinal disease or can occur secondary to extra-intestinal disease. Examples, of primary intestinal disease include dysautonomia and chronic intestinal pseudo-obstruction. Examples, of diseases that can secondarily affect small intestinal motility include postoperative ileus, opioid induced bowel dysfunction, parvovirus enteritis, and hypothyroidism.

In a research setting monitoring the passage of radiopaque markers or a wireless motility capsule along the intestinal tract can be performed to assess small and large bowel transit times. These techniques are not routinely used in clinical practice. Therefore, the diagnosis of small intestinal hypomotility is based on a combination of consistent clinical signs and diagnostic imaging findings consistent with distended gas or fluid/gas filled sections of hypomotile intestine. When diagnosing small intestinal hypomotility it is very important to rule out mechanical obstruction. This is usually achieved with abdominal radiographs although in some case abdominal ultrasound examination is also helpful. Once is ileus is identified diagnostic testing should be performed to identify its underlying cause. For example, dysautonomia is a multisystemic disease and is also associated with esophageal hypomotility, delayed gastric emptying, decreased tear production, atropine insensitive bradycardia, as well as urinary retention and overflow. The diagnosis of this condition is based on the presence of these clinical findings.
Where possible it is important to treat the underlying cause of small intestinal dysmotility, for example by providing thyroid supplementation to a dog with hypothyroidism. It is also important provide supportive care, for example, by maintaining hydration with intravenous fluids and feeding a fat restricted highly digestible diet. Prokinetic agents such as cisapride and sub-antimicrobial doses of erythromycin, which have are believed to have an effect on the small intestine, may also be indicated.

**Large intestinal hypomotility**

In the colon the fecal material is mixed by phasic contractions, migrating contractions, and non-migrating contractions, which slow the aborad propulsion of the intestinal contents. Giant motor complexes occur at intervals of approximately 10 hours and cause aborad propulsion of fecal material, resulting in defecation.

Reduced large bowel motility can result in constipation and obstipation. Non-obstructive constipation is more common in cats than dogs and is most commonly associated with feline idiopathic megacolon. Experimental suggests that cats with feline idiopathic megacolon have generalized colonic smooth muscle dysfunction. The end stage of this disease is dilated megacolon and obstipation, which often necessitate colectomy. Reduced large intestinal motility and constipation in dogs and cats may also be caused by dysautonomia, hypokalemia, hypocalcaemia, hypothyroidism, and with administration of drugs such as opioids or atropine.

As previously mentioned while it is possible to measure large intestinal transit times this is rarely done in clinical practice. The presence of large bowel hypomotility is therefore inferred in constipated patients when other causes have been ruled. Other potential causes of constipation include intramural obstruction, extramural obstruction, painful defecation due to inflammation of the rectum or anus, neurological dysfunction, and environmental factors in cats.

Feline idiopathic megacolon is treated with medical management initially and if this is not successful colectomy may be performed. Medical management consists of a combination of dietary management, enemas when needed, various classes of laxatives, and prokinetic agents. As cisapride has a prokinetic effect on the colon it is my drug of choice in this situation. Where non-obstructive large bowel hypomotility occurs secondary to another disease it is important to try to address it.
The use of “hepatoprotectants” in canine and feline liver disease

Nutraceuticals and other hepatoprotectants are often used in the management of dogs and cats with liver disease. Unfortunately there are very few clinical trials in dogs and cats that assess their efficacy. This can make it difficult for clinicians to know when their use is justified. By understanding how these agents work it is easier to make rational treatment decisions.

Because of its role in metabolism the liver is very susceptible to oxidative damage. Oxidative damage is important in the pathogenesis of a range of hepatic diseases. Reduced hepatic concentrations of the antioxidant glutathione have been found in dogs and cats with variety of severe hepatic diseases. S-adenosyl methionine (SAMe) is a precursor of glutathione. The main rationale for using this agent is that it helps prevent oxidative damage by preventing depletion of hepatic glutathione. It has also been purported that SAMe may have anti-inflammatory properties, modulate apoptosis, and be anticarcinogenic. However, these effects have not been documented in dogs or cats. At the recommended dose of 20 mg/kg PO q12 hours SAMe has rarely been reported to have side effects in dogs or cats other than occasional vomiting and decreased appetite after dosing. Potential indications for SAMe include liver disease where there is oxidative stress i.e. necroinflammatory, cholestatic, and metabolic liver disease. However, it is important to note that there currently is little evidence that SAMe is efficacious in dogs and cats. Oral administration of SAMe has been shown to increase hepatic glutathione concentrations when given to healthy dogs and cats and to reduce oxidative stress but not histological changes consistent with vacuolar hepatopathy in dogs receiving prednisone.

Silymarin is extracted from the milk thistle plant. Silibinin is the most biologically active component of silymarin. Silymarin is believed to have antioxidant effects by scavenging free radicals and reducing lipid peroxidation. It is also believed to have anti-inflammatory and antifibrotic properties. Additionally, silymarin may be a choleretic agent. At commonly used doses silymarin does not appear to cause side effects although its bioavailability is low. Potential indications for silymarin include necroinflammatory, cholestatic, and metabolic liver disease of dogs and cats. Again there is very limited evidence to support its efficacy in the veterinary literature. In one study of Beagles administered Amanita phalloides toxin, 11 dogs treated with intravenous silibinin survived whereas four out of twelve control dogs died. Although, statistical analysis was not reported in this manuscript, this difference was not statistically significant, possibly due the small number of dogs enrolled. Additionally the dogs treated with silibinin had smaller increases in serum liver enzyme activities, bilirubin, and prothrombin time than those that were not, again statistical analysis was not reported. Another study did not find strong evidence that silymarin has a protective effect after carbon tetrachloride ingestion in dogs. In a study of dogs being treated with the chemotherapy agent CCNU, dogs treat with a product containing silymarin, SAMe, and phosphatidylcholine (Denamarin) were shown to have smaller increases in serum ALT and ALP activities than those that were not, suggesting a hepatoprotective effect.

Ursodeoxycholic acid (UCDA) was found to be the active compound in the traditional Chinese remedy of dried black bear bile. Ursodeoxycholic acid is a hydrophilic bile acid that is believed to have multiple beneficial properties including: choleretic effects, displacement of other more toxic bile acids from the circulating pool, an anti-apoptotic effect, and immunomodulatory effects. When used at a dose of 15 mg/kg/day PO this drug has few side effects other than causing occasional diarrhea. Because of its choleretic effect and the displacement of more toxic hydrophobic bile acids it makes sense to use this drug in dogs and cats with cholestasis. This drug is often used in cats with cholangitis. The use of UCDA in dogs and cats with complete bile duct obstruction is controversial as some clinicians are concerned about the possibility of gall bladder rupture. Other clinicians feel comfortable using UCDA in this situation and studies in rats where bile duct ligation has been performed indicate that it has a beneficial effect. Additionally, UCDA is sometimes used in the medical management of canine gall bladder mucoceles. Due to its claimed immunomodulatory and anti-apoptotic there is a theoretical reason to use UCDA in dogs with chronic hepatitis. However, evidence supporting the use of UCDA in dogs is limited to case reports and to the author’s knowledge there have been no clinical studies in cats.

Vitamin E is actually a family of eight lipid soluble vitamins. The main role of vitamin E is is as an antioxidant, protecting phospholipids from oxidative injury by scavenging free radicals. Generally vitamin E is well tolerated and side effects are not observed. Because of these properties consider using this supplement in dogs and cats with liver diseases that can lead to oxidative damage, such as, cholestatic disease, feline hepatic lipidosis, copper associated chronic hepatitis, and certain hepatotoxins. However, it is important there is no clinical evidence supporting the efficacy of vitamin E in dogs or cats with hepatobiliary disease.

Treatment of hepatic encephalopathy

Supportive care is very important when treating dogs and cats with hepatic encephalopathy (HE). It is important to identify and manage factors that potentially precipitate HE such as, gastrointestinal bleeding, infection, dehydration, dehydation, electrolyte abnormalities, and alkalosis. Patients who have had or are having seizures should be treated with anticonvulsants.
Benzodiazepines should be avoided as they are thought to precipitate HE in humans. Phenobarbital has been used to control seizures in dogs and cats with HE but the liver metabolizes this drug. Levetiracetam (20 mg/kg PO q8 hours) acts rapidly and has few side effects. Fluid therapy may also be required in some patients. When raised intracranial pressure is suspected, mannitol should be administered (0.5−1 g/kg IV).

Severe protein restriction is no longer recommended for dogs with hepatic encephalopathy (HE) as this can lead to protein malnutrition. It is important to also note that dogs with liver disease that do not have signs of HE likely do not benefit from dietary protein restriction. Diets formulated for dogs with liver disease are moderately protein-restricted and often have other characteristics such as reduced copper and sodium contents, and are supplemented with zinc and antioxidants. Non-meat protein based diets are often recommended for dogs with HE. Once the signs of HE are controlled with a commercial hepatic support diet, it is recommended to add non-meat protein to the patient’s diet to help prevent protein malnutrition. Severe protein restriction is inappropriate for cats. Commercial hepatic support diets with moderate levels of high quality protein have been recommended for cats with HE due to congenital portosystemic shunts. Cats with feline hepatic lipodisosis (FHL) should be fed a high quality protein diet that contains adequate arginine and taurine.

Lactulose is commonly used to treat HE in dogs and cats. Lactulose can be given orally to patients with chronic HE. It is usually started at a dose of 1−3 mL per 10 kg of body weight every 6−8 hours for dogs and cats. The dose is then adjusted until the patient passes three to four soft stools per day. In patients that are stuporous or comatose, lactulose can be given per rectum after a cleansing warm water enema. Neomycin is a poorly absorbed aminoglycoside antibiotic that is sometimes used to treat HE in dogs and cats. The gastrointestinal absorption of neomycin is very low, but can be increased in patients with decreased gastrointestinal motility or bowel wall damage. Substantial systemic absorption can cause ototoxicity and nephrotoxicity. In humans, neomycin is no longer used in the treatment of HE for these reasons. Metronidazole is another antimicrobial that is sometimes used for the treatment of HE in dogs and cats. Metronidazole is usually given at a dose of 7.5 mg/kg PO q8−12 hours in dogs and cats with HE. Metronidazole is hepatically metabolized and can have neurological side effects that mimic those of HE. However, these are more likely to occur at the higher dosages used for other purposes.

**Treatment of canine chronic hepatitis**

Although the hepatoprotectant agents described above are often used and may be beneficial in treating used in dogs with chronic hepatitis they are not a substitute for treating the underlying causes of the liver disease when this is possible and hepatic biopsy is required to diagnose chronic hepatitis.

Hepatic accumulation of copper can lead to hepatocellular injury due to oxidative stress and therefore chronic hepatitis in dogs. Sometimes copper accumulates in the liver secondary to cholestasis, in which case its distribution tends to be perportal. Even when copper accumulation occurs secondary to cholestasis it can potentially contribute to hepatocellular injury. Copper accumulation can also be the primary cause of chronic hepatitis in which case it tends to be centrolobular in distribution. A genetic defect of the COMMD1 gene has been identified as the cause of copper associated chronic hepatitis in Bedlington Terriers. Other breeds such as Dalmatians, Skye Terriers, West Highland White Terriers, and Labradors may also be at increased risk. Hepatic copper concentrations between 120−400 ppm are considered normal and concentrations >1,500 ppm are considered diagnostic for hepatic copper retention. However, I consider treating dogs with concentrations >1,000 ppm with copper chelating agents, especially when there is centrolobular copper accumulation or when there is necrosis associated with copper containing macrophages. The dogs should also be started on a copper restricted diet such as one of the commercial liver support diet. D-penicillamine is my first choice of chelating agent for dogs (10−15 mg/kg q12 hours before feeding). This drug may cause side effects such as vomiting. The exact time for which chelation should occur is not known as prolonged therapy can result in copper deficiency. Monitoring the dog’s clinical signs and liver enzymes can provide some indirect information regarding the efficacy of treatment. A study in Labradors suggested that 6−10 months of chelation is adequate. Ideally at this point hepatic biopsy and copper quantification is performed. Trientine (10−15 mg/kg q12 hours) may be used in penicillamine is not tolerated. At this point, if hepatic copper concentrations, when measured, have returned to normal, treatment, with zinc acetate at a dose of 5−10 mg/kg of bodyweight is initiated. The dog should be continued on a copper restricted diet. A copper causes oxidative damage antioxidants such as SAMe and possibly vitamin E may also be beneficial.

There is limited information supporting the use of the anti-inflammatory drugs in the treatment of chronic hepatitis. One study of dogs with chronic liver disease showed prednisone had a positive effect on survival and another more recent retrospective study showed that prednisolone reduced hepatic inflammation, hepatic fibrosis, and abnormalities of coagulation in a subset of dogs with chronic idiopathic hepatitis. Where there is histological evidence suggesting a major component of inflammation the use of anti-inflammatory drugs such a prednisolone should be considered. Typically a dose of 1−2 mg/kg day is started initially and is then gradually tapered. It should be noted that high dosages of prednisolone/prednisone often cause vacuolar hepatopathy, which can be detrimental to these dogs. Other anti-inflammatory drugs that are sometime in place of prednisolone include azathioprine (2 mg/kg q48 hours) and cyclosporine (5−10 mg/kg/day).
Supportive care is also important for these dogs. Dogs with hepatic disease, especially those with portal hypertension are at increased risk of gastroduodenal ulceration. Consequently, treatment with omeprazole (1 mg/kg q12-24 hours) should be considered. The development of ascites in dogs with chronic hepatitis is a poor prognostic indicator. Furosemide can lead to hypokalemia and metabolic acidosis both of which can precipitate HE in humans. The aldosterone receptor antagonist spironolactone (2–4 mg/kg q12 hours) is a better choice. If this is ineffective furosemide can be added started at a low dose (1 mg/kg PO q12 hours).

**Treatment of feline hepatic lipidosis**

Most cats with FHL have some kind of underlying disease such as pancreatitis, inflammatory bowel disease, diabetes, or upper respiratory tract infections. In order to optimize the patient’s treatment it is essential to identify and if possible manage these concurrent disorders. Cats with feline hepatic lipidosis should initially be stabilized before feeding can be started and fluid therapy often plays a big part of this. Balanced electrolyte solutions are a good choice. Some clinicians avoid using lactate-containing fluids because they are concerned that the hepatic metabolism of lactate is compromised in these cats. I use lactated Ringer’s solution in patients with hepatic disease without apparent adverse effects. Hypokalemia is common and can causes severe muscle weakness. Therefore, intravenous fluids should be supplemented with potassium chloride as needed. Hypophosphatemia is also common, especially when the cats are initially fed. Therefore, supplementation with potassium phosphate is often required. Occasionally intravenous supplementation of magnesium is needed. Cats with FHL have intrahepatic cholestasis and so may be vitamin K deficient. Treatment with vitamin K (0.5–1.5 mg/kg subcutaneously every 12 hours for 3 doses) is recommended. This is important to start before invasive procedures such as hepatic biopsy or esophageal feeding tube placement are performed. Cats with FHL are often nauseous so antiemetics are indicated. Ondansetron (0.2 mg/kg IV q8–12 hours) and maropitant (1 mg/kg SQ q24 hours) are my preferences. Mirtazapine (3.75 mg per cat PO q72 hours) is an appetite stimulant that is sometimes used in cats. This drug is not a substitute for placing a feeding tube in most cats. Cyproheptadine (1–4 mg per cat q12–24 hours) is also an option but diazepam should be avoided as it can lead to acute hepatic injury in some cats. Oxidative injury is part of the pathogenesis of FHL and so antioxidant drugs are indicated. Initially, N-acetylcysteine (an initial dose of 140 mg/kg IV, followed by subsequent doses of 70 mg/kg IV q6–8 hours) is used as it can be given IV to anorexic cats. When oral medications can be given, the cat should be switched to an oral SAMe supplement. Some clinicians also treat with vitamin E. L-carnitine has been shown to increase the beta-oxidation of fatty acids in cats during weight loss. Therefore, it is reasonable to supplement cats suffering from FHL with L-carnitine (250 mg per cat PO q24 hours). Cobalamin deficiency is not uncommon and cats with serum cobalamin concentrations <400 ng/L should be supplemented with cyanocobalamin (250 μg SQ q7 days for 6 weeks the once monthly).

It is essential to ensure the adequate nutritional for cats with feline hepatic lipidosis. As previously mentioned these cats should be fed a high quality protein diet that contains adequate arginine and taurine. Of the macronutrients, protein is the most important in resolving FHL. Once the cat has been stabilized, unless it is eating an adequate caloric intake voluntarily, a feeding tube should be placed. If the cat is not stable enough for anesthesia a nasoesophageal feeding tube can be placed. However, these tubes necessitate feeding a liquid diet. Commercial liquid recovery diets that are suitable to feed cats with FHL are available. My preference is to briefly anesthetize the cat and place an esophageal feeding tube. I prefer esophageal tubes to gastrostomy tubes as they can be removed as soon as the cat is eating well and have a reduced rate of serious complications. Commercial canned recovery diets contain adequate protein and can be fed via esophageal/gastric feeding tubes as they can be liquidized and have an adequate calorie density. In order to avoid refeeding syndrome and because these patients cannot tolerate large volumes of food in their stomach, it is important to feed small amounts of food initially. The cat’s resting energy requirement should be estimated using the formula: RER (kilocalories) = 70 × lean body weight (kg) 0.75. Typically 25% of resting energy requirement is fed on the first day then if tolerated this amount is increased by 25% of RER each day. The food should be divided into 4–6 meals and these should be fed slowly over 10–20 minutes or given as a continuous rate infusion. If feeding are not tolerated the meal size/rate of infusion should be decreased.
Lung Patterns Made Easy
Robert Obrien, DVM, MS, DACVR
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Lung disease
The most important question to ask yourself is: Is the lung too opaque or too lucent? If the lung are diffusely or focally too opaque then use the pattern system (below).

Pattern method
The pattern approach to interpreting lung lesions simplifies your life. For reasons of simplicity we will not discuss mixed patterns. Clinically when faced with a mixed pattern, identify the most severe (i.e. alveolar or nodular).

- normal variants causing increased lung opacity
  - Expiration: mild interstitial pattern
  - Underexposure: mild interstitial pattern
  - Geriatric patients: mild bronchial and interstitial patterns
  - Obesity: mild interstitial pattern
  - Nipples, ticks, dirt, and costochondral junctions: mimic pulmonary nodules.

Alveolar
This is the most mis-underdiagnosed pattern. The silhouette sign (=border effacement) is the hallmark radiographic sign of an alveolar disease. This manifest as the inability to see margins of heart, vessels or diaphragm. A particular form of the silhouette sign is the air bronchogram. This is the ability to see air in bronchial lumen surrounded by opaque lung. The analogy is “black tree branching in a snow storm”. The lobar sign indicates that the disease margins are limited precisely by the lung lobe margin and the disease seems to completely fill one lobe.

- Causes: (HELP ME acronym)
  - Blood (Hemorrhage)
  - Water (Edema)
  - Cells (neoplasia; Lymphoma in dogs, primary pulmonary neoplasia in cats)
  - Pus (pneumonia; viral, bacterial or fungal)
  - Atelectasis (detected by the Mediastinal shift when the alveoli are Empty)

Bronchial
The hallmark of this pattern is thickened bronchi. This may be due to infiltration with inflammatory cells or edema.

- Causes include:
  - bronchitis
  - dogs: bacterial > allergic (eosinophilic)
  - cats: allergic > bacterial (Mycoplasma)

Vascular
Enlarged vessels the sole cause of increased opacity (see heart notes)

Nodular interstitial
These are soft tissue nodules or masses in the lung

- Causes
  - Metastatic neoplasia
  - mycotic pneumonia
  - granuloma
  - abscess
  - hematoma, hematocoele

Unstructured interstitial
This pattern is the most commonly over diagnosed pattern. It is very common as a normal variant due to expiration or underexposure, and seen in geriatric or obese patients. It requires a high degree of skill to differentiate variants from true disease.

- Causes
  - Lymphoma
  - nonalveolarized edema (edema in transition: forming or resolving)
  - Left-side heart failure (see above)
  - Vasculitis (see above)
  - atypical allergic/infectious pneumonitis
So a flow diagram for decision-making regarding pulmonary patterns is:

- Is there evidence of border effacement? If yes, Alveolar
  - No? (down)

- Are the bronchial walls more opaque or thickened? If yes, Bronchial
  - No?

- Are there nodules or masses? If yes, Structured interstitial
  - No?
  - Then… Unstructured interstitial

References
Reading the Entire Thoracic Radiograph
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1. Introduction
The goals of this lecture are to provide you with techniques of radiography and radiology of the dog and cat thorax. Thoracic radiology remains the main imaging modality in the interpretation of pulmonary and other intra-thoracic diseases. These techniques should provide the basis for production of diagnostic images and ability to derive a reasonable set of differential diagnoses.

A few key points to remember:
- Radiographs provide information NOT answers
- answers are derived from proper interpretation of the radiographic signs in concert with other clinical aspects of the case
- radiographs may lead you to ask more or different types of clinical questions
- if poor quality, radiographs are a waste of personnel time and client money
- without a systematic approach to film interpretation, the information may be on the radiograph, but goes unseen
- without a good knowledge of clinical medicine, the changes are noted on the radiographs but incorrect conclusions are reached

What is a radiograph
Radiographs are images on photographic film by x-rays that have passed through tissue. The interaction of x-ray photons with the intensifying screen in the cassette produces photons of visible light. The light interacts with silver in the film to produce a latent image. The latent image is converted into the blacks and whites by the developing process.

The whiteness of the film is termed “opacity”. There are five radiographic opacities:
- metal
- mineral (bone)
- soft tissue
- fat
- air

The resultant opacity of the image is a function of both the object density and the thickness of the structure (which is why some end-on blood vessels can appear as opaque as a rib). The film has characteristics that allow us to image structures as varied as air-filled to metallic objects on the same radiograph. We are very dependent on proper technique, positioning, and developing for production of diagnostic images.

A radiograph is medical legal document and needs to be diagnostic, identify the patient, date, clinic name and properly marked with patient positioning (lateral views are marked by the side closest to the cassette)and anatomical sidedness (left versus right).

2. Thoracic radiography
Any “weak link in the chain” of positioning, technique or developing can lead to a nondiagnostic image. If hand developing then chemicals need regular maintenance. Remember to use time-temperature developing (not guesswork or “experience”). If you want consistent high quality radiographs with minimal maintenance, purchase an automatic processor. Use rare earth screens and a grid with bigger patients ( > 10 cm thick) for optimal film quality.

a. Positioning
The diagnostic value of a radiograph is more dependent on positioning than any other single factor. Remove all foreign objects: collars, leashes, bandages, dirt, water or blood. Restrain the patient either chemically, physically, or both. Restraint techniques are limited by clinical concerns and patient compliance. Clever use of sand bags, rope, tape and straps minimize the radiation dose to holders. The front legs need to be pulled forward so that they are not superimposed on the chest. On VD/DV views, the spine MUST be superimposed on the sternum. On lateral projections, elevation of the sternum is often necessary so that the sternum and spine are the same distance above the cassette.

- Features of the properly positioned lateral projection include:
  - ribs extent equally and are parallel
  - costal arches do not extend more ventral than the sternum
  - ribs do not extend more dorsal than the spine (unless symmetrically)

- Features of the properly positioned VD/DV include:
  - sternum superimposed on the spine throughout the entire length of the thorax
  - symmetrical shape to ribs
  - spine is in a straight line
b. Views
Enough should be taken to provide the complete set of information. Typical studies include three views; left and right lateral and VD views. Opposite laterals provide better detection for focal diseases (lobar pneumonia and nodules). The VD view “opens” the chest providing better lung disease detection. The VD view is indicated with suspected pleural effusion.

Exceptions to the above listed recommendations are important to remember. The DV view provide a “better” view of the heart base and caudal lobar vessels. The VD view may be better tolerated by dysneic patients, especially cats. Patients should not die while we attempt a diagnostic procedure.

With severely dyspneic patients:
- be judicious and efficient
- premeasure the patient before transport to radiology
- set the machine technique and gown up before bringing the patient
- position the cassette and collimate the beam before the patient arrives
- MAYBE take only one view: a lateral view is the least stressful
- MAYBE wait until tomorrow!

c. Technique
Technique refers to the balance of KvP and mAs. We want a high KvP-low mAs technique because the thorax has inherent very high contrast. A low mAs means a very short exposure time will stop the breathing motion. Remember that interpreting a film that is a little too grey is easier than one that is too black and white. A technique chart should be derived for all species and body parts imaged. The technique chart is based on the maximum dimension, usually at the level of the last rib. Inaccurate measurements invalidate the technique chart insuring improperly exposed radiographs. Technique charts can be constructed from standing or recumbent patient positioning. Be consistent. If the technique chart was made assuming recumbent positioning, then measure your patients in the appropriate recumbency.

3. Thoracic radiology
   a. Film reading technique
Learn a system then use it! Make sure to look at the ENTIRE film. My system is listed below, but any system used consistently, is a good system:
   Peripheral structures in a clockwise direction starting cranially:
   1. forelimb
   2. neck (soft tissues, spine and trachea)
   3. thoracic spine (spinous processes, canal and bodies)
   4. diaphragm
   5. stomach
   6. liver (and any other intra-abdominal structure)
   7. falciform fat pad and other intra-abdominal fat
   8. sternum

Mediastinum and pleural spaces
Ribs for symmetry
Heart
Lungs

Inevitable some portion of the films will be “dark” (overexposed). To best view these areas use a bright light. Alternatively use a “bob-o-scope” (two lightly clenched hands arranged in series or an empty paper towel roll!). Either of these devices limit the extraneous light, size of the portion evaluated and thereby, increase acuity of detecting lesions in the darker areas of the film. Bright lights are more expensive but fewer people laugh at you!

4. Radiographic anatomy of the thorax
   a. Introduction
Knowledge of “what is normal” is essential for detection of lesions. “Normal” includes all the variations by age, breed, sex and body condition. Radiographic variations are as clinically important as, and more difficult to learn than, normal radiographic anatomy. Remember that cats are not little dogs.
b. Radiological variations
Expiration causes increased lung opacity. Decreased amount of air in the lung results in proportional increased interstitial pattern. Overlap of the diaphragm and caudal cardiac silhouette should alert you to this variation. (see comments below on obese patients)
Underexposure causes increased lung opacity. Poor penetration of the spine, especially superimposed on the scapula, should alert you to this variation. Especially a problem with obese patients if the technique is not adjusted accordingly.
Flexion of the neck causes bending of the trachea in the lateral projection. Undulation of the trachea should not be mistaken for “dorsal deviation” secondary to a cranial mediastinal mass. Repeating the radiograph with the neck hyperextended tests the validity of the tracheal positioning due to head position.
Rotation of the chest in the lateral projection makes the heart base appear larger. Without foam support beneath the ventrum, an increased opacity in the heart base mimics left atrium enlargement and hilar lymphadenopathy.
Oblique positioning on VD/DV projections distorts the cardiac silhouette mimicking chamber enlargements.
c. Geriatric patients
With increased age we see a large number of changes to the appearance of the thorax. The most common change in cats and dogs is increased lung opacity. This is mostly due to combined increased bronchial and interstitial patterns. The bronchial pattern is due to dystrophic mineralization in the walls. The interstitial component is thought to be due to pulmonary fibrosis. mineralized costal cartilages and costochondral junctions are seen in the ventral thorax. Spondylosis deformans is a radiographic change (more common in dogs than cats) associated with smooth bone formation extending (= originating) from the vertebral end plates towards the adjacent vertebral end plate. This change thought to be a degenerative of the annulus fibrosis part of the intervertebral disk and, as an isolated finding, is an incidental finding. Heart orientation often changes in older patients. The heart in older animals (more common in cats) tends to be less upright (= “falls forward”, “leans over”) than in young animals. This exaggerates the appearance of the aortic arch on both the lateral and VD/DV views.
d. Obesity
With increased obesity, increased lung opacity. This is mostly due to a increased interstitial pattern. This is due to relative expiration. The weight of the thoracic wall fat limits chest wall excursions and intra-abdominal fat decreases caudal movement of the diaphragm. Increase the KvP 10 to 15% compared to a normal conformation patient of the same measurements.
The heart size is apparent increased in obese patients. The smaller lung volume makes the heart appear larger (= out of proportion). This is a challenge with both the subjective interpretation and when using cardiac measuring schemes that utilize intercostal spaces or percent of chest width.
In obese patients increased width of the mediastinum is seen. Fat infiltration in the cranial mediastinum can mimic a mass (cats and dogs). This increased width usually has parallel sides, as seen on the VD/DV view, unlike an enlarged lymph node or thymoma. In the middle mediastinum the fat adjacent to the heart may silhouette with the cardiac outline mimicking heart enlargement. Caudal mediastinal widening, between the accessory and caudal left lung lobes can be mistaken for pleural effusion.
Finally, increased distance between lung lobes or between lung and inner body wall is often noted. Fat can accumulate in pleural fissures or on the inner aspect of the chest wall mimicking pleural effusion.
e. Breed variations
Brachycephalic dogs often have smaller diameter to trachea (normal > other brachycephalic breeds > bulldogs). Additionally, they have apparently larger heart size (result of wide, shallow conformation). A bulldog is not a bulldog without a caudal thoracic hemivertebra. Dachshund and greyhound hearts measures big using the vertebral heart scale. Collies commonly have heterotopic bone formation in the lungs (mimic nodules).

5. Some old techniques reinvented
a. How many views
Whilst the norm may seem to be 2-views we have discovered that the 3rd view is requested so frequently that is was more efficient to always take 30views. The reason to take both laterals was because middle lung field disease is hidden when that disease is in the dependent lung. For example, right middle lung pneumonia is NOT seen in a right lateral projection.
Similarly, in dogs with suspected dynamic large airway disease, the ability to detect collapse of the intra-thoracic portions is greatly reduced on inspiratory-phase images. So, an expiratory-phase radiograph is indicated to demonstrate collapse, or at least the propensity to collapse, of the intra-thoracic trachea and larger bronchi. This is so common that it has become our traditional 4-view thorax.
In our most dyspneic patients we either add an additional view (“5-view”) or replace the expiratory view with a lateral projection of the neck, including the nasopharynx to the level of the thoracic inlet. This view provides information on the extra-thoracic trachea, larynx, pharynx and soft palate. Seeing air-filled lateral laryngeal ventricles supports normal or laryngeal paralysis. Opaque lateral ventricles supports laryngeal collapse (everted saccules) and mass-lesion diagnoses. Laryngeal inflammation and mass lesions are common in cats. In these cases the thoracic portion of the series may be normal or indicate a global thoracic wall conformation change associated with upper airway obstruction. This conformation will be discussed in the lecture.
b. Other views?
The reason take other views depends on the clinical history, clinical exam findings and concurrent radiographic findings.

1. Placing barium on suspected cutaneous lesion is very helpful to evaluate possible nodules seen on routine images. Ticks, nipples, skin tags and other skin lesions can show up when located in the nondependent portion of the patient, making interpretation of nodules difficult.

2. Horizontal beam radiographs are indicated to more accurately determine the presence or absence, more accurately characterize the volume, and to diagnose the concurrent fluid component of a patient with pneumothorax. The VD view is the worst at detecting pneumothorax. Horizontal beam view more are more accurate than other projections at providing volume of the pneumothorax in the nondependent hemithorax and detecting the fluid component in the dependent hemithorax. This technique require the use of thick open cell foam pads (8-12 inches thick) to elevate the patient off of the radiology table and ability to 1) lower, and 2) rotate the x-ray tube to a horizontal position. Both horizontal VD views are taken with the dog in right and left lateral u

3. The cranial lung regions bilaterally. On standard VD views the scapulae are superimposed upon the left and right cranial lobes obscuring the lungs. By pulling the arms caudally, alongside the chest wall (similar to a person standing with their arms at their sides) on the VD projection, the scapulae are rotated and are no longer superimposed on the lungs. This positioning will be discussed in greater detail during the lecture.

6. Summary
Thoracic radiographs are powerful tools for the detection and characterization of lung, heart, mediastinal, pleural and body wall lesions. Through knowledge of normal variants (according to age, breed, species, and body conformation) differentiation of disease from a normal variant is possible. Through utilization of additional creative radiographic views, lesions are seen better or better differentiated from normal anatomy.
The normal vascular flow to the liver is dual with a larger portion coming portal vein (80%) than the hepatic arteries (remaining 20%). The efferent flow follows the hepatic veins to the caudal vena cava. Within the liver the hepatic portal veins are seen as anechoic, branching, tapering tubular structures. Hepatic arteries and hepatic ducts cannot be seen in normal patients. Color Doppler facilitates the identification of the hepatic veins and helps us verify which vessel we are examining.

Portosystemic shunts represent amongst the most common vascular anomalies. These represent an abnormal communication between the portal vasculature and either the caudal vena caval or azygos veins. Intra-hepatic shunts are more common in large breed dogs and extrahepatic shunts in small breed dogs. Microvascular dysplasia is most common in Yorkshire terriers. Multiple acquired shunts are only seen in acquired cirrhosis or developmental hepatic arterial dysplasia patients. The methods for evaluation portosystemic shunt include ultrasound, ultrasound combined with radiography or computed tomography. This lecture will discuss all three modalities with an emphasis towards more modern forms of imaging, concluding with CT angiography by multi-detector modern systems

Ultrasound is the mainstay of the characterization portosystemic shunts in general practice. However, it is amongst the most rigorous ultrasound examinations due to the wide variety of manifestations of these anomalies. While many tools are used to simplify the ultrasound search for portosystemic shunts, most will not cover shunts under all circumstances. For the evaluation of portosystemic shunts the measurements of the portal vein, immediately before entering the liver, compared to the diameter of the aorta at the level where the aortic crosses the diaphragm is useful. These measurements are typically made in transverse section and the normal portal vein is more than one half the diameter of the aorta. However, this measurement scheme does not include intrahepatic shunts, acquired hepatic shunts, or microvascular dysplasia. So, for the evaluation of solitary extra-hepatic shunts a strong level of suspicion the patient has a shunt would be reached if the portal vein was less than one half the diameter of the aorta. This is a reasonably easy measurement to obtain in most patients by utilizing a right-sided intercostal approach.

Additional schemes for evaluating portosystemic shunts include evaluation of the caudal vena cava. The normal caudal vena cava has no turbulent flow. Any evidence of turbulent flow, especially between the level of the right renal vein and the diaphragm should provide strong suspicion of an abnormal vessel representing a portosystemic shunt. Aberrant vascular drainage into the vena cava results in turbulent flow. Often we can find the exact site of the beginning of the turbulent flow and follow the vessel draining in at that level. This may often be traced to the origin of the shunt, usually the portal vein, gastric vein or splenic vein branches. Alternatively, you can look for sites where flow is leaving the portal vein. Flow departing from the portal vein is always abnormal since all portal vein branches enter the portal vein. Additional features of portosystemic shunts, while not specific they are supportive, include small liver, hypovascular liver, large kidneys and bladder stones. These bladder stones are lucent on radiographs because they are of urate composition. Approximately 10% of all portosystemic shunt patients present with urinary tract signs associated with the urate stones.

While many studies indicate the sensitivity and specificity of ultrasound for the diagnosis and portosystemic shunts, most radiologists confirm the challenge of both the detection of shunts as well as verification that the dog is normal in a large percent of patients. Therefore, additional modality should be considered to improve the accuracy of portosystemic shunt detection and better characterization. This includes the combination of ultrasound and radiography. Historically angiography has been used as an intraoperative tool for the characterization of portosystemic shunts. However, this requires a surgical exploratory and catheterization of a jejunal vein. A newer test has been proposed whereby the splenic vein can be injected with iodinated radiographic contrast for subsequent radiographic angiogram. Typically these patients should be heavily sedated or anesthetized, placed in right lateral recumbency with the spleen in the upper most part of the abdomen available for imaging with ultrasound. Using ultrasound guidance, a 25gauge needle can be directed into a large splenic vein, subsequent aspiration on the attached syringe should indicate strong blood flow indicating localization of the needle tip within the large vein lumen and thereafter 3 to 5 ml (depending on patient weight) of contrast is injected. The radiograph is taken after initiation of the injection but before the end of the injection. This test has been proven to be very sensitive and specific for shunts at the level of cranial to the entrance of the splenic vein into the portal vein. This represents approximately 95% of all portosystemic shunts. The additional advantage is that it also is helpful for acquired and intrahepatic shunts. There is no imaging test for the diagnosis of microvascular dysplasia.

The final diagnostic test, and that preferred by the lecturer, is CT angiography. Historically CT angiography has been a rigorous CT procedure including at least three separate data collection points including survey CT, a test injection to calculate the timing of portal vein enhancement of the liver and the final CT angiogram. This procedure was established during the era of single detector CT and is no longer necessary with multi-detector CT systems. With newer systems (greater than 4 detectors), a single CT angiographic
study is all that is necessary. This study is composed of three consecutive, rapid, limited abdominal scans after a hand injection of intravenous contrast in a peripheral vein. This study is referred to as a triple phase CT angiogram for portosystemic shunts. Usually the shunt is seen best in the second phase of this triple phase study. The rigor of this study is no longer the technical expertise of the imager, in this case a technician running the CT equipment, but rather the radiologists interpretation of the angiogram on the subsequent imaging set. A review using this technology demonstrated 100% accuracy for portosystemic shunts in patients in a clinical setting. These studies typically require approximately 10 minutes to perform, required no advanced radiologic expertise available during the scan, and open the opportunity for this advance modality in places where there is no boarded radiologist available. These techniques are easily taught to CT technicians and can readily be performed in an accurate and timely fashion in any practice setting.

In summary, the imaging of patients with suspected portosystemic shunt runs the gamut of ultrasound, radiology and computed tomography. Improved ultrasound equipment provides increased accuracy for the detection of shunts with ultrasound. The use of Doppler sonography greatly improves the characterization of the aberrant flow and possible turbulence associated with the shunt vessel. Measurement of the aorta compared to the portal vein often give strong suggestion of a portosystemic shunt, but has a large number of exceptions that limits utility of this tool. Ultrasound guidance of the injection of an iodinated contrast into a splenic vein with subsequent radiographic angiography is a simple, but technically rigorous test with a high degree of accuracy and better anatomic characterization of the portosystemic shunts for the surgeon. Finally, new advances in multi-detector CT demonstrate that this tool is the current superior test for the evaluation of portosystemic shunts. CT angiography is now a very simple, rapid and highly accurate test without the requirement of boarded radiologist available during the scan. This CT protocol is easily taught to anyone with a working knowledge of CT and images can thereafter be sent for evaluation of the CT angiogram.

References
In the dark ages of ultrasound, small intestinal loops were merely black rings on the ultrasound screen. It was only within the last 20 years that we were able to discern the various layers of all parts of the gastrointestinal tract. Within that short period of time we defined the appearance of many diseases and have advanced the technology necessary to perform minimally invasive ultrasound guided procedures. In this talk we will discuss the appearance of the normal gastrointestinal tract and cats and dogs and the ultrasonographic appearance of the surgical and medical diseases.

In both dogs and cats, all portions of the gastrointestinal tract have 5 acoustic layers. The outermost layer is the serosa, followed by an inner black layer of muscularis, submucosa, thicker black mucosa and finally the inner mucosal interface. The serosa and mucosal interface are not real histologic layers, but represent interfaces between the adjacent fat (serosa) and luminal contents (mucosal interface) of that portion of the intestinal tract.

Measurement should not be made of these layers. The remaining 3 layers represent histologic subdivisions within the gastrointestinal tract and are variable in thickness and proportion depending on the species and portions of the tract being evaluated.

<table>
<thead>
<tr>
<th>Thickness (mm)</th>
<th>Dog</th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Duodenum</td>
<td>5.1 – 5.7</td>
<td>3</td>
</tr>
<tr>
<td>Jejunum</td>
<td>4.1 – 4.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Ileum</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Colon</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

When scanning the gastrointestinal tract, measurement should be made of all these layers as part of a normal scan. I only measure total wall thickness, although I always subjectively evaluate the proportion of each sublayer. The measurement of the stomach assumes a mild amount of luminal contents, since a completely empty stomach is almost impossible to measure the wall thickness because of accumulation of exaggerated rugal folds. Similarly, I assume modern moderate contents in all patients and assume that the wall will be thin because of this effect. You may read thicker measurements of the colon assuming patients that have no luminal volume.

During the remaining portion of this presentation, we will discuss causes of thickness and loss of layering. We'll discuss surgical and nonsurgical conditions in each of the sub sections of the gastrointestinal tract. We will discuss the major differences between cats and dogs. It will discuss the necessity for imaging adjacent structures and affiliated structures associated with malignancy.

Of special note are certain surgical conditions that should not be missed during an ultrasound examination of a dog or cat. These include mechanical obstruction. To reach a diagnosis of mechanical obstruction you need 3 components; 1) fluid distended segment, 2) empty segment and, 3) transition point with lesion identified. Lacking any one of these 3 components should leave you in doubt as to whether the patient has a surgical condition. Possible lesions at the transition point include foreign body, neoplastic mass or intussusception. Most foreign bodies have a very hyperechoic interface and are very hyper attenuation (shadowing).

Linear foreign bodies are another very important surgical condition. The exaggerated plicated appearing folds of intestines form the basis of this diagnosis. Often the linear form body itself can be identified by hyperechoic interface and shadow artifact. This assumes a larger foreign body, but very thin foreign bodies may not have a shadow. The plicated appearance needs to be differentiated from corrugations and examples will be given in the lecture. Corrugation is intestinal wall spasticity and is caused by medical conditions, whereas plication is a surgical condition.

Finally regardless of the location of the gastrointestinal lesion, we must always be on the lookout for metastatic disease. A complete evaluation of the draining lymph nodes is paramount for evaluation of metastatic disease. For gastric lesions we evaluate the gastric lymph nodes which lie between the liver and stomach. For duodenal and jejunal lesions we evaluate the lymph nodes at the root of the mesentery (jejunal lymph nodes). At the ileocolic junction cats we evaluate the right colic lymph nodes. For all lesions of the gastrointestinal tract you should consider evaluating the sternal lymph nodes. These lymph nodes drain the cranial abdomen and are involved with both neoplastic and reactive diseases. These are easily evaluated and only add a few seconds to a complete a
abdominal ultrasound scan. They are often the easiest site to perform a fine needle aspirate upon, in cases of a deep cranial abdominal primary mass lesion.

Gastrointestinal disease is extremely common. In our clinical caseload, primary gastrointestinal disease forms at least 25% of all cases. Diseases such as lymphoma and inflammatory bowel disease are extremely common in cats need to be recognized in clinical cases. In both cats and dogs surgical conditions need to be recognized so that patients are promptly taken the surgery. Ultrasound has the advantage of prompt, real-time imaging and ability to take samples within a relatively short period of time. The modality has very little overhead costs associated with it with the exception of clinical experience and skill of the ultrasonography.
Recent research, both at other institutions and the University of Illinois, indicates that the pre-conceived notion of pulmonary edema causing a cough is somewhat misguided. Previous research has demonstrated mixed interpretations to the correlation between a large left atrium and large airway collapse. The most likely manifestation of pulmonary edema is increased respiratory rate and weakness. In those dogs with mitral valve degenerative disease, those same patients are at very high risk for the generation of their larger airway walls (=tracheal collapse syndrome, =chondromalacia, =broncomalacia). In this lecture we will go through a series of case examples demonstrating interdependency of left atrial enlargement, large airway collapse, and the likelihood of concurrent pulmonary edema.
Respiratory tract disease is both serious and extremely common. For 95% of all patients the only imaging modality available has been radiography. Radiography has the advantage of a strong historical basis, a good overview of everything within the thorax and inherently good contrast to identify the underlying structure involved. However, we are extremely limited in the characterization of mild or less classic abnormalities. Additionally, radiographs are quite poor for the evaluation of heart size in cats and may not be indicated in extremely dyspneic patients early in the course of therapy. During this election we will discuss more advanced respiratory imaging, especially computed tomography, and its role in both emergency and general veterinary practice.

Considerations to advanced conventional radiography are many. In our practice we routinely take 3 views for the evaluation of the most common diseases, including metastatic lesions. The 3rd view is the opposite lateral which allows us to see the middle lung field without superimposition. We often add a lateral neck section for dogs where laryngeal or tracheal disease are likely. This includes dogs with suspected tracheal collapse (small breed dogs and miniatures) or cats where laryngeal masses. Additionally dogs with laryngeal paralysis or laryngeal collapse will benefit from a lateral neck projection. Laryngeal collapse is seen in brachycephalic breeds. Laryngeal paralysis is seen in large breed dogs and certain miniature breeds. A 5th view is added when a dynamic large airway disease is suspected, such as collapse of either the trachea or larger bronchi. This is extremely common in our small breed dogs.

We routinely take horizontal beam VD radiographs in our trauma patients. These projections greatly improve our ability to detect small volumes of pneumothorax and better characterize the volume in more serious cases. Additionally, it allows us to evaluate for concurrent free fluid in the dependent portion of the chest. Examples will be given that display the improved characterization and detection of pleural disease with horizontal beam radiography.

Video fluoroscopy is very useful in cases of dynamic disease. This is especially true with the esophagus, which is beyond the scope of this lecture. Classically this modality has been used for the evaluation of collapsing trachea. However, given the prevalence of collapse of additional large airways including the principal and lobar bronchi, video fluoroscopy does not perform as well for those large airways. Multiple recent papers indicates that collapse of these large bronchi is more common than true tracheal collapse in dogs with chondromalacia.

Perhaps the most exciting new form of respiratory imaging is being performed with multiple slice CT. Multi-slice CT provides extremely rapid imaging and therefore opens the door to imaging patients on an emergency basis for evaluating functional lesions. CT has greatly improved spatial resolution and also allows for contrast enhancement of any space occupying lesion within the chest.

Combining this new technology with novel motion limiting devices provides the basis of the new wave of emergency respiratory imaging. The paradigm for the future should be imaging dogs that are awake, without any sedation or anesthesia if possible, to better demonstrate the lesions under disease states (rather than exaggerated or minimized by the effects of anesthesia). Many novel motion limiting devices have been proposed. Most allow for the administration of both oxygen and intravenous fluids during the imaging. The device should provide no additional artifacts or stress to the patient. It should be a device that could be additionally used in an emergency or intensive care setting for the administration of oxygen even without imaging being performed. It should be relatively inexpensive to manufacture and rugged for routine clinical use.

CT has greatly improved contrast resolution compared to radiology. Lung lesions are much better characterized on CT. Lung lesions can be detected even when surrounded by pleural lesions. The ability to perform contrast enhanced CT greatly improves on this contrast resolution. Angiographic CT also provides the ability to diagnose pure vascular lesions such as lung lobe torsion and pulmonary thromboembolic disease. Both of these lesions have been imaged and awake patients using modern systems and novel CT protocols.

Under certain emergency circumstances, echocardiography is relatively contraindicated due to the stress associated with restraint for the procedure. This is especially true in cats. By delaying echocardiography until the patient is more stable often results in unacceptable delays in appropriate therapy. CT has the unique capability of characterizing the size of the left atrium compared to the size of the aortic root on survey imaging. The importance of this cannot be exaggerated on an emergency basis. The implications are that a patient without an IV catheter and too dyspneic for echocardiography can be imaged without any handling or restraint within a motion limiting device and determination made for all the components necessary for the diagnosis of left–sided congestive heart failure; pulmonary edema and large left atrium. Additionally, this imaging can be performed in approximately 15 seconds without the need for any initial scanning to determine location of the body part of interest.

Finally, and perhaps most exciting, is the ability of CT to evaluate for large airway collapse. This takes us beyond the diagnosis of tracheal collapse into the region of principle and lobar collapse. A particularly difficult clinical situation has been in circumstances of the cardiac murmur and concurrent cough. There is a tendency to over diagnose this clinical scenario as being a cardiogenic cough due
to pulmonary edema with the ensuing overtreatment with diuretics and other cardiac medications. Recent evidence indicates that costs are quite unlikely with pulmonary edema and that the most common cause is bronchial collapse due to chondromalacia. CT is uniquely able to make this diagnosis in an awake patient. Cases will be discussed that exemplify this clinical situation. There is some suggestion that bronchomalacia (caused by chondromalacia) may be genetically associated with another cartilaginous degenerative disease; and endocardiosis. Therefore concurrence of the lesion should be expected rather than thought an unlikely combination of two unassociated diseases.

In summary, traditional ready graphic projections are easily made to improve respiratory imaging and cats and dogs in general practice. Video fluoroscopy adds to the sensitivity and characterization of functional diseases, especially involving the esophagus. But it is with CT that we can make major improvements in respiratory tract imaging that involve both primary pulmonary lesions, large airway characterization and vascular lesions that are so common in dogs and cats.
Contrast Studies that are Still Being Used Today
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The inherent poor contrast within the abdomen and the fact that soft tissue and fluid can not be differentiated radiographically means that contrast media are required for assessment of luminal surfaces, and therefore wall thicknesses of the gastrointestinal tract. Contrast studies are most commonly performed to identify anatomy not visible on plain radiographs and to evaluate the integrity of the hollow viscous organs. They may be used to determine function, as in gastric emptying and small intestinal transit.

Contrast media
Positive contrast media includes barium and iodinated options. The choice may depend on clinical, cost and availability limitations. The most important variable is the clinical situation.

Barium is very, very opaque and very inexpensive. We depend on barium contrast media for routine studies of most components of the gastrointestinal tract. Barium is inert, relatively palatable, has no osmotic potential and coats the mucosal of the gastrointestinal tract very well. Barium may be mixed with food for esophageal studies, although this will compromise a subsequent upper GI series. Barium is formulated as a suspension is not osmotically active.

Barium sulphate comes in a variety of centractions, normally classified by “weight-to-volume” (w/v). We usually dilute the concentration to make it 60% w/v for esophageal or 30% w/v for gastric and intestinal studies. Aspiration of barium has morbidity associated more with the volume and concurrent acidic gastric contents, then from any direct effect of the barium sulphate. Barium is relatively contraindicated in species with extremely slow transit time (especially reptiles) and with known gastrointestinal tract rupture.

Iodinated media
Iodinated contrast media are based on attachment of the iodine molecule to benzene ring compounds. These tri-iodinated monomers or dimmers protect against many adverse reactions of unprotected iodine in the body. Iodinated media are water soluble and therefore osmotically active. Iodinated agents are preferred if endoscopic evaluation of the GI tract is being consider after the GI radiographic contrast study.

High-osmolar iodinated contrast media
These are less expensive than low-osmolar agents. There are contraindications to the high osmolarity and when used as a gastrointestinal agent the contrast material becomes more dilute as it passes along the GI tract. This may be clinical important in dehydrated or neonatal patients. The high osmolarity irritates the GI mucosa and GI transit times are faster with iodinated agents, compared to barium agents. Aspiration of high osmolar agents results in severe pulmonary edema. These agents are diluted by their osmolar effects pulling fluid in from the interstitium into the lung alveoli.

Low-osmolar iodinated contrast media
Both ionic and non-ionic agents are available in this category of ionic agents. These agents result in fewer adverse effect including pulmonary edema if aspirated. Low-osmolar agents are preferred for the GI tract because they are not diluted as they pass through the GI tract.

Survey radiographs
Survey radiographs provide the basis of our contrast imaging of patients. In the abdomen we gain a tremendous amount of information regarding the gastrointestinal tract; overall dimensions, content and evidence of regional disease. Survey radiographs fall short of providing a definitive diagnosis when our confidence is low, there are ambiguous radiological findings, the radiological findings conflict with the clinical signs or the disease is entirely occult on survey radiographs.

Esophagography
Esophagography is very useful to identify a cause of regurgitation or to rule-out a possible stricture, perforation or foreign body. Other differentials include broncho-esophageal fistula, hialtal hernia and gastroesophageal hernia. Verify location of pulmonary mass in relationship to esophagus. A dose of 1 ml/10 lb body weight of barium suspension per os is usually sufficient. However, extravasation of barium into the mediastinum is a relative contraindication and may make the use of a nonionic iodinated contrast safer. The contrast is administered per os, trying to avoid overdosing while the patient alternatively breathes and swallows. Radiographs should be taken within 5 sec of start of contrast administration. Whilst this study is still ”state of the art” for functional pharyngeal disorders, these studies are dynamic and require videofluoroscopy and slow motion frame-by-frame analysis for complete evaluation.

Pneumogastrography
There are two location in the GI tract where use of a negative contrast study is indicated. The first is a the negative contrast gastrogram or pneumogastrogram. The most common indication is suspected lucent foreign body; ball, cloth, hair, toys. Air is administered by orogastric tube. I hardly think that this audience needs tutoring on passing an orogastric tube, but I usually
recommend as small a gauge as possible (we are not lavaging the stomach) and making sure to allow the dog to swallow each time the tube reaches a sphincter; upper and lower esophageal. The end point of "full gastric distension". Although a dosage (6 ml/lb body weight of air) is provided, I have always just blown into the tube a volume subjectively thought to be appropriate for the patient size. This study has the utility that if diagnostically negative, does not preclude a subsequent upper gastrointestinal series. However, if an ultrasound examination is being considered, than the US exam should be performed prior to any negative contrast study.

**Positive contrast gastrography**

This study is especially indicated to quickly determine stomach positioning or for suspected gastric or duodenal perforation. The contrast used depends on the indication. For cases of suspected perforation, nonionic iodinated contrast is indicated. Extravasation of barium suspension may cause unacceptable adhesions and barium granuloma formation if the surgery is delayed following the study. However barium extravasation is much easier to detect than iodine in cases of perforation, so decreased sensitivity must be balanced against surgical complications. If surgery can be performed immediately following the study, barium ids the contrast of choice. In either case the dose is 3 ml/lb body weight of contrast via orogastric tube.

**Upper gastrointestinal (UGI)**

Although largely supplanted by ultrasound, the UGI series may be a faster and more sensitive test for certain small intestinal diseases. Indications still include suspected gastrointestinal obstruction, intussusception or linear foreign body. The UGI series works best in an emergency setting with a proximal ("high") small intestinal lesions where the lesion is noted after only a brief wait for passage of barium. Distal lesions may require many hours for passage barium. Larger and older dogs have slower small intestinal transit, compared to cats or smaller and younger patients. Normal gastric emptying is 4 hours in dogs and 2 hours in cats. The dose for an UGI study is 6 ml/lb body weight of 20% weight/volume barium suspension via orogastric tube.

**Pneumocolonogram**

This is the most common gastrointestinal contrast study performed in our academic setting. The indication is suspected, but not highly suspected, small intestinal obstruction. Maybe there is one or two loops of intestine which are moderately enlarged and you can not tell whether they are small intestinal or colonic loops. This study very quickly provides the information as to "who is the colon". The dose is 4 ml/lb body weight via rectum by Foley catheter. The balloon of a large diameter catheter is very gently filled to seal the rectum and the air slowly infused. A single VD view may suffice, although lateral projections may augment the study.

**References**

Learning ultrasound is hard enough! Haven't we done enough just to make accurate descriptions and list most appropriate differential diagnoses? The short answer is maybe. In this talk we will discuss the pros and cons of ultrasound guided interventional procedures. We'll discuss the indications and contraindications and equipment that should be utilized. We will try to add a component of economic importance to this discussion.

At the University of Illinois that in her teaching hospital approximately 70% of all for some patients have an interventional procedure. This may be as simple as a sister some pieces or is complex is an extremely difficult core or fine needle aspiration. The prevalence of this procedure in our practice makes it vital for both providing high-quality medical care and is a major source of income to the hospital. It is very common for our clinicians not to be very concerned about the description of the ultrasonic graphic findings, but rather insist upon a diagnostic sample of liver, spleen, etc. Even many normal appearing organs may be a site to perform a fine needle aspiration under certain circumstances, such as the spleen in certain cases of mass cell tumor.

The indications to perform intervention are varied. It may be as simple as elevated liver enzymes of the appearance of nodules within the liver parenchyma. Generally, any nodule, mass, fluid pocket is fair game for a fine needle aspiration. Core biopsy is done very infrequently and only in very specific circumstances (e.g., liver in cases of copper storage disease or chronic active hepatitis). We've had very good luck with most diseases using fine needle techniques.

Equipment necessary to perform fine needle aspiration is quite simple and inexpensive. A 22 or 25gauge needle of appropriate length attached to a 5 to 10 mL syringe is all that is required. Limited patient preparation is required. Rarely do we need to assess platelet number or coagulation status for such a limited study. The gel is removed from the patient and isopropyl placed for coupling. Any residual gel in the needle path may result in a basophilic haze on the cytologic sample making it nondiagnostic. The needle is then inserted through the skin and into the area of interest whereafter multiple-agitations of the needle are made to pack the needle with cells and quickly withdrawn. We usually perform 3 aspirations but in certain circumstances may just perform a single aspiration. This is usually dependent on patient clinical concerns. Use of larger gauge needles should be considered when drainage is of interest. This would include pericardial sac, any abscess for even the peritoneum. I find that 25gauge often gives me a good diagnostic sample and is much less painful, especially in older cats. In one study performed in Australia, 25 gauge samples were as good as or better compared to 22gauge. However in our institution, there is a bias against 25gauge and our clinical pathologists prefer larger samples obtained with 22gauge needle. The downside to the larger gauge is increased likelihood of hemodilution and pain to the patient.

Problems associated with interventional procedures are usually limited and mild. Bleeding is inevitable but usually not detectable. An exception is with especially friable tissues such as livers with hepatic lipidosis or spleen with lymphoma. Many apparently dangerous structures may be samples with lower than anticipated morbidity, such as the pancreas. Although we were historically told not to perform fine needle aspirations when the pancreas was inflamed, there is no clinical basis to suspect that fna of this organ is more likely to result in serious clinical effects than any other organ. The most likely cause of morbidity is missing your target. This is very easy especially early in your learning curve. It is usually also associated with increased duration of your biopsy efforts. They longer the procedure, the more likely there will be morbidity. Fast and efficient should be your motto. However, this requires experience and appropriate skills.

Learning to perform these procedures will require a certain amount of confidence and a good quality ultrasound machine system. Beginning with phantoms is often preferred by neophytes. This could be a gel phantom made with cooking gelatin and flour mixture or a raw turkey breast. But eventually you will have to start performing procedures on your patients. I recommend beginning with cystocentesis. This is a procedure that you do not need ultrasound for, and therefore will feel more comfortable beginning your ultrasound guided efforts. This is relatively simple because, 1) the target is big, 2) the target is superficial, and 3) when you are inside the target the needle will be very bright against the dark black background. After you develop some comfort with this procedure I recommend beginners move on to free fluid sampling in the peritoneum. Eventually you will work up to the pleural space in the chest and other more exacting sites. The liver is probably the most common site for us to perform a fine needle aspiration. This is either due to liver enzymes being elevated or detection of echogenic lesions such as nodules. These can be easy or extremely difficult depending on the depth of the lesion, patient movement (such as panting) and other clinical concerns. Eventually you'll get down to very small lesions including the gastrointestinal tract, lymph nodes and other small nodules. The limit of targets is only based on your experience and skills. For example, how small of a nodule to feel comfortable performing at aspirate upon in the lung, knowing that if you miss the target you will cause pneumothorax? Again, everyone has their limitations where they say, " I don't think so".

In summary, interventional ultrasound techniques are extremely common and usually very safe. In addition they significantly add to the quality of medical care being provided to the patient's and provides a diagnosis of many diseases with a simple, brief procedure.
Just as important it is a substantial economic boost to your practice. Again, 70% of all of our patients in ultrasound have some form of interventional procedure performed. If you are performing 10 ultrasound examinations a day and with a hypothetical cost of $30 per fna, daily income would be over $200, not counting the additional fee for psychological evaluation with very little overhead involved. I strongly recommend that when your skill sets are at an appropriate level, that you take on the additional task of performing interventional ultrasound procedures. These procedures are clinically very rewarding as well as challenging on a daily basis.
(HAC) is one of the most, if not the most, common endocrinopathies of older dogs. Due to the high incidence and relatively non-specific clinical signs, older dogs are commonly screened for HAC. Diagnosis requires testing such as the low-dose dexamethasone suppression test (LDDST) or the standard ACTH stimulation test with measurement of serum cortisol pre- and post-ACTH injection. Unfortunately, neither test is perfect, however.

**Atypical or occult hyperadrenocorticism**

These terms are used to describe dogs in which clinical signs and response to treatment are consistent with a diagnosis of HAC, but the standard screening test (ACTH stimulation test, low-dose dexamethasone suppression test) results are within the reference range. The reasons for the clinical signs in these patients are currently unknown. It has been proposed that increased circulating concentrations of steroid adrenal hormones other than cortisol (e.g., progesterone, 17-hydroxyprogesterone, androstenedione, dehydroepiandrosterone) may be responsible for the clinical signs in occult HAC, but this is controversial except in the few documented cases of sex-hormones-secreting adrenal tumors. Sex-hormone-secreting adrenocortical tumors can be identified because of the presence of an adrenal mass; in these dogs cortisol concentration after ACTH administration is typically suppressed below the reference range. Although dogs with apparent, pituitary-dependent occult HAC have been reported in the literature they are rare. Other potential reasons for normal screening test results in occult HAC patients may include individuals with increased sensitivity to glucocorticoids, inappropriately high reference ranges for cortisol in dogs with early or mild HAC, as well as rare forms of HAC such as food-dependent HAC.

The first report of clinical signs thought to be due to elevations in adrenal-derived sex hormone concentrations described diffuse bilaterally symmetrical alopecia and hyperpigmentation in 7 Pomeranians. Classic HAC was ruled out. Progesterone, 17-hydroxyprogesterone (17OHP), 11-deoxycortisol, dehydroepiandrosterone sulfate (DHEAS), testosterone, androstenedione, and estradiol were measured pre- and post-ACTH in 7 affected Pomeranians, 12 unaffected Pomeranians and 19 non-Pomeranian control dogs. Only ACTH-stimulated 17OHP concentrations were different between affected and unaffected Pomeranians, but ACTH-stimulated progesterone and DHEAS concentrations were significantly higher in both affected and unaffected Pomeranians as compared to the controls. Based on the findings, it was hypothesized the alopecia was due to a partial deficiency of 21-hydroxylase, an enzyme needed for cortisol synthesis. In humans with 21-hydroxylase deficiency and resultant congenital adrenal hyperplasia (CAH), cortisol is not synthesized and cortisol precursors, most notably 17OHP and androgens, accumulate. Since affected Pomeranians had normal serum cortisol concentrations, the enzyme deficiency was assumed to be partial. Family members of people with CAH have sex hormone elevations to a lesser magnitude and no clinical signs, thus explaining the abnormalities in the unaffected Pomeranians (many of the affected and unaffected Pomeranians were related). Subsequently, 3 Alaskan Malamutes with Alopecia X were reported to have ACTH-stimulated 17OHP concentrations above the reference range and that were significantly higher than those in 3 normal Alaskan Malamutes.

More recently, a study of 23 dogs all of which had clinical and routine laboratory findings suggestive of HAC was reported. Of the 23 dogs, 11 were assigned to Group 1 that had typical HAC with an elevated cortisol response to ACTH. Of 10 dogs with a normal ACTH response, 6 had a positive LDDST (Group 2A), 4 had a negative LDDST (Group 2B) and 3 had low plasma cortisol concentrations throughout an LDDST (Group 2C). However, all 23 dogs had elevated ACTH-stimulated 17OHP concentrations. It was concluded that ACTH-stimulated serum 17OHP concentration is elevated in dogs with classic as well as occult HAC and measurement of serum 17OHP concentration is a marker of adrenal dysfunction. Numerous other studies have also documented elevations in sex hormone concentrations in dogs with various forms of hypercortisolemia, either pituitary-dependent HAC (PDH) or due to an adrenal tumor (AT). More specifically to the point, in cases where cortisol and sex hormones are both elevated, which hormones are causing any of the clinical signs of HAC present is difficult to impossible to determine. However, sporadic reports exist of dogs with sex hormone-secreting AT and low serum cortisol concentrations but in which clinical signs of HAC were present, ostensibly due to the sex hormones.

Two mechanisms have been proposed for progesterone's ability to cause signs of glucocorticoid excess. Synthetic progestins, compounds with progesterone-like actions, may either bind glucocorticoid receptors or may displace cortisol from its binding protein, thereby elevating serum free cortisol concentrations. Indeed, progestins suppress endogenous ACTH secretion and cause adrenal atrophy, an action suggestive of glucocorticoid activity. Accordingly, progesterone may do the same. Examination of Pomeranians with Alopecia X, however, refutes the likelihood of either mechanism occurring. If elevated serum 17OHP concentration as seen in those dogs is sufficient to cause clinical disease due to glucocorticoid actions of 17OHP, endogenous ACTH concentration should be
suppressed due to negative feedback effects of glucocorticoids on the pituitary. To the contrary, Pomeranians with elevated serum 17OHP concentrations had higher plasma ACTH concentrations than healthy dogs. Similarly, during diestrus when serum progesterone concentrations are highest, adrenal secretion of cortisol in response to ACTH is greatest.

Sex hormones can be elevated in dogs with either PDH or AT. However, in most cases, whether hypercortisolemia or the sex hormones are causing the clinical signs is impossible to distinguish. Sex hormone elevations, however, have been documented to cause clinical signs of HAC even in cases where cortisol concentrations are suppressed. On the other hand, in humans and intact female dogs, sex hormone elevations do not always cause clinical signs or cause signs associated with the reproductive function of the hormone and not of occult HAC. A mechanism by which sex hormones could cause the signs of occult HAC or by which adrenal glands would shift their hormone production in PDH is lacking. Occult HAC, if it does exist, has only truly been possibly documented in a handful of cases.

In dogs with either Alopecia X or purported occult HAC, treatment with agents that affect pituitary or adrenal function has resulted in resolution of clinical signs. Melatonin alters sex hormone concentrations in intact dogs; it was administered initially in 29 dogs with Alopecia X. Of the 29 dogs, 15 had partial hair regrowth. In 3 Alaskan Malamutes with Alopecia X, treatment with trilostane resulted in complete hair regrowth within 6 months. Of 16 Pomeranians and 8 miniature poodles with Alopecia X, 14 Pomeranians and all poodles had hair regrowth in response to trilostane. In another study on occult HAC, 9 dogs in groups 2A, B or C (i.e., were diagnosed with HAC but had normal ACTH-stimulated cortisol concentrations) were treated with trilostane or mitotane, and all had clinical improvement. Decreased ACTH-stimulated cortisol and/or 17OHP concentrations were documented in 4 of the 9. Lastly, in 1 dog with clinical signs of HAC and normal post-ACTH stimulated cortisol and LDDST results but an elevated ACTH-stimulated 17OHP concentration, clinical signs resolved with mitotane therapy.

Although successful therapy has been reported, 2 main problems exist. First, not all dogs respond to melatonin, mitotane or trilostane. Response has no apparent correlation to sex hormone concentrations; hair regrowth can be seen even in dogs in which serum sex hormone concentrations do not improve. Secondly, serum sex hormone concentrations can even increase yet the clinical signs resolve. It is hard to explain how further elevations in sex hormones can be associated with remission if the sex hormones are causing the clinical signs.

**Conclusion**

Whether occult HAC is due to adrenal secretion of sex hormones has never been conclusively proven. In the literature, both human and veterinary, evidence exists both in favor and against the theory. Using the research into Alopecia X as an analogy for occult HAC, although occult HAC was originally thought to be due to sex hormone abnormalities and elevations in sex hormone concentrations were widely documented in dogs with Alopecia X, later research was unable to detect a correlation between elevations in any hormone and a clinical abnormality. The specificity of adrenal sex hormone panel testing needs to be closely evaluated as evidence suggests that sex hormone concentrations may be easily elevated non-specifically due to NAI. Furthermore, not all dogs diagnosed with occult HAC respond to therapy directed at minimizing adrenal secretion. Sex hormones may be elevated even further by therapy, yet dogs improve clinically.

The possibility remains that "occult HAC" may exist as a syndrome, but one that is not caused by sex hormone secretion. Given the response of Alopecia X in some cases to therapy directed at hormone secretion, it is possible that local factors such as enzymes, growth factors or hormone receptors may contribute to the hair cycle abnormalities and be acted upon by substances secreted by the adrenals to manifest the clinical signs. The same could be true of occult HAC - abnormal local tissue response to cortisol, for example, could cause the syndrome. Much work remains to be done to understand both the adrenal and local tissue contribution to occult HAC.
The principles of therapy for immune-mediated hemolytic anemia (IMHA) and immune-mediated thrombocytopenia (ITP) include:

- Treat the underlying disease, where applicable
- Inhibit red blood cell and/or platelet phagocytosis
- Decrease auto-antibody production
- Monitor and potentially undertake prophylactic therapy for complications
- Provide supportive care

Treating the underlying disease

If a secondary cause of IMHA or ITP is identified, treatment of the cause may diminish the need for prolonged immunosuppressant therapy. Therefore a thorough investigation for a potential cause is recommended. This investigation should include a detailed history of medications/supplements as well as travel, comprehensive physical examination, complete blood count, blood film evaluation, serum biochemistry, urinalysis, full body imaging, and testing for blood-borne parasites. Depending on the geographic location of the practitioner and travel history of the patient, treatment for rickettsial disease with doxycycline (5 mg/kg PO q 12 hr or 10 mg/kg PO q 24 hr) may be recommended even despite negative screening test results.

Immunosuppressive therapy

Immunosuppressants work by a variety of methods to decrease phagocytosis of red blood cells or platelets by the mononuclear phagocyte system and to decrease anti-erythrocyte and anti-platelet production by lymphoid tissue. For either primary IMHA or ITP, it is important to prepare the owners for months of therapy, typically greater 6 months. Medications are tapered slowly, usually by decreasing the dose by 25% of the initial dosage every 2-4 weeks. If a patient is on multiple immunosuppressant medications, only one medication should be tapered at a time. Typically the medication causing the most annoyance to the owners at the time – whether that is by side-effects or financial burden – is the one chosen to be tapered. Some patients may require life-long therapy.

Glucocorticoid therapy is the mainstay of immunosuppressive therapy. Glucocorticoids exert a relatively rapid effect (i.e. within days) upon the immune system by reducing Fc-mediated phagocytosis of red blood cells and/or platelets by macrophages. With chronic use, glucocorticoids may also inhibit antibody production in some patients. Of all the immunosuppressive medications, glucocorticoids have the least financial burden for the owner. However, for all the benefits of glucocorticoids, they come at a high cost in terms of adverse effects. Side effects include iatrogenic hyperadrenocorticism, gastrointestinal ulceration, insulin resistance and secondary diabetes mellitus, loss of muscle mass and muscle strength, increased risk of ligamentous injury, impaired wound healing, increased susceptibility to infection, and behavioral changes. Symptoms of iatrogenic hyperadrenocorticism (e.g. polydipsia, polyuria, polyphagia) can be so severe as to hinder owner compliance.

Some clinicians prefer to start with an injectable dose of glucocorticoids such as dexamethasone (0.25 mg/kg IV q 24 hr.) before transitioning to oral therapy, but there is no evidence as to whether this hastens recovery. However, it is a reasonable choice in an anorectic patient or a patient otherwise challenging to administer oral medications. Prednisone or prednisolone can be dosed at 2 mg/kg/day. There is no additional immunosuppressive benefit to higher doses; simply more severe side-effects will be seen. Since the adverse effects of glucocorticoids tend to be more dramatic in large breed dogs, the speaker uses allometric scaling when dosing prednisone for large breed dogs, using a dose of 40 mg/m²/day.

It is up to clinician preference whether to start a patient with IMHA or ITP at the time of diagnosis on single-agent glucocorticoid therapy or a combination of a glucocorticoid plus a secondary immunosuppressant. It may be reasonable in a patient with milder primary disease or in most cases of secondary disease to start with only prednisone. A secondary drug may be added in at a later date if the patient fails to respond to the prednisone or develops intolerable side-effects. The speaker prefers to start a secondary immunosuppressant at the time of diagnosis for patients with fulminant disease (e.g. an IMHA patient with macroagglutination or severe anemia, an ITP patient that is transfusion dependent) and in large-breed dogs.

Azathioprine (2 mg/kg PO q 24 hr for 5-7 days then q 48 hr) is a drug with a long history of use as an immunosuppressive agent in veterinary medicine. It is a purine analogue. By competing with purine for incorporation into RNA and DNA, nonfunctional DNA and RNA is created. This disruption of DNA and RNA synthesis inhibits the proliferation of fast-growing cells. Lymphocytes in particular are affected as they lack a salvage pathway for purine biosynthesis. In addition to interfering with lymphocyte proliferation, azathioprine also decreases T-cell-dependent antibody synthesis. It can take several weeks for azathioprine to exert its full effect.

While generic azathioprine is very inexpensive – monthly drug costs are less than prednisone – azathioprine requires diligent bloodwork monitoring for side-effects. The cost of additional bloodwork adds to the costs for the owner. There may be mild gastrointestinal side-effects at the start of therapy, but more concerning is the potential for hepatotoxicity or myelosuppression. These
adverse events appear to be non-dose-dependent idiosyncratic reactions and are typically reversible if recognized promptly. Therefore complete blood counts and a serum biochemistry should be regularly monitored (e.g. initially q 1-2 weeks, eventually monthly) during azathioprine therapy.

Metabolites of azathioprine are methylated by thiopurine methyltransferase (TPMT). TPMT activity varies from patient to patient. In humans it has been shown to correlate both to the therapeutic efficacy of azathioprine in a particular patient as well as the risk of azathioprine-induced myelosuppression. Cats as a species have reduced levels of TPMT as compared to dogs or humans, which may account for their risk of myelotoxicity to the drug. However, reduced TPMT activity did not correlate with myelosuppression in dogs in one study.

Cyclosporine (3-6 mg/kg PO q 12 hr) inhibits calcineurin, an intracellular enzyme that activates gene transcription factors. Activation of T-cells is blocked by calcineurin inhibition, as is production of interleukin-2 and other cytokines. Thus cyclosporine disarms cellular immunity but has little effect on humoral immunity. It has a relatively fast onset of action and has the potential for less systemic adverse effects. Mild gastrointestinal upset is the most common side effect. It is often transient or responsive to dose reduction. Anecdotally, keeping the drug chilled or frozen diminishes this side-effect. In rare cases, nausea or anorexia may be severe enough to require drug discontinuation, however. Hypertrichosis and gingival hyperplasia may occasionally be seen. Rare side-effects include psoriasiform-lichenoid-like dermatosis, opportunistic infections, and lymphoproliferative disorders.

The two biggest drawbacks to cyclosporine are its cost and bioavailability. It is one of the most expensive oral immunosuppressant agents regularly used in veterinary medicine. This may tempt the clinician to seek out alternative sources of versions of the drug. However oil-based formulations (i.e. formulations labeled as bioequivalent to Sandimmune®) should not be used in veterinary patients as they have very poor gastrointestinal absorption. Microemulsions (i.e. formulations labeled as bioequivalent to Neoral®) have improved gastrointestinal absorption. Atopica® is a microemulsion that is an approved veterinary product. Novartis often offers patients as they have very poor gastrointestinal absorption. Microemulsions (i.e. formulations labeled as bioequivalent to Neoral®) have improved gastrointestinal absorption. Atopica® is a microemulsion that is an approved veterinary product. Novartis often offers rebates for Atopica, making it cost competitive with human products. However, even with microemulsions use, bioavailability is variable from one patient to the next.

Because of the unpredictable bioavailability of cyclosporine, therapeutic monitoring may be performed. Measurement of blood trough levels has been the method used the longest in veterinary medicine. Target trough levels 400-600 ng/mL were extrapolated from canine and feline renal transplant studies. However, trough levels do not reliably predict clinical response in patients with immune-mediated disease. Human transplant medicine has moved to using peak cyclosporine levels to adjust cyclosporine dose, but target peak concentrations have not been established in veterinary medicine. Mississippi State University Pharmacodynamic Laboratory now offers a novel method for therapeutic monitoring. They can perform qRT-PCR assays of activated T-cell mRNA IL-2 and IFN-γ to measure the adequacy of immunosuppression in dogs to individually tailor cyclosporine dosing.

Mycophenolate mofetil (MMF; 10 mg/kg PO q 12 hr) is a newer immunosuppressant drug that is gaining favor in treatment of a variety of immune-mediated diseases in veterinary medicine. MMF selectively inhibits de novo purine synthesis. Both T and B lymphocytes are entirely dependent on the de novo pathway for differentiation, proliferation and immunoglobulin production. As with cyclosporine, MMF has a relatively fast onset of action and has the potential for less systemic adverse effects. The main side-effect is diarrhea, most commonly seen at higher dosages. The diarrhea is not self-limiting and often persists as long as the patient remains on MMF. Occasionally it can be severe enough to lead to drug discontinuation. While MMF is not an inexpensive drug, it is significantly less expensive than cyclosporine.

Leflunomide (2-4 mg/kg PO q 24 hr) is another newer immunosuppressant drug. As with cyclosporine and MMF, leflunomide has a relatively fast onset of action and the potential for less systemic adverse effects. Self-limiting gastrointestinal upset is the most commonly encountered side effect. Rarely bone marrow suppression and cutaneous vasculitis have also been seen. While there is a case report of two dogs treated with leflunomide for ITP, anecdotally this drug has appeared more useful for treatment of immune-mediated polyarthritis than for IMHA or ITP. In addition, leflunomide is currently three times the cost of cyclosporine. For these reasons, leflunomide is not recommended for routine use in IMHA or ITP cases.

Both cyclophosphamide and danazol are no longer recommended for treatment of IMHA or ITP. In the case of cyclophosphamide, studies suggested increased morbidity and increased incidence of serious adverse effects in patients receiving the medication. In the case of danazol, studies suggested it is not efficacious.

Adjunctive immunosuppressive therapy

Vincristine (0.02 mg/kg IV once) is a useful adjunctive therapy for treatment of ITP. Vincristine binds to tubulin, a major component of platelet microtubules. When the vincristine-loaded platelets are consumed by macrophages they act as a Trojan horse, selectively delivering cytotoxic doses of vincristine to the macrophages involved in platelet destruction. In addition, vincristine stimulates releases of platelets by megakaryocytes in the bone marrow. Aggregation studies have shown that these platelets have normal function. Circulating platelet numbers thus increase within days of vincristine administration and platelet life-span is enhanced. The addition of vincristine to treatment for ITP has been shown to shorten hospitalization time by several days compared to prednisone alone in a non-randomized, unmasked trial. Vincristine is inexpensive and usually well tolerated at the dose used for ITP. There is the
possibility it can cause leukopenia and gastrointestinal upset, however. Finally, vincristine is a vesicant, so care must be taken during administration lest extravasation occur.

Human intravenous immunoglobulin (hIVIG, 0.5 g/kg IV once over 6-12hrs) appears to be useful in treatment of ITP, but has been shown to not improve survival in IMHA. The immunosuppressive effect of hIVIG has been attributed to blockade of Fc-mediated phagocytosis of platelets by macrophages but it probably works by other mechanisms as well. In a randomized double-blind, placebo-controlled trial, dogs receiving hIVIG had significantly faster recovery times compared to prednisone therapy alone. However the extreme cost of hIVIG and limited availability typically limits the use of hIVIG to severe, refractory cases. The major risk to the patient of hIVIG treatment is development of an acute hypersensitivity reaction from the foreign protein. 

Splenectomy is the treatment of choice for humans with chronic IMHA or ITP. Splenectomy removes a major site of antibody production and extravascular hemolysis and platelet destruction. In veterinary medicine few clinicians are eager to recommend such an invasive treatment in a critical patient and thus reserve it as a therapy of last resort. However, one small study looked at proactive splenectomy early in the course of treatment for IMHA and found increased survival. A more thorough evaluation of splenectomy would be ideal before widely recommending its use; however, it is likely an appropriate treatment for clinicians to consider in select patients.

Melatonin (3 mg PO q 12 hr < 30 lb, 6 mg PO q 12 hr > 30 lb) has anecdotally been used as an adjunctive therapy for ITP as well as for many other refractory immune-mediated diseases, including IMHA. Its use has been extrapolated from human medicine, where there are small case series of patients with refractory ITP that responded to melatonin. No controlled studies have been performed on the human or veterinary side, and the possible mechanism of action of melatonin is unknown. It is extremely inexpensive, readily available over-the-counter, and has a low rate of side-effects (drowsiness).

**Thromboprophylactic therapy**

Thromboembolism is a major complication of IMHA and a major cause of mortality. Not only does the disease inherently cause hypercoagulability, but our mainstay therapy – glucocorticoids – also contributes to the hypercoagulable state. Dogs with ITP are likely also prothrombotic, but their thrombocytopenia is likely “self-treating” their risk. Although larger studies are needed to definitively prove they improve survival, either aspirin (1 mg/kg PO q 24 hr) or clopidogrel (2-3 mg/kg PO q 24 hr) appear to be suitable thromboprophylaxis treatments. Both aspirin (when used at this ultra-low dose) and clopidogrel are well-tolerated. Unfractionated heparin is no longer recommended due to unpredictable bioavailability and expense associated with monitoring. While low molecular weight heparin may surmount some of these problems, the effective dose is currently unknown and the expense of low molecular weight heparin is unrealistic for most patients.

**Supportive care**

Patients receiving high-dose, long-term treatment with glucocorticoids are considered to be at higher risk for development of gastroduodenal ulceration. For this reason, many clinicians who start a patient on immunosuppressive doses of prednisone also prescribe one or more gastroprotectants (e.g. famotidine, omeprazole, misoprostol, and/or sucralfate). However, there is no evidence in the human or veterinary literature that any of these medications actually decrease the risk of steroid-induced ulcer development. The clinician should balance the burden of polypharmacy on the owner versus the unknown benefit from these drugs when contemplating the addition of these medications to the treatment plan. Even if there is minimal benefit from these medications, with the exception of misoprostol, they all tend to be well-tolerated.

**Cost considerations**

Unfortunately, financial constraints are an important cause of mortality in patients with IMHA and ITP. Initial hospitalization and multiple blood transfusions can run up a considerable bill. In addition, the ongoing costs of medications can be daunting. If your owners are filling prescriptions at a pharmacy, it may behoove them to compare prices between pharmacies. Drug prices are neither fixed nor regulated; there can be significant differences in mark-up from one pharmacy to the next. Owners can also seek out discount plans. For example, members of AAA have access to a pharmacy discount card as part of their membership. The website GoodRx.com is a free resource that scans currently available discounts and coupons and prints savings cards for owners.

Average cost of the first month supply of medications based on prices obtained from 1-800-Pet-Meds, Fosters & Smith, Pet360, and Walgreen’s pharmacies.
<table>
<thead>
<tr>
<th>Drug</th>
<th>30 kg Golden retriever</th>
<th>12 kg Cocker spaniel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>$24</td>
<td>$23</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>$16</td>
<td>$8</td>
</tr>
<tr>
<td>Atopica</td>
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<td>$204</td>
</tr>
<tr>
<td>Generic cyclosporine</td>
<td>$438</td>
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</tr>
<tr>
<td>Mycophenolate mofetil</td>
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<td>$104</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>$1227</td>
<td>$592</td>
</tr>
<tr>
<td>Aspirin</td>
<td>$&lt;1</td>
<td>$&lt;1</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>$169</td>
<td>$86</td>
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<tr>
<td>Melatonin</td>
<td>$8</td>
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</tr>
</tbody>
</table>
Fever is defined as an elevated body temperature (>103°F (>39.5°C)) due to an altered hypothalamic set point. Fever of unknown origin (FUO) is defined in human medicine as an illness of at least 3 weeks duration with a fever, for which a cause is not identified after 3 hospitalized days or outpatient visits. A consensus veterinary definition has not been developed, but many practitioners would agree diagnosis of FUO is justified when an elevated body temperature has been documented on several occasions (typically over a period of several days) in the absence of confounding factors such as anxiety or warm ambient temperatures. Temperatures consistently >105°F (>40.6°C) are uncommon in FUO and temperatures >106°F (>41.1°C) are more common with nonfebrile hyperthermia (e.g., physical exertion, heat stroke, muscle fasciculations).

Since FUO is, by definition, not easy to localize, there are no simple algorithm to provide an inclusive approach to achieving a diagnosis in all patients. The goal of the diagnostic plan should be to begin with simple, relatively non-invasive, inexpensive, and easy to interpret tests to identify an abnormality. Once an abnormality is identified, it can be used as the basis for more targeted diagnostic testing. A stepwise approach to testing will minimize the chances of overlooking any potential diagnostic differentials. The diagnostic plan should evolve as results of each diagnostic test become available. Finally, the plan should allow for repetition of simple and basic diagnostic tests.

Practitioners should be mindful that the investigation of FUO demands patience and often also considerable financial commitment from the client. When planning the diagnostic investigation, it is essential for practitioners to explain to clients that investigation of FUO can be time consuming and frustrating. Many diagnostic tests may be necessary, and certain tests may need to be repeated. However, practitioners should also reassure clients that the fever itself is rarely harmful to patients and a diagnosis is ultimately obtained in the majority of cases.

### Etiology

Infectious, immune-mediated, and neoplastic etiologies are the most common causes of FUO. There are a smattering of other diseases that can cause FUO that defy this categorization. See the chart below for a listing of frequently encountered etiologies.

#### Infectious
- Localized or systemic bacterial infections: diskospondylitis, osteomyelitis, bacterial endocarditis, septic arthritis, prostatitis, pyelonephritis, septic meningitis, cholangiohepatitis, abscesses, pyothorax, peritonitis, pneumonia, pyometra, catheter site infections
- Specific bacterial infections: leptospirosis, borreliosis, brucellosis, mycobacterial infections, bartonellosis, hemotropic Mycoplasma (**Haemobartonella**), tularemia, salmonellosis
- Viral: canine influenza, canine distemper virus, parvovirus/panleukopenia, feline leukemia virus, feline immunodeficiency virus, feline infectious peritonitis, systemic calcivirus
- Rickettsial: ehrlichiosis/anaplasmosis, Rocky Mountain spotted fever (**Rickettsia rickettsii**), Salmon poisoning (**Neorickettsia helminthoeca**)
- Fungal: histoplasmosis, blastomycosis, coccidioidomycosis cryptococcosis, systemic aspergillosis
- Protozoal: babesiosis, leishmaniasis, trypanosomiasis, hepatozoonosis, toxoplasmosis, cytiauxzoonosis

#### Immune mediated
- Immune-mediated polyarthritis, systemic lupus erythematosus, rheumatoid arthritis, vasculitis, meningitis, pemphigus, immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, transfusion reaction

#### Neoplastic
- Histiocytic sarcoma, lymphoma, leukemia, multiple myeloma, necrotic solid tumors

#### Other
- Pancreatitis, drug induced (tetracyclines, penicillins, sulfas), toxins, metabolic bone disorders, hyperthyroidism, tissue necrosis

#### Initial database

A detailed history and comprehensive physical examination should be performed in all patients with FUO. The history should include vaccination status, heartworm preventative, other medication history, previous illnesses, and surgeries. Travel history, lifestyle, and the home environment in particular may key the clinician in to specific differentials. The examination should include a rectal examination in dogs, dilated fundic examination, thorough oral examination, full orthopedic and neurological examinations, and a meticulous examination of the skin. Rectal examination may reveal sublumbar lymphadenopathy, prostatomegaly, and rectal or anal sac masses. Dilated fundic examination may reveal granulomas, hemorrhages, retinal detachments or chorioretinitis. Oral examination
may reveal pain or difficulty opening the mouth, draining tracts, swelling caudal to the last maxillary molar or sublingual or pharyngeal masses. Orthopedic and neurologic examinations may reveal long bone pain, joint pain, joint effusion, spinal pain or cranial nerve deficits. Meticulous examination of the skin may reveal draining tracts, abscessation or masses.

The initial laboratory work-up in a febrile patient should include a CBC, serum biochemistry profile, urinalysis, and retrovirus testing in cats. A blood smear evaluation must be performed, as reliance solely on automated CBCs will miss significant abnormalities such as a degenerate left shift, toxic change, blood parasites or circulating neoplastic cells. Thoracic radiographs should be performed to evaluate for evidence of masses, effusions or pulmonary infiltrates. Abdominal radiographs should be performed to evaluate for masses, effusion or free gas. If the initial work-up fails to identify an abnormality responsible for the fever, a urine bacterial culture and sensitivity should be performed in all cases even if urine sediment is inactive.

Advanced diagnostics
If the initial database fails to identify an abnormality to direct the investigation, advanced diagnostics will need to be pursued. However, it can be rewarding to repeat the initial database and other simple diagnostic tests periodically throughout the investigation as findings can change as the underlying disease progresses. Advanced diagnostics typically progress from less invasive to more invasive as the investigation continues. Relatively less invasive advanced diagnostics appropriate for the next round of testing include abdominal ultrasound to evaluate for pyelonephritis, prostatitis, pyometra, masses or otherwise abnormal organs; echocardiogram to evaluate for vegetative valvular lesions particularly if a new murmur is present; spinal, long bone, and joint radiographs to evaluate for evidence of diskospondylitis, pre- and post-prandial bile acids testing to evaluate for portosystemic shunting; serial blood cultures to detect bacteremia associated with diskospondylitis, endocarditis or other foci of infection; cytology of lymph nodes, masses or abnormal organs to evaluate for neoplasia or infectious agents; and serology and/or PCR for infectious diseases. If infectious disease is suspected and initial titers are negative, convalescent titers should also be performed. Arthrocentesis, while a slightly more invasive test, should be considered at this stage of diagnostic testing in dogs. Immune-mediated polyarthritis is a common cause of FUO and may not always present with obvious joint effusion. The higher tier of advanced diagnostic tests consists of relatively invasive or expensive diagnostics. They include cerebrospinal fluid analysis, bone marrow aspirates and/or biopsy, bronchoalveolar lavage, CT or MRI, and exploratory surgery with biopsies.

Therapeutic trials
The goal in all cases of FUO should be to obtain a specific diagnosis and treat accordingly. A therapeutic trial should be initiated only when a specific diagnosis cannot be ascertained. This most commonly occurs because diagnostics are curtailed by the owner, but in rare instances can occur despite an exhaustive work-up. Drug therapy trials without a definitive diagnosis may interfere with future diagnostics and exacerbate the underlying condition into a life threatening one. Broad-spectrum antibiotic therapy may be initiated after all culture specimens have been collected. Therapy should be based on the agents most likely present, their known antibiotic sensitivity, and the organ or system affected. If no response is seen after 72 hours, another antibiotic may be chosen, however the practitioner should first re-evaluate if a bacterial infection may be the underlying cause. Commonly used empiric antibiotics include:

- For broad-spectrum coverage: amoxicillin-clavulanate, 10-20 mg/kg PO q 8-12 hour and enrofloxacin 5-10 mg/kg (dog), 5 mg/kg (cat) PO q 24 hour
- If anaerobic infection is suspected: metronidazole 10-15 mg/kg PO q 12 hour or clindamycin 5-15 mg/kg PO q 8-12 hour
- If tickborne disease is suspected: doxycycline, 10 mg/kg PO q 24 hour or 5 mg/kg PO q 12 hour

In areas where systemic mycoses are endemic, antifungal agents may be used in patients with typical signs of fungal infection. The response to antifungal therapy may take days to weeks. Commonly used empiric antifungals include:

- Itraconazole (Sporanox, Janssen), 5-10 mg/kg PO q 24 hour or 5 mg/kg PO q 12 hour
- Fluconazole, 5-15 mg/kg PO q 12-24 hour

A glucocorticoid trial should be used only when infectious disease has been ruled out as the immunosuppressive effects of glucocorticoids can cause a life-threatening exacerbation of an infectious disease. A dramatic response (fever reduction) should be seen within 24-48 hours. Be aware that glucocorticoids may mask clinical signs even if an immune-mediated disease is not the underlying cause due to their anti-inflammatory effects. Commonly used empiric glucocorticoids include:

- Prednis(ol)one, 1 mg/kg PO q 12 hour
- Dexamethasone, 0.2 mg/kg IV q 24 hour
Management Strategies for Constipated Dogs and Cats
Karen Teft, DVM, MVSc, DACVIM
The Ohio State University
Columbus, OH

Constipation is a clinical sign characterized by absent or infrequent defecation associated with retention of feces within the colon and rectum. As the feces remain in the colon, the mucosa continues to absorb water from the fecal mass, which gradually results in hard, dry, impacted feces. Terms associated with constipation include:

- **Dyschezia**: A clinical sign characterized by difficult or painful defecation. It is usually associated with lesions in or near the anal region.
- **Tenesmus**: A clinical sign characterized by ineffective or painful straining to defecate. It usually accompanies dyschezia.
- **Obstipation**: A condition of intractable constipation. The colon and rectum have become so impacted with excessively hard feces that defecation cannot occur.
- **Megacolon**: A condition of colonic hypomotility and dilation. The changes associated with megacolon are usually irreversible.

**Etiology of constipation**
Underlying causes and predisposing factors for constipation include fluid and electrolyte imbalance, environmental factors, pain on defecation or posturing to defecate, dietary factors, neuromuscular disease, obstruction, and drug-induced. In addition, there are several conditions that may cause the owner to erroneously describe constipation as the presenting complaint. Lower urinary tract obstruction, particularly in male cats, is an important imposter to remain aware of. Malnutrition/starvation, wherein the pet is literally not being fed enough food to regularly produce feces, is another unfortunate mimic.

**Fluid and electrolyte imbalance**
Dehydration can cause the feces to become excessively dry and hard. Hypokalemia and hypercalcemia can impair colonic smooth muscle function. A combination of these factors may explain why constipation can frequently be seen in cats with chronic kidney disease.

**Environmental factors**
Environmental conditions that are not conducive to defecation or a change from the daily routine from which the pet is accustomed may cause the pet to inhibit the urge to defecate. This may occur when the pet is kept in strange surroundings, such as while boarding or hospitalized. Indoor cats may suppress the urge to defecate if their litterbox is dirty or if there is territorial conflict with other cats in the household.

**Ingested foreign material**
Indigestible fibrous material (e.g. hair, cloth, plant material) or abrasives (e.g. bones, rocks) may become incorporated into the fecal mass and result in the formation of hard fecal impactions that are difficult and/or painful to pass.

**Painful anorectal or orthopedic conditions**
Painful anorectal diseases (e.g. anal sacculitis, perianal fistulae, perianal trauma with abscess or cellulitis) or painful orthopedic disease (osteoarthritis of the stifles, hips or spine) that limit posturing to defecate may result in voluntary inhibition of defecation.

**Neuromuscular disorders**
Neuromuscular disorders may lead to constipation by interfering with colonic innervation (e.g. Manx tail deformity, dysautonomia), smooth muscle function (e.g. hypothyroidism, idiopathic megacolon) or the ability of the animal to posture to defecate (e.g. lumbosacral disease, degenerative myelopathy).

**Anorectal or colonic obstruction**
Obstruction may result from extramural compression (e.g. benign prostatic hypertrophy, prostatic carcinoma, paraprostatic cyst, or malunion pelvic fracture), intramural obstruction (e.g. neoplasia) or intraluminal obstruction (e.g. rectal stricture, foreign body, perineal hernia, pseudocoprostasis).

**Drug-induced**
Drug-induced constipation may be a side-effect of motility-modifying drugs (e.g. anticholinergics, opiates, and opioids), diuretics, antihistamines, adrenergic blockers, calcium channel blockers, phenothiazines, benzodiazepines, aluminum hydroxide antacids, sucralfate, barium sulfate, and iron. Chronic overuse of laxatives ironically can lead to constipation.

**Clinical signs**

**Reduced of absent defecation**
Constipated animals are usually presented because the owners have noted a failure to defecate over a period of days. The owner may have also noted tenesmus or frequent attempts to defecate with little or no passage of feces.

**Abdominal discomfort**
Constipated animals may develop a hunched-up appearance or cry out as they attempt to defecate.

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**Paradoxical diarrhea**
Mucosal irritation caused by impacted feces may provoke secretion of fluid and mucus that bypasses the retained fecal mass and is expelled paradoxically as diarrhea during attempts to defecate.

**Other signs**
Prolonged constipation may lead to anorexia, weight loss, lethargy, vomiting, and dehydration.

**Diagnostic work-up**
Constipation can be established as a problem from history and physical examination. The goal of the diagnostic work-up is to identify the underlying predisposing factors.

**Digital rectal examination**
To detect painful or obstructive lesions of the anorectal area and pelvic canal. Sedation may be required for examination.

**Orthopedic and neurologic examinations**
To detect pain or difficulty with posturing.

**Minimum database (CBC/chemistry/urinalysis)**
To detect underlying systemic disease leading to dehydration or electrolyte imbalance that could contribute to constipation. In severely obstipated animals, especially those with vomiting and dehydration, this also detects the metabolic consequences of obstipation.

**Thyroid panel**
To detect hypothyroidism in dogs or hyperthyroidism in cats.

**Abdominal radiographs**
To determine the extent of colonic impaction and degree of colonic dilation. In addition, abdominal radiographs can identify underlying causes of constipation such as ingestion of radio-opaque foreign material; pelvic, coxofemoral or spinal skeletal lesions; prostatomegaly; or sublumbar lymphadenopathy.

**Advanced diagnostics**
Abdominal ultrasonography can evaluate the urogenital tract when prostatic disease or pelvic canal neoplasia is suspected. CT/MRI can further evaluate the pelvic canal as well as the lumbosacral spinal cord. Barium enema contrast radiography can evaluate the lumen of the colon when an intraluminal obstructive lesion is suspected. Colonoscopy can evaluate the lumen of the colon and perform biopsies.

**Treatment**
Mild constipation (mild-to-moderate impaction of feces without systemic signs such as depression, vomiting, dehydration) can be managed on an outpatient basis using dietary adjustment, increased water intake, suppositories, and/or laxatives. The patient should be re-evaluated after 48 hours.

Severe constipation and obstipation may initially require correction of dehydration and potential electrolyte imbalances before deobstipation is performed. Subsequent to deobstipation, measures such as dietary modification, laxatives, and promotility agents should be prescribed to eliminate or control the underlying causes of constipation to prevent recurrence.

**Dietary therapy**
High-fiber, bulk-forming diets and additives promote soft feces, decrease intestinal transit time, and reduce the force needed to defecate. The indigestible polysaccharides and cellulose comprising these high-fiber diets are hydrophilic, which traps water in the feces, keeping it softer. The increased bulk of the feces enhance distension of the colon, which helps trigger contraction. High-fiber diets require adequate patient hydration to work; otherwise they will contribute to further fecal impaction. Options for high-fiber diets include commercial diets, wheat bran, oat bran, canned pumpkin (1-5 tbsp/meal), or psyllium (1-5 tsp/meal).

**Suppositories**
Suppositories work either to soften the stool or to stimulate colonic contractions. 1-3 pediatric suppositories can be administered to veterinary patients. Options for safe suppositories include glycerin (lubricant laxative), docusate (emollient laxative), and bisacodyl (stimulant laxative).

**Enemas**
Enemas work to soften hard, impacted feces to promote defecation. Warm the enema solution prior to instillation and use a lubricated rubber catheter or feeding tube to administer the calculated dose slowly so as to not induce vomiting. Commonly used enema solutions include warm isotonic saline or tap water (5-10 ml/kg) with a mild soap and/or lubricant jelly, docusate (5-30 ml) or mineral oil (5-30 ml). Do not mix mineral oil and docusate. Docusate promotes mucosal absorption of mineral oil. Mineral oil coats the feces, preventing the emollient effect of docusate. Caution: Never use Fleet enemas (sodium phosphate solution) in cats and small dogs as they can lead to potentially fatal hypernatremia, hyperosmolality, hyperphosphatemia, and hypocalcemia.

**Manual deobstipation**
In severe obstipation cases, the patient may need intravenous correction of dehydration and electrolyte imbalances followed with manual extraction of feces from the colon with the patient under general anesthesia. Colonic irrigation with warm isotonic saline as an enema can help soften the feces. The fecal masses can be removed by gentle transabdominal manipulation to milk the feces into the
distal rectum for digital or forceps removal. To avoid excessive bowel trauma, it may be advisable to stage colon evacuation over a period of days.

**“Hands-free” deobstipation in cats**

Intravenous correction of dehydration and electrolyte imbalances should be performed first. Then a nasoesophageal or nasogastric tube is placed. A polyethylene glycol solution (e.g. Colyte, Golytely) is trickled through the tube initially at 5 ml/kg/hr. If that is tolerated, increase to 10 ml/kg/hr. The average total dose needed is 100 ml/kg. Bowel movements typically start in 6-8 hours after starting the trickle.

**Oral laxative therapy**

Laxatives can be used to treat mild constipation and to prevent recurrence. Laxatives lubricate feces, promote water penetration to soften feces, enhance intestinal mucosal fluid and electrolyte transport, or stimulate colonic propulsive motility. They are classified by their properties and mechanisms of action as bulk-forming, lubricant, emollient, osmotic, stimulant or promotility. Many oral laxatives require normal water intake and patient hydration for optimal activity. The use of an oral laxative often must be individualized by adjusting the dose until the desired frequency and consistency of defecation is achieved.

1. **Lubricant laxatives**: Lubricate the feces to facilitate evacuation. Overuse can cause fat-soluble vitamin malabsorption. A classic example is flavored white petrolatum products (i.e. “hairball” remedies). Caution: Never use mineral oil orally as a laxative as accidental aspiration can lead to a fatal lipid pneumonia.

2. **Emollient laxatives**: Promote water penetration into the feces. They should not be used in dehydrated patients. A classic example is docusate.

3. **Osmotic laxatives**: These disaccharides or inert osmotic agents work to retain water in the bowel lumen. Examples include lactulose (0.5-1 ml/kg q 8-12 hr) or PEG (Miralax; 0.25 tsp/cat q 12 hr).

4. **Stimulant laxatives**: Increase propulsive motility of the bowel. Overuse of stimulant laxatives can damage the myenteric plexus. They are also contraindicated in the presence of an obstructive lesion. A classic example is bisacodyl (5-20 mg q 24 hr).

**Promotility therapy**

Promotility agents stimulate colonic smooth muscle contractions. They are contraindicated in the presence of an obstructive lesion. The most effective promotility agent is cisapride (0.5-1.5 mg/kg q 8-12 hr). It is a serotonergic agonist. Currently cisapride is only available through compounding pharmacies as it was taken off the human market due to the development of fatal ventricular arrhythmias that occurred in humans (but have not been documented in dogs and cats). Tegaserod (0.05-0.3 mg/kg q 12 hr) and mosapride (5 mg/cat q 12 hr) are newer serotonergic agonists that have also been investigated for use in cats and dogs.

**Ancillary treatment**

Following evacuation of constipation, other measures to prevent and control recurrences of constipation include: preventing ingestion of constipating or abrasive materials such as bones; regular grooming to prevent ingestion of loose hair; providing fresh drinking water; providing clean litter for cats; encouraging regular exercise; and correction of obesity.

**Megacolon**

Megacolon is a condition in which the colon becomes extremely and irreversibly dilated and hypomotile. Recurrent constipation and obstruction are the primary signs. Episodes of constipation usually become more frequent and severe with progression over time. In 70% of cases, feline megacolon is an idiopathic hypomotility disorder involving colonic smooth muscle. Idiopathic megacolon is usually irreversible. In up to 25% of cases, megacolon is secondary to an underlying cause of persistent rectocolonic obstruction, such as perineal hernia, anorectal stricture, anorectal neoplasia, or pelvic canal stenosis caused by fracture malunion. This hypertrophic megacolon is potentially reversible with early removal of the obstruction. After 6 months, however, obstructive megacolon is usually irreversible. Finally, neurologic dysfunction may account for 5% of megacolon cases; for example, lumbosacral spinal cord disease, Manx cat deformity, or dysautonomia.

Radiographs are important in the diagnosis of megacolon as they can help screen for an obstructive cause and differentiate a simple episode of constipation from megacolon. A ratio of the maximal colonic diameter to the length of the fifth lumbar vertebra can aid differentiation of constipation from megacolon. In a study by Trevail, et al, a ratio less than 1.28 is suggestive of a normal colon. A ratio of 1.28-1.48 suggests constipation, while a ratio greater than 1.48 is suggestive of megacolon. While high fiber diets can be beneficial in the management of cats with simple constipation, highly digestible low-residue diets are preferable once a cat is diagnosed with megacolon. The increased bulk from fiber will no longer stimulate colonic contractions and instead will just contribute to further fecal impaction. In addition to dietary management, promotility therapy is also indicated for management of megacolon. Subtotal colectomy is often the most effective way to manage cats with advanced megacolon and recurrent obstruction. In the previously mentioned study, all cats with a ratio greater than 1.62 required subtotal colectomy for management.
Coughing is a complaint that should be actively pursued in cats. Small airway disease – asthma – is the most common underlying cause of feline coughing. Other differentials to consider, however, include *Mycoplasma* infection and other pneumonias, heartworm associated respiratory disease, bronchogenic adenocarcinoma, tracheal disease, and pleural space disease. Unlike in dogs, cough is very rarely associated with feline congestive heart failure.

The overall prevalence of asthma in cats is less than 1% of the feline population. However, the Siamese breed is predisposed and has a prevalence rate of approximately 5%. Classically, asthma initially presents in middle-aged cats; the median age at initial presentation is 5 years old. The clinical signs of asthma can vary, likely representing a continuum of disease. Some cats may present for a chronic waxing and waning cough with mild to moderate exercise intolerance, whereas other cats will not have a chronic cough history, but present with acute respiratory compromise consisting of a sudden onset of dyspnea, tachypnea, and orthopnea.

Asthma develops as the cat becomes sensitized to aeroallergens. These allergens activate T-Helper 2 lymphocytes, which then produce cytokines. These cytokines trigger allergen-specific IgE inflammatory cell influx (the hallmark of which is the eosinophil), airway hyper-reactivity, and remodeling changes in the lung. The airway inflammation and hyper-reactivity provoke bronchoconstriction, which leads to the clinical signs of cough and dyspnea. The remodeling changes to the airway in the chronic asthmatic consist of smooth muscle hypertrophy and goblet cell hyperplasia. This further reduces the luminal diameter of small airways. Reduction in the diameter of small airways impairs expiration over inspiration. This accounts for the expiratory push observed in asthmatic cats and the phenomenon of “air trapping” seen on thoracic radiography.

In humans, diagnosis of asthma relies upon specific pulmonary function studies. While these studies are used in the investigation of experimental models of feline asthma, for the most part they are not feasible in a clinical patient. Therefore the majority of asthma diagnoses in patients rely on clinical criteria.

1. A history that includes one or more of: acute wheeze, tachypnea, and respiratory distress. History often also includes a rapid response to treatment with a combination of oxygen, steroids, and/or bronchodilators.
2. Radiographic evidence of bronchial wall thickening (“doughnuts” and “tram lines”) and air trapping (diaphragm flattening). In addition, atelectasis, particularly of the right middle lung lobe, may be present in 10% of cases. In severe cases, fluffy, ill-defined heavy interstitial infiltrates in multiple lung lobes may be appreciated. However, 23% of asthmatic cats can have normal thoracic radiographs.
3. Exclusion of other differentials such as heartworm associated respiratory disease via serology.
4. Evidence of airway inflammation, particularly eosinophils. A peripheral eosinophilia may be seen in 17-49% of cases.

Bronchoalveolar lavage or endotracheal wash can be used to collect samples for cytology and culture in the coughing cat. Unfortunately, either of these procedures can carry significant risk for a cat that already has respiratory compromise, therefore the clinician may want to consider empiric treatment first, and reserve airway sampling for refractory cases. On cytology of fluid from airway sampling, an asthmatic will have increased amounts of mucus (the pathologist may comment on seeing Curschmann's spirals) and mixed inflammation with increased eosinophils. Aerobic culture should have no growth. However, 25% of cats with chronic airway disease will culture positive for *Mycoplasma*.

The role of *Mycoplasma* in feline airway disease is a bit of a “chicken and the egg” scenario. *Mycoplasma* is not found in the lower airways of healthy cats, but it is difficult to determine if it is a true primary pathogen or a secondary opportunistic pathogen. *Mycoplasma* can degrade neutral endopeptidase, which is an enzyme responsible for the biodegradation of substance P. In turn, substance P is capable of causing bronchoconstriction and edema in the feline airway. Therefore, *Mycoplasma* may indirectly prolong the effects of substance P in the airway and therefore exacerbate asthma.

**Management of the acute asthmatic crisis**

Many asthmatic cats may present to the veterinarian initially on emergency for respiratory distress. There may not have been much coughing previous to the onset of respiratory distress or the owner may have attributed previous coughing fits to unsuccessful attempts to “hack up a hairball.” Therefore, on initial presentation, the clinician may not initially know if they are facing a patient with congestive heart failure, asthma, pleural effusion, or some other cause of respiratory distress.

All cats in respiratory distress should receive oxygen therapy immediately. This should be continued until it is established that the cat no longer requires it. Oxygen can be provided to cats by flowby, mask or oxygen cage. Oxygen cages tend to be the least stressful, however they may be least effective at delivering the highest oxygen concentration. Also, you cannot examine the patient without compromising oxygen delivery. While oxygen delivery via nasal cannulas provides the highest amount of oxygen delivered to the...
patient and you to examine the cat while delivering oxygen, it is not often employed in cats as it is extremely stressful to place the cannulas.

Limiting stress in the dyspnic cat is essential. In addition to low-stress oxygen delivery, severely dyspnic cats should be restrained as little as possible. This means no restraint for a full physical examination, for placement of an intravenous catheter or for diagnostic procedures such as radiographs. Perform a “barebones” triage examination consisting of mucous membrane evaluation, thoracic auscultation, thoracic compression, and observation of the respiratory pattern. Consider sedation with a low dose of butorphanol (0.1-0.2 mg/kg IM or IV). In many cases, therapeutic intervention may need to be performed (e.g. thoracocentesis) without a confirmed diagnosis (e.g. identifying pleural effusion on radiographs). Keep a laryngoscope and appropriately sized endotracheal tubes within reach in case the cat decompensates.

While you await the effects of the sedation to decrease the cat’s anxiety, you can begin collecting a history from the owners. How long have clinical signs been present and have they progressed? What other signs referable to the respiratory tract have the owner’s witnessed? Has then been any vomiting or regurgitation? The cat’s environment and recent changes in the environment should be questioned. Also, particularly in endemic areas, it should be asked if the cat is on heartworm preventative.

Other than oxygen and sedation, other emergency interventions that should be considered in the dyspnic cat include a dose of furosemide (1 mg/kg IM or IV), particularly if crackles are ausculted. A single dose of furosemide is unlikely to be deleterious to a patient if they are not in congestive heart failure. In addition, particularly if wheezes are ausculted, a dose of dexamethasone (0.2-0.5 mg/kg IM or IV) and albuterol (90 mcg inhaled) or terbutaline (0.01 mg/kg SQ or IM) should be given. Again, a single dose of these drugs is unlikely to be deleterious to a non-asthmatic cat. As dexamethasone has negligible mineralocorticoid effects it is not expected to significantly exacerbate congestive heart failure.

Long-term management of the asthmatic
There are three cornerstones to the long-term management of the asthmatic: identify and avoid inciting triggers, decrease airway inflammation, and enhance bronchodilation. The first step, identifying and avoid inciting triggers, is recommended for all asthmatic cats, regardless of the severity of their disease. Triggers include allergens and irritants such as mites, pollen, mold, dust, smoke, powders, aerosols, and scents. Washing bedding in hot water every two weeks and minimizing carpeting will help minimize dust mites. Feeding canned cat food will limit the exposure of the cat to storage mites, which can be found in dry foods. Using HEPA air filters in the areas the cat spends the majority of their time will limit pollens and other small particulate matter in the air. Use of incense, candles, and wood burning stoves should be limited or discontinued if possible. The owner should not smoke in the presence of their cat. Finally a course of azithromycin (5 mg/kg PO q 24 hr for 5 days, then q 72 hr for 3 weeks) or doxycycline (5 mg/kg PO q 12 hr for 4 weeks) should be considered for potential underlying Mycoplasma infection.

To decrease airway inflammation, corticosteroids are the most effective treatment. Cats with infrequent symptoms (less than weekly) may not be started on heart steroid therapy as they are suspected to have limited or even absent chronic active airway inflammation. For cats with signs that occur more than once a week, prednisolone (2 mg/kg PO q 24 hr.) should be started. Most cats have greatly diminished signs within one week. The dose can then be slowly tapered over 2-3 months to the lowest effective dose. The long-term side effects of corticosteroids can be undesirable. Inhaled steroids will greatly decrease the risk of these side effects. Therefore, in a cat that has a positive response to oral prednisolone, a transition to inhalant therapy is recommended. Fluticasone propionate (Flovent; mild-to-moderate disease 110 mcg q 12 hr; severe disease 220 mcg q 12 hr) is the inhaled steroid of choice. It is the most potent inhaled steroid with the longest half-life and lowest oral bioavailability. Onset of action takes 1-2 weeks. Fluticasone can be tapered to once daily once good control is achieved, but most asthmatic cats cannot be tapered to every other day. The cat’s face should be wiped down after fluticasone has been administered, as localized demodicosis has been reported in cats on chronic inhaled steroid therapy.

A spacer chamber will be needed for use of fluticasone or other inhaled therapies. Metered dose inhalers allow for delivery of a pre-set dose in aerosolized form, but their use requires coordination of actuation and inhalation. A spacer chamber avoids this need. The Aerokat spacer chamber is recommended for use as it was specifically designed based on the tidal volume of cats and has an indicator for the owner to easily visualize each breath the cat takes. Despite cat’s notoriously suspicious behavior, a study by Padrid found that 70% of cats accept a spacer chamber immediately and 20% will accept it within a week with some positive reinforcement. Only 10% of cats will never accept the spacer chamber. There are numerous instructional videos on YouTube published by owners demonstrating proper use of a spacer chamber and training methods.

For cats who cannot be pilled, will not tolerate an inhaler, and have severe asthma, parenteral long-acting steroids such as methylprednisolone (10-20 mg IM q 4-8 wks) can be considered as a last resort. However, this is very likely to result in significant side effects including weight gain, diabetes, and reduced immunity. Methylprednisolone should never be considered a routine or first line treatment for asthma. A very frank discussion should be held with the owner, informing them of the risks, before proceeding.
To enhance bronchodilation, β2-agonists are the bronchodilators of choice. They are the most effective bronchodilators with the least side-effects. They enhance relaxation of the smooth muscle in bronchial, vascular, and uterine tissues. However, chronic use will lead to tachyphylaxis, so they should only be used on an as needed basis. If several consecutive days of treatment are needed to control symptoms, the owner should alert the veterinarian so that other treatments can be added or adjusted. β2-agonists should be used with care in patients sensitive to their adrenergic effects, such as patients with heart disease, diabetes, hyperthyroidism, hypertension or seizure disorders. Terbutaline (0.1-0.2 mg/kg PO q 8 hr.) and albuterol (90 mcg inhaled PRN) are the most commonly used β2-agonists. Also be aware that chronic use of inhaled albuterol will paradoxically lead to increased airway inflammation.

Methylxanthines such as theophylline are another class of drug that can cause bronchodilation. However, they are less effective, have a narrow safety margin, and have many drug interactions. Their use is not recommended. Cyproheptadine (2-4 mg/cat PO q 12 hr.) will not cause bronchodilation, but it can help block antigen-induced smooth muscle contraction by blocking serotonin receptors. Serotonin is the primary mediator released from mast cells in feline airways that causes bronchoconstriction. Cyproheptadine’s use can be considered in cats already on maximal dose of steroids and β2-agonists.

For asthmatic cats refractory to the standard treatments of allergen avoidance, steroids, and β2-agonists other therapies that may be considered include allergen-specific immunotherapy and cyclosporine. Allergen-specific immunotherapy has been used to treat an experimental model of feline asthma. Cats were sensitized to Bermuda grass allergen, inducing an asthmatic state. They were then treated with immunotherapy to Bermuda grass pollen and dust mite allergens. The clinical signs and airway inflammation progressively decreased in these cats. Cyclosporine (3-6 mg/kg PO q 12 hr) has been used in human asthmatics refractory to steroids. Cyclosporine inhibits T-lymphocytes, which blocks the inflammatory cascade in the airways. While both immunotherapy and cyclosporine have been investigated in experimental models of feline asthma, there have been no controlled studies in naturally occurring asthmatic cats.