Megaesophagus and Focal Myasthenia Gravis in Dogs

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Megaesophagus refers to a specific syndrome characterized by a dilated hypoperistaltic esophagus and should be differentiated from other causes of esophageal dilation (e.g., foreign body, vascular ring anomaly, mucosal stricture, neoplasia) which may or may not be characterized by abnormal peristalsis. Megaesophagus is one of the most common causes of regurgitation in dogs. Megaesophagus can be congenital or acquired. Acquired megaesophagus can be idiopathic or caused by a specific syndrome, e.g., myasthenia gravis, hypoadrenocorticism, lead toxicity, and others. It is always important to perform tests to determine if an underlying disease is present, as successful treatment of the primary disease may in some cases lead to resolution of esophageal hypomotility, either completely or at least partially. Failure to recognize an underlying cause can significantly complicate matters and make it more difficult to manage the patient successfully, and can also lead to sudden demise of the patient demise if catastrophic aspiration pneumonia occurs.

In the past it was thought that most dogs with megaesophagus had a poor prognosis. Experience has shown, however, that many dogs with this potentially devastating disease can be managed well for a number of years by very dedicated pet owners. The keys to success include identifying and treating any underlying cause and finding a way to successfully provide nutritional support with delivery of nutrients to the stomach, while minimizing episodes of regurgitation since these can lead to aspiration of food to the airways, debilitating pneumonia, and death in some cases. Feeding dogs in a *completely* upright position using high chairs (e.g., Bailey chair) has made a significant difference in our ability to manage dogs more successfully for long periods of time.

Megaesophagus and Myasthenia Gravis

Megaesophagus is a frequent finding in animals with myasthenia gravis (MG). There are two main types of MG in dogs, a generalized form and a focal form. MG can be congenital or acquired. Acquired MG is an immune-mediated disease in which antibodies (in most cases IgG) are formed against the nicotinic acetylcholine (Ach) receptors, resulting in decreased numbers of receptors on the postsynaptic membrane. These autoantibodies can alter the receptor function by one of several mechanisms, and the result is a decrease in normal neuromuscular junction (NMJ) transmission which then results in muscle weakness.

Acquired MG can present as one of three different clinical syndromes: focal MG, generalized MG, and acute fulminating MG. Acquired MG has been associated with other diseases, therefore, when planning the diagnostic approach the clinician should keep these diseases in mind.
These diseases include:

- hypothyroidism and other autoimmune diseases
- thymomas
- thymic cysts
- nonepitheliotropic cutaneous lymphoma
- cholangiocellular carcinoma
- anal sac adenocarcinoma
- osteogenic sarcoma

In dogs, a high risk for MG exists in several breeds, including Akitas, several terrier breeds, German Shorthaired Pointers, and Chihuahuas. The German Shepherd dog and Golden Retriever demonstrate the highest morbidity.

Generalized MG patients have skeletal muscle weakness that may be induced or exacerbated by exercise as a hallmark sign. In contrast, focal MG presents as a weakness of isolated muscle groups, particularly the esophageal, pharyngeal, laryngeal, and facial muscles. *There is an absence of appendicular muscle weakness in focal MG.* Acute fulminating MG is a severe and rapidly progressing form of MG.

Clinical Signs Associated with Megaesophagus

The dominant clinical sign of megaesophagus is regurgitation. It is essential that the clinician make a clear differentiation between regurgitation and vomiting at the outset. Failure to recognize the difference between regurgitation and vomiting often leads to inappropriate testing (i.e., tests most useful for diagnosis of abdominal disorders are generally performed), misdiagnosis, and the use of ineffective treatment regimens. Valuable time is wasted when tests for vomiting rather than regurgitation are pursued. Therefore, the first diagnostic step is to obtain an accurate history and to personally observe the actions of the patient so that an accurate determination of regurgitation vs. vomiting can be made.

Regurgitation refers to a *passive,* sometimes almost effortless retrograde movement of ingested material to a level proximal to the upper esophageal sphincter. Usually this occurs before ingested material reaches the stomach. There usually are few additional premonitory signs (e.g., retching, signs of nausea) except ptyalism in esophageal inflammatory or obstructive disease. Vomiting refers to an *active* process with forceful ejection of gastric content and often proximal small intestinal contents as well through the mouth. The vomiting act involves three stages: nausea, retching, and vomiting. Regurgitated material does not contain bile, whereas vomited material frequently does. In fact, content of ejected material is an important point of discussion with clients. Dogs with regurgitation often bring up food with foam and saliva, but there is no bile present, unless the dog has *both* regurgitation and vomiting. Both regurgitation and vomiting are *clinical signs* of many disorders and should not be considered a primary disease. Regurgitation is usually a clinical sign of an esophageal disorder.

The esophagus is a tremendously dilatable muscular tube that acts via a series of well-coordinated peristaltic contractions to move ingesta from the mouth to the stomach. Regurgitation in most cases results from abnormal esophageal peristalsis, esophageal obstruction, or asynchronous function of the gastroesophageal junction. Significant complications of regurgitation include aspiration pneumonia and chronic wasting disease. All patients with esophageal dysfunction are at risk for sudden death related to aspiration and subsequent upper airway obstruction.

Regurgitation may occur minutes to hours after eating. Frequency varies from several episodes per week to many (10 to 20) episodes in a single day in some patients. It must be recognized that the degree of esophageal function does not always correlate with the severity of clinical signs.

Other clinical signs may include acute or chronic cough that may or may not be associated with dyspnea and fever. These signs are most consistent with aspiration pneumonia, which is the most complication of megaesophagus. Coughing may also be related to compression of lung tissue and airways by the enlarged esophagus and its contents. Occasionally coughing is the only clinical sign demonstrated by a dog with megaesophagus. Weight loss and emaciation occur secondary to inadequate food intake. Inappetence or salivation of both may result from discomfort caused by esophagitis.

In patients in which megaesophagus is associated with an underlying disorder, other clinical abnormalities that may be noted include generalized muscle weakness (generalized MG, polymyopathy, hypoadrenocorticism), neurologic deficits (MG, central nervous system disease, polyneuropathy), generalized muscle atrophy or pain with myositis, vomiting (hypoadrenocorticism, lead poisoning, obesity

and alopecia with hypothyroidism, and oropharyngeal dysphagia with generalized neuromuscular dysfunction.

Diagnosis

Acquired megaesophagus is most commonly diagnosed by the presence of generalized esophageal dilation on survey thoracic radiographs, without evidence of obstruction. Once the presence of megaesophagus is confirmed, appropriate ancillary tests should be performed in search of an underlying cause (e.g., MG, hypoadrenocorticism, etc.). Details are described in the following sections.

Diagnostic Imaging

Survey Radiographs

The normal esophagus is not often seen in the canine patient although a small amount of fluid may accumulate within the caudal thoracic esophagus creating a soft tissue tubular appearing structure midway between the caudal vena cava and aorta especially in thin dogs positioned in left lateral recumbency. A small amount of gas within the esophageal lumen especially caudal to the cranial esophageal sphincter, at the level of the thoracic inlet and dorsal to the heart may be within normal limits. The inability to visualize the esophagus on thoracic images does not rule out esophageal disease. One unusual situation to be aware of is that in cases where animals are severely dyspneic (for example with severe pneumonia) the esophagus may become dilated with gas. If this is indeed a secondary problem then with resolution of the dyspnea the megaesophagus will also resolve.

Radiographic Changes with Megaesophagus: Definitive diagnosis of megaesophagus requires the identification of a dilated esophagus on radiographs. In some cases survey radiographs may demonstrate the etiology of the esophageal dilation (e.g., foreign body, mass lesion, hiatal hernia, GDV, etc.). Megaesophagus is one of those conditions that covers a broad range of severity. Radiographs may show an esophagus dilated with air, fluid, ingesta/foreign material or a mixture of these. The esophagus can have a mild or severe, focal, segmental/regional or generalized dilation. It is also supportive if there is more than one radiograph demonstrating persistent dilation.

If megaesophagus is diagnosed on survey radiographs an esophagram is generally not necessary. Some believe that an esophagram may pose a significant risk of aspiration especially with barium contrast that pools in the esophagus. Evaluation of lungs for aspiration pneumonia as a common sequela of megaesophagus is also of utmost importance.

Esophagram/Barium Swallow Changes for Megaesophagus: If the patient has signs of a swallowing disorder or regurgitation, and megaesophagus is suspected but not appreciated on survey images, administering barium contrast and taking a radiograph will be enough to demonstrate the outline of the dilated esophagus (see description of technique below). Fluoroscopy or sequential images is very valuable in more subtle cases since the motility in real time or over time can be observed. Once the diagnosis of megaesophagus has been made, additional radiographs or fluoroscopy may be indicated in monitoring response to treatment, or for response to treatment of secondary disease such as aspiration pneumonia.

Contrast Study: Esophagram

Esophagram is the positive esophageal contrast study necessary for further characterization and evaluation of almost all cases of morphologic and dynamic esophageal diseases. Dynamic or functional disease may need sequential images with contrast or fluoroscopy. Sedation should be avoided as it may affect esophageal motility.

Technique: An esophagram is done using either barium liquid or barium paste. These products provide both great radiopacity and may demonstrate adherence to the mucosa of the esophagus (barium paste does a much better job of this). In some cases where animals have problems swallowing solids and not liquids or have a suspected esophageal stricture or dysfunction barium may be mixed with either canned or dry dog food.

A survey radiograph should always be taken prior to any contrast study. The entire esophagus should be evaluated on survey images including from the proximal esophagus to the junction of the esophagus with stomach. Since the esophagus is a midline structure and will remain superimposed with spine and sternum on VD images, an oblique 15 to 30 degree VD should be utilized instead for orthogonal view to lateral image. Approximately 10 to 30 ml of contrast should be given orally to induce swallowing and potentially coat the esophagus before radiographs are taken (enough time should be given to allow contrast to fully pass to stomach). This can be repeated several times if necessary.

Normal Appearance of Esophagus on Esophagram: The canine esophagus normally appears as a series of parallel longitudinal folds. Between these folds there may be small thin linear accumulations of positive contrast. On VD or VD oblique images the esophagus will pass to the left of the trachea at the level of the thoracic inlet. If a bolus of contrast is seen on esophagram a subsequent image should be taken to make sure it is not present on multiple images.

There are a few variations in the normal appearance of the esophagus that you should recognize. The first one is a small amount of air in the cervical esophagus, just caudal to the cricopharyngeus muscle. The second variation of normal is a small thin pocket of air in the thoracic esophagus, just cranial to the heart base. With a three-view thoracic series, there will often be some fluid in the caudal esophagus on the left lateral projection. This is most likely because the esophagus and cardia of the stomach are on the left, and the increased pressure from abdominal organs causes some reflux of gastric contents. The key to recognizing all of these variations of normal is that they are transient. If another radiograph is performed, they should be gone.

Laboratory Tests

A baseline CBC and biochemical profile should be run in all patients with megaesophagus to look for evidence of underlying problems. Specific tests to evaluate for systemic disorders such as hypoadrenocorticism (ACTH stimulation), systemic lupus erythematosis (antinuclear antibody), and serum lead levels are done if the history and/or physical examination indicate that these primary disorders may exist. **Focal myasthenia gravis should be considered in any patient with megaesophagus.** The test of choice is an acetylcholine receptor antibody titer assay. The assay is specific and sensitive and documents an autoimmune response against acetylcholine receptors. The acetylcholine receptor antibody test is run at the Comparative Neuromuscular Laboratory in La Jolla, CA. This laboratory is headed by a veterinary internist, Dr. Diane Shelton, who is highly experienced in diagnosis and management of neuromuscular disorders. The laboratory is an international reference center dedicated to the diagnosis and study of spontaneous neuromuscular diseases in companion animals. Contact the laboratory for forms, sample submission instructions, and interpretation of results.

The address is:
Comparative Neuromuscular Laboratory
9500 Gilman Drive
Basic Science Building, Rm. 2095
University of California, San Diego
La Jolla, CA 92093-0709
Phone: (858)534-1537 **Fax:** (858)534-0391
Web: http://vetneuromuscular.ucsd.edu/
Email: musclelab@ucsd.edu

An Ach receptor antibody concentration of greater than 0.6 nmol/L is positive for dogs. False positive tests are extremely rare and therefore a positive result is considered virtually definitive for acquired MG. The serum Ach receptor antibody concentration is usually lowest in dogs with focal MG and highest on dogs with fulminant MG.

REPEAT TESTING MAY BE NECESSARY: In some cases the ACh receptor antibody titer test may be within normal reference range on initial testing, but then may be abnormal on re-check testing performed 2-3 months later. VERY IMPORTANT: Clinicians should re-test any patient that is still considered to possibly have focal MG. If a subsequent test is positive, then there is clear direction at that time on how to manage the patient more specifically in addition to using elevated feedings for megaesophagus (i.e., use drug therapy for MG).

Treatment

General Management Principles for Megaesophagus

The main objectives of treatment for regurgitation disorders are to remove the initiating cause as early as possible, minimize chances for aspiration of esophageal content, and maximize nutrient intake to the GI tract. In most cases, idiopathic megaesophagus is incurable, and treatment involves an individually tailored feeding regimen with the patient eating in an elevated position. Medical management is indicated for such secondary causes of esophageal dilation as myasthenia gravis, hypoadrenocorticism, hypothyroidism (a rare cause of megaesophagus), lead toxicity, and systemic lupus erythematosis. Any occurrences of aspiration pneumonia should be treated aggressively.

Megaesophagus patients are best fed with the upper body in an elevated position of at least 45 degrees (more if possible). It is important that proper positioning be clearly demonstrated to the client so that there is no misunderstanding. The elevated position should be maintained for a full 10 minutes after ingestion of food is completed. Various props to aid in the elevation process have been used successfully, including ladders, stairs, ramps, tables, and chairs. Since the esophagus is virtually never completely empty in a megaesophagus patient it is often helpful to hold the animal in an elevated position for 5 to 10 minutes at a time sometime between meals and at bedtime.

A recent Advance: Use of Special Feeding Chairs

Bailey Chair: There is a lot of information available on the internet about a special feeding chair that was designed by Donna and Joe Koch, the owners of a dog named “Bailey.” “Bailey” had been diagnosed with megaesphagus. The dog sits in a totally upright (“begging”) position to eat, drink, or take medication and gravity aids transit of anything ingested to the stomach. Basically we are turning the patient into a biped from a quadruped. Use key words “Bailey Chair” for an internet search and information on how to acquire or build a Bailey chair (also see support group information below).

Megaesophagus patients are ideally fed 2 to 4 times daily. This depends, of course, on the caregiver’s time constraints. We have had the best success feeding soft moist to solid (chopped) canned food consistency. We only recommend trying gruels if the semi-moist consistency is not well tolerated. Some patients do well when fed a series of “meatballs” fashioned from canned food. Others can tolerate dry food fairly well. A key point is that each patient is an individual and clients should be instructed to experiment with various food consistencies in order to determine the best approach for their own pet.

Many patients with idiopathic megaesophagus can be managed successfully for months to years. We have known many dedicated owners who have managed to find the time required to care for their pets. As a result of this experience we try to offer as much encouragement as possible at the time of diagnosis. The most worrisome complications that can occur are aspiration pneumonia and significant weight loss. The prognosis is guarded to poor in patients that suffer recurrent episodes of pneumonia.

Gastric Feeding Tube Placement

An option in cases where frequent regurgitation remains an ongoing problem with or without aspiration events, is to place a gastric feeding tube (e.g., percutaneous endoscopy-guided gastrostomy tube [PEG]). All food and water can then be administered through the feeding tube (some patients have been maintained for as long as 4 or more years in this way). Periodic tube replacement will be necessary. Low profile feeding tubes often work best for long term tube feeding.

Megaesophagus Client Information and Support Group
www.caninemegaesophagus.org
Provides information on the causes of congenital and idiopathic *canine megaesophagus*, the clinical signs, risk factors and accompanying disorders, with lots of feeding tips.

A Support Group for owners of dogs that have, had or may have megaesophagus, was established at Yahoo Groups in 2002 by Dave Kay and Katy Weeks, in memory of their Golden Retriever, Rusty. Members of the group can provide suggestions and ideas for feeding and care of dogs with megaesophagus. A veterinarian monitors the group as an advisor and offers suggestions for members to discuss with their veterinarians. The group is at: http://groups.yahoo.com/group/megaesophagus/ and requires membership.

Medical Management of Focal Myasthenia Gravis
Each patient needs to be carefully assessed and an individual treatment plan developed. With an accurate diagnosis and early treatment, autoimmune MG is a treatable disease. It is not uncommon for dogs with MG, unlike humans, to go into spontaneous remission. Treatment duration can range from several months to several years, depending on the severity of disease. Drug therapies can include cholinesterase inhibitors (cornerstone of therapy and recommended for all dogs with MG), corticosteroids, and other immunosuppressive drugs. It is advised that veterinarians who have not had much experience managing dogs with focal or generalized MG actively consult with veterinary neurologists or internists who have much more experience in this area, so that each patient will have the benefit of the expertise needed to navigate the decisions on which drugs to use and when to make adjustments.

Anticholinesterase drugs prolong the availability of Ach for binding to Ach receptors by inhibiting degradation of acetylcholinesterase. Pyridostigmine bromide (Mestinon) is administered to dogs at 0.5 – 3 mg/kg PO every 8 to 12 hours. Start low and titrate upwards gradually to achieve the best clinical response while avoiding cholinergic side effects, which can include hypersalivation, vomiting, and muscle fasciculations based on response. Adverse effects may be reduced by administering small doses of atropine or giving the medication after meals when feasible. Tablet and syrup forms are available. The syrup formulation should be diluted 50:50 in water because gastric irritation may result if it is given straight. The response to anticholinesterase therapy can be variable depending on the patient, with some responding significantly and others minimally. Also, anticholinesterase therapy seems to exert greater effect on improving appendicular muscle weakness (in generalized MG) than it does on improving esophageal function in dogs with megaesophagus.

Use of immunosuppressive therapy in dogs with acquired MG is based on the underlying pathophysiology, which includes an autoimmune destruction of functional Ach receptors. However, there can be concerns related to use of immunosuppressive therapy, including immunosuppressing dogs with aspiration pneumonia, a common sequela of megaesophagus. Glucocorticoid therapy can also cause a worsening of muscular weakness. Further, the increased water consumption associated with steroid use can be problematic in dogs with swallowing difficulties or are regurgitating. Therefore, the decision to use steroids should be made carefully with consideration of the entire clinical picture, and steroids are withheld until pneumonia is resolved. In some cases it may be best to first try pyridostigmine and if there is a suboptimal response steroids are initiated at a conservative dose.

When using corticosteroids, it may be best to start with a lower anti-inflammatory level dose of prednisolone, e.g., 0.5 mg/kg given every 24 hours. Beneficial effects of steroids may be related to inhibitory effects of prednisone on the formation and release of inflammatory agents, lymphocyte division, lymphocyte reactivity to Ach receptors, and leukocyte chemotaxis.

Other immunosuppressive drugs that may be beneficial include azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil (MMF). Controlled clinical trials are needed to help determine which drugs are the most effective and what the best protocols are for dogs that require more than pyridostigmine and steroids.

Azathioprine has been the most commonly used immunosuppressive agent for acquired MG, after prednisolone. Bone marrow suppression is the most common adverse event, and occasionally pancreatitis can occur as well. The recommended dose is 1.1 to 2.2 mg/kg once every 24 hours. Alternate day therapy is given later when the patient is well controlled. There is a lag phase of 2 to 4 weeks. Azathioprine allows for lowering of the steroid dose once it has reached therapeutic levels ("steroid sparing" effect). A complete blood count should be run 7 to 10 days after azathioprine is initiated and then monthly thereafter for the first 3-4 months.

Mycofenolate mofetil has been widely used in human medicine. It is being used more commonly now in veterinary medicine but studies are needed to further define indications and effectiveness in dogs.

Monitoring Dogs with Acquired MG

There is value in monitoring the Ach receptor antibody titer test, especially in dogs that are not on immunosuppressive therapy. Therapy should be continued as long as the test remains positive. Dr. Diane Shelton has reported that at her laboratory there has been an excellent correlation between resolution of clinical signs, including megaesophagus, and return of Ach receptor antibody titers to within the reference range. Once remission occurs, recurrence of MG is rare. Caution: A decrease in the Ach receptor antibody titer in dogs that are on immunosuppressive therapy and that are no longer demonstrating clinical signs should not be interpreted as a sign of remission. It is known that once the immunosuppressive drug dosage is decreased clinical signs can return.

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ESOPHAGITIS

Inflammatory diseases of the esophagus occur more commonly than they are recognized. Inflammatory changes can range from mild mucosal inflammation that may or may not be grossly evident, to moderate to severe ulceration and transmural involvement. Any disorder that causes acute or chronic frequent vomiting has the potential for causing esophagitis. This especially includes causes of severe vomiting, such as intestinal foreign bodies, gastric foreign bodies, acute pancreatitis, parvovirus enteritis, and gastrinoma. Dogs with parvovirus enteritis that are debilitated and recumbent are especially at risk. Vomited fluid that is retained in the esophagus is not cleared adequately in weak and recumbent patients. As a result the esophageal mucosa is bathed with gastric acid and activated enzymes that will cause mucosal injury.

Other causes of esophagitis include esophageal foreign bodies, chemical and thermal injuries, injury from lodged medication (doxycycline capsules in cats can become lodged and cause esophagitis and even stricture formation), gastroesophageal reflux, and anesthesia related reflux.

Diagnosis of Esophagitis

The clinical signs of esophagitis vary considerably, depending on the degree of inflammation present. The clinician must maintain a high index of suspicion because in many cases only subtle clinical signs may be evident. With mild esophagitis there may be increased swallowing motions, salivation, and inappetence. In more severe cases there may be gulping, regurgitation, dysphagia due to pain, total anorexia, and signs that suggest esophageal pain, such as reluctance to move, standing with the head extended, reluctance to lie down, and trembling. Heartburn pain in humans can be quite intense, and it is suspected that a similar situation exists in animals. Esophageal hemorrhage may occur in severe cases. Signs such as increased attempts at swallowing, salivation, and regurgitation, and inappetence that occur within 1 to 4 days of an anesthetic procedure strongly suggest reflux esophagitis. Chronic reflux esophagitis occurs most commonly in patients with hiatal hernia disorders.

Radiographic survey and contrast studies are often normal in patients with mild to moderate esophagitis. Survey films may show increased esophageal density in moderate to severe esophagitis. There may also be various degrees of esophageal dilation, since esophageal inflammation may inhibit motility. Persistent contrast in the thoracic esophagus or esophageal dilation, or both, suggest the possibility of gastroesophageal reflux.

A definitive diagnosis of esophagitis is most often made by endoscopic visualization of the esophageal mucosa. Variable degrees of mucosal erythema or isolated patches of eroded mucosa may be seen. However, as also occurs in humans, some animals with esophagitis do not have gross esophageal abnormalities, and in these cases symptom patterns in conjunction with positive response to therapy are the key components to a presumptive diagnosis.

Treatment of Esophagitis

It is important to note that, although the esophagus is physically a very tough and resilient structure, once it is injured it does not always heal very quickly. For inflammatory disorders fairly aggressive combination drug therapy is often required. Treatment may include dietary modification, proton pump inhibitors (PPIs), H2-receptor antagonists, GI promotility agents, anti-inflammatory drugs, and mucosal protectant therapy. Single or combination drug therapy may be required, depending on factors that include whether treatment is designed mostly for prevention, duration or severity of mucosal injury, and clinical signs. Most affected dogs and cats are managed with either an H2-receptor antagonist or a PPI (e.g., omeprazole). Additionally, high-protein and low-fat diets, a promotility drug, and cytoprotective medication are indicated in some cases.

Mild reflux esophagitis is often asymptomatic and generally resolves without therapy. If clinical signs suggestive of reflux esophagitis occur within several days of an anesthetic procedure, treatment should be instituted, regardless of whether endoscopy is available for definitive diagnosis. Treatment in this situation

usually includes an H2-receptor antagonist or a PPI, the cytoprotective drug sucralfate, and a promotility drug (metoclopramide or cisapride). The duration of therapy will typically be 7 to 14 days. A longer duration will be required if clinical signs persist.

PPIs are drugs that completely inhibit gastric acid secretion in response to all modes of stimulation. This class of drug is used when esophagitis is moderate to severe, as H2-receptor antagonists are not as effective in reducing acid levels. PPIs include omeprazole (Prilosec), lansoprazole (Prevacid), esomeprazole (Nexium), pantoprazole (Protonix), and rabeprazole (Aciphex). Omeprazole is the PPI that has been used most frequently in animal patients. PPIs decrease acid secretion by inhibiting H+, K+ ATPase (commonly called the proton pump), thereby blocking the final, common step in the secretion of gastric acid. PPIs control both basal and meal-stimulated acid secretion. Therefore, the acid suppression achieved by a PPI is more complete and longer lasting than can be attained with an H2-receptor antagonist. The recommended dosage for omeprazole is 0.7 - 1.2 mg/lb once daily.

Moderate to Severe Esophagitis – IV PPI Protocol
The PPI drug pantoprazole is currently available in an injectable preparation. Lansoprazole was available in an IV formulation at one time but this is not currently available. In situations where the patient is NPO or where more rapid effective blood levels are needed, pantoprazole is administered IV.

Pantoprazole (Protonix) IV, 40 mg/vial
Marketed by: Wyeth(R) Pharmaceuticals Inc.

Dose: 0.32-0.4 mg/lb q24 hours (but it can be dosed at q22 hours to get 2 doses out of 1 bottle since it's $$)

Administration: The Protonix should be reconstituted with 10mL of 0.9% NaCl and then further diluted with 100mL of 0.9%NaCl, LRS or 5%Dextrose.

Final concentration = 0.4 mg/mL

Give over 15-20 minutes

H2-receptor antagonists are used to decrease gastric acid production, thereby decreasing acid volume available for reflux. H2-recptor antagonists also reduce the volume of gastric acid that is produced. There is no adverse effect on resting or stimulated LES pressure levels. Ranitidine (1 mg/lb [dog], 1.5 mg/lb [cat] orally every 12 hours), or famotidine (Pepcid, 0.5 to 0.6 mg/lb orally every 24 hours, or every 12 hours if there is severe esophagitis) is generally used for 2 to 3 weeks in dogs and cats with acute reflux esophagitis. I have preferred to use famotidine (Pepcid) because of its long dosage interval and the fact that it is associated with fewer side effects. Another H2-receptor antagonist that can be tried is nizatidine (Axid). The dosage is 1.25 to 2.5 mg/lb orally every 24 hours. Ranitidine and nizatidine also have a gastric prokinetic effect. Long-term therapy should be used in hiatal hernia patients with chronic reflux esophagitis if corrective surgery either is not performed or is unsuccessful.

Esophagitis Associated with Frequent Vomiting
Clinicians are especially cautioned to be more attentive to patients that might have esophagitis secondary to frequent or severe vomiting (e.g., caused by GI foreign bodies, parvoviral enteritis, acute pancreatitis, or renal failure). Esophagitis can easily develop in these situations, and it no doubt adds significantly to the discomfort that the patient is already experiencing. In these cases, both sucralfate and an H2-receptor antagonist are used to treat esophagitis. I use famotidine (Pepcid) injectable at 0.25 mg/lb IV BID. An antiemetic drug such as maropitant (Cerenia) is injected to help decrease the frequency of vomiting. Sucralfate is given orally, in suspension form so as to better coat the esophagus, usually 30 to 60 minutes after antiemetic therapy has been administered.

The duration of therapy in patients with reflux esophagitis depends on the cause and degree of inflammation. For moderate to severe esophagitis, 4 to 8 weeks of therapy or more may be required to achieve full healing of the esophagus. For esophagitis related to frequent or severe vomiting, treatment is usually administered 5 to 7 days, and only longer if clinical signs or endoscopic findings warrant.

Suggested Reading

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Tams TR: Diseases of the esophagus. In Tams TR, ed: *Handbook of Small Animal Gastroenterology*, ed 2, pp. 118-158. Philadelphia, 2003, WB Saunders.

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Diagnosis of Acute and Chronic Vomiting in Dogs and Cats

Vomiting is among the most common reasons that dogs and cats are presented for evaluation. Because there are a multitude of causes of vomiting, ranging from simple to complex, this can be a challenging problem for clinicians to accurately diagnose and manage. The problem also causes significant concern for pet owners, especially when there is an onset of frequent severe vomiting or when the occurrence becomes more chronic and intermittent without adequate control. However, by following a systematic approach beginning with an accurate history, a thorough physical exam, and appropriate baseline testing (Stage 1), then performing tests more specific for certain conditions or organ systems (e.g., bile acids assay, leptospirosis serology, baseline cortisol or ACTH stimulation, ultrasonography) (Stage 2), and finally where indicated performing advanced procedures for more thorough examination and biopsy or definitive therapy (endoscopy, exploratory laparotomy), most cases can be diagnosed successfully and managed judiciously. Vomiting does not constitute a diagnosis in itself. It is emphasized that vomiting is simply a *clinical sign* of any of a number of disorders that can involve any organ system in the body. In fact, one diagnostic registry service listed over 400 potential causes of vomiting in dogs! These notes summarize diagnostic approach and various treatment options for managing dogs and cats with vomiting.

Vomiting refers to a forceful ejection of gastric and occasionally proximal small intestinal contents through the mouth. The vomiting act involves three stages: nausea, retching, and vomiting. Serious consequences of vomiting include volume and electrolyte depletion, acid-base imbalance, and aspiration pneumonia.

It is essential that the clinician make a clear differentiation between regurgitation and vomiting at the outset. Regurgitation is defined as passive, retrograde movement of ingested material, usually before it has reached the stomach. Failure to recognize the difference between regurgitation and vomiting often leads to misdiagnosis. Regurgitation may occur immediately after uptake of food or fluids or may be delayed for several hours or more.

A Detailed, Accurate History is ESSENTIAL

One of the most important early considerations is to determine if any toxins or foreign objects may have been ingested. Some compounds can cause life threatening sequelae. The earlier a toxicity is identified, the greater the chance for successful management. Currently, xylitol toxicity is being recognized more frequently, and sago palm plants, which can cause severe hepatotoxicity in dogs and cats, are found in more homes and yards than in previous years. Cocoa mulch toxicity (theobromine) is also occasionally seen. Many animals that have ingested toxins are presented with vomiting as a prominent sign.

History and Clinical Assessment: Clinical Features Of Vomiting

Because of the wide variety of disorders and stimuli that can cause it, vomiting may present the clinician with a major diagnostic challenge. A complete historical review with emphasis on all body systems is essential for determining a realistic and effective initial work-up plan and treatment protocol. All too often concentration on only the gastrointestinal tract leads to an incorrect diagnosis and inappropriate treatment. Consideration of the following features is useful in assessing and diagnosing a patient with vomiting:

(1) duration of signs
(2) signalment and past pertinent history
(3) environment and diet
(4) systems review (e.g., history of PU/PD, coughing and sneezing, dysuria or dyschezia, etc.)
(5) time relation to eating (vomiting of undigested or partially digested food more than 8-10 hours after eating often indicates a gastric motility disorder [more common] or gastric outlet obstruction [less common])
(6) content of the vomitus (food, clear fluid, bile, blood, material with fecal odor), and
(7) type and frequency of vomiting (projectile?, chronic intermittent?, cyclic?, morning vomiting only?).

Most Common Causes of Acute or Chronic Vomiting in Dogs

First need to Rule-Out:

Dietary/ingestive problem (always investigate for any potential environmental materials that the patient may have been chewing on (plants [toxins], debris carpet, etc)

- Indiscretion (e.g., table scraps, sudden diet change, garbage ingestion; toxins, foreign body, ingesting plants in home or yard)
- Food adverse reaction (dietary sensitivity)
- True food allergy

Parasites

- Intestinal (including *Giardia*)
- Gastric (*Physaloptera*)

Drug related problems

- NSAIDS must always be considered
- Other drugs (e.g., cardiac glycosides, antibiotics, chemotherapeutic agents)
- *Any* drug can potentially cause vomiting, always ask about any supplements that are being given to a pet

Metabolic disorders

- Renal disease
- Liver disease
- Electrolyte abnormalities
- Addison's disease (some are glucocorticoid and mineralocorticoid deficient and will demonstrate typical electrolyte abnormalities; others are only glucocorticoid deficient and require ACTH stim for diagnosis (JAVMA April 15, 2007, p. 1190-1194)

Rule-Outs for Chronic Vomiting, Once the Causes Listed Above are Ruled Out:

Main Categories:

Motility Disorders

- Gastric hypomotility (an underappreciated disorder)

Inflammatory Disorders

- Chronic gastritis (with or without *Helicobacter*)
- Inflammatory bowel disease

Obstructive Disorders

- Foreign body not already diagnosed (including cases with a partial small bowel obstruction that has eluded early diagnosis)
- Hypertrophic gastropathy (uncommon)

Neoplasia

Most Common Causes of Chronic Vomiting in Cats

Dietary problem

- Food adverse reaction (dietary sensitivity), up to 25% of cases

IBD
Hyperthyroidism
Liver disease
Renal disease
GI lymphoma (intestinal is more common)
Chronic pancreatitis
Heartworm disease

Intermittent Chronic Vomiting

Chronic intermittent vomiting is a common presenting complaint in veterinary medicine. Often there is no specific time relation to eating, the content of the vomitus varies, and the occurrence of vomiting may be very cyclic in nature. Depending on the disorder, other signs such as diarrhea, lethargy, inappetence, and salivation (nausea) may occur as well. When presented with this pattern of clinical signs, the clinician should strongly consider chronic gastritis, inflammatory bowel disease, irritable bowel syndrome, and gastric motility disorders as leading differential diagnoses. A detailed work-up including gastric and intestinal biopsies is often required for definitive diagnosis in these cases. It is important to note that chronic intermittent vomiting is a common clinical sign of inflammatory bowel disease in both dogs and cats.

Vomiting from systemic or metabolic causes may be an acute or chronic sign and generally there is no direct correlation with eating and no predictable vomitus content.

Diagnostic Plan

If reasonable concern is established based on the history (e.g., patient is inappetent, ingested a toxin, is vomiting frequently) or physical assessment (e.g., patient is listless, dehydrated, in pain), then a minimum data base of **CBC**, **complete biochemical profile** (or specific tests for evaluation of liver, kidney, pancreas, electrolytes), complete **urinalysis** (pre-treatment urine specific gravity extremely important for diagnosis of renal failure), and **fecal examination** is essential. The best way to screen for GI parasites on a single fecal sample is to run *both* a centrifugal flotation test and a *Giardia* antigen test. If only a single zinc sulfate centrifugal flotation is run, 25-30% of *Giardia* cases will be missed. **T4 and both a heartworm antibody test and heartworm antigen test** are considered routine baseline tests for vomiting cats (approximately 40% of cats with adult heartworms will have vomiting as a clinical manifestation of the disease). **Survey abdominal radiographs** are indicated if thorough abdominal palpation is not possible or suggests an abnormality (e.g., foreign body, pancreatitis, pyometra). Some institutions now routinely order 3 view abdomen films on patients presented for vomiting (both laterals and a VD). Unfortunately these tests are often not done early enough. Even if baseline results are unremarkable they are more than justified because they help to rule out serious problems at the outset (e.g., vomiting due to renal failure, diabetes mellitus, liver disease). Alternatively, any abnormalities provide direction for initial treatment and further diagnostics.

The decision for performing more in-depth diagnostic tests is based on ongoing clinical signs, response to therapy, and initial test results. These tests include **baseline cortisol** or **ACTH stimulation** to confirm hypoadrenocorticism in a patient with an abnormal Na:K ratio or to investigate for this disorder if electrolytes are normal, **complete barium series** or **BIPS study** (for gastric or intestinal foreign body, gastric hypomotility, gastric outflow obstruction, partial or complete intestinal obstruction), **cPLI* or fPLI***(canine and feline lipase immunoreactivity, respectively, for diagnosis of pancreatitis in dogs and cats), and **serum bile acids assay** (to assess for significant hepatic disease). **Barium swallow with fluoroscopy** is often necessary for diagnosis of hiatal hernia disorders and gastroesophageal reflux disease. **Serum gastrin levels** are run if a gastrinoma (Zollinger-Ellison Syndrome) is suspected.

Pancreatitis: Pancreatitis continues to be a challenging disorder to accurately diagnose, short of thorough direct examination and biopsy. Assays for amylase and lipase are of very limited value, especially in cats. In general, the following can be stated regarding the various diagnostic tests for pancreatitis:

Value of the Various Diagnostic Tests for Pancreatitis

Amylase/Lipase

- of value as a screening test in dogs only
- need to be 3x or > above normal reference range in order to suggest pancreatitis
- normal does *not* rule-out pancreatitis

Abdominal Ultrasound
- highly specific, but not very sensitive, especially in cats

Serum PLI
- highly sensitive for pancreatitis

Pancreatic Lipase Immunoreactivity (cPLI and fPLI)
- Exocrine Pancreatic Insufficiency (EPI)
  - cPLI is reliably significantly decreased
  - cPLI is specific for EPI
- Chronic Renal Failure
  - Increased, but usually still within reference range
- Dogs with Biopsy Proven Pancreatitis
  - cPLI sensitivity is > 80%
  - currently recommended cutoff value for *dogs* is >200 ug/L
  - results are also promising for cats

Negative contrast gastrography.
An excellent technique to quickly evaluate the stomach for presence of a nonradiopaque foreign body.
Technique:
Gastric tube, tranquilize as needed
(definitely tranq cats)
Dogs: 8-10 ml/lb air or stop if the animal shows discomfort
Cats: 5 ml/lb air
Remove tube, take rads immediately
(left lateral, VD first)
Can also use 60 ml carbonated beverage (e.g., Mountain Dew)

BIPS are barium impregnated polyethylene spheres. Traditionally, veterinarians have relied on barium liquid as the contrast agent of choice for gastrointestinal studies. However, recognized limitations of barium liquid have led to the development of barium-impregnated solid radiopaque markers for the diagnosis of motility disorders and bowel obstructions. Barium liquid contrast studies are of limited value in detecting hypomotility. Radiopaque markers can be used to investigate a number of common gastroenteric problems. These spheres have been specifically validated for use in dogs and cats and are the only radiopaque markers with which there is extensive clinical experience in veterinary medicine. BIPS are manufactured in New Zealand and are now available in many countries. Information on availability of this product, including instructions on use and interpretation of radiographic studies, can be found at (www.medid.com; 800-262-2399).

Ultrasonography can be useful in the diagnostic work-up of a number of disorders that can cause vomiting. Among the problems that may be detected with ultrasonography are certain disorders of the liver (e.g., inflammatory disease, abscessation, cirrhosis, neoplasia, vascular problems), gall bladder (cholecystitis, choleliths, gallbladder mucocele), GI foreign bodies, intestinal and gastric wall thickening, intestinal masses, intussusception, kidney disorders, and others. Needle aspirations and/or biopsies can be done at many sites under ultrasound guidance.

One of the most reliable and cost efficient diagnostic tools currently available for evaluation of vomiting is **flexible GI endoscopy**. Endoscopy allows for direct gastric and duodenal examination, mucosal biopsy from these areas, and in many cases gastric foreign body retrieval. Endoscopy is considerably more reliable than barium series for diagnosis of gastric erosions, chronic gastritis, gastric neoplasia, and inflammatory bowel disease (a common cause of chronic intermittent vomiting in dogs and cats). It is stressed that biopsy samples should always be obtained from stomach and whenever possible small

intestine regardless of gross mucosal appearance. Normal gastric biopsies may support gastric motility abnormalities, psychogenic vomiting, irritable bowel syndrome, or may be noncontributory (i.e., look elsewhere for diagnosis). Many dogs with vomiting due to inflammatory bowel disease have no abnormalities on gastric examination or biopsy. If only gastric biopsies are obtained, the diagnosis may be missed.

Abdominal exploratory is indicated for a variety of problems including foreign body removal, intussusception, gastric mucosal hypertrophy syndromes, procurement of biopsies, and for resection of neoplasia.

***fPLI** is available at Texas A&M University. Serum samples can either be sent directly to the GI Laboratory at Texas A&M University, or they can be forwarded to Texas A&M by a commercial laboratory.

The address is:
GI Lab at Texas A&M University
College of Veterinary Medicine
TAMU 4474
College Station, TX 77843-4474
979-862-2861
www.cvm.tamu.edu/gilab

Diagnosis of Vomiting

Stage 1—Baseline Assessment

- History and physical examination
- Conservative vs. more aggressive diagnostic plan based on patient's condition and clinician's concern

Conservative Approach	**Serious or Systemic Clinical Signs**
Fecal examination[a]	Complete blood count
Selected diagnostics	Complete biochemical profile
Specific/symptomatic therapy	Urinalysis
	Fecal examination[a]
	Parvovirus test if indicated
	Survey abdominal radiographs
	T4 (cats)
	Heartworm antibody and antigen test (cats)
	Appropriate specific/supportive therapy

Stage 2—Further assessment (if vomiting persists or initial tests indicate further investigation should be performed promptly):

- **Special Blood Tests**
  - —Corticotropin stimulation
  - —cPLI or fPLI (pancreatitis)
  - —Leptospirosis serology and/or lepto PCR
  - —Bile acids assay (to asses liver function)
  - —Coagulation tests (consider in patients with hematemesis/melena)

- **Contrast Radiography**
  - —Barium contrast
  - —Air contrast gastrogram (to further assess for gastric foreign body)
  - —BIPS (barium-impregnated polyethylene spheres; with food to assess GI motility)
- **Ultrasonography**
  - —Evidence of GI or non-GI disease
  - —Aspirates or biopsy
  - —Abdominocentesis
- **Nuclear Scintigraphy**
  - —Transcolonic portal angiography for detection of portosystemic anomaly
  - —GI motility study

Stage 3—Invasive Procedures

- **Flexible GI endoscopy**[b] (minimally invasive)
  - —Examination, biopsy, foreign body retrieval
- **Laparoscopy**
  - —Biopsies (e.g., liver, pancreas)
  - —Aspirates (e.g., gall bladder, lymph nodes, mass lesion)
  - —Intestinal biopsy
- **Surgical intervention**
  - — Therapeutic or exploratory with multiple biopsies

[a]GI parasites, including *Giardia*, should always be considered in dogs with acute or intermittent vomiting. Best baseline testing on a single fecal sample includes centrifugal flotation and *Giardia* antigen test.

[b]Endoscopy is a diagnostic or therapeutic tool that can be used in Stage 1, Stage 2, or Stage 3, depending on the clinical situation.

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Drug Therapy for Vomiting in Dogs and Cats

Pharmacologic Control of Acute Vomiting

Initial nonspecific management of vomiting includes NPO (in minor cases a 4-12 hour period of nothing per os may be all that is required), fluid support, and antiemetics. Initial feeding includes small portions of a low fat, single source protein diet starting 6-12 hours after vomiting has ceased. Drugs used to control vomiting will be discussed here.

The most effective antiemetics are those that act at both the vomiting center and the chemoreceptor trigger zone. Vomiting is a protective reflex and when it occurs only occasionally treatment is not generally required. However, patients that continue to vomit should be given antiemetics to help reduce fluid loss, pain and discomfort.

For many years I strongly favored **chlorpromazine (Thorazine),** a phenothiazine drug, as the first choice for pharmacologic control of vomiting in most cases. The HT-3 receptor antagonists **ondansetron (Zofran)** and **dolasetron (Anzemet)** have also been effective antiemetic drugs for a variety of causes of vomiting. **Metoclopramide (Reglan)** is a reasonably good central antiemetic drug for dogs but not for cats. **Maropitant (Cerenia)** is a superior broad spectrum antiemetic drug and is now recognized as an excellent first choice for control of vomiting in dogs. Studies and clinical experience have now also shown maropitant to be an effective and safe antiemetic drug for cats. While it is labeled only for dogs, clinical experience has shown it is safe to use the drug in cats as well. In addition to antiemetic effect, maropitant also provides visceral analgesic effect. Maropitant is also the first choice for prevention of motion sickness vomiting in both dogs and cats.

Metoclopramide (Reglan) is a gastric prokinetic drug that also has central antiemetic effect. Metoclopramide increases gastric and proximal small intestinal motility and emptying without causing acid secretion, decreases enterogastric reflux, and provides inhibition of the chemoreceptor trigger zone. The central antiemetic effect is mediated through antagonism of dopaminergic D2 receptors in the chemoreceptor trigger zone of the medulla to inhibit vomiting induced by drugs, toxins, metabolic disease, and acid-base imbalances. Metoclopramide is a less effective central antiemetic drug in cats than in dogs because serotonin receptors, rather than dopaminergic receptors, predominate in the CTZ of cats. For vomiting in cats, I generally usually use metoclopramide only if a prokinetic effect is desired. Chlorpromazine, dolasetron, ondansetron, or maropitant should be used as a first or second choice to control acute frequent vomiting in cats. Parvovirus can cause gastric hypomotility and therefore the promotility effects of metoclopramide may prove beneficial. However, maropitant, dolasetron, or ondansetron are more effective drugs than metoclopramide for managing vomiting caused by parvovirus. Further, maropitant also helps provide visceral analgesia and is the best single drug choice in parvo cases.

The recommended injectable dose of metoclopramide is 0.2 to 0.5 mg/kg IM or SC given TID to QID as needed. Metoclopramide can also be given IV as a constant rate infusion (1 - 2 mg/kg over 24 hours). Metoclopramide should not be used if gastric outlet obstruction or GI perforation is suspected, or in patients with a seizure disorder.

Metoclopramide - Clinical Applications for Chronic Vomiting

Several clinical applications for use of metoclopramide in dogs with chronic vomiting have been identified. These include gastric motility disorders, gastroesophageal reflux disease (GERD), primary or adjunctive therapy for antral and pyloric mucosal hypertrophy, and as treatment for nausea and vomiting caused by various other disorders. While cisapride is a superior prokinetic drug, metoclopramide is an effective drug and is often the first choice for prokinetic effect, with cisapride used as a second choice if metoclopramide is not effective. Other drugs that are sometimes used for prokinesis are low dose erythromycin and the H2-receptor blocker ranitidine (Zantac).

Gastric motility disorders have been recognized with increased frequency in veterinary medicine, but are still overlooked. Gastric stasis, characterized by abdominal discomfort, periodic bloating, borborhygmus, nausea and vomiting may be associated with a number of clinical states that include inflammatory disorders (e.g., chronic gastritis, IBD), gastric ulcers, gastroesophageal reflux, infiltrative lesions (e.g., neoplasia), and chronic gastric dilatation. Metabolic disturbances that may cause gastric stasis include hypokalemia, hypercalcemia, acidosis, anemia, and hepatic encephalopathy. Short-term continued vomiting that is observed in some cases after apparent recovery from viral enteritis may be due to abnormal gastric motility. Transient (3 to 14 days) gastric hypomotility may also occur after gastric or abdominal surgery. Motility disorders with no organic cause may be best classified as idiopathic. For any of the disorders listed, the primary cause should be treated, and metoclopramide may be a valuable short-term adjunct to therapy in these cases, along with feeding low fat foods in divided amounts. Metoclopramide alternatively may be used as the primary treatment on a long-term basis for idiopathic hypomotility disorders. Metoclopramide has also been useful in treatment of dogs that have chronic vomiting characterized by episodes occurring routinely in the early morning and containing bilious fluid.

In general, patients less than 4.5 kg (10 lb) receive 2.5 mg per dose), 4.5 to 18 kg (11-40 lb) 5 mg per dose, and greater than 18 kg (40 lb) 10 mg per dose. Metoclopramide is given 30 to 45 minutes before meals and again at bedtime. Animals that require chronic medication may need only 1 to 2 doses daily. Because of its short half-life, the drug is not effective when given by intravenous or intramuscular bolus injection for purposes other than when only one treatment would be administered (i.e., to aid in evacuating the stomach if an anesthetic procedure in a non-fasted patient becomes necessary, pre-radiologic contrast study). Subcutaneous administration into fat may be of benefit when oral therapy is contraindicated and an intravenous line is not available.

Metoclopramide is less effective as a promotility drug than cisapride (see later discussion). While many animals with gastric hypomotility respond well to metoclopramide, some have a less than desired response. If a patient with a suspected gastric hypomotility disorder has an inadequate response to metoclopramide, cisapride should be tried next.

Side Effects

Some adverse effects may occur if metoclopramide is given in the usual therapeutic doses. Clients should be apprised of these before the medication is prescribed. These effects are uncommon in animals, and somewhat more common in humans.

Motor restlessness and hyperactivity may occur; and when observed, these signs usually begin 20 to 30 minutes after a dose and last 4 to 5 hours. The reaction can range from mild to quite dramatic. Alternatively, drowsiness and depression occasionally occur. Side effects are infrequent in cats, but clients have reported disorientation, frenzied behavior, and hiding tendencies associated with the medication. Hospitalized animals may chew excessively at catheter sites or be more aggressive toward hospital staff. Sometimes these effects are subtle and nursing staff need to be observant. These side effects are reversible (diphenhydramine [Benadryl 2.2 mg/kg IV] or discontinuing the drug) but generally do not subside when lower doses are given. Unless side effects are infrequent, the use of metoclopramide should be discontinued if adverse reactions are seen. Cisapride does NOT cause these same type of adverse reactions. Metoclopramide crosses the blood brain barrier, cisapride does not.

In general, metoclopramide should not be given to epileptic patients. Other contraindications include evidence of significant mechanical obstruction, simultaneous use of anticholinergic agents (antagonism of metoclopramide's effects), and pheochromocytoma.

Ondansetron - Clinical Applications for Acute Vomiting

Ondansetron (Zofran) is a potent antiemetic drug that has proven to be effective in both humans and animals for control of severe vomiting. It has been used in human cancer patients undergoing cisplatin therapy, a drug that frequently causes nausea and severe vomiting, with very good results. Ondansetron

acts as a selective antagonist of serotonin S3 receptors (a principal mediator of the emetic reflex). S3 receptors are found primarily in the CTZ, on vagal nerve terminals, and in the gut in enteric neurons. The principal site of action of ondansetron is in the area postrema, but it also has some peripheral gastric prokinetic activity.

In my experience, ondansetron has produced very good results in either controlling or at least significantly decreasing the frequency of vomiting in dogs and cats with frequent or severe vomiting, including in dogs with severe parvovirus enteritis, in pancreatitis patients, and cats with hepatic lipidosis. The recommended dose is 0.5 to 1 mg/kg IV given as a slow push every 6 to 12 hours (based on patient response). Frequently dogs that appear quite distressed due to nausea and vomiting look much more relaxed and comfortable within 15 minutes of receiving ondansetron. There are no reports of any significant side effects such as diarrhea, sedation, or extrapyramidal signs in human and animal trials. While Zofran was quite expensive for many years, it came off patent in 2007 and is now more affordable for use at any small animal hospital. *Currently, however, my top antiemetic drug of choice is maropitant (Cerenia), because it is a highly effective antiemetic drug but also because it provides visceral analgesic effects as well.* Animals with significant liver disease may be best managed with ondansetron or dolasetron, as maropitant should be used with caution in animals with significant hepatic dysfunction (although it is not contraindicated – some clinicians have used maropitant successfully and safely in animals with liver disease).

Dolasetron

Dolasetron (Anzemet) is also a 5-HT3 receptor antagonist antiemetic drug, with action similar to ondansetron. It is a slightly less expensive alternative to ondansetron and only needs to be administered once daily. Indications are the same as for ondansetron, namely, for control of frequent vomiting that is poorly responsive to lesser expensive front-line antiemetic drugs. The dose is 0.5-1 mg/kg IV once daily. Dolasetron is generally well tolerated in animals.

A NEWER ANTIEMETIC DRUG FOR DOGS

Most drugs used to control vomiting in animals have been developed for use in humans. There has been a need for a broad-spectrum antiemetic drug for use in animals that is effective in a variety of situations, has a rapid onset of action, is safe and affordable, and is available in both injectable and oral preparations. **Maropitant citrate (Cerenia)** is a newer broad-spectrum antiemetic drug that is indicated for the treatment of acute vomiting in dogs. Maropitant is a neurokinin receptor antagonist that blocks the pharmacologic action of the neuropeptide substance P in the central nervous system. Substance P is found in significant concentrations in the nuclei comprising the emetic center and is considered a key neurotransmitter involved in emesis. By inhibiting the binding of substance P within the emetic center, maropitant provides broad-spectrum effectiveness against both neural and humoral causes of vomiting. Clinical trials and recent clinical experience, since August 2007 when the drug was released for use in the U.S., have shown maropitant to be very effective for control of a variety of causes of acute vomiting in dogs. It is administered as a once-daily injection (0.45 mg/lb [1 mg/kg] SC for dogs), which is a significant advantage over many other antiemetic drugs, and has a rapid onset of action. Maropitant is also available in tablet form for outpatient use, which makes it a very attractive choice for use in small animal practice. It is the drug of choice for dogs with motion sickness.

CAUTION: Use at a reduced dose for animals with significant hepatic dysfunction, OR select an alternative antiemetic for animals with liver disease – e.g., ondansetron or dolasetron.

The issue of stinging on injection: Information from clinical experience and studies indicates that there is less likelihood for stinging to occur with maropitant injections when the product is kept refrigerated. The current guidance is that the solution should be kept refrigerated and drawn up and injected right away at refrigerated temp.

CATS: Studies have now been done using maropitant in cats and some clinicians in general practice have been using it since 2008. In May 2012 Cerenia was approved for use in cats and also in puppies as young as 8 weeks of age.

Recommended dose of maropitant for cats:
Injectable: 0.5-1 mg/kg SC or IV (give SLOWLY over 60-90 seconds if administering IV)
Oral: (1 to 2 mg/kg). This is the starting dose recommended for prevention of motion sickness in cats as well; i.e., somewhat lower than the canine dose for motion sickness.

How long can Cerenia be used on a consecutive days schedule?
The label states that Cerenia should not be given for more than 5 consecutive days (injectable or oral at the anti-emesis dose) and for 2 days at the motion sickness prevention dose. However, experience has shown that in some patients Cerenia has been used safely and effectively on a longer term basis (anecdotal reports, e.g., patients with neoplasia or renal disease that were experiencing ongoing nausea, vomiting, and inappetence). Many of these patients have a much better quality of life while on Cerenia, as they have less nausea and vomiting and a much better appetite. There are cats that have been treated with a daily oral dose for months to several years. Use of Cerenia in this fashion is being investigated further.

A study was presented at the Veterinary Cancer Society (VCS) meeting in San Diego Oct. 29-November 1, 2010, and then subsequently at the ACVIM Forum in Denver in June 2011:
Pharmacokinetics of maropitant citrate dosed orally to dogs at 2 mg/kg and 8 mg/kg once daily for 14 consecutive days. Two groups of eight healthy beagle dogs were administered maropitant citrate at 2 or 8 mg/kg orally once daily for 14 days. Concentrations of maropitant and its metabolite were measured in plasma using a LC-MS/MS assay. Pharmacokinetic parameters were estimated using non-compartmental pharmacokinetic techniques and a modeling approach was used to estimate steady-state.

Results: The model estimate for the number of doses required to reach 90% of steady-state was 4.30 for 2 mg/kg and 8.09 for 8 mg/kg. Four dogs experienced a single dose of vomiting.

Conclusions: Dosing maropitant citrate beyond the label duration was well tolerated by healthy dogs. During the 14 days of dosing there was accumulation, however, steady-state was reached after approximately 4 doses for daily 2 mg/kg dosing and 8 doses for daily 8 mg/kg oral dosing.

Use of Oral Maropitant (Cerenia)

- Confident there is no GI foreign body (i.e., do not use ongoing antiemetic therapy if there could be a foreign body ledged in the GI tract)
- Prevent vomiting during cyclosporine, azithromycin, or other drug induction period (use for 3-5 days in conjunction with the start of a drug that might cause vomiting)
- Vomiting flare-ups in IBD patients (or other chronic disorders)
- Pancreatitis, parvovirus, etc for a few days after vomiting is fairly well controlled with injectable maropitant. Excellent control of nausea may help improve appetite and earlier food intake
- Prevention of vomiting in chemotherapy patients
- Prevention of motion ("car") sickness
- Renal disease patients – and perhaps chronic use (these patients may benefit tremendously and we have observed many patients that eat better, do not vomit or exhibit nausea, and feel better overall. Studies are ongoing).

Cisapride

Cisapride is a potent GI prokinetic drug and is superior in action to metoclopramide. It is no longer on the market for use in humans, as of 2000, because of an association with fatal arrhythmias. There are no reports of similar complications existing in dogs and cats, however, and cisapride continues to be readily available to veterinarians through compounding pharmacies.

Cisapride has broader promotility effects than metoclopramide (e.g., cisapride has demonstrated excellent efficacy in management of colonic inertia and small intestinal ileus). In contrast to metoclopramide, which has central effect at the CRTZ in addition to its peripheral effects, cisapride has no known direct antiemetic properties. Another contrast is that metoclopramide's prokinetic effect is most significantly on the stomach. It is NOT a reasonable choice for treatment of small intestinal ileus.

The most relevant uses of cisapride in animal patients include treatment of gastroparesis, especially in patients that experience significant side effects from metoclopramide (e.g., hyperactivity and other dystonic reactions) or where metoclopramide is not sufficiently effective, idiopathic constipation, gastroesophageal reflux disease (if H2-receptor antagonists or proton pump inhibitors and dietary management alone are not effective), and postoperative ileus.
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Cisapride is extremely well tolerated by animal patients. I have used cisapride in dogs and cats that have experienced neurologic side effects from metoclopramide. I have observed no adverse reactions to cisapride in any of these patients, even in those whose side effects to metoclopramide included very bizarre behavior changes. The suggested dose of cisapride is similar to what has been recommended for metoclopramide (see earlier discussion).

Acute and Chronic Diarrhea in Dogs and Cats

Giardia, *Clostridium perfringens* Enterotoxicosis, *Tritrichomonas foetus*, and Cryptosporidiosis

Introduction

These seminar notes will focus on the diagnosis and management of important and sometimes challenging to diagnose causes of diarrhea in dogs and cats, with particular emphasis on *Giardia*, *Clostridium perfringens* enterotoxicosis, cryptosporidiosis, and *Tritrichomonas foetus*. These disorders should be investigated early in the course of diarrhea, whether it is persistent or intermittent, along with evaluation for dietary causes of GI signs (including both dietary indiscretion and adverse reactions to specific foods), nematode parasites, bacterial and viral causes, and acute idiopathic colitis. This group of disorders constitutes a thorough differential list for animals with acute and intermittent diarrhea (Table 1).

The challenge to veterinarians is in making an accurate diagnosis, so that the most indicated therapy can be instituted as early as possible. This will then lead to the best opportunity for successful control of the medical disorder. It is also important to recognize that some animals may have several disorders at the same time (co-morbidities), so a thorough diagnostic approach is recommended. This is why it is often best to run tests for these disorders at the same time, through use of a "fecal diagnostics panel" that is now available at many commercial laboratories. A single fecal sample is submitted to the lab, and tests for each of these disorders is done at the same time. This provides a prompt and thorough analysis for important clinical disorders of the GI tract. The clinician then has more clear direction on how to proceed with treatment, or other diagnostic tests in the event that none of these disorders is identified.

It is also important to include blood tests for complete blood count, urinalysis, and complete biochemical profile to help evaluate for any major organ abnormalities (e.g., liver, kidneys, hypoproteinemia associated with protein losing enteropathy), especially in cases in which diarrhea does not resolve with the initial therapies and dietary changes. Only animals should have these tests done early in order to establish a minimum data base.

Table 1: Common Causes of Acute Diarrhea in Dogs and Cats

Young Animals	***Older Animals***
Dietary problems	**Dietary** problems
Parasites	**Parasites** less common but always possible
- nematodes	- nematodes
- protozoa (*Giardia*, *Trichomonads*)	- protozoa (*Giardia*, *Trichomonads*)
- coccidia (including *Cryptosporidium*)	- coccidia (including *Cryptosporidium*)
Viral and bacterial	Viral causes uncommon in older animals
Clostridium perfringens enterotoxicosis	**CPE** (common in older animals)
(CPE)	**Acute colitis** (fairly common cause of diarrhea in older animals)

Giardia is an important cause of diarrhea, and for some patients other GI signs as well. It is an important pathogen in dogs and cats, as well as humans and other species. Historically, a*ccurate* diagnosis of *Giardia* has posed a significant challenge to veterinary practitioners, but there are now much more

sensitive tests readily available for veterinarians to use on a routine basis. Because of the impact that this organism can have on animals, and also humans because of its zoonotic potential, it is important that veterinarians perform accurate diagnostic testing on animals to determine whether or not an animal is infected with *Giardia*. These notes will emphasize steps for accurate diagnosis, and also management of giardiasis.

Clostridium perfringens enterotoxicosis is a common cause of intermittent diarrhea in dogs and cats. Veterinary practitioners should test for the enterotoxin whenever faced with a patient that has unexplained diarrhea.

Cryptosporidiosis is now recognized to be a more common disorder in dogs and cats than was previously thought. It can cause significant abnormalities, and it has zoonotic potential. Cryptosporidiosis can be fatal in people that also are immunosuppressed (e.g., on chemotherapy or corticosteroids, carriers of HIV). Therefore, it is incumbent on veterinarians to test for this disorder, as there are important implications to both the patient as well as to humans who may come in contact with an infected animal.

Early Diagnostic Screening in Animals with Diarrhea

Diarrhea – Making the Correct Diagnosis(es)

Acute Diarrhea – DOGS (initial screening)	**Acute Diarrhea – CATS (initial screening)**
☐ Direct smear in house (fresh sample (perform by <1hr)	☐ Direct smear in house (fresh sample (perform by <1hr)
☐ $ZnSO_4$ w/centrifugation	☐ $ZnSO_4$ w/centrifugation
☐ Giardia antigen test	☐ Giardia antigen test
☐ Parvo test if indicated	
Later if Persistent:	**Later if Persistent:**
☐ Repeat all of the above	
☐ Cryptosporidium IFA	☐ Repeat all of the above
☐ Clostridium perf enterotoxin assay	☐ Cryptosporidium IFA
	☐ Clostridium perf enterotoxin assay
	☐ Large bowel signs??
	> R/O Tritrichomonas foetus (special tests)

****Negative results do not make a rule-out. Be persistent, as retesting can be very important.**

Diagnosis and Management of *Giardia*

Diagnosis

Standard diagnostic tests used in any practice setting should include **fresh saline fecal smears** and zinc sulfate flotation with centrifugation. **Zinc sulfate flotation with centrifugation**, rather than gravity

flotation alone, is a somewhat more sensitve means of testing for *Giardia* and other parasites. Trophozoites are more likely to be found in loose stools, while cysts are more often found in semi-formed or formed stools. Performing both zinc sulfate concentration with centrifugation and a ***Giardia* antigen test** together constitutes the most accurate means of evaluating a patient for the presence of *Giardia*. This has been recognized as the "gold standard" in human medicine, and is true also in veterinary medicine.

Direct Saline Smear

Direct smears should be performed on fresh fecal samples as soon as possible after being passed, but definitely within 1 hour. A fresh saline smear is made by mixing a drop of feces with a drop of saline on a glass slide. A coverslip is applied and the preparation is examined immediately under 40x magnification. Trophozoites are pear-shaped and have a characteristic concave ventral disk. They demonstrate rolling/wobbling motion (e.g., like a falling leaf). Adding a drop of Lugol's solution of iodine on the edge of the coverslip can be done as an optional procedure and this will enhance the morphologic features of the organisms and make them easier to find. The iodine kills the parasite, so motion will no longer be seen if this procedure is used. Differentiation of trichomonads from *Giardia* is based on a different motion pattern (more forward motion with trichomonads versus rolling motion with *Giardia*), the absence of a concave disk, a single nucleus, and the presence of an undulating membrane. Identification of *Giardia* trophozoites is diagnostic, while their absence in fecal samples does not rule out presence of infection.

Zinc Sulfate Concentration with Centrifugation

Many studies have now shown that zinc sulfate concentration with centrifugation is the most reliable test available for demonstration of *Giardia* cysts in fecal samples. The test can be done in any practice setting, and the technique is described below. Alternatively, because the best accuracy in detection of *Giardia* is achieved through well trained and experienced lab personnel consistently setting up the assay and studying the microscopic specimens on time, many practices now submit fecal samples for centrifugation assays to a commercial laboratory.

Zinc sulfate centrifugation is also a very effective method for identifying nematode eggs in feces. It is therefore now used as the standard test for screening for intestinal parasites in most academic and many private practices. Studies have shown that approximately 70-75 percent of *Giardia* positive dogs can be identified on a single zinc sulfate centrifugation test (as opposed to approximately 40 percent of dogs after 3 separate saline smear preparations). Slides should be examined within 10 minutes of preparation because the cysts may begin to shrink. **Since animals shed *Giardia* on an intermittent basis it is recommended that a series of zinc sulfate concentration tests be run over a 3 to 5 day period in order to maximize chances of accurately diagnosing or ruling out *Giardia* in animals with chronic diarrhea (or, alternatively, an antigen test can be run at the same time to help increase diagnostic efficiency and accuracy – this is what I recommend now as a standard practice).** Diagnostic efficiency increases to 95 percent when 3 zinc sulfate examinations are conducted over a 3 to 5 day period. A positive result on any of the tests warrants treatment for *Giardia*.

Caution: It is not uncommon for plant spores, yeast bodies, and other amorphous debris to be mistaken for *Giardia* cysts. In fact, *Giardia* is frequently misdiagnosed – either it is being diagnosed incorrectly, or the wrong tests are being run and animals with *Giardia* are being missed. Giardia cysts are 11-13 u in size, and the subtle characteristics of the nuclei, axostyles, and median bodies are often more easily observed under 100X oil immersion magnification. Sometimes there are crescent shaped indentations of the cyst wall. Yeast bodies are similar to *Giardia* in size, shape, and color. Yeast bodies appear to be far more common than *Giardia*.

Zinc Sulfate Concentration - Summary

- Zinc sulfate is the flotation solution of choice in small animal practices (excellent for detection of *Giardia* as well as nematodes)

- Zinc sulfate concentration *with* centrifugation is the best test for identification of *Giardia* cysts
- Causes less distortion of *Giardia* cysts than standard salt solution

Giardia Antigen Testing

Other diagnostic tests for *Giardia* include an enzyme-linked immunosorbent assay (ELISA) test for *Giardia* antigen in feces, a direct immunofluorescent assay, duodenal aspiration under endoscopic guidance, and the peroral string test. The latter two tests are impractical for routine use in small animal practice, especially when the effectiveness of today's fecal tests is recognized.

The fecal ELISA test detects *Giardia* antigen that is produced by dividing trophozoites. The test is very sensitive in humans and reportedly detects 30 percent more cases of *Giardia* than does zinc sulfate. Studies have now confirmed that this is also an excellent test for use in animals. One advantage of the ELISA test is that, since it detects *Giardia* specific antigen in the feces, it avoids the problem of intermittent cyst excretion in the feces. This test can be a significant aid in accurate diagnosis of *Giardia* in any private practice setting, and I highly recommend that veterinarians utilize this test in order to more consistently make an accurate diagnosis of giardiasis in their small animal patients.

Indications for Running *Giardia* Antigen Test:

- Cases of acute or chronic diarrhea in which zinc sulfate centrifugation tests are negative for parasites
  *Including young dogs with suspected viral or bacterial enteritis – *Giardia* and other parasitic infections can significantly compromise animals with these conditions. **I recommend that all puppies with parvoviral enteritis be screened early for parasites with a combination of zinc sulfate with centrifugation and a *Giardia* antigen test (both tests day one or two on a single fecal sample)**
- Cases in which it is unclear whether *Giardia* cysts are being seen on flotation tests (e.g., vs. plant spores)
- For evaluation of animals with unexplained weight loss, unthriftiness, abdominal pain
- Acute or chronic vomiting **(some animals with disease related to *Giardia* have only vomiting as a clinical sign)
- **Many hospitals are now using the ZnSO4 with centrifugation *and Giardia* antigen combination assay as a routine screening test for GI parasites and wellness testing.** This is because there are animals that have *Giardia* but that do not have any GI signs (loose stools, vomiting, etc) at the time of the exam. The addition of the antigen assay significantly improves the diagnostic sensitivity for *Giardia.* In summary, this approach offers: Better more sensitive diagnostic testing, more convenience to the client (one sample only), and ultimately it is more economical.

Treatment of *Giardia*

For many years the primary treatment for *Giardia* in dogs and cats has involved metronidazole. For dogs in which metronidazole proved ineffective, quinacrine was often used in the past. However, although quinacrine has been shown to be more effective than metronidazole, it frequently causes side effects, including lethargy, anorexia, and vomiting. It was also used in cats. Quinacrine is no longer available, however. More recently it was shown that albendazole (Valbazen) is highly effective in controlling *Giardia*. I recommended albendazole as an effective treatment for Giardia from 1993-1997, but experience with albendazole in dogs and cats has shown that it can cause bothersome side effects; including

leukopenia, lethargy, and inappetence. Therefore, I have not recommended albendazole for many years. I mention it here because some veterinarians still do use it.

Fenbendazole (Panacur), well known for its effectiveness against a variety of intestinal parasites, also appears to be very effective against *Giardia*. In a controlled trial at Cornell University 6/6 dogs were effectively treated in an initial study. The same dose that is used to treat roundworms, hookworms, whipworms, and the tapeworm *Taenia pisiformis* (50 mg/kg orally once daily for 5 consecutive days [there have been treatment failures occasionally when therapy is given for only 3 days]) is used to treat *Giardia*. If the infection is not cleared on this regimen, a longer course of therapy is used (7 days). Fenbendazole has a proven track record for being very safe and is thought to not have any teratogenic effects. ***Fenbendazole is therefore the drug of choice for treatment of Giardia in pregnant animals.*** This is now also the preferred treatment for *Giardia* in cats.

Drontal Plus (Bayer Animal Health) is also an excellent choice for treatment of *Giardia*. This product includes febantel in addition to praziquantel and pyrantel pamoate. Febantel is the drug component that treats *Giardia*. Febantel is metabolized into fenbendazole and oxyfenbendazole after oral administration. Drontal Plus is administered once daily for 3 to 5 consecutive days for treatment of *Giardia*. Drontal Plus has been approved for use in dogs. Drontal Plus has been administered to cats empirically at a dosage of two small dog tablets per cat (about 50 mg/kg febantel) orally for 5 days with subsequent demonstration of decreased shedding of cysts (Scorza, Radecki, and Lappin).

Metronidazole is still a useful drug for treating *Giardia*, and it has the added advantage of having antibacterial as well as antiinflammatory properties. In situations in which it is unclear whether diarrhea is due to giardiasis, bacterial overgrowth, or mild inflammatory bowel disease, metronidazole is an excellent choice, especially when a client requests empirical therapy rather than definitive diagnostic testing. Metronidazole is only 67-74 percent effective in eliminating *Giardia* from dogs, however, and if a positive diagnosis is made fenbendazole or febantel would also be a reasonable choice. Potential side effects of metronidazole include anorexia, vomiting, and neurologic problems (ataxia, vestibular problems, seizures). In my experience these side effects are not common. They are more likely to occur when the anti-*Giardia* dose is used (25 to 30 mg/kg orally every 12 hours for 5 to 7 days). *The total dose of metronidazole should not exceed 65 mg/kg per day (30 mg/lb per day).* A lower dose (10 to 20 mg/kg every 12 hours) is used in treatment of intestinal bacterial overgrowth and inflammatory bowel disease. Side effects are infrequent at this dose. In the past, if a 5 to 7 day course of metronidazole failed to eliminate *Giardia*, a longer follow-up course (10 to 14 days) was often used. With the availability of fenbendazole and Drontal Plus it is recommended that one of these drugs be used instead in this situation.

Metronidazole neuro toxicity can be resolved more quickly by administering diazepam for several days. This is likely related to modulation of the GABA receptor within the cerebellar and vestibular systems.

In addition to use of pharmacotherapy to eradicate *Giardia*, it is important to consider environmental control so as to minimize chances of reinfection, especially in kennel or cattery situations. Cysts present in a cool environment can remain infective for a long period of time. Cages and runs should be thoroughly cleaned of all solid fecal material. Steam cleaning, or treatment with a quaternary ammonium compound (e.g. A 33) are both very effective measures for killing cysts. Allowing time for thorough drying is important, to desiccate any remaining cysts.

Bathing: Steps to prevent reinfection play an important role in resolution of giardiasis in dogs. Dogs may be reinfected with cysts from the hair or the environment, and bathing at the time that drug therapy is concluded, thereby removing cysts that could be licked from the hair coat by the animal, may be a very helpful additional step in decreasing the chances of reinfection. Changing the environment, if possible, can also be beneficial.

Dietary Therapy and Supplementation:

In animals that are known to be chronic carriers of *Giardia*, it may be benefical to supplement the diet with fiber. Increased dietary roughage may make it more difficult for *Giardia* trophozoites to attach to the small intestinal mucosa (use either commercial diets or simply add a fiber source such as Metamucil or pumpkin, for example, to the animal's standard diet

Rx for Chronic Giardiasis: <u>Will Probiotics Help</u>?

- *Lactobacillus johnsonii has been shown to inhibit Giardia proliferation in vitro*
  - ✓ Due to alterations in pH from production of lactic acid
  - ✓ In guinea pigs, in vivo, prophylactic feeding of Lj greatly reduced fecal shedding following experimental inoculation with *G. intestinalis*

- Enterococcus faecium SF68 fed to mice
  - ✓ Stimulated increase in anti-Giardia intestinal IgA and circulating IgG
  - ✓ Increased CD4+ immunocytes
- Reduced shedding and more rapid clearance of *Giardia?*
- **Studies are ongoing**

Zoonotic Potential: Current information indicates that zoonotic potential may exist with some Giardia genotypes, but certainly not all. When both animals and humans living in the same environment become infected, a common source of infection rather than direct transmission must also be considered.

Are most *Giardia* spp. infections shared between animals and man? The genus *Giardia* contains multiple species of flagellated protozoans that are indistinguishable morphologically. Host specificity was thought to be minimal for *Giardia* spp., but not all small animal isolates cause disease in human beings. There have been varying results concerning cross-infection potential of *Giardia* spp.. Human *Giardia* isolates usually grow in cell culture, animal isolates often do not. Recent genetic analysis has revealed 2 major genotypes in people. Assemblage A (*G. duodenalis*) has been found in infected humans and many other mammals including dogs and cats. Assemblage B (*G. enterica*) has been found in infected humans and dogs, but not cats. It appears that there are specific genotypes of *Giardia* that infect dogs (*G. canis*; Assemblages C and D) and cats (*G. felis*; Assemblage F) but not people. Accordingly, healthy pets are not considered significant human health risks for HIV infected people by the Centers for Disease Control (<u>www.cdc.gov/hiv/pubs/brochure/oi_pets.htm</u>).

Should Giardia Positive But Asymptomatic Animals Be Treated?
The question whether animals that are asymptomatic carriers of *Giardia* should be treated is often asked. *Giardia* cysts have been found in many animals with well-formed feces. *Giardia* is clearly not pathogenic in some animals, while in others it causes significant enteritis. And there may be others that experience intermittent GI upsets that could potentially be related to chronic parasite carriage, and that may benefit in the long term from more effective parasite control. Because the public health considerations must still be considered, **I do recommend that all animals with fecal samples that are positive for *Giardia* be treated, using these guidelines:**

- ✓ *Administer Fenbendazole (Panacur) 5 days*
- ✓ *Re-check fecal at 14-28 days, not later – use the zinc sulfate w/centrif assay, NOT the antigen test (we don't know how long it takes to go negative)*
- ✓ *If positive on O&P, treat once more*
  - ✓ Fenbendazole again, or febantel (in Drontal PLUS); could also combine with metronidazole for this second round of therapy
- ✓ *If still not clinical, stop here, don't re-check again*
  - ✓ Pet is not clinical and likelihood of transmission of any infectious agent to a human is very low
  - ✓ Is the Giardia even a significant problem for the patient?

NOTE: We do not want to overtreat! The antigen test should not be used as a recheck test in the immediate post treatment phase. The idea is to use the best diagnostic approach up front and then to manage the patient judiciously.

Preventing Infection/Premises Control

In controlled environments, the following methods should be used to keep the area as decontaminated as possible:

1. Decontaminate the environment
2. Treat all animals in the environment
3. Bathe at the conclusion of drug therapy to remove cysts from haircoats
4. Prevent reintroduction of infection

In hospital and kennel/cattery situations (controlled environments) moving animals away from contaminated areas so they can be cleaned and decontaminated is very important. Steam cleaning after all fecal material has been removed is very effective. Chemical disinfection can be effectively accomplished using quaternary ammonium (QUAT) – containing disinfectants (e.g. Roccal, Totil), which will inactivate cysts in one minute at room temperature. The area should be allowed to dry completely and if possible left open for a few days. Animals should be bathed with a general cleansing shampoo before being returned. In some situations, e.g., shelters, research facilities, it may also be advisable to bathe the animals a second time, especially around the perianal area, using a quaternary ammonium compound. These can be safely left on the coat for 3 to 5 minutes, before being thoroughly rinsed off (longer exposure can cause irritation). Allow the coat to dry thoroughly before returning the animal to the clean area, and then administer one more course of anti-Giardia therapy, preferably using a different drug than was used during the initial course. Subsequently, any new animals introduced to the kennel or cattery should be tested as a matter of routine, but also bathed and treated as well, regardless of whether the fecal tests are positive or negative for *Giardia.*

Tritrichomonas foetus

Tritrichomonas foetus is a recently identified enteric protozoan of cats. It causes chronic large bowel diarrhea (loose stools, presence of blood and mucus, straining to defecate), and is most commonly seen in young cats that have resided in densely populated housing such as catteries and shelters. The diarrhea may be intermittent or persistent. Loose stool may dribble out (lack of control) and the anal area may become edematous. The organism is present in the ileum, cecum, and colon as a trophozoite. The organism does not encyst, so trophozoites are the only recognized stage. Infection in feral cats and healthy cats appears to be uncommon.

Until 2005 no effective treatment had been identified. Unfortunately, some cats with chronic diarrhea and dyschezia were euthanized due to a lack of any therapy that could control the clinical signs. It was exciting news in 2005 when Dr. Jody Gookin and colleagues at North Carolina State University reported that the nitroimidazole drug ronidazole is effective in controlling *T. foetus*. Although the diarrhea eventually resolves over a period of time (months up to one to two years) in untreated cats, ronidazole is the recommended therapy once a diagnosis has been established. It is important that an accurate diagnosis be made so that clients can be counseled appropriately, i.e., they should expect that their cat(s) will continue to have abnormal stools for some period of time. Further, there can be side effects of significant concern related to ronidazole, so this is NOT a drug that should be used empirically in lieu of testing. Also, it is not uncommon for cats to be co-infected with *Giardia* or *Cryptosporidium* or even both, so a thorough evaluation for parasites is important (run a minimum of one zinc sulfate with centrifugation and a *Giardia* antigen test and consider IFA fecal assays to check for *Cryptosporidium*). Accurate and thorough testing is essential and once any causative agents are identified they can be treated appropriately for the benefit of the patient and its owner.

Tritrichomonas foetus is commonly mistaken for *Giardia* trophozoites on direct smear exam. All trichomonads possess three to five anterior flagella, an undulating membrane, and a recurrent flagellum attached to the edge of the undulating membrane. All flagella originate from an anterior basal body. An axostyle extends the length of the trichomonad and extends posteriorly. A cyst stage is not known for this genus. Video clips showing both *Giardia* and *Tritrichomonas* trophozoites are available on the North Carolina State University website cited in the reference list below.

Definitive diagnosis can be made in some cases by direct smear of fresh feces in saline and examined at 200 to 400x magnification. Sensitivity is low, however, for diagnosis by direct smear (only 14% in one study), so results can often be false negative. To increase the chance of finding Tritrichomonas trophozoites on direct smear, it is recommended that multiple direct smears be done on the same day. Whenever possible, a cat with suggestive signs should be hospitalized for part or all of a day so that each fecal sample that is passed can be examined quickly via direct saline smear.

Tritrichomonas foetus can also be grown from feces via incubation at 37 degrees C in Diamond's medium. A commercially available culture system is also available and is recommended for use in clinical practice (InPouch TF, Biomed Diagnostics Inc., San Jose, CA). The medium in InPouch does not support the growth of Giardia species or *Pentatrichomonas hominis* so presence of organisms is consistent with *T. foetus*. PCR is the most sensitive means for confirming a diagnosis. In one study of 36 cats with *T. foetus* infection, 20/36 were positive on the InPouch TF test and 34/36 were positive on PCR. Details on the PCR assay can be reviewed on the North Carolina State website.

Studies at North Carolina State University in 2005 showed that ronidazole is effective for treatment of *T. foetus*. The original dosage guidance was to administer 30 mg/kg BID for 14 days. **However, a study reported in 2008 provided new guidance: 30 kg/kg once daily is effective and safer, i.e., less likely to cause neurologic adverse events** (RONIDAZOLE PHARMACOKINETICS IN CATS AFTER IV ADMINISTRATION AND ORAL ADMINISTRATION OF AN IMMEDIATE RELEASE CAPSULE AND A COLON-TARGETED
DELAYED RELEASE TABLET; Levine, Papich, Gookin et al)**.**

Ronidazole is a nitroimidazole antimicrobial that is not licensed for any use in the U.S. The medication has become more readily available in the United States through compounding pharmacies. The drug has mutagenic properties, so it must be compounded the same way as chemotherapy drugs. We have had some cats experience mild neurological side effects to ronidazole, similar to what can be seen with metronidazole. These resolved upon discontinuation of the drug. It is expected that there will be fewer instances of neurotoxicity with the new schedule of 30 mg/kg on a <u>once daily</u> dosing schedule. It is important that an accurate diagnosis be made so that clients can be counseled appropriately, i.e., they should expect that their cat(s) will continue to have abnormal stools for some period of time until definitive treatment can be administered.

Other recommended steps during therapy include isolating cats to decrease the risk of reinfection and to discard any litter boxes the cat has used, after treatment is completed.

Follow-up testing: Dr. Gookin recommends testing by PCR at 1 to 2 weeks and 20+ weeks after treatment is completed. Negative results should be interpreted with caution since PCR cannot prove the absence of infection and prolonged symptomatic carriage of the organism after antimicrobial therapy may e common.

An alternative drug which can be tried is tinidazole. This is also a nitroimidazole antimicrobial. A dose of 15-30 mg/kg SID can be tried. It should be safe and may or may not be effective. Studies have been ongoing, however, and results have not been very impressive.

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****Website for periodic updates and video clips of motile trophozoites: www.JodyGookin.com. There is an excellent reference section titled AN OWNERS GUIDE TO DIAGNOSIS AND TREATMENT OF CATS INFECTED WITH *TRITRICHOMONAS FOETUS*.**

Clostridium Perfringens Enterotoxicosis

Over the last 12 years *Clostridium perfringens* enterotoxicosis (CPE) has emerged as a frequently recognized cause of chronic intermittent diarrhea in dogs. Although it is likely a less common cause of diarrhea in cats it is still diagnosed frequently enough that it should be considered in the diagnosis of diarrhea in cats as well. This is not a new disease. Frequent use of the definitive test (enterotoxin assay performed on feces) for this disorder has revealed that CPE is seen relatively commonly in clinical practice and that CPE is a disorder that should be considered in any dog or cat with intermittent or chronic persistent diarrhea.

C. perfringens is a normal vegetative enteric organism. Simply identifying *C. perfringens* on a fecal culture is meaningless. The pathogenesis of CPE is through an enterotoxin that is produced after certain strains of *C. perfringens* sporulate. The toxin damages epithelial cells of the distal ileum and colon. Inciting factors that promote sporulation are not clearly understood but may include stress, diet changes, concurrent disease, or inherent immune status.

The most common clinical signs are chronic intermittent or persistent diarrhea. In some animals acute diarrhea is the primary sign. In fact, some of the cases of hemorrhagic gastroenteritis (HGE syndrome), characterized by acute bloody diarrhea and an increased packed cell volume that most practitioners have seen over the years, may have been due to CPE. Many animals exhibit signs of large bowel diarrhea, but small bowel signs may be seen as well. In some cases signs may be seen for only a day or two at a time, with persistent recurrences on a weekly, monthly, or on a less frequent basis. Stressful events or diet changes may incite flare-ups of clinical signs. In other cases *C. perfringens* enterotoxicosis is one of several problems that an animal may have concurrently and diarrhea may be persistent.

Diagnosis

CPE must be considered whenever more than one animal in the environment has diarrhea (e.g., household, kennel, cattery). Transmission from animal to animal can occur. A presumptive diagnosis may be suggested on fecal cytology in which more than 3-4 spores per high power oil immersion field are observed (the spores have a safety pin appearance and are larger than most bacteria). However, **definitive diagnosis** is by identification of enterotoxin which is currently done via a fecal assay. Clinicians should be aware that simply seeing spores on fecal cytology does not establish a definitive diagnosis (see JAVMA February 1, 1999). Stool is submitted to the lab for enterotoxin analysis. Fecal samples that will be shipped off from the hospital directly to a laboratory should be sent on ice via overnight express. If a courier service will be picking up samples for transport to the laboratory it is sufficient to keep the sample refrigerated until pick-up. The courier service will keep the sample properly chilled during transport. The minimum amount of stool that should be submitted is the size of a pea. Typically I submit samples in a red top tube, without

serum separator. In animals with intermittent diarrhea the chances of a positive toxin finding are greater when abnormal rather than a normal stool is examined. *A negative result does not definitively rule-out CPE.*

Treatment

Several antibacterial drugs are effective in controlling CPE. Acute cases often respond well to amoxicillin (22 mg/kg BID) or metronidazole (10-20 mg/kg BID) for 7-28 days. Many clinicians have likely treated CPE with these medications empirically without knowing what they were treating. Chronic cases tend to respond best to tylosin powder. The recommended dose is: Animals greater than 23 kg ¼ tsp BID, 12 to 23 kg 1/8 tsp BID, 5 to 12 kg 1/12 tsp BID, and less than 4.5 kg 1/16 tsp BID (a "pinch"). Cats definitely do not accept the powder well at all, even when it is mixed in very tasty foods. It is best to have the powder reconstituted to capsule form for administration to cats. The medication is very safe. Some animals require treatment for several to many months (3 to12 months or more). Over time the dose may in some cases be successfully reduced to SID and then every other day dosage (after several months or more on a BID schedule).

Dietary fiber supplementation may also help control CPE. Probable mechanisms include decreased *C. perfringens* fecal concentration, lower colonic pH, which prevents sporulation, and increased concentrations of SCFA. Some patients may respond well to dietary fiber supplementation alone.

Follow-up testing at 3-6 months can be done to determine if toxin persists. Once daily to every other day tylosin in conjunction with dietary fiber supplementation are used in chronic cases.

Cryptosporidiosis

Infection with *Cryptosporidium* is much more common than most small animal practitioners recognize. Currently it is recommended that all dogs and cats with diarrhea, whether acute or chronic, be screened for *Cryptosporidium* in addition to testing for nematode and protozoan parasites. In 2004 the American Association of Feline Practitioners adopted a position statement recommending that all kittens and adult cats with diarrhea be screened for *Cryptosporidium.* It is recommended that the same policy be followed with dogs (given that the cause is not simple diarrhea related to an acute upset due to sudden change in diet or dietary sensitivity).

Cryptosporidium spp. are coccidians that reside in the gastrointestinal tract. Infection can be associated with diarrhea in both immunocompetent and immunodeficient hosts. In the past, most of the cases of mammalian cryptosporidiosis were attributed to *C. parvum.* However, molecular studies have demonstrated that cats are usually infected with the host-specific *C. felis,* dogs are infected with *C. canis*, and people are infected with *C. parvum* or *C. hominus* (Scorza and Lappin). In a recent study at Colorado State University, they documented the presence of *Cryptosporidium* spp. DNA in diarrhea from 24.3% of the 292 animals tested (180 cats, 112 dogs) (Scorza and Lappin). This highlights the importance of testing dogs and cats for cryptosporidiosis. PCR is much more sensitive than the tests that are used most commonly at this time (acid fast staining of fecal smears or IFA). In this same series with 24.3% positive on PCR, only 2.7% were positive on IFA.

All dogs and cats infected with *Giardia* or *Cryptosporidium* species should be considered potentially zoonotic, even though the number of cases in which humans are infected through contact with pets is probably not high. Infection in humans is sometimes fatal in the presence of severe immunosuppression. Acute symptoms may include diarrhea, abdominal pain, vomiting, fever, and listless behavior. Infection can also be subclinical in dogs and cats. Chronic unresponsive diarrhea has been associated with cryptosporidiosis in cats with serious underlying disease as well as in dogs.

Because *Cryptosporidia* oocysts are quite small (as little as one-tenth the size of common *Isospora* oocysts) and are usually present in the feces in small numbers, they are very difficult to detect on routine fecal flotation and microscopy. The best tests currently available for routine testing for *Cryptosporidium* are fecal IFA and acid fast staining of fecal smears; however, they lack sensitivity. These tests are readily available at commercial laboratories (acid fast staining can also be done in house). PCR is a much more sensitive test but is labor intensive, expensive and is only available at a limited number of laboratories. Antigen tests for detecting *C. parvum* in human species are not sensitive for use in dogs and cats. In time there will be more sensitive tests readily available.

Treatment

The following treatment regimens may be used for cryptosporidiosis:

Canine	**Feline**
Azithromycin 5-10 mg/kg, BID orally, for 14-28 days	**Azithromycin** 7-15 mg/kg, BID, orally, for 14-28 days
Paromomycin 150 mg/kg, SID orally, for 5 days	**Paromomycin** 150 mg/kg, SID orally, for 5 days
Tylosin 15 mg/kg, BID orally, for 21-28 days	**Tylosin** 15 mg/kg, BID orally, for 21-28 days

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INFLAMMATORY BOWEL DISEASE AND INTESTINAL LYMPHOMA IN CATS

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Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is not a specific diagnosis, rather it is a histological description of a syndrome resulting from a host hypersensitivity response to antigenic stimuli. In IBD there is an increase in the inflammatory cell population in the intestinal mucosa. The predominant inflammatory component in cats with IBD can be lymphocytic-plasmacytic (most common type), eosinophilic, or neutrophilic. Changes in mucosal architecture and cell morphology should also be noted (crypt lesions including abscesses, villus atrophy or fusion, edema, epithelial erosions or ulceration, fibrosis). The etiology of IBD is poorly understood. Primary causes of initiation and perpetuation of intestinal inflammation that should be considered include parasites, bacteria (specific agents including normal luminal bacteria or bacterial overgrowth), immune-mediated diseases, and food sensitivities. Many cases of IBD are likely idiopathic in nature.

Clinical Course

Inflammatory bowel disease (IBD) currently is recognized as a common and important medical problem in cats. Three general types of clinical presentations have been identified in cats with idiopathic IBD: (1) a clinical course characterized primarily by vomiting, (2) a clinical course characterized primarily by diarrhea, and (3) a clinical course that includes both vomiting and diarrhea as primary signs. Associated clinical signs can include change in appetite (anorexia, inappetence, or ravenousness), weight loss, and lethargy. In some cats, the clinical signs are cyclic; they seem to flare up and then abate in a predictable pattern.

Vomiting, one of the most frequent clinical signs of IBD in cats, is most often recognized as an intermittent occurrence for weeks, months, or years. As the disorder progresses, an increased frequency of vomiting often leads the owner to seek veterinary attention. In addition to vomiting, diarrhea is a common sign observed in feline IBD and most likely is due to derangement of normal mechanisms of absorption and motility caused by mucosal inflammation. In most cases, diarrhea is intermittent early in the course of the disorder, and there may be a transient response (weeks to several months) to dietary manipulation or any of a variety of medications (in some cases, however, dietary manipulation can effect excellent control and drug therapy may ultimately not be necessary). Later, the diarrhea becomes persistent and usually responds only to specific treatment, which is determined after a definitive diagnosis is made. Signs of small bowel diarrhea predominate, but signs of large bowel diarrhea may be evident as well if there is generalized intestinal tract involvement.

Appetite changes in cats with idiopathic IBD vary from decreased appetite to complete anorexia to ravenousness. Inappetence seems to occur more commonly in cats that have vomiting as the primary clinical sign and usually occurs during exacerbation of clinical signs, and vomiting or diarrhea is not

observed until later or not at all. The three leading differential diagnoses for a cat with a ravenous appetite, diarrhea, and weight loss are IBD, hyperthyroidism, and exocrine pancreatic insufficiency (uncommon).

Diagnosis

A definitive diagnosis of IBD can be made based only on intestinal biopsy (performed either at endoscopy or exploratory laparotomy, and ensuring that both upper and lower [ileum] biopsies are obtained). A definitive diagnosis of IBD *cannot* be made based on barium series radiography or ultrasonography. Diagnostic work-up prior to performing biopsies includes baseline testing to evaluate the overall health status of the patient and to rule out other disorders. Recommended baseline tests include a complete blood count, complete biochemical profile, urinalysis, fecal exams for parasites, serum thyroxine test, serum cobalamin level, and FeLV/FIV. Cats with chronic vomiting should be screened for heartworm disease. fTLI is done to rule-out exocrine pancreatic insufficiency. Ultrasonography is useful for assessing the abdominal organs, intestinal wall thickness, searching for any masses, and examining for lymphadenopathy. Dietary sensitivity is a common problem in cats with vomiting and/or diarrhea and food trials are an important part of the diagnostic work-up, especially early in the clinical course. Hydrolyzed protein and novel protein foods should be fed for 2-3 weeks at a time to determine if dietary therapy will either reduce or resolve the problem entirely.

Abdominal Imaging in Cats – IBD vs. Lymphoma

Radiology

Radiography is important for diagnosing intestinal diseases. During evaluation of the small bowel on survey radiographs, important factors that should be evaluated include location of small intestine (normally fills the abdomen where nothing else is present, not unusual to be mostly right-sided in cats), appearance of bowel contents (gas, fluid, or mottled material), contour of small bowel, and diameter of the small intestine. The normal diameter in cats is up to 12 mm.

In normal animals, intestinal luminal contents should appear as a homogeneous fluid opacity. Disease of the small intestine may be missed on survey films unless there is a change in bowel opacity (mineralized mass or foreign material), luminal diameter (functional ileus or complete or partial mechanical obstruction), or changes in contour of the small bowel (linear foreign body).

Contrast studies (upper GI series) are often necessary to identify normal or abnormal shape, diameter, or continuity of small bowel. The transit time of barium varies greatly in cats. It usually travels from the stomach through to the ileum in about 60 minutes, although it can take as long as 4 hours. The range of transit times for organic iodides through the small bowel is approximately 15–90 minutes. The organic iodide usually reaches the ileum and colon in less than 60 minutes.

Small Intestinal IBD

Diagnostic radiographs are recommended in the work-up of cats with gastrointestinal signs. Although survey and contrast radiographs are usually not specific/diagnostic for IBD, abdominal radiography is most helpful in defining extra-alimentary tract disorders causing gastroenteritis. Survey radiography might detect organomegaly (liver, kidney) unrelated to IBD or intestinal obstruction that might cause similar GI signs. Survey radiographs of inflammatory bowel disease are usually normal. There is no consistent radiological finding in cats with inflammatory bowel disease. The intestines may appear thickened (intestinal thickness *cannot* adequately be determined on survey radiographs), or luminal fluid maybe increased and there may be more gas than normal in the intestines, but these signs can occur in many conditions. Contrast examinations (upper GI series) are helpful in identifying a mass or obstruction. With contrast, assessment of the location and extent of the intestinal lesion may be more accurate than on survey images. Changes associated with IBD on barium study are often not present. With severe inflammatory however; changes may include: irregular mucosal lining abnormalities and thickened intestinal walls. In most cases contrast radiography is unrewarding.

Intestinal Lymphoma

Survey radiography might detect organomegaly (liver, kidney, lymph nodes) associated with lymphoma. Radiographic findings may reveal a mid-abdominal mass associated with the GI tract and/or mesentery, or localized or diffuse decrease, or loss, of serosal detail suggestive of peritoneal effusion. If a mass is suspected radiographically or historically, or a mass has been palpated, then compression radiography may be helpful to isolate and visualize the mass. Obstruction occurs more often with adenocarcinoma of the small intestine than with small intestinal lymphoma. Contrast examinations (upper GI series) are helpful in identifying the mass or the obstruction. With contrast, the location, bowel wall thickening, mucosal irregularity and extent of the intestinal lesion may be more accurate than on survey images.

Ultrasonography of the Feline Small Intestines
The small intestines can be seen throughout the abdomen, both end-on and longitudinally oriented. The duodenum has a slightly larger diameter than the rest of the small intestinal loops, and is the most lateral and ventral bowel loop in the right cranial abdomen. It can be located usually just ventral and lateral to the right kidney and followed cranially into the pylorus. The ileum has a distinct cross-sectional appearance (resembling spokes on a wheel) and can be visualized as it enters the colon, just medial to the right kidney. The colon typically
is gas-filled, with poor visualization of the lumen.

The following five layers are present in the intestinal wall, from outside to inside:
Serosa: Thin hyperechoic layer
Muscularis: Thin hypoechoic layer
Submucosa: Thin hyperechoic layer
Mucosa: Prominent hypoechoic layer (typically the thickest layer)
Mucosal surface–lumen interface: Hyperechoic layer in the center of the bowel

These individual layers are best visualized with higher-frequency transducers.

Normal wall thicknesses have been established in the cat for various segments of the GI tract:
Duodenum: 2.0–2.4 mm (mean of 2.2 mm)
Jejunum: 2.1–2.5 mm (mean of 2.3 mm)
Ileum: 2.5–3.2 mm (mean of 2.8 mm)
Colon: 1.4–l.7 mm (mean of 1.5 mm)

One to three contractions per minute should be seen with normal small intestinal peristaltic activity.

Ultrasonographic features of intestinal disease include bowel wall thickening, loss of wall layers, loss of motility, and regional lymph node involvement.

Intestinal Ultrasound: IBD versus Lymphoma
An abdominal ultrasound examination may be helpful in cases of suspected small intestinal disease. Abdominal ultrasound is superior to radiology in defining focal versus diffuse disease, loss of layering, intestinal thickening and mesenteric lymphadenopathy seen with IBD and lymphoma. Ultrasonography also allows for precise guidance of fine needle aspiration or biopsy for cytologic or histopathologic sampling of small intestinal disease and associated lymphadenopathy.

Ultrasonography can also be used to assess response to therapy noninvasively. A limitation of ultrasonography would be the difficulty in assessing the exact anatomic location (duodenum and ilium should be more easily identified by an experienced operator). Findings may be normal, especially in cases of low-grade small cell lymphoma or mild IBD

Changes of the small intestine may or may not be present dependent upon chronicity and/or severity. The changes may be diffuse or focal. The intestine may appear normal. Biopsy is indicated to confirm disease.

The most common finding with inflammation is normal to symmetric wall thickening with the layering retained. In comparison, neoplasia is usually localized with greater wall thickness and loss of normal layering. These categories can overlap, and therefore cytology or histopathology is required for definitive diagnosis. Acute enteritis or inflammatory bowel disease may demonstrate corrugation of the intestine on ultrasound examination.

Ultrasound of IBD

With inflammatory bowel disease, the intestine may be normal on ultrasound. The measurement of the intestinal wall thickness by ultrasound is neither specific or sensitive for diagnosing IBD. Changes, especially those of severe or chronic disease, have been reported as focal to diffuse thickening, altered echogenicity, poor intestinal wall layer definition, and mild enlargement of adjacent lymph nodes. Mucosal echogenicity may remain hypoechoic. Round, enlarged, hypoechoic lymph nodes may be more consistent with neoplasia, while inflammatory lymph nodes may be enlarged but tend to maintain their normal shape.

Ultrasonographic Measurements of Feline Abdominal Lymph Nodes

	US Length (mm)	US Diameter (mm)	Frequency of detection
Jejunal	20.2 (11.4-39.0)	5.0 (2.8-7.2)	90%
Colic	9.0 (4.6-12.1)	3.1 (1.9-5.2)	50%

Ultrasound of Intestinal Lymphoma

Perform abdominal ultrasonography to evaluate the extraintestinal organs in addition to GI tract wall thickness, layering, and motility. Lymphoma most commonly presents as transmural, circumferential, homogenous, hypoechoic thickening with loss of normal wall layering. Lymphoma tends to involve a long bowel segment or multiple bowel segments. Regional moderate, hypoechoic lymphadenopathy is generally present. Lymphoma is less likely to cause obstruction of the lumen.

Six major patterns of ultrasonographic features in feline lymphoma include: transmural-circumferential, symmetrical and asymmetrical, transmural-bulky, transmural-nodular, transmural-segmental, and mucosal infiltration. The transmural-circumferential pattern is most common. The transmural-bulky pattern has been described as a space occupying mass representing the thickened wall with areas of increased and decreased echogenicity. The transmural-segmental pattern has been described as wall thickening involving only a portion of the wall. The transmural-nodular pattern appeared as nodular wall infiltration and local nodular spread into the mesentery. Mucosal infiltration pattern demonstrated mild thickening of the intestinal wall associated with faint hyperechoic foci throughout thickened mucosal layer. In cats GI lymphoma can affect the intestinal tract without disrupting the wall layering.

Ultrasonographic Evaluation of Muscularis Propria in Cats with Diffuse Small Intestinal Lymphoma or IBD

It is difficult to detect small intestinal lymphoma or IBD in cats without a mass lesion, loss of layering or thickened bowel wall. Thickening of the muscularis propria is associated with diffuse infiltrative bowel disease such as lymphoma or IBD in cats. This has also been seen in normal cats as well. The most common ultrasound descriptions of GI lymphoma in cats are as mass lesions previously discussed.

Intestinal Biopsy Techniques

Endoscopic Biopsy: Endoscopy is a minimally invasive procedure in which multiple biopsies can be obtained and this procedure generally has greater client compliance than with surgery because it is less invasive and less expensive than exploratory abdominal surgical procedures. Endoscopy is considered a gold standard procedure for tissue collection. Operator experience and the quality and number of biopsy

samples obtained are very important. Endoscopy offers a means of examining the upper and lower small intestine, stomach, and colon. It is especially advantageous because biopsies can be obtained early in the course of the disorder, at a stage when a client will likely be reluctant to agree to an exploratory surgery for their pet. The degree of intestinal changes noted on biopsy also provides useful guidelines for both type and duration of therapy that will be needed to control the specific disorder.

Clinicians need to make sure they are taking an adequate number of endoscopic biopsy samples for accurate diagnosis. Even expert endoscopists report that in some cases one-fourth to one-third of the biopsy samples they take from a patient will have some degree of damage to the tissue that may preclude the samples from being useful or representative. Therefore, it is recommended that clinicians take 8 to 12 biopsy samples from the upper small intestine so that the pathologist will have enough tissue to work with. Also, it is recommended that both upper and lower GI endoscopy be done on cats with chronic GI signs (vomiting and/or diarrhea, weight loss). In this way biopsies from the ileum can be obtained by passing the endoscope along the full length of the colon up to the level of the ileocolic orifice. **It is very important that the effort be made to obtain ileum samples, since some cats with small cell lymphoma have disease in the ileum but not in the upper small intestine.** The diagnosis can be missed in these cats if only upper small intestinal biopsies are obtained.

When a pediatric diameter endoscope is used it is possible in most *dogs* over 4 to 5 kg to advance the endoscope through the ileocolic orifice and into the ileum, where it can then be advanced along the terminal ileum for exam and biopsies. However, in *cats* the ileocolic orifice is very small and in most cats it is not possible to advance the endoscope through this junction and into the ileum. In cats ileum biopsies are obtained blindly by advancing the endoscopic biopsy instrument through the ileocolic orifice with the endoscope tip positioned at the ileocolic sphincter area. Usually 3 – 4 samples are procured in this way. Colon biopsies are always obtained as well during colonoscopy in order to evaluate for inflammation in the colon.

Surgical Biopsy Techniques for Abdominal organs

Biopsy. Organ biopsy is usually required to confirm feline IBD and Lymphoma. This can be accomplished using either laparoscopic techniques or open abdominal surgery. Laparoscopic techniques have been well described for organ biopsy. These techniques are minimally invasive and well suited for tissue procurement, however, laparoscopy is not yet readily available as a diagnostic tool in most small animal clinics. Surgery on the other hand is an excellent way to obtain liver, pancreatic and intestinal biopsies. In addition to biopsy the liver should be cultured as well as bile aspirates for culture and cytology. We also currently culture the pancreas as well during laparotomy.

Intestinal Biopsy: One can obtain intestine using several techniques**.** A full thickness biopsy allows the pathologist to porovide the most accurate diagnosis. When taking an intestinal biopsy, the easiest way to guarantee you will get an adequate size, full thickness piece of intestine is to use a brand new 4mm or 6mm skin punch biopsy instrument. The skin punch is placed on the antimesenteric border of the proposed segment of intestine and 'drilled' through all layers of intestine until the biopsy punch can be felt to enter the lumen of the intestine. The skin punch is removed and the biopsy retrieved from the shaft of the skin punch biopsy. This technique is particularly useful for ileal biopsy as it is easy to biopsy between the mesenteric and antimesenteric vessels. Transverse closure of the biopsy site is recommended to eliminate the possibility of lumen compromise. The biopsy site is closed using a simple interrupted or simple continuous suture pattern. 3-0 or 4-0 monofilament absorbable suture with a swaged-on sharp taper or taper-cut (penetrating point) needle is recommended. Care is taken to ensure that at least 3 mm bites are taken into the intestine and the sutures are no more that 2-3 mm apart. This is Dr. Seim's preferred technique for intestinal biopsy.

An alternate technique for intestinal biopsy is to make a 2-3 mm long incision on the antimesenteric border of the intestinal segment. A #11 or #15 BP scalpel blade is used to penetrate the intestinal wall. The blade is withdrawn to create a 2-3 mm long incision. A second parallel incision is made 1 – 2 mm from the

original incision. A DeBakey forcep is used to grasp one end of the parallel incisions, a Metzenbaum scissor is used to cut out the piece of intestine. The surgeon should be careful not to crush the specimen with forceps. Only handle one end of the specimen while excising the biopsy specimen. If excessive trauma is created during biopsy, the pathologist may not be able to determine if the pathology is real or surgically created. The excised piece of intestine is examined closely to ensure that all layers have been included in the specimen. The biopsy site is closed using a simple interrupted or simple continuous suture pattern. 3-0 or 4-0 monofilament absorbable suture with a swaged-on sharp taper or taper-cut (penetrating point) needle is recommended. Care is taken to ensure that at least 3 mm bites are taken into the intestine and the sutures are no more that 2-3 mm apart. Complications associated with multiple intestinal biopsies are rare. Complications in patients undergoing intestinal surgical procedures are generally related to the surgeon's technical ability and not the patient's preoperative status.

Lymph node biopsy: All lymph nodes are encased in a layer of peritoneum. When performing a lymph node biopsy it is best to tent the peritoneal covering with forceps and incise it with metzenbaum scissors. The peritoneum is then gently dissected off the lymph node. The exposed lymph node is biopsied using a #15 or #11 scalpel blade. Generally, a thin section of lymph node is 'filleted' off and placed in a moistened gauze sponge. The peritoneum covering the remaining lymph node is sutured to create suture pressure to help control surface hemorrhage.

Liver Biopsy: Surgical biopsies obtained during exploratory laparotomy are described here. The simplest method is performed by cutting a strip of liver parenchyma 5 to 6 mm thick along the border of the liver lobe. Excessive bleeding is rarely a problem with this technique; hemorrhage is controlled via cautery or direct pressure. Diffuse liver disease must be present if this method is to be diagnostic.

A second technique involves placing an encircling ligature around a pedicle of liver tissue. As the ligature is tightened, it cuts through the hepatic parenchyma, ligating hepatic vessels and bile ducts. This technique, widely known as the Guillotine technique, has been criticized for leaving excessive amounts of devitalized parenchyma. This can be avoided by inserting scissors through the cut parenchyma and cutting hepatic vessels and bile ducts just distal to the ligature. This method requires the presence of diffuse liver disease to obtain a diagnostic biopsy unless the lesion is present in the distal aspect of the liver lobe.

More localized abnormalities can be biopsied by wedge resections or partial lobectomy. Wedge resections may be performed by placing a row of overlapping, full-thickness, interrupted mattress sutures of 0 or 2-0 Maxon or Biosyn along each side of the wedge to be removed; these sutures should commence at the edge of the liver lobe and meet proximally to form a "V". The sutures should be tied so as to compress the liver slightly but not cut into liver parenchyma. The wedge of tissue to be removed is incised about 5 mm from the suture line. Alternatively, the wedge may be removed prior to tightening the mattress sutures; preplaced mattress sutures are then gently tied with enough tension to control bleeding.

An alternate technique for use in patients with diffuse fibrotic liver disorders is performed by penetrating the affected liver lobe with a straight mosquito hemostat. The hemostat tip is placed on the surface of the liver lobe to be biopsied and gently plunged through the liver lobe until the tip of the hemostat is seen penetrating through the opposite side of the liver. The jaws of the hemostat are opened just wide enough to accept a piece of 2-0 or 3-0 Maxon or Biosyn suture. The suture is doubled on itself, the loop is passed into the jaws of the hemostats, and the loop pulled through the liver lobe. The exiting loop is cut leaving two strands of suture coursing through the liver lobe. Each strand is tied individually to "cut" through the liver. A "V" wedge is cut through the liver when both strands of suture have been tied. A number 15 BP scalpel blade is used to cut the V-shaped liver biopsy wedge from the sutures.

Pancreatic Biopsy: **Samples from the pancreas should be obtained in all suspected triaditis cases. The old wive's tale stating "don't touch the pancreas" needs to be put to rest in veterinary medicine. Gentle manipulation and biopsy of the pancreas is a predictably successful procedure with almost no incidence of postoperative pancreatitis. Biopsy of the pancreas is performed in a similar manner as**

biopsy of the liver. In patients that have diffuse pancreatic disease, a segment of the right or left limb of the pancreas is identified. An encircling ligature of 3-0 Biosyn is placed around the pedicle. As the ligature is tightened, it cuts through the pancreatic parenchyma, ligating vessels and pancreatic ducts. The distal pedicle of pancreas is carefully removed with a number 15 BP scalpel blade or metzenbaum scissors. Care is taken to avoid cutting the suture.

Treatment of IBD

It is important that the clinician formulate a treatment plan based on a correlation of clinical course, laboratory and gross findings, and histologic findings (considering both cellular infiltrate and morphology) rather than relying on histologic changes alone. Since food sensitivities can be a cause of IBD, dietary trials are an essential part of both the diagnostic and therapeutic strategy, utilizing hydrolyzed protein diets and novel protein diets and treating each patient as an individual (i.e., there can be variable responses to specific diets varying from patient to patient). Regarding pharmacotherapy, while corticosteroids have long been considered the cornerstone of treatment for idiopathic inflammatory bowel disorders, antimicrobial agents may play a role as well. Bacteria have been implicated in the pathogenesis of IBD.

Guidelines for corticosteroids in cats with IBD are as follows. Mild to moderate cases of IBD often respond to prednisolone (preferred over prednisone in cats) at a starting dose of 1 to 2.2 mg/kg divided twice daily for two to four weeks followed by a gradual decline in 50% increments at two week intervals. Cats with inflammatory changes graded as mild usually respond quite well to the lower dose and alternate day or every third day treatment can often be achieved by two to three months. Occasionally treatment can be discontinued altogether by three to six months.

If biopsies reveal disease that is moderate to severe a prednisolone dose of 2 to 4 mg/kg divided twice daily is used in cats for the first 2 to 8 weeks or until clinical signs resolve. This dose of corticosteroid is usually well tolerated in cats. In some cases a dose of 1 to 2 mg/kg per day may be necessary long term (months to years) to maintain clinical remission. Use of combination drug therapy may also be required at the outset to control clinical signs and prevent progression of the disease (e.g., metronidazole or tylosin plus prednisolone). Cats with hypoproteinemia and histologic changes graded as severe often respond quite well when an aggressive therapeutic course is undertaken.

Budesonide is a glucocorticoid that represents an alternative for management of IBD in dogs and cats, especially in severe cases that have proven to be refractory to prednisolone, metronidazole, azathioprine, chlorambucil, tylosin, and dietary management; or that are intolerant of the corticosteroids discussed above. Budesonide is one of a group of novel corticosteroids that have been in development for use in humans in an attempt to make available alternative preparations that will help limit toxicity associated with corticosteroid use.

Budesonide undergoes high first pass metabolism in the liver and 90% is converted into metabolites with low corticosteroid activity. It has minimal systemic availability. The potential for typical corticosteroid side effects is significantly reduced as a result of decreased bioavailability and the resulting limited systemic exposure, which makes this a particularly attractive drug for use in humans and animals that are poorly tolerant of other corticosteroids. Budesonide also has a high receptor-binding affinity in the mucosa. It has been referred to as a "locally acting" corticosteroid.

Therapeutic results with budesonide have been promising in humans with Crohn's disease, collagenous colitis and lymphocytic colitis, ulcerative colitis, either when administered as a retention enema or in oral form, and primary biliary cirrhosis.

Budesonide has been used by some veterinary clinicians in recent years to treat IBD in dogs and cats. Dose recommendations vary. In humans, a range of 6 mg to 9 mg per day has been used during initial therapy. In general, budesonide is administered to cats at 1 mg administered once per day (this dose level is prepared at a compounding pharmacy).

Budesonide can be used in combination with other drugs. Since cats tolerate corticosteroids very well, there is little indication to use budesonide as initial therapy for IBD. However, this may be a very attractive option for use in diabetic cats that also have IBD, or in patients where conventional therapies have not been sufficiently effective.

Potential adverse effects include PU/PD, when budesonide is used at the high end of the dose range, and GI ulceration. These reactions have been observed in some human patients. These problems would be more likely to occur in dogs than in cats. It appears to be very safe when used at the levels listed above.

When combination therapy is indicated metronidazole is usually the first choice to be used in conjunction with prednisolone. Metronidazole's mechanism of action includes an antiprotozoal effect, inhibition of cell-mediated immune responses, and anaerobic antibacterial activity. A dosage of 10 to 20 mg/kg two times daily is used for IBD. Ideally, at least several months of metronidazole therapy is given once it is started. In some cats with severe disease long term consecutive use or one to two month cycles of treatment may be required. Side effects to metronidazole at this low dose are uncommon in cats. Occasionally nausea or vomiting may be seen.

If a client is unable to successfully administer oral medications, methylprednisolone acetate (Depo-Medrol) can be used as sole treatment for cats with mild to moderate IBD or as adjunctive therapy when oral prednisolone and/or metronidazole are used as the primary treatment and flare-ups of clinical signs occur. Consistent control of clinical signs in cats with moderate to severe IBD is more difficult to maintain when methylprednisolone acetate is used alone, however. It is recommended that sole use of methylprednisolone acetate be reserved for situations in which the owner is unable to consistently administer tablet or liquid prednisolone preparations. Initially 20 mg is given subcutaneously or intramuscularly and is repeated at 2-week intervals for 2 to 3 doses. Injections are then given every 2 to 4 weeks or as needed for control.

If remission cannot be maintained with use of corticosteroids and metronidazole then chlorambucil (Leukeran) should be used. Azathioprine was used more in the past but it has been largely supplanted now by chlorambucil. Chlorambucil is an alkylating agent. Alkylating agents alter DNA synthesis and inhibit rapidly proliferating cells. Chlorambucil is administered initially at 0.1 to 0.2 mg/kg/day in conjunction with prednisolone at 2.2 mg/kg/day. The small pill size of chlorambucil (2 mg) allows for easy dosing. Most cats receive one-half tablet (1 mg) per day. Various dosage schedules for cats have been published. An alternate schedule is 0.15 to 0.3 mg/kg every 72 hours. Toxicities are uncommon in cats but may include anorexia, vomiting, and diarrhea, but these problems generally resolve rapidly when chlorambucil is reduced from daily to every other day administration. Bone marrow suppression is possible but uncommon, and is mild and rapidly reversible when it does occur. Once the desired clinical response is achieved, chlorambucil is gradually tapered over several months while prednisolone is continued as the primary maintenance drug.

Cyclosporine is another immunosuppressive drug that can be used in management of IBD. Cyclosporin inactivates calcineurin phosphorylase in T cells, preventing transcription of interleukin-2 (IL-2) as well as other cytokines. Cyclosporin inhibits activation of T cells, natural killer cells, and Langerhans (i.e., antigen-presenting) cells. Suppression of the Th1 or Th2 response induces antigen tolerance. The dose is 5 mk/kg once daily. Once sufficient response is achieved the dosage interval can be reduced to administration of a full dose every 48 hours and subsequently even further, on an individual patient basis.

Cobalamin therapy in cats: Significant tissue level cobalamin deficiency is present in some animals with GI disease. This is usually secondary to reduced cobalamin absorptive capacity. It is essential that all cats with any form of GI disease (including involvement of liver, stomach, pancreas, intestines) have a serum cobalamin level run to determine if the patient is hypocobalaminemic. Response to therapy will be limited if low cobalamin levels are not resolved. The reference range for cobalamin in cats is 290-1500 ng/L.

Therapy is given if the value is less than 500 ng/L (i.e., in the low part of the reference interval; don't wait until the level drops below the low end point of the reference range).

Therapy involves administering injectable cobalamin at the following schedule for cats: 250 ug subcutaneously once a week for 6 weeks, then every 2 weeks for the next 6 doses, then dose monthly. Most generic cobalamin preparations contain 1 mg/ml (1000 ug/ml). It is important to note that multi-vitamin and B-complex injectable formulations contain significantly lower concentrations of cobalamin and they also cause pain when injected. Therefore, it is recommended that these preparations not be used for cobalamin supplementation. Unless the intestinal disease is totally resolved, long-term and perhaps lifelong supplementation with cobalamin may be necessary. The frequency of injections on a long-term basis is determined by regular measurement of serum cobalamin concentration.

Because dietary allergens may play a role in the cause if IBD, specific dietary therapy may be beneficial. Often, moderate to severe degrees of IBD are either temporarily responsive or only minimally responsive to careful dietary manipulations. However, long term control of IBD with as minimal a drug administration schedule as possible may be aided by specific dietary management. This should be started as soon as a diagnosis is made and continued as drug therapy is decreased later. Feed elimination (novel protein) or hydrolyzed protein diets. Chicken, duck, lamb, fish, or venison based diets are often tried initially. Elimination diets have been found to be very beneficial in cats.

Poor responses to treatment of cats with IBD usually result from:

1. Inadequate initial or long-term maintenance corticosteroid dosage in cats with more severe forms of IBD (moderate t severe disease).
2. Failure to use ancillary medications (metronidazole, chlorambucil, cyclosprinetylosin) in cases where disease is moderate to severe.
3. Failure to recognize and treat a concurrent condition (e.g., gastric hypomotility disorder that may either be secondary to IBD or idiopathic in nature, hyperthyroidism, parasitism [e.g., *Giardia*, *Cryptosporidium*], *Clostridium perfringens* enterotoxicosis, cholangitis/cholangiohepatitis, chronic pancreatitis).
4. Treatment for only small intestinal inflammatory disease when colitis is present as well. Some cats with concurrent IBD and colitis may show minimal or no clinical signs of colitis.
5. Failure to recognize and treat low body cobalamin levels (measure serum cobalamin).
6. Failure to identify an effective diet.
7. Poor client compliance

What If Biopsies are Not Definitive for Either IBD or Small Cell Lymphoma?

It can be difficult to definitively differentiate benign IBD from small cell intestinal lymphoma, even when full thickness intestinal biopsies are obtained. If the biopsies were obtained via endoscopy, one option is to proceed to exploratory laparotomy to obtain full thickness samples. However, this is not practical in some cases and involves a more invasive procedure and more expense. Further, there is no guarantee that the differentiation can be made even when full thickness samples are obtained. Another option that is employed more commonly now is to perform special tests to help differentiate benign IBD from low-grade, small cell lymphocytic malignant lymphoma. Specific immunohistochemical techniques can be done to identify populations of malignant B and T lymphocytes (i.e., phenotyping) and molecular (PCR) testing is done for clonality. Clients should be given the option of ordering these additional tests if the pathologist indicates on the initial histopathology interpretation that the differentiation can't be made definitively between IBD and lymphoma. If the client declines to have the additional tests performed, the clinician then needs to decide whether or not to just go ahead and treat for the disease that poses greater concern, i.e., lymphoma. Low grade small cell lymphoma is often treated with the combination of prednisolone and chlorambucil (see later discussion on treatment details in the next section).

Treatment of Intestinal Lymphoma in Cats

Lymphoma is the most common feline neoplasm. It is also the most common form of gastrointestinal neoplasia in cats. Gastrointestinal lymphoma is often referred to as either well differentiated (low grade or lymphocytic), poorly differentiated (high grade, lymphoblastic, or immunoblastic), and intermediate (or mixed). Endoscopy has been shown to be a very useful modality for diagnosis of intestinal lymphoma in cats, especially when multiple biopsies are obtained using proper technique and instruments that can procure adequate size tissue samples. Immunohistochemical stains are beneficial for differentiating IBD from intestinal lymphoma in cases where it is difficult for the pathologist to distinguish between the two. Full thickness intestinal biopsies may be required in a very limited number of cases in order to establish the correct diagnosis.

Many cats respond favorably to treatment for intestinal lymphoma, especially with the low grade or chronic lymphocytic type. Clinical signs can be very similar to cats with IBD. Therefore, it is strongly recommended that cats with chronic GI signs undergo a biopsy procedure as early as possible, so that the correct diagnosis can be established and the best course of therapy be made available for each individual cat. Biopsies should be obtained from *both* the upper and lower (ileum) small bowel.

Multi-agent chemotherapy is recommended for all cats with GI lymphoma. Surgery is done only if there is an isolated mass that is causing some degree of luminal obstruction. Survival times in excess of 12 to 18 months are not unusual. In some cats the response is somewhat shorter (three to six months). The prognosis for longer survival time is much better if the diagnosis is made before clinical signs become chronic and debilitation results.

One study has reported excellent results in cats with chronic lymphocytic lymphoma using a protocol of prednisone (10 mg PO per cat per day) and chlorambucil (Leukeran) at a dosage of 15 mg/m2 PO, once every day for 4 days, repeated every 3 weeks (Note: prednisolone is used routinely at this time, rather than prednisone, in cats). Sixty-nine percent of the cats with lymphocytic lymphoma treated with this regimen achieved a complete remission. The median disease free interval for cats that achieved complete remission was 20.5 months (range, 5.8-49 months). The median survival for all cats with lymphocytic lymphoma treated with chemotherapy was 17 months (range, 0.33-50 months). Cyclophosphamide (Cytoxan) was used for rescue in some of the cats that were entered in this protocol (225 mg/m2, PO, every 3 weeks). For further reference on this protocol, see Richter,K: Feline gastrointestinal lymphoma, ACVIM Proceedings 2001, p. 547-549.

The protocol that Dr. Tams has used most often for cats with the more aggressive lymphoblastic form of GI lymphoma was originally published by Cotter in 1983. Dosage levels have been modified slightly since that time. This protocol utilizes cyclophosphamide, oncovin, and prednisolone (COP). This protocol can be easily managed in any practice setting. Vincristine is administered intravenously at a dose of 0.5-0.75 mg/m^2 once weekly for 4 consecutive weeks and then once every 3 weeks. The initial doses are often decreased by approximately 25 percent for cats that are inappetent or debilitated. If well tolerated the dose can then be gradually increased. Care is taken to ensure that none of the vincristine is given extravascularly. The average volume that is administered is quite low (0.1 to 0.15 ml for many cats, using a vincristine concentration of 1 mg/ml). Cyclophosphamide is given orally at a single dose of 225 mg/m2 every 3 weeks (50 mg tablets are used with dosage adjusted to the nearest 25 mg on the low side of the calculated dose). Prednisolone is given orally at 10 mg per cat per day. Although cyclophosphamide and vincristine can be given on the same day I often prefer to have the owner administer the cyclophosphamide 2 to 3 days after the oncovin. A CBC is done several times during the first month and then every 3 weeks to be sure that adequate granulocytes are present before treatment. At least 3,000 granulocytes/ul must be present before cyclophosphamide is given. If the granulocyte count drops to less than 1,000/ul 5 to 7 days after cyclophosphamide, the dose for subsequent treatments is reduced by 25 percent. The highest non-toxic dose is most likely to result in the greatest tumor cell kill.

The COP protocol is generally well tolerated, although side effects may occur and dosage or interval adjustments may be necessary. Side effects of COP in cats may include anorexia, vomiting, lethargy, and severe tissue irritation if any vincristine is given extravascularly. Also, the haircoat may become thinner, but complete hair loss does not occur. Cats do tend to lose whiskers. Cats should be carefully observed for sepsis especially during the induction phase. Prophylactic antibiotics are not indicated, but any infections that occur should be treated aggressively. Advantages of this protocol include hospital visits at only 3 week intervals after the first 4 weeks, lower cost to the owner, and a treatment interval that allows recovery of normal cells between treatments. I would like to emphasize that with careful monitoring and use of a dosage schedule that is tailored to each individual cat few problems are encountered It is our general practice to encourage owners of most cats with GI lymphoma to pursue treatment that includes chemotherapy.

Nutritional and metabolic support are also important. If inappetence is a problem cyproheptadine can be administered as an appetite stimulant (1 to 2 mg orally every 12 to 24 hours) on an as needed basis (long-term if necessary). Mirtazapine is another appetite stimulant that can be used (one-fourth of a 15 mg tablet every three days). Intermittent vomiting, nausea, and inappetence is managed with maropitant (Cerenia) administered at 4 mg for most cats once orally daily as long as it is needed. If there is concurrent renal disease with azotemia or if dehydration is a problem owners are taught how to administer subcutaneous fluids at home (e.g., lactated Ringer's 100 to 150 ml every 24 hours to 48 hours, based on each individual cat's needs). Special attention is given to ensuring that low cobalamin levels are addressed, if serum tests indicate that hypocobalaminemia is present.

Rarely chemotherapy can be discontinued after one year. This is done only if follow-up endoscopic intestinal biopsies indicate that there is no remaining lymphoma. Most cats remain on treatment for the remainder of their lives. If chemotherapy is poorly tolerated and reduced dosages and increased intervals between treatment times are unsuccessful in adequately decreasing side effects chemotherapy should be suspended. Prednisolone should be continued however because it may help maintain remission for a period of time. Doxorubicin (Adriamycin) can also be used in cats.

For clinicians inexperienced in administering chemotherapy, or who have not treated many cats with intestinal lymphoma, it is recommended that a veterinary oncologist or internist be consulted for guidance on protocol selection and ongoing management. Many cats with intestinal lymphoma can be managed successfully for some period of time!

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