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: 1.4–1.7 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

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<th>US Length (mm)</th>
<th>US Diameter (mm)</th>
<th>Frequency of detection</th>
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<td>Jejunal</td>
<td>20.2 (11.4-39.0)</td>
<td>5.0 (2.8-7.2)</td>
<td>90%</td>
</tr>
<tr>
<td>Colic</td>
<td>9.0 (4.6-12.1)</td>
<td>3.1 (1.9-5.2)</td>
<td>50%</td>
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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 provide 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 then 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, cyclosporinetylosin) 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* enterotoxictosis, 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/m^2, 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/m^2 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!

References
