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

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

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

**Indications**

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

Gastroduodenoscopy is a very important diagnostic procedure in cats that chronically vomit. The author performs endoscopy, rather than upper GI barium studies, because endoscopy offers the following advantages: 1) direct mucosal inspection; 2) directed mucosal biopsy; 3) ability to remove foreign bodies; 4) ability to visualize subtle mucosal lesions; 5) assessment of respectability of neoplastic masses; and, 6) is rapid to perform. Some potential disadvantages of endoscopy include: 1) necessity of general anesthesia; 2) inability to examine the entire small intestine; 3) inability to detect lesions in the muscularis and serosa; and, 4) inability to evaluate gastric motility and emptying. Gastric and small intestinal mucosal samples can be collected via endoscopy with less morbidity than exploratory celiotomy with gastrotomy and enterotomy.

Therapeutically, gastroduodenoscopy is indicated if foreign bodies are visualized on radiographs or if an owner has observed or suspects foreign-body ingestion. In cases of suspected foreign body ingestion radiographic studies should always confirm the presence of a foreign body prior to endoscopy. Endoscopic retrieval of gastric foreign bodies is readily accomplished in most cases. Foreign bodies in the small intestine are very difficult to remove endoscopically and exploratory surgery is indicated in most cases.

A final indication for gastroduodenoscopy is placement of percutaneous endoscopic gastrostomy tubes (PEG). This rapid and simple procedure provides a convenient avenue for nonstressful enteral nutritional support in cats with prolonged anorexia or oral, pharyngeal, or esophageal disorders.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 2 - Disorders diagnosed by endoscopy

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

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

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

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

Table 3 - Unique features of endoscopy in cats vs dogs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Many drugs are available to treat the clinical signs associated with GI diseases or to treat the disease process itself. A thorough knowledge of these drugs, including several of the newer developments, is necessary for the practitioner to effectively treat dogs and cats with GI diseases.

**Antiemetics**

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

**Metoclopramide**

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

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

**Ondansetron**

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

**Maropitant – cerenia™**

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

**Erosion and ulcer therapy**

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

**H-2 receptor blockade**

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

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

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

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

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

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

References


Chronic diarrhea is a common problem in dogs and cats. Diagnosis can be difficult and challenging for veterinarians due to the large number of possible causes of chronic diarrhea. Following a logical and thorough diagnostic plan is essential to efficiently arrive at an accurate diagnosis. This seminar will review the author's approach to the diagnosis of chronic diarrhea.

Clues obtained during the history and physical examination may suggest a diagnosis or help to rank the differential diagnosis. A thorough description of the diarrhea should be obtained (Table 1: diarrhea history form). The dietary history should include the diet being fed, meal size, meals / day, past diet changes and effects on clinical signs, supplements, and the existence of dietary indiscretion. Dietary indiscretion includes a recent sudden diet change, feeding of table scraps, free roaming behavior allowing ingestion of garbage, ingestion of foreign objects, exposure to toxins (including house plants), excessive ingestion of hair, or feeding a low-quality poorly digestible diet. The duration of the problem should be identified and the diarrhea should be categorized as continuous or intermittent. If intermittent, how long are the episodes and how frequently do they occur? Are there any inciting factors the owner can relate to the origin of the diarrhea or that make the clinical signs worse? Examples include any stress, travel thunderstorms, new pet, loss of a pet, new family member, household move, etc. Does vomiting accompany diarrhea? How many times a day does vomiting occur, how many days / week, what is its association with eating, and what does the vomitus look like? What is the animal's deworming history? What previous treatments have been used, including dosage, frequency / day, and duration, and what response has been seen?

Specific information should be obtained describing and characterizing the diarrhea. What is the frequency / day, is there melena or hematochezia, mucus, tenesmus, or accidents in the house? What is the volume of stool / defecation, compared to what is normal for the dog or cat? Is the animal's appetite normal, reduced, or increased? Has weight loss occurred, and how much? Finally, the consistency of the stool should be graded from 1 (watery diarrhea) to 5 (formed stool). The above characteristics should be based on the animal's average clinical signs during the period prior to your examination. Based on a thorough history, the initial step in evaluation of dogs and cats with chronic diarrhea is to determine if diarrhea is of small bowel, large bowel, or mixed bowel origin (Table 2). Small bowel diarrhea is characterized by weight loss, a mildly increased frequency of defecation, and a large quantity of stool produced per defecation. Blood, if present, is partially digested (melena). On the other hand, large bowel diarrhea is characterized by the absence of weight loss, and a moderate to greatly increased frequency of defecation, with a reduced to scant volume produced per defecation. Tenesmus, excess fecal mucus, and frank blood (hematochezia) is often present. Mixed bowel diarrhea has some characteristics of both. This initial distinction between small and large bowel is extremely important because the diagnostic plans and differential diagnoses are different.

Physical examination is often normal in dogs and cats with chronic diarrhea with the exception of weight loss. Mildly thickened bowel wall may be palpated. If a severe episode of clinical signs is present, signs of dehydration may be detected (delayed capillary refill time, enopthalmos, decreased skin turgor, tachycardia, pale mucous membranes, and cold extremities). Careful attention should be devoted to abdominal palpation to detect abnormalities such as dilated (gas, fluid, or ingesta) loops of bowel or extremely thickened bowel wall, abdominal masses, intraluminal foreign bodies, or ascites. These abnormalities are detected in <5% of cases seen at the author's hospital. Digital rectal examination may elicit pain and reveal an intraluminal mass, rough corrugated mucosa, sublumbar lymphadenopathy, narrowed lumen, foreign material, blood on the glove, or a perineal hernia.

Laboratory diagnosis of chronic diarrhea

Many laboratory tests may be used in the diagnosis of patients with chronic diarrhea. Routine complete blood count, biochemical profile and urinalysis is often normal. Evidence of anemia and hypoproteinemia may reflect protein and blood loss into the GI tract. Anemia initially may be regenerative, but as iron deficiency develops, it may become nonregenerative. In addition, a nonregenerative anemia associated with chronic disease may be found. Eosinophilia may reflect the presence of inflammatory bowel disease or gastrointestinal parasites. Hypoproteinemia associated with protein losing enteropathy is a panhypoproteinemia with decreased albumin and globulins. The FeLV / FIV test may be positive. Serum thyroxine levels may be elevated in older cats with hyperthyroidism and chronic small bowel diarrhea.

Perhaps the most important test for evaluation of dogs and cats with chronic diarrhea is fecal examination for parasites. Many problem diarrhea cases are caused by the protozoan parasite Giardia. Routine fecal flotation techniques rarely identify this parasite. The zinc sulfate sedimentation technique is sensitive for the diagnosis of Giardia and other GI parasites. One to two grams of feces is well mixed in a tube with a 33% zinc sulfate solution and strained. The tube is centrifuged for 3-5 minutes at 1,500 rpm. If a free-swinging head centrifuge is used, the tube is topped with a coverslip and the coverslip examined for parasites. If a fixed-head
centrifuge is used, a drop of the surface layer is collected and examined. A single zinc sulfate floatation has identified approximately 75% of *Giardia* infected dogs, while 3 samples examined every other day identified >95% of infected dogs! The SNAP *Giardia* fecal ELISA is a recent addition to aid in the diagnosis of *Giardia*. In most cases the author feels that a single zinc sulfate floatation combined with a *Giardia* SNAP test are adequate to diagnose the presence or absence of *Giardia*.

Feces can also be examined microscopically by adding a few drops of saline to a thin smear of fresh feces. This may allow visualization of trophozoites. *Giardia* trophozoites move across the field as a leaf falls from a tree. A saline fecal smear been shown to detect about 20% of dogs infected with *Giardia*. By repeating the test on three successive stool samples, detection rates have increased to approximately 40%. In addition, highly motile, spiral-shaped bacteria may suggest a *Campylobacter* infection.

Fecal or rectal cytology can also be performed by staining a thin fecal smear with Wrights stain. A rectal cytology specimen can be collected by scraping the rectum with a gloved finger and gently rolling the finger across a glass slide. Alternatively, a moistened cotton swab or conjunctival spatula can be used. Normal fecal or rectal cytology should contain colonic epithelial cells, a mixed population of bacteria, yeast, and unidentifiable debris. Increased numbers of white blood cells or red blood cells may be indicative of inflammatory, infectious, or hemorrhagic disorders. The presence of more than 3-5 spores / hpf of *Clostridium perfringens* suggests the possibility of enterotoxicosis. Spores appear as large rods with a clear center and dark staining ends (safety pins). *Campylobacter* organisms may appear gull-shaped. Occasionally, neoplastic cells may be seen or inclusions may be found within macrophages suggesting fungal infection with *Histoplasma*.

The gold standard test for diagnosing pancreatic exocrine insufficiency in dogs is determination of serum trypsin-like immunoreactivity. Trypsinogen, a pancreas specific substance, leaks from the pancreas into blood. It is filtered by the kidney. After a 12-hour fast, one ml of serum can be assayed. Concentrations >5 ug/l indicate normal pancreatic exocrine function. The test has recently been validated for cats, although this is a rare condition in this species.

Determination of serum vitamin B₁₂ and folic acid concentration can be beneficial in diagnosis of bacterial overgrowth of the small intestine (SIBO) in dogs. These bacteria bind and metabolize vitamin B₁₂ and produce additional folic acid, resulting in decreased B₁₂ levels and increased folic acid levels. However the test is insensitive and only fairly specific. Diagnosis of SIBO requires quantitative aerobic and anaerobic culture of duodenal juice. However, many cats with chronic GI are deficient in vitamin B₁₂, and benefit from parenteral supplementation.

Radiographic evaluation of dogs and cats with chronic diarrhea is not a very high yield procedure. Changes seen on survey films may include dilated, gas-filled loops of small bowel, an abdominal mass, radiodense foreign body, or ascitic fluid. An upper GI contrast series may demonstrate evidence of enteritis, a dilated loop of bowel not previously identified, a soft tissue mass, or decreased motility. Abdominal ultrasound can be useful in the cases with palpable abdominal abnormalities detected during physical examination. Masses, thickened bowel walls, and mesenteric lymphadenopathy can be localized and fine needle aspiration or Tru-Cut biopsy samples obtained. Abdominal ultrasound should be done in animals in which lymphoma or other neoplasms are high on the rule out list. In a group of dogs with chronic diarrhea the following factors were associated with a higher diagnostic utility of abdominal ultrasound: the presence of weight loss, palpation of an abdominal or rectal mass on initial physical examination, localization of diarrhea to mixed bowel (vs. large bowel), diseases that commonly have mass lesions that should be visible on ultrasound examination, and a clinical diagnosis of GI neoplasia.

For many small intestinal disorders biopsy is necessary for diagnosis. Endoscopic examination of the duodenum with mucosal biopsy is a minimally invasive method of obtaining tissue. In the author's experience, evaluation of the duodenum and proximal jejunum results in accurate diagnosis in at least 75% of dogs and cats with chronic small bowel diarrhea. A duodenal aspirate for *Giardia* can be performed. If endoscopy is not available, exploratory celiotomy can be performed. Multiple full-thickness biopsies of the small bowel should be taken, mesenteric lymph nodes biopsied, and a duodenal aspirate examined for *Giardia* trophozoites. Ten ml of saline can be injected into the duodenum, aspirated, centrifuged, and the pellet examined for motile trophozoites.

For animals with large bowel diarrhea, colonoscopic examination is a high yield diagnostic test. Rigid colonoscopy allows evaluation of the descending colon which should be diagnostic in approximately 90% of cases with large bowel diarrhea. Flexible colonoscopy allows evaluation of the transverse and ascending colon, cecum, and possibly the ileum. Proper preparation for colonoscopy is essential to allow visualization of the entire mucosal surface. The animal should be held off food for 24 hours. Two doses of GoLYTELY should be given 2 hours apart, the afternoon prior to endoscopy. Dogs receive 60 ml/kg via orogastric tube while cats get 30 ml/kg via nasoesophageal tube. A warm water enema should follow each GoLYTELY and a third prior to anesthesia. When doing endoscopy, biopsies should always be taken, even if the mucosa looks normal.

Bacterial culture is a low yield diagnostic procedure. Specific pathogens that should be cultured for include *Salmonella*, *Campylobacter*, and *Yersinia*.
Differential diagnosis
Table 3 lists some causes of chronic small and large bowel diarrhea. The most common causes of small bowel diarrhea include GI parasites, highly digestible diet-responsive small bowel diarrhea, and inflammatory bowel disease. In cats, it is important to consider hyperthyroidism and infection with FeLV / FIV. Common causes of chronic large bowel diarrhea include *Trichuris vulpis*, highly digestible diet-responsive large bowel diarrhea, plasmacytic lymphocytic colitis, irritable bowel syndrome, *Clostridium perfringens* enterotoxosis, fiber-responsive diarrhea, and neoplasia.

Diagnostic plan (figure 1)
Based on history and physical examination, diarrhea should be localized to the small bowel, large bowel, or mixed bowel. In cases of small bowel diarrhea, the next distinction to be made is based upon abdominal palpation. If abdominal palpation is abnormal (<2% of cases) diagnostic evaluation should proceed with survey abdominal radiographs, abdominal ultrasound, a barium upper GI series, and exploratory laparotomy. If neoplasia is very likely, 3-view thoracic radiographs should be performed to evaluate the presence of metastasis. Many practitioners will skip the barium series and go straight to surgery, reducing the cost to the client and the time to diagnosis.

If abdominal palpation is normal, multiple fecal examinations should be performed to rule out gastrointestinal parasites. Treatment for *Giardia* with metronidazole or fenbendazole is indicated prior to invasive diagnostic procedures. In addition, a dietary trial using a highly digestible diet for 3-4 weeks is also indicated. The diet should contain a highly digestible carbohydrate, be low in fat, low in fiber, and lactose and gluten-free. Many commercially available diets are available, including several diets for cats.

If diarrhea continues despite negative fecal examinations, treatment for *Giardia*, and a 3-4 week dietary trial, further evaluation should include measurement of serum trypsin-like immunoreactivity in dogs with a strong clinical suspicion of exocrine pancreatic insufficiency. In cats, tests for FeLV / FIV should be performed. Middle-aged and older cats should be tested for hyperthyroidism.

Further evaluation should include a complete blood count, biochemical profile, and urinalysis. Survey abdominal radiographs may be taken (or abdominal ultrasound performed) to rule out any abnormalities not detected by palpation. Multiple small intestinal biopsies should be collected by endoscopy if available, or via exploratory laparotomy. Serum B12 and folic acid may be measured to indirectly assess bacterial overgrowth, if a diagnosis has not been reached or the dog is not responding to appropriate therapy.

If chronic large bowel diarrhea is present, the initial diagnostic plan should consist of multiple fecal examinations for parasites, a 3-4 week dietary trial with a highly digestible diet, therapeutic deworming for whipworms and rectal cytology. In cases of large bowel diarrhea, a dietary trial utilizing higher levels of fiber may be beneficial. If diarrhea persists after these steps, an expanded database should include a complete blood count, biochemical profile, urinalysis, T4 and FeLV / FIV testing for cats, and colonoscopy with multiple mucosal biopsies. If available, fecal assay for Clostridium enterotoxin or a therapeutic trial with amoxicillin should be performed prior to colonoscopy. If the colon is found to be normal with rigid endoscopy and a flexible endoscope is not available, a barium enema may be administered to evaluate the transverse and ascending portions of the colon. On rare instances, fecal cultures should be submitted, especially if increased numbers of neutrophils are seen on colonic or fecal cytology.

Figure 1- Chronic diarrhea history
Date ________________
Duration of diarrhea: Continuous or intermittent (circle)
If intermittent: Length of episode: Frequency of episode:

Inciting factors (dietary indiscretion, stress, travel, thunderstorms, separation anxiety, nervous temperament etc.):

When diarrhea is present:
Frequency / day
Blood (indicate melena or hematochezia):
Mucus:
Tenesmus:
Accidents in house (how often):
Volume of stool: decreased normal increased (circle):
Stool grade: 1-5:
Appetite (circle) normal or slightly reduced or greatly reduced or none or increased (circle)

Weight loss? Yes or No (circle)
If present how much?

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Abdominal pain? Yes or No (circle)

Excessive borborygmus / flatulence? Yes or No (circle)

Vomiting? Yes or No (circle)
If present: frequency / day:
days / week:
association with eating:
character of vomitus:

Diet (type, changes, effects):

Meals / day:

Maintenance medications:

Previous treatments (drug, dose, duration, response): continue on back of form if necessary

small bowel  large bowel  mixed bowel  (circle)

Answer each question for the average clinical sign. If frequency or severity has progressed, indicate (frequency was 5/day, during last 4 weeks 9/day).

**Chronic diarrhea activity index (CDAI)**
Score each of the categories based on the severity of clinical signs during the 2 weeks prior to the animal’s visit.

<table>
<thead>
<tr>
<th>Category</th>
<th>Points possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attitude / activity</td>
<td>0 – normal</td>
</tr>
<tr>
<td></td>
<td>1 – slightly reduced</td>
</tr>
<tr>
<td></td>
<td>2 – moderately reduced</td>
</tr>
<tr>
<td></td>
<td>3 – severely reduced</td>
</tr>
<tr>
<td>Appetite</td>
<td>0 – normal</td>
</tr>
<tr>
<td></td>
<td>1 – slightly reduced</td>
</tr>
<tr>
<td></td>
<td>2 – moderately reduced</td>
</tr>
<tr>
<td></td>
<td>3 – severely reduced</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 – none</td>
</tr>
<tr>
<td></td>
<td>1 - &lt; 4/week</td>
</tr>
<tr>
<td></td>
<td>2 - &lt; 8/week</td>
</tr>
<tr>
<td></td>
<td>3 - &gt; 7/week</td>
</tr>
<tr>
<td>Stool consistency</td>
<td>0 – Mostly grade 4 or 5</td>
</tr>
<tr>
<td></td>
<td>1 – Mostly grade 3, some grade 4</td>
</tr>
<tr>
<td></td>
<td>2 – Mostly grade 2, some grade 3</td>
</tr>
<tr>
<td></td>
<td>3 – Mostly grade 1, some grade 2</td>
</tr>
<tr>
<td></td>
<td>4 – Always grade 1</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>0 – normal</td>
</tr>
<tr>
<td></td>
<td>1 – 1-2x normal</td>
</tr>
<tr>
<td></td>
<td>2 – &gt;2-3x normal</td>
</tr>
<tr>
<td></td>
<td>3 - &gt;3x normal</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0 – none</td>
</tr>
<tr>
<td></td>
<td>1 - &lt; 5%</td>
</tr>
<tr>
<td></td>
<td>2 - &gt;5 - &lt;10%</td>
</tr>
<tr>
<td></td>
<td>3 - &gt;10%</td>
</tr>
<tr>
<td>Blood – Melena or hematochezia</td>
<td>0 – none</td>
</tr>
<tr>
<td></td>
<td>1 – positive</td>
</tr>
<tr>
<td>Mucus</td>
<td>0 – none</td>
</tr>
<tr>
<td></td>
<td>1 – positive</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>0 – none</td>
</tr>
<tr>
<td></td>
<td>1 - positive</td>
</tr>
</tbody>
</table>

Total Points
Table 2: Localization of chronic diarrhea

<table>
<thead>
<tr>
<th>SIGN</th>
<th>SMALL BOWEL</th>
<th>LARGE BOWEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Frequency</td>
<td>Normal - mild</td>
<td>Normal - Moderate - large increase</td>
</tr>
<tr>
<td>Volume</td>
<td>Normal - Increased</td>
<td>Normal - Decreased</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Blood</td>
<td>Melena</td>
<td>Hematochezia</td>
</tr>
<tr>
<td>Mucus</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Table 3: Chronic diarrhea- differential diagnosis

Chronic small bowel diarrhea
- Giardia, hookworms, roundworms
- Dietary indiscretion / Highly digestible diet - responsive
- Pancreatic exocrine insufficiency
- Inflammatory bowel disease
- Stagnant loop syndrome
- Feline hyperthyroidism
- Lymphosarcoma - diffuse
- Lymphangiectasia
- Neoplasia
- Antibiotic responsive diarrhea / Small intestinal bacterial overgrowth
- Feline leukemia virus
- Feline immunodeficiency virus
- Histoplasmosis

Chronic large bowel diarrhea
- Whipworms,
- Dietary indiscretion / Highly digestible diet - responsive
- Plasmacytic lymphocytic colitis
- Irritable bowel syndrome
- Neoplasia
- Fiber-responsive diarrhea
- *Clostridium perfringens* enterotoxicosis
- Histoplasmosis
- Eosinophilic colitis
Chronic diarrhea case 1

Signalment
2.5 yr SF Irish setter

History
- Diarrhea of 5 months duration
- Frequency: once every 4-5 days, gradually progressed to 2/day
- Quantity/defecation: normal
- Tenesmus, hematochezia, excess mucus, Grade III
- No weight loss, good appetite
- Fecal examination: hookworms, treated with pyrantel
- Treated with mebendazole and fenbendazole
• Negative fecals x3
• Diet i/d and Ken-L-Ration Biscuit
• Environment: fenced in yard
• Other pets: 3 dogs, 4 cats all normal

Past history
Hit by car: traumatic myocarditis, acetabular fracture, stray dog

Physical examination

Normal

Localization of diarrhea (Circle one) –
Small bowel - Large bowel - Mixed bowel

Differential diagnosis
• IBD - plasmacytic lymphocytic / eosinophilic colitis
• Clostridium perfringens enterotoxosis
• Fiber-responsive large bowel diarrhea
• Irritable bowel syndrome
• Lymphoma

Diagnostic plan
• Fecals x3 - done
• RX whipworms - done x2
• GI diet - done
• Rectal cytology
• RX Clostridium
• +/- Clostridium enterotoxin
• Colonoscopy

Diagnostic results/diagnosis
• Fecal neg
• Rectal cytology - normal
• Clostridium enterotoxin neg
• Colonoscopy - 15 cm superficial erosion, histopathology - PL colitis

Therapy
• Hypoallergenic diet - d/d
• FU 4 weeks - 2 short episodes diarrhea, colonoscopy - hemorrhagic ascending colon, granular descending colon, histopathology - PL colitis with inc eosinophils, RX sulfasalazine 1 g TID
• FU 3 months - infrequent diarrhea, colonoscopy and histopathology normal, tear production dec 50%, dec sulfasalazine 500 mg TID
• FU 7 months - diarrhea with dec sulfasalazine, RX tylosin 20 mg/kg BID - no response
• FU 28 months - prednisone 1 mg/kg SID tapered to 0.25 mg/kg q 48H

Chronic diarrhea case 2

Signalment
Male German shepherd dog, 2 yrs

History
• Diarrhea for 4 months, 20 kg weight loss, voracious appetite.
• Frequency: 3-8 times/day
• Large amount of feces per defecation, Grade II
• Environment: runs lose on farm
• Diet: Purina dog chow and canned Alpo

Previous therapy
• Metronidazole 1 gm SID x 6 days
• Fenbendazole 50 mg/kg SID for 3 days
• Pancreatic enzyme powder (1 TBS/meal)
• No improvement

Physical examination

Localization of diarrhea (circle one)
Small bowel - Large bowel - Mixed bowel
Differential diagnosis

- Giardia
- PEI
- IBD
- SIBO
- Lymphoma
- Lymphangiectasia
- Partial SI obstruction

Diagnostic plan

- Fecals x3, SNAP Giardia
- STLI
- +/- abdominal radiographs
- +/- abdominal ultrasound
- CBC, biochemical profile, UA
- Endoscopy
- +/- serum B12 / folate
- Exploratory laparotomy

Diagnostic results/diagnosis

- MDB normal
- Fecal x3 neg, SNAP Giardia not available
- STLI <1 (5-35)
- B12 352 (225-660)
- Folate 21.7 (6.7-17.4)
- Endoscopy and histopathology normal, quantitative aerobic anaerobic duodenal culture - ?
- DX - PEI with secondary bacterial overgrowth

Therapy

- Pancreatic enzyme powder 2 TBSP TID
- Low fat diet
- Doxycycline 5 mg/kg BID x 21
- FU day 3 - normal stool
- FU day 14 -3 kg weight gain, died mesenteric volvulus

References


Leib MS, Monroe WE, Codner EC. Performing rigid or flexible colonoscopy in dogs with chronic large bowel diarrhea. Vet Med 1991; 86; 900-912.


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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Helicobacter gastritis in dogs**

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

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

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

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

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

### Table 1 - Some causes of chronic vomiting

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

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

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

<table>
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<th>Diagnosis</th>
<th>Survey Rad</th>
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<td>+++++</td>
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Chronic vomiting case 1

Signalment
Himalayan, 3.5 years, NM

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

Physical examination
Normal

Regurgitation or vomiting (circle one)

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

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

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

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

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

**Chronic vomiting case 2**

**Signalment**
6 year old, MN, Shetland sheepdog

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

**Physical examination**
Normal

**Regurgitation or vomiting (circle one)**

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

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

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

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

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

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

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

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

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

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

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

Other clinical signs are dependent on the cause of icterus. Prehepatic, or hemolytic cases, are often weak, lethargic, and tachypneic, and may have dark discolored urine, a systolic heart murmur, not previously detected, or hepatosplenomegaly. Animals with hepatic or post-hepatic disorders may have some of the following signs: anorexia, weight loss, pyrexia, vomiting, diarrhea, abdominal distention, encephalopathy, polyuria / polydipsia, or bruising or bleeding tendencies. Abdominal distention due to hepatomegaly or ascites or cranial abdominal pain may be detected during physical examination.
Diagnostic plan
The most important initial diagnostic step with the icteric patient is to evaluate the hematocrit to determine if prehepatic, or hemolytic icterus, is present. Moderate or severe anemia with a normal total protein suggests hemolysis. The presence of hemolysis is also supported by hemoglobinuria or autoagglutination, although neither must be present. Further evaluation of hemolysis should include a review of red blood cell morphology for spherocytosis, hemoproteozoa, determination of the reticulocyte count, a Coombs test, and a FeLV ELISA test in cats.

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

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

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

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

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

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

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

<table>
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<tr>
<td>PCV</td>
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<tr>
<td>BUN (6-28)</td>
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<tr>
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<tr>
<td>ALT</td>
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<tr>
<td>AP</td>
</tr>
<tr>
<td>Cholesterol</td>
</tr>
<tr>
<td>USG</td>
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<td>Urine bilirubin</td>
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</table>

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

### Differential diagnosis – hepatic icterus

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

### Diagnostic plan

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

### Diagnostic results

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

### Therapy

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

### Case follow-up

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

### References


Giardia and Tritrichomonas Foetus: An Update

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Giardia

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

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

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

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

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

Differential diagnosis and diagnostic plan

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

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

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

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

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

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

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

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

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

Treatment
The author recommends using either metronidazole or fenbendazole for treating giardiasis in dogs and cats. The dosage of metronidazole should be 50 mg/kg SID for 5 days. It has been previously suggested to split the dosage and administer it BID. In one study it was effective in 67% of infected dogs at 22 mg/kg BID for 5 days. In a different study in a group of research cats, 25 mg/kg BID of metronidazole benzoate suspension resulted in negative fecal samples 15 days after treatment. Tablets should not be divided as the medication is bitter and unpalatable. Compounding with tasty flavors, such as tuna or sardine juice, will increase palatability for cats and small dogs that receive less than one tablet. Some authors have found that a lower dosage, 10 mg/kg BID, is effective in cats. Severe neurologic side effects, including seizures and coma, have been reported in dogs receiving higher dosages or prolonged treatment. However, neurologic signs can occur with lower dosages, but are usually reversible if the drug is discontinued. Metronidazole is a potential mutagen and carcinogen, so treatment of pregnant animals should be avoided. Metronidazole enters the parasite by passive diffusion. Under anaerobic conditions, the compound is reduced, forming toxic derivatives that bind to DNA, RNA, and other proteins, leading to denaturation and strand breakage. In humans, metronidazole is metabolized in the liver. Sixty to eighty percent of the metabolites and parent compound is eliminated by the kidney. Approximately 15% is eliminated in the feces. Drug interactions are uncommon, but phenobarbital and prednisone may increase hepatic metabolism while cimetidine may decrease it.

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

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

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

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

**Trichomoniasis**

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

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

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

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

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

Treatment of cats is difficult. The best currently available treatment is ronidazole 30mg/kg SID-BID for 10 days. Many cats will develop reversible neurologic toxicity 3-9 days into treatment. Clinical signs include anorexia, lethargy, trembling, agitation, instability, and a blank stare. In many cats, signs of toxicity will resolve 6-10 days after stopping the treatment. Feces often become normal within 10 days of treatment. Treatment with paromomycin cannot be recommended as acute renal failure may occur!

**References**


Medication-induced esophageal strictures in cats
Doxycycline is commonly used in cats to treat many potentially infectious diseases. The drug is acidic and can be caustic to esophageal epithelial cells. It may accumulate within epithelial cells, where it can decrease protein synthesis and potentially decrease mucosal repair. Esophagitis can progress to stricture formation after doxycycline administration in cats. These strictures result in dramatic reduction of the esophageal lumen and severe regurgitation and dysphagia. Clinical signs usually develop within 7-10 days of administration of doxycycline. Treatment requires repeated endoscopic balloon dilation, with is an expensive and invasive procedure. Doxycycline induced esophageal strictures in cats usually occur in the proximal esophagus. Stricture diameter is often very small (often 1-5 mm) at initial diagnosis, smaller than strictures associated with anesthesia and gastroesophageal reflux. Usually re-stricturing is a major problem and affected cats often require more frequent dilations than cats with strictures due to other causes. Intral esional corticosteroid injection may reduce the frequency of repeated dilations. Post-dilation treatments often include and H2 blocker, metoclopramide, sucralfate, prednisone, and in some cats placement of a PEG tube. Oral feeding with a liquid or blenderized diet is often necessary after dilation.

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

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

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

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

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

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

**New treatments for IBD**

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

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

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

**Helicobacter gastritis in dogs**

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

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

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

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

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

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

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

**Giardiasis and zoonosis**

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

**References**


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

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

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

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

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

**Lymphangiectasia**
Dilation of small intestinal lymphatics and rupture into the lumen leads to protein losing enteropathy and low serum proteins in dogs. Cases may be idiopathic, or secondary to chronic inflammatory conditions of the small intestine. The aim of dietary management is to decrease lymphatic flow by supplying a very low fat diet. Reduced fat diets used for weight control, such as Hills r/d, Purina OM, Iams reduced calorie dry, or Royal Canin calorie control dry can be effective. Caloric supplementation with medium chain triglyceride oil (MCT) may be necessary. Medium chain triglycerides are absorbed into the venous system, not via lymphatics, and do not stimulate lymphatic flow. Ultra-low fat home made diets consisting of low fat cottage cheese, rice and potatoes can be very effective.
Plasmacytic lymphocytic enterocolitis – Inflammatory bowel disease
Inflammatory bowel disease is a common idiopathic condition in dogs and cats that causes vomiting and/or diarrhea of small and/or large bowel origin. Diagnosis requires histologic demonstration of intestinal inflammation in the absence of known causes of intestinal disease. Increased mucosal permeability leads to penetration of the mucosa by food antigens and initiation of hypersensitivity, that worsens the inflammatory process. It is also possible that dietary hypersensitivity may play a role in the initiation of mucosal damage.

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

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

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

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

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

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

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

Chronic idiopathic large bowel diarrhea
I routinely add soluble fiber to a highly digestible diet in dogs with chronic idiopathic large bowel diarrhea, even if irritable bowel syndrome has been diagnosed. In cases of fiber-responsive large bowel diarrhea (FRLBD), chronic intermittent or continuous large bowel diarrhea is usually accompanied by hematochezia, excess fecal mucus, and tenesmus. Abdominal pain and vomiting can occur in some dogs. Nervousness, abnormal personality factors, and stressors have been identified in approximately 40% of cases. However, in some of these cases, a temporal relationship to the diarrhea could not be established.
Soluble fiber, psyllium hydrophilic mucilloid (Metamucil®, Procter & Gamble), added to a highly digestible diet (i/d® Hills), has resulted in excellent or very good results in approximately 80% of dogs with chronic idiopathic large bowel diarrhea. In the authors' cases, the median amount of Metamucil® added to the diet was two TBSP / day which was approximately 1.3 g psyllium / kg / day. I have not been able to identify any clinical findings that help to predict whether a dog will respond to fiber supplementation. In some dogs, the amount of fiber added to the diet can be reduced or withdrawn entirely, while in others the highly digestible diet can be replaced with a grocery store brand of food after the diarrhea resolves.

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

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

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

Table 1. Some limited antigen foods

<table>
<thead>
<tr>
<th>Company</th>
<th>Food name</th>
<th>Major ingredients</th>
<th>dog or cat</th>
<th>dry or canned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hills</td>
<td>d/d</td>
<td>Egg, rice</td>
<td>dog</td>
<td>dry</td>
</tr>
<tr>
<td>Hills</td>
<td>d/d</td>
<td>Duck, rice</td>
<td>dog</td>
<td>dry</td>
</tr>
<tr>
<td>Hills</td>
<td>d/d</td>
<td>Salmon, rice</td>
<td>dog</td>
<td>dry</td>
</tr>
<tr>
<td>Hills</td>
<td>d/d</td>
<td>Lamb, rice</td>
<td>dog / cat</td>
<td>canned</td>
</tr>
<tr>
<td>Purina</td>
<td>LA</td>
<td>Salmon, trout</td>
<td>dog</td>
<td>dry</td>
</tr>
<tr>
<td>Iams</td>
<td>Response FP</td>
<td>Catfish, potato</td>
<td>dog</td>
<td>dry, canned</td>
</tr>
<tr>
<td>Iams</td>
<td>Response KO</td>
<td>Kangaroo, oats</td>
<td>dog</td>
<td>dry</td>
</tr>
<tr>
<td>Innovative Veterinary Diets</td>
<td>Limited ingredient diet</td>
<td>Lamb, potato</td>
<td>dog, cat</td>
<td>dry, canned</td>
</tr>
<tr>
<td>Innovative Veterinary Diets</td>
<td>Limited ingredient diet</td>
<td>Venison, potato</td>
<td>dog, cat</td>
<td>dry, canned</td>
</tr>
<tr>
<td>Innovative Veterinary Diets</td>
<td>Limited ingredient diet</td>
<td>Duck, potato</td>
<td>dog, cat</td>
<td>dry, canned (dog only)</td>
</tr>
<tr>
<td>Innovative Veterinary Diets</td>
<td>Limited ingredient diet</td>
<td>Rabbit, potato</td>
<td>dog, cat</td>
<td>dry, canned</td>
</tr>
<tr>
<td>Innovative Veterinary Diets</td>
<td>Limited ingredient diet</td>
<td>Whitefish, potato</td>
<td>dog</td>
<td>dry, canned</td>
</tr>
<tr>
<td>Royal Canin</td>
<td>Sensitivity RC, LR</td>
<td>Catfish, rice</td>
<td>dog</td>
<td>dry (RC), canned (LR)</td>
</tr>
<tr>
<td>Royal Canin</td>
<td>Sensitivity RD, VR</td>
<td>Duck, rice</td>
<td>cat</td>
<td>dry (RD), canned (VR)</td>
</tr>
<tr>
<td>Wysong</td>
<td>Anergen</td>
<td>Lamb, rice</td>
<td>dog, cat</td>
<td>dry, canned</td>
</tr>
<tr>
<td>Nature’s Recipe</td>
<td>Allergy</td>
<td>Venison rice</td>
<td>dog</td>
<td>dry, canned</td>
</tr>
<tr>
<td>Nature’s Recipe</td>
<td>Allergy vegetarian</td>
<td>Rice, soy, barley</td>
<td>dog</td>
<td>dry, canned</td>
</tr>
<tr>
<td>Natural Life</td>
<td>Lamaderm</td>
<td>Lamb, rice</td>
<td>dog, cat</td>
<td>dry, canned</td>
</tr>
<tr>
<td>Sensible Choice</td>
<td></td>
<td>Lamb, rice</td>
<td>dog</td>
<td>dry</td>
</tr>
</tbody>
</table>
References
The “GI Panel”:
Use, Abuse, and Interpretation
Craig Ruaux, BVSc, PhD, DACVIM
Oregon State University
Corvallis, OR

The components of the “GI panel”
Most clinicians, when referring to a GI panel, are referring to the measurement of serum concentrations of specific pancreatic lipase immunoreactivity (Spec-cPL in the dog, Spec-fPL in the cat), serum trypsin-like immunoreactivity (cTLI in the dog, fTLI in the cat), and the serum concentrations of two water soluble, B-group vitamins, cobalamin (Vitamin B12) and folate (Vitamin B9). Together, these compounds can provide valuable information regarding the presence and localization of disease in the pancreas and small intestine, and they may also suggest the need for therapeutic supplementation. The normal physiology and significance of abnormalities of these compounds are discussed individually below. While most clinicians will use the full panel of all four compounds, particularly in cases where clinical signs are vague or inconsistent, in some situations it can be cost effective to measure only one of the pancreas markers. For instance, if the clinical suspicion is of exocrine pancreatic insufficiency in a dog, due to the presence of compatible clinical signs, little additional value is obtained from measuring Spec-cPL, cTLI is the test of choice. Equally, in a dog with a strong suspicion of pancreatitis there is usually little additional value in measuring cTLI and Spec-cPL is the test of choice. In the cat, however, the clinical signs and histories of both exocrine pancreatic insufficiency and pancreatitis are sufficiently vague and non-specific that it is generally advisable to at least initially measure both fTLI and Spec-fPL in this species.

Trypsin-like immunoreactivity (cTLI, fTLI)
The serum concentration of trypsin-like immunoreactivity represents the presence of (mainly) trypsinogen and (rarely) active trypsin in the circulation. Trypsinogen, the zymogen precursor to active trypsin, is essentially exclusively synthesized in the pancreatic acinar cells, where it is packaged in secretory granules before excretion into the pancreatic duct system. Pancreatic acinar cellular damage, for instance with pancreatitis, can result in the loss of trypsinogen into the pancreatic interstitium and circulation, resulting in a higher than normal concentration. Loss of acinar cell mass, as occurs in both pancreatic acinar atrophy in dogs and as an end stage of chronic pancreatitis in dogs and cats, can result in subnormal concentrations of TLI. Detection of a serum TLI concentration <2.5µg/L is highly sensitive and specific for the diagnosis of exocrine pancreatic insufficiency in the dog. In the cat, a serum fTLI concentration ≤8 µg/L is suggestive of exocrine insufficiency. Values within the reference range, even if “low normal”, rule out exocrine insufficiency due to reduced functional acinar cell mass.

Elevations in serum TLI will be seen in some animals with acute pancreatitis. Serum TLI concentrations rise rapidly early in the course of acute inflammatory disease of the pancreas, but also return to baseline relatively rapidly, and are typically at or slightly below baseline values within 48 to 72 hours after the onset of a bout. Consequently, a normal serum TLI concentration does not reliably rule out the presence of inflammatory pancreatic disease.1 In the context of the GI panel, the greatest utility of the serum TLI concentration lies in the diagnosis or ruling out of exocrine pancreatic insufficiency as a cause of small intestinal diarrhea.

In some cats the serum fTLI concentration is mildly to moderately elevated, even though the clinical signs reported (diarrhea, weight loss) are more consistent with small intestinal disease. In many of these cats, serum Spec-fPL concentrations are normal. While the mechanism underlying this pattern of results is uncertain, it likely relates to a loss of normal negative feedback from the small intestine to the pancreas. This particular pattern of results (high TLI, normal PLI) in the cat is strongly suspicious of small intestinal disease, and warrants assessment of the serum cobalamin and folate concentrations.

Specific pancreatic lipase (Spec-cPL™, Spec-fPL™)
As with trypsin/trypsinogen, specific pancreatic lipase is synthesized only in the exocrine pancreas. Release of enzymes into the circulation is via leakage, and increased release is generally held to be consistent with acinar cellular damage occurring during pancreatitis. Generally speaking, serum concentrations of PLI show greater magnitudes of increase and longer durations of elevation above baseline than TLI in the same patient.

Detection of elevated serum concentrations of specific pancreatic lipase (fPLI or Spec-fPL) has a higher reported sensitivity and specificity than fTLI for diagnosis of pancreatitis in the cat. In one study, where fTLI achieved overall sensitivity and specificity of 28% and 82%, respectively, fPLI achieved overall sensitivity and specificity of 67% and 67%, respectively.2 In the same study, sensitivity of fPLI for the diagnosis of “moderate to severe” pancreatitis was 100%. A larger study (n=182 cats) of the Spec fPL assay reported an overall sensitivity for this test of 79%, with a specificity of 82% for detection of pancreatitis in this group.3 Overall, the Spec-fPL assay has the highest currently reported sensitivity and specificity of any diagnostic modality for the detection of pancreatitis in the cat.1

While pancreatic lipases are highly specific for the exocrine pancreas, the normal range of these assays in both dogs and cats includes values close to or equal to zero. Consequently, the Spec-c/fPL assays cannot be used to diagnose exocrine pancreatic

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Serum folate
Folate is a water-soluble, B-group vitamin (Vitamin B₉) that is abundant in most small animal diets. As dietary deficiency of this vitamin is highly unlikely, the serum concentration of folate is an indicator of the small intestinal absorptive capacity for this vitamin. Folate monohydrate, the major form of folate absorbed from the small intestine, is absorbed exclusively via a receptor mediated process in the duodenum, thus a low serum folate concentration suggests a lack of duodenal receptors, and implies duodenal mucosal disease with a very high specificity.

Folate availability from the GI tract can be increased in some disease states. Many intestinal bacteria, including some Lactobacillus spp and representative flora from the large intestine, are net synthesizers of folate and release significant quantities of folate into their environment. In the dog an increased serum concentration of folate has traditionally been considered suggestive of bacterial overgrowth (see below), based on the assumption that a more “large intestinal” flora has migrated up into the small intestine. However, as mentioned above, some Lactobacillus organisms are net folate synthesizers as well as being “desirable” flora. With increasing use of partially fermentable fiber sources such as fructose-oligosaccharides in pet diets, there has been a population wide increase in serum folate concentrations.

Relatively recent studies of dogs with chronic enteropathy and suspected small intestinal bacterial overgrowth have found no difference is serum folate concentrations between dogs that responded to antibiotic therapy and those that did not. In the author’s experience at least, elevated folate concentrations are common in many animals with minimal to no evidence of typical “bacterial overgrowth”, and this finding is of little impact to the management of clinical cases. The obverse of this observation, though, is that a low serum folate is highly meaningful and a strong indicator of significant small intestinal disease of some form.

Serum cobalamin
Cobalamin is also a water-soluble, B-group vitamin (Vitamin B₁₂). In common with folate, this vitamin is abundant in small animal diets and it is extremely difficult to induce cobalamin deficiency in companion animals via dietary means. Also in common with folate, the serum concentration of cobalamin reflects the small intestinal absorptive capacity for this vitamin. Cobalamin undergoes a complex receptor-mediated absorptive process that occurs exclusively in the ileum in all species studied to date, including both dogs and cats. As the absorption of cobalamin occurs exclusively in the ileum, a low serum concentration of this vitamin strongly suggests ileal mucosal dysfunction.

Absorption of cobalamin relies on the formation of complexes between cobalamin and a binding protein called intrinsic factor, this protein is synthesized in the pancreas and gastric mucosa in dogs, and exclusively in the pancreas in the cat. Thus exocrine pancreatic insufficiency is almost invariably associated with low cobalamin concentrations in cats. As the clinical signs of exocrine insufficiency in many cats are vague and often dominated by weight loss and poor appetite, it is important to measure serum fTLI in cats with low cobalamin to help rule in/rule out this disease. While exocrine insufficiency is certainly a potential cause of low cobalamin in cats, it is not the primary cause. Infiltrative disease of the ileum, either inflammatory enteropathies or lymphoma, remain the most common cause of low serum cobalamin in cats and dogs.

Some enteric bacteria, particularly some species of Clostridium, are able to degrade the cobalamin/intrinsic factor complexes and then utilize the cobalamin for their own needs, thus patients with the conditions referred to as “bacterial overgrowth” may present with low serum cobalamin due to bacterial competition. Decreased serum cobalamin concentration was identified in 16/29 dogs with chronic enteropathies, however there was no differences noted in dogs with differing definitive diagnoses.

Cobalamin malabsorption can lead to a state of body-wide cobalamin deficiency, with deleterious effects on many cell types in the body, including enterocytes. Recognition of low serum cobalamin and parenteral supplementation to address this is an important part of the management of dogs with chronic enteropathies. Interestingly, low serum cobalamin concentration has been identified as a negative prognostic factor for dogs with chronic enteropathies, and cats with gastrointestinal lymphoma.

The combination of low serum cobalamin and folate concentrations is a very specific indicator of diffuse small intestinal mucosal pathology of some form. Any infiltrative disease, including the various forms of inflammatory bowel disease and intestinal lymphoma, may lead to this combination of abnormalities. Documentation of this combination of abnormalities in a dog with clinical signs of a chronic enteropathy warrants further, more invasive diagnostic testing, such as endoscopy with mucosal biopsy or exploratory laparotomy with biopsy.

Folate and cobalamin are intrinsically linked biochemically, with most enzyme systems that rely on cobalamin as a co-factor also utilizing folate as a methyl group donor. This means that animals that are cobalamin deficient are often not utilizing folate particularly efficiently, which can result in accumulation of folate in the circulation. When the low cobalamin is detected and supplementation begins, it is common for serum folate concentrations to drop quite markedly, in some cases folate drops low enough to suggest the presence of duodenal mucosal disease.
The clinical significance of elevated cobalamin concentrations remains unclear. At least one publication in the veterinary literature has associated high cobalamin concentrations with some hepatic and neoplastic diseases in cats, but similar data are lacking for dogs.

Common patterns of results and interpretation for cobalamin and folate

The table below summarizes the common patterns of results that may be detected when measuring serum cobalamin and folate concentrations in dogs and cats with gastrointestinal disease. It is important to remember that these tests have high specificities due to the very localized absorption sites, but they have relatively low sensitivities and thus these tests cannot be used to rule out the presence of small intestinal mucosal disease.

<table>
<thead>
<tr>
<th>Cobalamin</th>
<th>Folate</th>
<th>Potential DDx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Diffuse SI mucosal diseases: Infiltrative (IBD, LSA) Structural (lymphangectasia, Short Bowel Syndrome)</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>Disturbed intestinal flora: “SIBO”. Diffuse SI mucosal Exocrine Pancreatic Insufficiency (particularly in cats), check [TLI]</td>
</tr>
<tr>
<td>Low</td>
<td>Normal</td>
<td>Distal SI disease (infiltrative or structural) MOST LIKELY Abnormal bacterial population/dysbiosis Exocrine Pancreatic Insufficiency (particularly in cats), check [TLI]</td>
</tr>
<tr>
<td>High</td>
<td>Normal</td>
<td>Possible association with hepatic and neoplastic disease in cats, consider iatrogenic sources, coprophagia</td>
</tr>
<tr>
<td>Normal</td>
<td>High</td>
<td>Intestinal dysbiosis if compatible signs Possibly no significance, consider iatrogenic sources, coprophagia</td>
</tr>
</tbody>
</table>

Indications for supplementation

As well as acting as a marker for intestinal mucosal disease, there is an increasing body of evidence that cobalamin deficiency, which can manifest with serum cobalamin concentrations in low end of the normal range for both dogs and cats, is associated with poorer response to therapy and poorer prognosis in a variety of diseases. While a full discussion of cobalamin supplementation dosing and schedules is outside the scope of these notes, a substantial amount of information is available from the GI Lab at Texas A&M website, at: [http://vetmed.tamu.edu/gilab/research/cobalamin-information](http://vetmed.tamu.edu/gilab/research/cobalamin-information)

Low serum folate concentrations will also often prompt supplementation, and anecdotally there does appear to be a link between low serum folate and poorer response to therapy, but objective data regarding thresholds for supplementation and doses required are lacking at this time. The author typically recommends folic acid supplementation, 5-10 µg/kg per os daily for dogs and cats with serum folate concentrations <4.5µg/L. Additionally, animals with low normal serum folate and subnormal cobalamin concentrations receive folate supplementation preemptively, due to the common occurrence of low folate following cobalamin supplementation.

References


Chronic gastrointestinal disease is one of the most common reasons for companion animal owners to seek veterinary care. Clinical signs such as diarrhea, vomiting and inappetance are common in dogs and cats with chronic gastrointestinal disease, these signs are distressing to owners. Many underlying diagnoses can lead to chronic gastrointestinal signs, and conclusive diagnoses are often difficult to achieve. Successful management of these cases relies on a multi-pronged approach, involving dietary manipulations, identification and elimination of parasites, assessment of gastrointestinal function and, in some cases, pharmacological manipulation to mitigate inflammation.

A common feature of many of the diseases leading to chronic gastrointestinal signs is the presence of gastrointestinal inflammation, this inflammation may be the result of dietary intolerance (so called “Food-Responsive Diarrhea”), intestinal dysbioses or chronic colonization by bacterial pathogens (so called “Small Intestinal Bacterial Overgrowth” or “Antibiotic-Responsive Diarrhea”), or may be idiopathic. As classically understood, canine idiopathic inflammatory bowel disease (IBD) is characterized by persistent or recurrent clinical signs of GI disease of unidentified cause, associated with histologic evidence of inflammatory infiltration of the intestinal mucosa. The final diagnosis of an individual patient as food-responsive, antibiotic-responsive or idiopathic inflammatory bowel disease depends upon rigorous completion of therapeutic trials to rule out the food- and antibiotic-responsive diseases. In many cases a definitive diagnosis cannot be made due to imprecise or non-specific findings from diagnostic tests and the difficulty of accurately assessing the GI tract in an non-invasive manner. Thus many authors prefer the less restrictive term “chronic enteropathy” to refer to patients with these signs. This term throughout these notes in recognition that in many patients a true diagnosis of idiopathic inflammatory disease cannot be made with a high degree of certainty.

Historical and clinical findings
The small intestine is the main site of digestion and absorption of dietary nutrients. Disease in the small intestine may result in decreased ability to digest dietary nutrients (maldigestion syndromes) or decreased ability to absorb the products of digestion (malassimilation). In most small intestinal diseases both of these processes, i.e. maldigestion and malassimilation are present to varying degrees. Normal digestive function in the small intestine relies on the maintenance of a normal luminal pH, presence and function of normal brush border enzymes on the microvilli and the maintenance of normal tight-junction function, amongst other critical factors. Any disease process affecting the small intestine may potentially interfere with one or more of these processes, leading to clinical signs of small intestinal disease.

Typically small intestinal disease leads to clinical signs of diarrhea and weight loss. Reduced absorptive surface area in the small intestine, decreased brush border enzyme activities and compromise of the epithelial tight junctions may all decrease the ability of the small intestine to absorb the products of digestion. The products of digestion are typically small molecules, and with the loss of the ability to absorb these molecules effectively there is an increased osmotic pull into the small intestinal lumen, leading to increased fluidity of the small intestinal content. This is manifested as diarrhea in most cases. As there is a failure of small intestinal absorption and increased net water losses from the small intestine, small intestinal diarrhea typically manifests with large volume bowel movements, the total volume of feces passed in the day is increased. In animals where the disease is isolated to the small intestine, the large intestine may be able to increase its water absorptive function and produce feces with only mildly increased water content. Clinical signs such as tenesmus, urge incontinence and excessively frequent defecation are more suggestive of large intestinal disease. In many patients, however, both the small and large intestine are involved in the disease process and a mixture of small and large intestinal diarrheal signs may be seen.

If the large intestinal water absorptive capacity is able to cope with the increased fluid input from the small intestine, diarrhea may not manifest and the major clinical sign may be weight loss. Vomiting and inappetance are also common complaints in animals presenting with small intestinal disease. In many animals there is an increased appetite and polyphagia, a consequence of the decreased efficiency of utilization of nutritional input. Clinical signs of weight loss or failure to thrive, polyphagia and large volume diarrhea are also typical of exocrine pancreatic insufficiency, and it is important to conclusively rule this condition in or out during the diagnostic assessment of an animal with a chronic enteropathy.

Approach to the assessment of a chronic enteropathy patient
Routine biochemistry and complete blood count panels are indicated in the initial approach to a chronic enteropathy patient. As there are no specific tests that directly assess the small intestine in either of these panels, it is not unusual for a patient with a chronic enteropathy to have a complete lack of abnormal findings. This step is important, however, to assess the physiology of the patient,
screen for signs of other disease processes that may result in weight loss and diarrhea, and as a preliminary step before anesthesia in many patients for the collection of biopsy samples. Identification of significant abnormalities in other organ systems (i.e., azotemia/uremia, elevated liver enzyme activities, abnormal Na⁺:K⁺, elevated cholesterol or triglycerides) may prompt the clinician to work up the patient for other diseases.

In addition to routine clinical chemistry and complete blood count, a group of more specialized tests should be considered during the work up of a gastrointestinal disease case. For companion animals with small intestinal diarrhea, the author recommends measurement of serum TLI, cobalamin and folate concentrations. These tests are described in more detail below. Unless pancreatic inflammatory disease is suspected, the addition of a pancreatic lipase immunoreactivity assay (Spec cPL/Snap cPL or Spec fPL/Snap fPL) rarely advances the diagnosis and is not recommended for most chronic enteropathy patients as a first line diagnostic test.

Direct, specific assessment of the small intestine is complicated by the difficulty of accessing the tract for collection of samples. Ideally, a marker for small intestinal disease should be sensitive (i.e., detect most diseased patients) and specific (able to rule out disease in normal patients). At this time there are no non-invasive diagnostic tests for small intestinal disease that are both highly sensitive and highly specific. The most commonly used, minimally invasive tests currently available involve the measurement of serum concentrations of specific water-soluble vitamins to establish a lack of mucosal absorption. Specifically, the serum concentrations of cobalamin and folate can be measured, and abnormalities in these vitamins may indicate the presence of mucosal disease. The practical assessment of “The GI Panel” in dogs and cats with chronic enteropathies is discussed in more detail in separate proceedings for this meeting.

“Inflammatory bowel disease”

Inflammatory bowel disease is one of the most commonly diagnosed, and likely one of the most commonly missed, small intestinal diseases in the dog. Ironically, this condition is also likely over-diagnosed, or diagnosed inappropriately in animals that have not had a sufficiently thorough work up. In essence, inflammatory bowel disease is an idiopathic diagnosis based on histological findings, which means that we really should not be making the diagnosis of idiopathic IBD without intestinal biopsies and a complete, quite stringent work up to exclude other diseases (such as food responsive and antibiotic responsive enteropathies) that have similar histopathologic appearances. Intestinal inflammation falls in to a variety of histological categories. These types are summarized in Table 1 below.

Table one – Histopathological categories of inflammatory bowel disease in dogs

<table>
<thead>
<tr>
<th>Histological Category</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic/Plasmacytic</td>
<td>~60%</td>
<td>The most common form of inflammatory bowel disease diagnosed in dogs nationwide. Often idiopathic, but the same histological changes are seen with dietary intolerance/allergy.</td>
</tr>
<tr>
<td>Eosinophilic</td>
<td>~15%</td>
<td>As with LP disease, may be idiopathic or associated with dietary intolerance/allergy. Often associated with GI parasitism. Relatively common in the Rottweiler. Anecdotally, more common in the Pacific Northwest than elsewhere.</td>
</tr>
<tr>
<td>Neutrophilic</td>
<td>&lt;5%</td>
<td>Common in humans, often antibiotic- or probiotic-responsive.</td>
</tr>
<tr>
<td>Granulomatous</td>
<td>Rare</td>
<td>In veterinary medicine, granulomatous colitis of boxers is the most common manifestation of granulomatous intestinal inflammatory disease encountered.</td>
</tr>
</tbody>
</table>

Inflammatory bowel disease is, by definition, a histological diagnosis. The majority of cases diagnosed with inflammatory enteropathies via intestinal biopsy are lympho-plasmacytic or eosinophilic, with some regional variations in prevalence. Unfortunately there is a lack on consensus on histological descriptions and definitions of the severity of disease amongst veterinary histopathologists. Histopathology scores, as currently assigned, correlate poorly with the clinical severity of inflammatory bowel disease in canine patients and suffer from poor inter- and intra-observer consistency. Histopathology remains useful for definitive diagnosis of an inflammatory disease process and identification of differential diagnoses such as lymphoma or lymph drainage abnormalities such as lymphangectasia.

**Therapeutic planning in patients with chronic enteropathies**

On diagnosis of an inflammatory enteropathy, therapeutic planning can take place. A remarkably large proportion of dogs with a diagnosis of lymphocytic/plasmacytic enteritis will show at least partial food responsiveness. A dietary exclusion trial is indicated in most cases, the author’s preference is for use of a novel protein source diet selected on the basis of a thorough dietary history. Partially hydrolyzed and modified antigen diets may also be beneficial. The patient is started on the elimination diet exclusively for a minimum period of 14 days. In most patients with diet-responsive disease a notable improvement in clinical signs will have occurred at 14 days, and those that have failed to show a good response are unlikely to show much benefit from a longer period on the diet. If the dog responds to the diet change, the diagnosis becomes one of food-responsive diarrhea or dietary intolerance. “Dietary allergy” implies
tylosin, is able to control clinical signs adequately. Some patients require constant, lifelong tylosin therapy. Clinical signs to recur within weeks of antibiotic withdrawal. In some patients a pulse therapy approach, with 2 weeks on and 1 week off tylosin (Tylan Powder™, Elanco), at a dose of 20-25 mg/kg per os SID, typically in the morning, for at least 14 days. If clinical signs are well controlled at this time, a gradual taper to the minimum effective dose is begun, with dose reductions of approximately 25% per week. In some animals, more aggressive immune suppressive therapy may be required. Azathioprine (2mg/kg SID to every other day) has traditionally been the next step for immune suppression, this drug requires several weeks to manifest full effect. Recent publications have examined the utility of cyclosporine-A in therapy of dogs with refractory IBD and saw benefit in many patients, however expense may limit the use of this drug in some patients.7 Drugs such as mycophenolate mofetil and leflunomide have been investigated for use in these patients, but to date limited information is available regarding their efficacy.

Most patients respond well to dietary change and judicious use of anti-inflammatory or immune-suppressive medical therapy and have a fair to good prognosis. Some animals, unfortunately, show more refractory disease and the prognosis is more guarded. In a review of risk factors for adverse outcomes with inflammatory bowel disease in dogs, 18% of patients were eventually euthanized due to intractable disease.8 High clinical severity scores, severe changes visible on endoscopy, low serum cobalamin and hypoproteinemia were all associated with a higher likelihood of an adverse outcome.8 Where low serum cobalamin or folate concentrations are detected, supplementation of these vitamins is recommended.

“Ecological” diseases – “SIBO”, ARD and tylosin-responsive diarrhea

The small intestine is home to a large, diverse population of bacteria and other microflora. The microflora is essential to the normal anatomy and physiological function of the gastrointestinal tract, and abnormalities in this microflora are commonly associated with clinical signs of disease. The total number of organisms present in the canine GI tract has been a point of controversy. The term “Small Intestinal Bacterial Overgrowth” (SIBO) was originally defined in the context of culture studies that defined the upper limit of normal for the bacterial population of the duodenum as $10^7$ colony-forming units/ml.2 We now know from more recent culture-based and genetic diversity studies of the canine intestinal microflora that these original culture studies likely underestimated the numbers and diversity of bacteria present.7 The term “antibiotic-responsive diarrhea” is gaining currency in the recent literature, recognizing the antibiotic responsive nature of this condition without applying arbitrary criteria regarding expected bacterial numbers.

Disturbances in the gastrointestinal flora are likely common in dogs with other chronic enteropathies, such as idiopathic IBD or dietary intolerances. The maintenance of the normal flora relies on normal mucosal function, secretory function of the stomach and pancreas and gastrointestinal motility. Any of these functions may be abnormal in dogs with small intestinal disease, leading to an abnormality in the gastrointestinal flora.

In many dogs with chronic enteropathies, therapy directed against the bacterial flora may be advantageous. As the disturbed flora is typically secondary to some other disease process, and these primary disease processes are usually managed rather than cured, long durations of therapy are necessary. Given the need for repeated or chronic therapy, alternative approaches via dietary modification or supplementation are desirable. Potential modalities include supplementation with prebiotic compounds, such as fructo-oligosaccharides or inulin, that are preferentially fermented by “beneficial” organisms (typically Lactobacillus or Bifidobacterium spp). Empirically, diets containing these compounds (for instance, many of the “intestinal health” diets) are often helpful in managing dogs with chronic enteropathies. Probiotic organisms may also act via a displacement mechanism, and in some cases they are of benefit. There is a plethora of probiotic products on the market with very little data from well-controlled studies.

A more traditional approach would be to use antibiotic medications. The author’s preference is to use tylosin (Tylan Powder™, Elanco), at a dose of 20-25 mg/kg per os BID. Treatment is given for a minimum of 6 weeks, however it is not unusual for clinical signs to recur within weeks of antibiotic withdrawal. In some patients a pulse therapy approach, with 2 weeks on and 1 week off tylosin, is able to control clinical signs adequately. Some patients require constant, lifelong tylosin therapy.

References
Diagnosing and Managing Pancreatitis in the Era of PLI
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The conclusive diagnosis of inflammatory disease of the pancreas in dogs and cats is difficult. While the presence of compatible clinical signs such as vomiting, abdominal pain, dehydration, and pyrexia increase our index of suspicion for the disease, no specific findings on clinical examination are pathognomonic for pancreatitis.

As there are no specific findings on clinical examination or in an animal’s history that point conclusively to pancreatitis, confirmation of this clinical suspicion is based on clinical pathology results, imaging studies and the use of more specialized tests. The purpose of this presentation is to overview the various methods now available to the clinician that are used for the diagnosis of pancreatitis and their clinical utility in both diagnosis and management of dogs and cats with pancreatic inflammatory disease. With the availability of semi-quantitative ‘cage-side’ diagnostic tests measuring pancreatic lipase immunoreactivity, increasing numbers of animals are diagnosed with pancreatic inflammatory disease in practice. With this increased ability to specifically diagnose exocrine pancreatic disease, we are realizing that pancreatic disease may be more common, and more variable, than previously appreciated.

Markers of pancreatic disease
The most commonly used markers of pancreatic disease, and more specifically pancreatitis, are digestive enzymes. Serum amylase and lipase activities are the “traditional” markers used to support a clinical diagnosis of pancreatitis, in the presence of compatible history and findings on examination.

Low or normal serum lipase activity has been said to “almost always rule out the possibility of pancreatitis” in dogs, but increased serum lipase activity is not pathognomonic for pancreatic disease.1 While serum lipase activity is often empirically felt to be of higher sensitivity and specificity for the diagnosis of pancreatitis in dogs, controlled studies to demonstrate this are lacking. In cats, the performance of amylase and lipase as diagnostic markers of acute pancreatitis is even worse than in dogs. Experimentally, lipase and amylase activities are increased in induced pancreatitis in cats, but in spontaneous clinical cases these enzymes have no value in making the diagnosis. This likely relates to the typical timing of presentation of cats with pancreatitis, and the underlying pathological process in most cats, as discussed later.

While amylase and lipase activities may be the easiest biochemical markers of pancreatic inflammation to measure in dogs, the pancreas is a source of many other potential marker compounds. Of the digestive enzymes other than amylase and lipase, the enzymes most studied with respect to pancreatic disease are trypsin-like-immunoreactivity (cTLI and fTLI) and specific pancreatic lipase (Spec-cPL™ and Spec-fPL™).

Experimentally, serum TLI concentrations increase rapidly following induction of pancreatitis or ligation of the pancreatic duct in both dogs and cats. Serum TLI concentrations then drop rapidly, and are often back to normal or slightly sub-normal concentrations within 48 to 72 hours after disease induction. This is probably due to a protective down-regulation of trypsin synthesis by the pancreatic acinar cells, without further production of trypsinogen the serum concentrations decline rapidly.

Lipase produced in the pancreas is structurally distinct from the other lipases in circulation, although it shares the same substrate specificity. This means that, while activity assays are relatively non-specific for pancreatic disease, immunoassays for pancreatic lipase have a much higher specificity.

Canine pancreatic lipase immunoreactivity (PLI) has been measured via several differing immunoassay methods in recent years. The original studies using immunoassays to measure this protein were carried out at the GI Laboratory at Texas A&M University, using an ELISA method. Subsequently, the assay was commercialized as Spec cPL™ by IDEXX Laboratories, using differing antibodies and a recombinant protein for standards.2,3 Finally, IDEXX has produced “cage-side” diagnostic tests, SNAP cPL and Snap fPL, that measures the same protein in a semi-quantitative manner, defining a patient as normal or abnormal by reference to the intensity of the color spot developed. These assays are absolutely species specific, feline pancreatic lipase immunoreactivity cannot be determined using Spec cPL or the SNAP cPL tests, and vice versa.

As pancreatic lipase is found only within pancreatic acinar cells, an increase in the serum concentration of PLI is consistent with increased release of this enzyme from the acinar cells. The most common mechanism whereby pancreatic lipase is likely to be released is through increased “leakiness” of the acinar cells, this may occur as a result of mishandling of enzyme granules by the acinar cells, or due to compromised acinar cellular membrane permeability secondary to inflammation.

While the pancreatic lipase protein (and trypsinogen/TLI) are pancreas-specific, and thus elevated concentrations of these compounds in a serum sample are strongly suggestive of pancreatic pathology, the actual serum concentration of these compounds is altered by several factors other than just the presence and degree of pancreatitis. In particular, differences in the routes and speed of clearance of these proteins from the circulation can have a great bearing on the concentration measured.
Changes in the serum concentrations of TLI and PLI with pancreatitis

Trypsinogen, the precursor to active trypsin and the major protein measured in the TLI assay, is a relatively small protein with an overall negative charge. These factors both favor clearance by renal mechanisms, and the clearance half-life of trypsinogen is relatively short. Active trypsin is also detected by the TLI assay, however this protein is very rapidly complexed to scavenger proteins in the circulation and cleared from the circulation within minutes, thus active trypsin is rarely a significant contributor to the serum TLI concentration. This rapid clearance of trypsinogen/TLI, in combination with the dramatic down-regulation of pancreatic enzyme synthesis discussed above, results in serum TLI concentrations within the reference range, or in some cases even below the reference range, in many animals with pancreatic inflammatory disease. These rapid changes in TLI concentration following onset of the disease contribute to the relatively low sensitivity of serum TLI concentrations for the diagnosis of acute pancreatitis in both dogs and cats.

In comparison to trypsinogen/TLI, the PLI protein in both dogs and cats is much larger (approximately twice as large) and has an overall positive charge. These features both prevent renal clearance of the PLI protein. The actual mode of clearance of PLI from the circulation is unknown at this time, but it is presumed to be via the hepatic reticuloendothelial system. The actual clearance half-life of pancreatic lipase in the dog has been reported to be about 90 minutes, however the duration of elevation of PLI in dogs with pancreatitis is often a week or longer. This slower return to baseline/cessation of pancreatic lipase release increases the sensitivity of the test for detection of pancreatitis, as the clinician is more likely to be sampling a patient when the concentration is increased. In the cat, with experimentally induced pancreatitis, the degree of elevation of PLI is greater than that of TLI, and the serum PLI concentration remains elevated for an average of 10 days.

One of the many factors influencing pancreatic enzyme synthesis and release is feedback regulation from the small intestine. When active proteolytic enzymes enter the distal small intestine, a negative feedback signal that cuts off pancreatic enzyme synthesis and release is generated by the small intestinal mucosa. In the cat (but, interestingly, not the dog), small intestinal disease is often associated with a mildly but persistently increased serum TLI concentration. This most probably results from the mucosal disease and the loss of this negative feedback signal. This effect often leads to confusion amongst clinicians, as the clinical signs of marked small intestinal disease in the cat (steatorrhea, marked small intestinal diarrhea, weight loss, ± polyphagia) are often remarkably similar to exocrine pancreatic insufficiency. In many cats with significant small intestinal disease the serum TLI concentration is elevated, while the PLI concentration is within normal.

Test selection and interpretation in animals with suspected pancreatic disease

When selecting TLI or PLI tests for use in clinical patients, appropriate test selection will depend upon the clinically suspected diagnosis and the duration of clinical signs. In most cases where the clinician suspects the presence of pancreatitis, either acute or chronic, the PLI test is the best choice. Care must be taken with interpretation when using the “Snap” tests. These test are interpreted on the basis of the degree of color development seen, not as positive or negative (i.e. color development is expected in most cases, a very dark spot indicates high serum PLI). A positive Snap test should be confirmed by running the quantitative version of the test at a reference laboratory.

One consequence of the increasing availability of the PLI tests has been the recognition that chronic pancreatic disease, particularly chronic pancreatitis, is both much more common and in many cases more subtle than we originally thought. Particularly in the cat, most cases of pancreatic disease appear to be chronic and often clinically silent. In a case with chronic pancreatitis, the expectation is that the serum concentrations of PLI will remain persistently elevated. As the average time for decline to below the cut off value for a diagnosis of pancreatitis is around ten days, documentation of persistent elevation of PLI in serum samples taken at least 14 days apart can support the clinician’s suspicion of chronic pancreatitis. If the PLI returns to within the normal range at 14 days, this supports a retrospective diagnosis of an isolated bout of acute pancreatitis. These distinctions can be important, as the therapeutic approach to chronic pancreatitis is in many respects different to our approach to a patient who has had a single bout of acute pancreatitis and subsequently recovered.

Do TLI or PLI concentrations have prognostic value?

The degree of elevation of TLI or PLI in an animal with pancreatic inflammatory disease, as discussed above, is influenced by many factors. The amount of tissue compromised, the time from the beginning of the disease process, factors such as fluid losses that influence clearance; all of these factors may influence the final concentration measured in a patient. To date there is a limited amount of well-controlled data assessing the prognostic importance of varying degrees of abnormality in serum PLI concentrations. In one recent study, cats hospitalized for pancreatitis with serum Spec-fPL concentrations >20µg/L on the day of hospitalization were more likely to die or be euthanized.4

Within an individual, resolution of elevated PLI concentrations, or a trend towards normality, appear logically to indicate progress towards a more “normal” state. Certainly the persistence of elevated PLI concentrations in a patient who continues to show clinical signs of pancreatic disease is consistent with ongoing inflammation in the pancreas, and an increasing concentration in this patient would be consistent with worsening or deterioration of the patient’s condition. The absolute degree of abnormality, however, does not seem to correlate with the symptoms seen or the duration of illness in many spontaneous pancreatitis cases.

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Some observations on therapy for acute pancreatitis

Acute pancreatitis is an unusual disease process as total loss of exocrine pancreatic function is not immediately life threatening. Most general practitioners will be familiar with dogs that have pancreatic acinar atrophy leading to exocrine pancreatic insufficiency. These dogs may have virtually no functional exocrine pancreatic tissue, yet they do not suffer immediate life-threatening biological derangement because of this lack of pancreatic tissue. By comparison, the complete loss of hepatic, renal, cardiovascular, or respiratory function is associated with immediate, life threatening metabolic disturbances. While loss of pancreatic exocrine function is not typically life threatening, inflammation of this gland will often induce systemic metabolic derangement and organ failures distant from the pancreas itself. These distant organ failures, rather than the failure of the pancreas itself, are commonly the causes of death in acute pancreatitis.

In animals with complicated pancreatitis of high severity, the replacement and maintenance of circulating fluid volumes, attention to plasma colloid oncotic pressure, and the promotion of oxygen delivery to the tissues are all critical to successful therapy. Dogs with severe acute pancreatitis have a form of circulatory shock with many similarities to septic shock, and the clinical approach to these two forms of shock is essentially identical. Animals with pre-existing severe inflammatory disease, hypoalbuminaemia and multiple organ failure as a result of acute pancreatitis are beyond the therapeutic and management capabilities of most veterinary hospitals, and typically require referral for intensive care if treatment is desired. The prognosis for dogs with acute pancreatitis once they have developed this extent of metabolic derangement is guarded to grave, with mortality rates greater than 75% in some studies.

‘Feeding through’ bouts of acute pancreatitis, multimodal antiemetics

The idea that the pancreas should be “rested” during the treatment and recovery period from acute pancreatitis has long been held in the veterinary world. The theoretical basis for this recommendation was to decrease pancreatic enzyme synthesis and secretion, under the assumption that release of enzymes into the pancreatic interstitium and circulation was responsible for many of the clinical signs and complications of pancreatitis. While this approach still has some currency in the veterinary community, it flies in the face of our current understanding of the best management of critically ill patients. Animals with acute abdomen presentations are typically in a catabolic state, have additional metabolic demands due to the inflammatory process, and the development of functional ileus can result in substantial additional morbidity.

One of the main reasons for the nil per os approach to treatment of acute pancreatitis was in an attempt to reduce frequency and severity of vomiting in these patients. In recent years we have had a dramatic increase in the number of effective antiemetic medications available to us, most notably the neurokinin-1 receptor antagonist maropitant citrate (Cernia®, 1 mg/kg q24 hr), and the 5-HT₃ receptor antagonists such as dolasteron (Anzemet®) or ondansetron (Zofran®), 0.3-0.5 mg/kg IV q24 hr. These medications are highly effective at controlling vomiting and nausea in our patients, and have the advantage that they can be administered by injection or orally, and need only once daily dosing. They act via different mechanisms, and there does not appear to be any meaningful interaction between these drug classes. Maropitant also has some benefit as a visceral analgesic, which is of significant benefit in acute pancreatitis cases.

With the use of a multimodal antiemetic regime, vomiting and nausea are controlled rapidly in most cases of acute pancreatitis. This allows consideration of an early return to feeding. While controlled studies of early enteral nutrition in severe pancreatitis in veterinary species are relatively few, the data available so far suggest that early enteral nutrition in dogs with acute pancreatitis is associated with less incidents of vomiting, lower incidences of complications than parenteral nutrition, and no difference in outcomes. The author’s approach to dogs with pancreatitis is to reintroduce feeding as soon as possible, often within hours of ICU admission. Early enteral nutrition of cats with pancreatitis is arguably even more important, due to the risk of hepatic lipidosis in this species.

Dietary manipulations in the management of chronic pancreatitis

In the dog, use of a fat-restricted diet in the post-recovery period from a bout of acute pancreatitis is commonly accepted, and most authors will recommend fat restriction in dogs with chronic pancreatitis. The use of fat restricted diets is not recommended in cats, however, as this species has an obligate requirement for relatively high intake of essential fatty acids. Additionally, most fat-restricted commercial diets substitute carbohydrates for fat to maintain an iso-caloric formulation, this represents a problem for cats as their obligate carnivore nature means that they are less able to adapt to carbohydrate rich diets, and have a tendency towards protein catabolism if dietary fat is restricted. In many cats pancreatitis accompanies enteritis and cholangitis or cholangiohepatitis, so-called “triaditis” or “feline inflammatory syndrome.” While the underlying pathology of triaditis is not fully understood, overall it appears that the presence of inflammatory disease in the small intestine may be a common precipitating factor. Given the relatively low sensitivity of non-invasive tests for small intestinal disease in cats, and the low frequency with which biopsies are obtained, it is reasonable to assume that many cats with chronic pancreatitis will actually also have intestinal inflammatory disease that goes undiagnosed. Many cats with these diseases respond to dietary protein-source modification, using either a novel protein source or a modified antigen type diet. The author’s typical approach to a cat with a diagnosis of chronic pancreatitis is identical to the approach for inflammatory disease of the intestine, with carefully managed dietary elimination trials and screening for comorbid deficiencies in...
water soluble vitamins such as cobalamin and folate. The protein type of the diet, rather than dietary fat content, has a much greater
influence on diet selection in feline chronic pancreatitis cases.

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Protein-Losing Enteropathies: The Black Diamond Cases
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Protein loss through the GI tract (protein-losing enteropathy, PLE) presents in a spectrum of severities, ranging from cases with insidious weight loss and mild diarrhea through to highly challenging cases complicated by the development of ascites, peripheral edema and coagulopathies. Recognition of PLE can be quite challenging, particularly in cases where overt hypoproteinemia is not yet present. The presence of PLE in dogs with chronic inflammatory enteropathies has been shown to be a negative prognostic factor in these cases, and warrants more aggressive therapy. While cases with PLE secondary to inflammatory enteropathies tend to be the most challenging to manage, a variety of other mechanisms can result in significant intestinal protein losses. Selection of the appropriate therapy for a PLE case depends upon accurate identification of the pathology present, as differing modes of therapy are indicated for some of the non-inflammatory, structural diseases.

Clinical signs in PLE
Depending on the degree of severity and duration of the disease, clinical signs of PLE can range from the development of ascites, peripheral edema or acute severe respiratory distress due to pulmonary thromboembolism, through to vague signs such as weight loss and poor appetite. If an inflammatory enteropathy is present diarrhea may be noted, but many cases with PLE present with normal stools. Consequently, PLE should be considered as a differential diagnosis for any dog presenting with hypoalbuminemia, even if gastrointestinal signs as lacking.

Mechanisms of protein loss in PLE cases
With some specific breed-related exceptions, the major mechanisms of protein loss in most cases of PLE in dogs (and cats, but this condition is recognized infrequently in that species) can be divided into two major groups: primary lymphatic drainage abnormalities such as lymphangectasia, lipogranulomas or mesenteric lymphatic obstructions, and secondary to mucosal inflammatory disease. While these major categories account for the majority of PLE cases encountered in clinical practice, gastrointestinal ulcers, significant gastrointestinal parasitism and gastrointestinal neoplasms (both lymphosarcoma and carcinoma) can also result in marked GI protein loss. Intestinal motility accidents, such as intussusception, partially obstructing foreign bodies, and diverticulae can also result in quite marked protein loss, however their clinical signs and initial examination findings are usually sufficiently distinct from the more typical PLE cases to allow rapid identification.

Breed predispositions
While any dog can present with PLE, particularly as a complication of severe inflammatory enteropathies, some breeds are recognized to have particularly marked breed predispositions. Often the manifestations of PLE in these breeds are quite severe.

Lymphatic drainage abnormalities such as lymphangectasia have been reported in the Rottweiler, Yorkshire terrier, Shar-pei and the Maltese terrier. In the Rottweiler lymphangectasia commonly accompanies eosinophilic inflammatory disease of the intestine, but a direct relationship between these two conditions has not been established and both diseases are commonly diagnosed in this breed in isolation.

As well as primary lymphangectasia, the Yorkshire Terrier is commonly diagnosed with significant inflammatory lesions of the intestinal crypts. These crypt lesions are commonly associated with severe gastrointestinal protein loss. The mechanism of crypt abscess formation in these dogs has not been well defined, but there does not appear to be any association with bacterial invasion.

The Norwegian Lundehund, a relatively rare dog breed in the USA, has been reported to have 50% or more of individuals affected with intestinal lymphangectasia, with associated PLE.

The Soft-coated Wheaten terrier presents with a breed specific PLE and protein-losing nephropathy that can be quite challenging to manage. This disease has been linked to food hypersensitivities in this breed, and is apparently worsened by high level exposure to gluten and other dietary allergens, but does not appear to be a true gluten hypersensitivity. Soft-coated Wheaten terriers may present with protein-losing enteropathy alone, protein-losing nephropathy alone, or may have both conditions simultaneously.

Diagnostic approaches to a suspect PLE case
In most dogs with PLE, the suspicion that this disease is present first arises when a low serum albumin concentration is detected. This may be noted as part of the work up for chronic gastrointestinal disease, but as noted above many dogs with significant PLE may first present with ascites or edema and with little in the way of gastrointestinal signs, thus the presence of a low albumin should always prompt the consideration that PLE may be present.
When presented with a case with low albumin (typically <2.0g/dL), we have a relatively limited number of ways in which this could have come about. Major routes for protein loss include via the kidneys (protein-losing nephropathies), through significant skin lesions or open wounds, through the gastrointestinal tract, and as a result of hepatic synthetic failure/hepatic insufficiency.

A rational approach to a suspect PLE case with hypoalbuminemia, then, is to screen for and rule out as many of these conditions as possible. Protein losses due to cutaneous lesions or open wounds can be readily ruled out via physical examination, as the extent and severity of these lesions necessary to cause this volume of protein loss is quite dramatic. Protein losses due to protein-losing nephropathies can be ruled out by the detection of a normal protein-creatinine ratio. It is important to remember that lower urinary tract infections, or any other disorder leading to an active urinary sediment, can also cause an elevation in urinary protein:creatinine, screen for and if necessary treat urinary tract infections first before assessing this test for evidence of a protein-losing nephropathy.

Detection of hepatic insufficiency and synthetic failure can be more complicated, as liver enzyme activity elevations and hyperbilirubinemia are not present in many animals with end stage liver disease. Other common clinical chemistry findings with hepatic failure, such as low cholesterol and blood urea nitrogen, are also common findings with PLE.2

The best method for non-invasively assessing hepatic function is to perform a pre- and post-prandial bile acids tests. Normal pre- and post-prandial bile acid concentrations rule out hepatic insufficiency as a cause of hypoalbuminemia with a high degree of certainty. Some clinicians will measure only the resting, pre-prandial bile acid concentration, but this reduces both the sensitivity and specificity of this test. Some animals with synthetic failure are still able to clear bile acids to a normal pre-prandial value while fasting, and evidence of loss of hepatic function is only seen after the bile acid challenge. Alternatively, animals with gastrointestinal disease can show mildly to moderately elevated pre-prandial bile acids due to the reduced efficiency of clearance of bile acids from the portal circulation that have undergone bacterial deconjugation.12

In a suspected PLE case with hypoalbuminemia, where skin disease and protein-losing nephropathy have been ruled out and pre-/post-prandial bile acid tests are normal, the diagnosis of PLE can be made with a high degree of certainty through simple exclusion. The diagnosis of PLE in dogs that have not reached a state of overt hypoalbuminemia is more challenging. This can be quite important in dogs from the breeds previously listed with predispositions for PLE, as some of the adverse outcomes of PLE such as hypercoagulability and thromboembolic potential can manifest before the albumin is markedly low, and thus in these breeds early diagnosis and management is important.

Unfortunately, albumin itself cannot be detected in stool samples as it undergoes bacterial degradation. A surrogate for albumin losses, α-1 Proteinase Inhibitor (α-1PI), is able to survive transit through the GI tract and can be detected in fecal samples.13,14 This protein has a very similar molecular mass and charge to albumin, thus elevated α-1PI in stool samples is suggestive of increased albumin loss into the GI tract. This test is somewhat complicated, requiring multiple stool samples to be collected and stored frozen, and is only available from one laboratory (The GI Lab at Texas A&M). The author typically only uses this test in the previously mentioned, predisposed breeds, particularly if they present with weight loss and mild GI signs without hypoalbuminemia. The majority of PLE cases seen in our clinic are diagnosed by exclusion, as detailed above, and a combination of diagnostic imaging and endoscopic biopsy findings.

**Diagnostic imaging findings with lymphangiectasia of the intestine.**

Abdominal ultrasound examination is a valuable modality for the assessment of dogs with potential PLE. As well as giving some idea of the hepatic size and potentially revealing the presence of low volume ascites, occasional dogs will show characteristic hyperechoic striations in the intestinal mucosa, often referred to as a “tiger stripe pattern”. This finding is strongly suggestive of intestinal lymphatic dilatation, either due to lymphangectasia or distal lymphatic obstruction.15

**Therapy for PLE: “Uncomplicated” cases**

As the mechanism of protein loss in many “uncomplicated” cases of PLE revolves around loss of intestinal lymph, strategies to reduce lymph loss are useful in the management of PLE cases. The major driver of intestinal lymph production is the intake of dietary fat. (Recall that the intestinal lymphatics are called “lacteals” due to the presence of high concentrations of fat in chylomicrons.) Thus the use of extremely low fat diets is recommended in most dogs with PLE, and is the mainstay of treatment for most dogs with primary lymphangectasia.2 The use of ultra-low fat diets has been shown to be effective in dogs with lymphangectasia that had failed to respond to glucocorticoid therapy or showed a relapse as glucocorticoid doses were reduced.16

The author’s first choice of diet for management of relatively uncomplicated PLE cases is typically one of the commercially manufactured, ultra-low fat diets such as Royal-Canin’s LF or Hill’s I/D-LF (NB: the I/D low fat formulations. I/D GI health is too high in fat). Alternatively, home cooked diets have been described for dogs that are also extremely low in fat, and with careful attention to vitamin and mineral supplementation can be used long-term.7

Many dogs with PLE due to lymphatic drainage abnormalities within the mucosal will also develop lipogranulomas or other inflammatory lesions in the mesenteric lymphatics. Patients showing only partial response to ultra-low fat diets after 2-3 weeks of
therapy will often benefit from the addition of prednisone at 1-2 mg/kg/day. This will also assist in management of secondary inflammatory disease in these patients.

**Therapy for PLE: “Difficult” cases**

“Difficult” PLE cases fall into two main groups: severe disease with marked hypoalbuminemia, ascites and/or edema, and cases where the PLE is a complicating factor for other diseases, such as severe inflammatory enteropathies.

Cases with markedly severe hypoalbuminemia represent a significant therapeutic challenge. Ideally, colloid oncotic support should be given before any invasive diagnostic intervention, to reduce the risk of wound dehiscence and anesthetic complications due to embolic events. Fresh frozen plasma transfusions can be very useful, as they replace clotting factors as well as albumin, but the volumes of plasma necessary to replenish albumin in many dogs can become cost prohibitive. If available, 20% human albumin solutions can provide rapid oncotic support at relatively low cost and risk in dogs, but this product is often difficult to obtain.

Synthetic colloids may also be used, often in combination with fresh frozen plasma.

Ascites fluid is usually not drained, except if the volume of fluid is sufficient to cause respiratory compromise. Only sufficient fluid should be drained to relieve respiratory compromise. Removal of large volumes induces a large body-wide protein deficit in the patient that will promote a catabolic state and cachexia, and also activates the renin-angiotensin-aldosterone system to normalize blood pressure following substantial volume loss, this can increase blood pressure and increases the rate of further ascites accumulation. Animals who are recurrently effusive may benefit from diuretic therapy.

Animals with this degree of PLE are usually assumed to be hypercoagulable. This hypercoagulable state persists in many dogs after therapy that increases albumin, and thus these dogs should be considered at long-term risk for thromboembolic complications.\(^1\)^ The reason for this difference is not clear, but at least in this one study the differences in outcome were quite dramatic (azathioprine-prednisolone group had a median survival of 30 days, while chlorambucil-pred group did not reach a median survival as 10/14 were still alive at the end of the study).

The presence of significant PLE in dogs with inflammatory enteropathies is a poor prognostic sign, and the early use of more aggressive immune suppression therapy is indicated. Interestingly, in a recent study of dogs with inflammatory enteropathies and PLE, patients treated with chlorambucil-prednisolone showed a better outcome than those treated with azathioprine-prednisolone.\(^1\)^ The reason for this difference is not clear, but at least in this one study the differences in outcome were quite dramatic (azathioprine-pred group had a median survival of 30 days, while chlorambucil-pred group did not reach a median survival as 10/14 were still alive at the end of the study).

**References**

Blastocystis: A New Pathogen, or Just a “Thing”
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The genus *Blastocystis* is a complex grouping of enteric protozoa commonly detected in a broad variety of species, including most mammals, many avian species, reptiles and amphibians. Phylogenetically, *Blastocystis* is a member of the Stramenopiles (phylum Heterokonta), an extremely diverse and complex phylum of predominantly algal genera. This organism is one of the most common gastrointestinal parasites of human beings, with reported prevalence rates ranging from 5% in some western countries to >76% in some parts of the developing world.1,2 Originally, species were named on the basis of the host organism (i.e. *Blastocystis hominis, B. ratti*), however it is now well recognized that there is no single species that infects only humans (or any other host organism), and the entire group of organisms is now identified as genus *Blastocystis* with numbered subtypes, these subtypes being determined by small subunit ribosomal DNA (SSU-rDNA) gene sequences.3 At the time of writing there are at least 14 known subtypes of *Blastocystis* identifiable on the basis of SSU-rDNA sequences.

In addition to the remarkable genetic diversity within this genus, there is a high degree of morphologic variation, with vacuolar, “granular”, amoeboid, and cystic forms identified. Any subtype from any host organism may be identified in any of the morphologic forms, although the amoeboid form is thought to be closely linked to disease in humans.4 Transmission is thought to be predominantly fecal-oral; there is also some evidence for water-borne transmission. The high prevalence rates reported from human beings in the developing world likely reflect differences in public sanitary infrastructure, closer exposure to open sewers, and closer exposure to animal waste than in the developed world.

**Blastocystis as a human enteric pathogen**

There exists considerable controversy in the human medical literature regarding the pathogenic potential of *Blastocystis* organisms.5 Many workers feel that there is a link between this organism and irritable bowel syndrome (IBS) in humans,6-8 and some reports have shown a relatively high risk of carriage in human patients with ulcerative colitis.7 Interestingly, there appears to be quite marked geographic and subtype differences in the potential pathogenicity of this organism. Workers in the developing world have demonstrated increased risk of *Blastocystis* carriage in human patients with IBS and inflammatory bowel disease,7,8 while workers in the developed world (particularly Europe) have reported a low prevalence of these organisms in human patients with chronic gastrointestinal disease.9,10

When considered a specific disease entity, Blastocystosis in humans is associated with anorexia or hyporexia, diarrhea, bloating, abdominal pain, skin rashes, steatorrhea, and weight loss.1 The natural history of this disease can be prolonged (months to years), there are no known reliably effective therapies, and spontaneous resolution, rapid re-infection following apparently successful therapy, and resolution of clinical signs without effective clearance of the organism have all been reported.11

**Possible mechanisms of pathogenicity**

While the actual pathogenic potential of the various *Blastocystis* subtypes for their hosts is an area of ongoing controversy, there are recognized characteristics of these organisms that are consistent with a potential role as a gastrointestinal pathogen. At least some isolates of Subtype 4 (previously *B. ratti*) are able to induce apoptosis, actin rearrangement and loss of barrier function in cultured rat intestinal epithelial cells.12 This same strain has been shown not to activate toll-like receptor signaling in a human monocyte cell line, suggesting that the parasite may be able to avoid recognition by the innate immune system.13 In unpublished data from my laboratory, we have observed this same lack of induction of TLR-2 in CACO-1 cells, along with apparent inhibition of the serotonin-reuptake transporter protein.

Several subtypes have been shown to produce a variety of cysteine proteinases, these proteases have been shown to be capable of cleaving secretory IgA, and similar proteases are recognized as virulence factors in other enteric protozoal pathogens, including a variety of *Trichomonas* spp., *Giardia* spp. and *Entamoeba histolytica*.14,15

In a recently reported study of fecal microbiome structure and diversity in humans with IBS symptoms, infection with *Blastocystis* was associated with decreased numbers of *Faecalibacterium prausnitzii* and *Bifidobacteria*,16 a pattern that is commonly recognized in a variety of chronic enteropathic and dysbiotic diseases. Interestingly, this pattern was also present in asymptomatic male control patients that were positive for *Blastocystis*, but at this time this finding is one of correlation rather than causation.

**Diagnosis (in human beings)**

In human beings the most commonly used method for diagnosis of *Blastocystis* carriage is via direct light microscopy of either unstained, wet mount or stained fecal preparations. Enrichment culture and fecal PCR are also commonly used, with fecal PCR
Fecal PCR has greater sensitivity than direct light microscopy.17

Clinical presentation (in human beings)
Interestingly, there appears to be quite marked geographic and subtype differences in the potential pathogenicity of this organism in human beings. Workers in the developing world have demonstrated increased risk of Blastocystis carriage in human patients with IBS and inflammatory bowel disease, while workers in the developed world (particularly Europe) have reported a low prevalence of these organisms in human patients with chronic gastrointestinal disease. When considered a specific disease entity, Blastocytosis in humans is associated with anorexia or hyporexia, diarrhea, bloating, abdominal pain, skin rashes, steatorrhea, and weight loss. The natural history of this disease can be prolonged (months to years), there are no known reliably effective therapies, and spontaneous resolution, rapid re-infection following apparently successful therapy, and resolution of clinical signs without effective clearance of the organism have all been reported.

Within the veterinary and parasitology literature there is a remarkable dearth of data regarding any link between Blastocystis carriage and clinical signs of disease in companion animals. A solitary case report describes a significant parasite burden in a mixed-breed dog with vomiting, diarrhea, and weight loss. This animal was definitively diagnosed with exocrine pancreatic insufficiency and marked hypocobalaminemia, which is sufficient to explain the observed clinical signs.18

Prevalence in companion animals, zoonotic potential?
The true prevalence of Blastocystis carriage in companion animals is unclear at this time, with most of the parasitology literature in this area focused on the domestic dog. Early data from subtropical and tropical environments suggested quite high carriage rates for Blastocystis in dogs, with rates as high as 70% reported for carriage in shelter-resident dogs in a subtropical environment,19 although this finding has been thrown into some doubt by recent PCR-based studies from the same environment.20 Carriage rates as high as 100% have been reported in domestic dogs from Thailand, however this was in a limited number of samples (n=3).21 By comparison, in a cross-sectional study of military working dogs and personnel at a military dog center in Thailand, the prevalence in 189 dogs was 3.7%, while the prevalence in military personnel (n=317) at the same center was 14.5%.22 This pattern of lower prevalence in dogs than humans is repeated in several other studies, leading some authors to conclude that dogs are unlikely to act as either natural hosts or primary zoonotic reservoirs for infection.20

In a study of asymptomatic individuals and pet animals living in the same household as humans symptomatic for Blastocytosis (n=11), 8/8 in-contact animals (5 dogs, 3 cats) were positive for Blastocystis via fecal PCR, with 7/8 of the in-contact animals carrying the same strain as the symptomatic in-contact human.23 Interestingly, none of the in-contact animals or in-contact humans (n=17) in this admittedly small study showed clinical signs consistent with Blastocytosis. These data suggest that transmission between humans and companion animals is possible, however this is most likely a transient phenomenon and it appears unlikely that domestic dogs and cats represent a significant risk for zoonotic transmission.

Data recently reported from our laboratory assessed the prevalence and subtypes of Blastocystis in shelter-resident and client owned dogs in the US Pacific Northwest (specifically, Portland, OR and the southern Willamette valley).24 In this study, we screened 104 shelter-resident dogs, 105 shelter-resident cats, 51 client-owned dogs and 52 client owned cats using a standard nested PCR methodology. In this study 10/103 dogs and 12/105 cats were positive for Blastocystis, however only 4/22 identified Blastocystis were of Subtype 1 (a potential human pathogen strain), with the remainder being Subtypes 10, 8 and 14, none of which are typically considered human enteric pathogens. All of the animals testing positive for Blastocystis in this study were shelter-resident, only one client-owned dog showed a faint positive result on PCR, this finding could not be replicated and thus the sample was considered negative. Shelter-resident animals (both cats and dogs) were significantly more likely to test positive for Blastocystis than client-owned animals, this is consistent with several prior observations that shelter-resident animals are more prone to enteric parasite infection.25,26

Is blastocystis a pathogen in companion animals?
Within the veterinary and parasitology literature there is a remarkable dearth of data regarding any link between Blastocystis carriage and clinical signs of disease in companion animals. A solitary case report describes a significant parasite burden in a mixed-breed dog with vomiting, diarrhea, and weight loss. This animal was definitively diagnosed with exocrine pancreatic insufficiency and marked hypocobalaminemia, which is sufficient to explain the observed clinical signs.18

In our recent study of Blastocystis prevalence in companion animals in the Pacific Northwest we assessed the relationship between the presence of a parasite burden and signs of gastrointestinal disease of any kind. While records of gastrointestinal disease signs, typically diarrhea, were common in the medical records of the shelter-resident cats (26/105, 24.7%) and less so in dogs (9/103, 8.7%), there was no significant relationship seen between carriage of Blastocystis and the presence of gastrointestinal signs in the shelter-resident animals. Four of 52 (7.7%) client owned cats showed owner-reported gastrointestinal signs in the week prior to collection,
while 2/51 (3.9%) of client-owned dogs showed gastrointestinal signs in the week prior to collection. None of the client-owned animals showing gastrointestinal signs tested positive for *Blastocystis*. Shelter-resident cats were significantly more likely to have gastrointestinal disease signs overall than client-owned cats (P=0.0099, Relative Risk 3.21, Fischer’s Exact Test), while there was no significant relationship between shelter-residence and presence of gastrointestinal signs in dogs (P=0.339, Fischer’s Exact Test). Similar data regarding the frequency of diarrhea in shelter-resident dogs and cats have been reported previously. From the data reported in this study, it appears unlikely that the presence of *Blastocystis* infection is a significant contributor to diarrhea in shelter-resident cats in the Pacific Northwest of the USA.

**Conclusions**

At this time there is a distinct lack of evidence for a relationship between *Blastocystis* carriage and the presence of gastrointestinal disease in companion animals, however the rate of infection and subtypes present in animals with chronic enteropathies is currently unknown. There is at least some concern that animals in contact with humans with Blastocystosis may act as secondary reservoirs for infection, but there is little evidence at this time that domestic animals represent a significant source of zoonotic spread of these organisms to uninfected human beings. Given the widely varying apparent pathogenicity of differing subtypes, and apparent geographic variation in common subtypes in other species, it would be interesting to determine if similar differences in prevalence and common subtypes are present in domestic animals in differing geographic areas.

**References**


Exocrine pancreatic insufficiency (EPI) is a syndrome characterized by maldigestion, malassimilation and marked, large volume small intestinal diarrhea. In the dog, this condition is usually the result of complete loss of pancreatic acinar tissue secondary to Pancreatic Acinar Atrophy (PAA). This condition is well known in the German Shepherd Dog, and is usually easy to recognize. In the cat, the underlying pathology leading to loss of exocrine pancreatic tissue mass is more likely to be chronic pancreatitis. This presentation will review the general features of EPI in both cats and dogs, including pathophysiology and diagnostic testing. Therapy of dogs with EPI is usually straightforward, and will be reviewed. In cats, therapy can be more challenging and other issues, including chronic cobalamin deficiency, must be addressed to ensure a good outcome. While most cases of EPI are the consequence of complete loss of exocrine pancreatic tissue, apparent selective pancreatic enzyme deficiencies have recently been recognized in several dogs, resulting in atypical presentations of exocrine insufficiency that can be diagnostically challenging.

Pathophysiology of diarrhea in exocrine pancreatic insufficiency
A lack of digestive enzyme synthesis and release into the small intestine results in a lack of digestion of dietary substrates. The osmotic draw produced by the unabsorbed, partially degraded nutrients within the small intestine will then produce an osmotic diarrhea. Fats are particularly strong inducers of diarrhea, as bacterial degradation of the fat produces large quantities of free fatty acids. These fatty acids can not be absorbed, and thus are potent osmotic agents, and in many cases the fatty acid products of bacterial fat degradation are toxic to the enterocytes, setting up secondary inflammation and motility disorders.

The pancreatic duct system, which is the source of pancreatic bicarbonate secretion, is spared in most dogs with EPI, and thus pancreatic bicarbonate secretion is normal. Trophic factors for the intestinal mucosa are lost, resulting in secondary abnormalities in structure and surface area of the villi and loss of brush-border enzymes. The exocrine pancreas has a sizable reserve capacity, and clinical signs are usually not seen until there has been a loss of >90% of the acinar tissue.

Pancreatic acinar atrophy vs. chronic pancreatitis
In the dog, the most common cause of primary pancreatic exocrine insufficiency is pancreatic acinar atrophy (PAA). This condition is associated with progressive loss of pancreatic acinar tissue, in at least some groups of dogs PAA appears to be associated with or preceded by a lymphocytic/plasmacytic pancreatic infiltrate. In both German Shepherd dogs and the Rough-coated Collie there is evidence for heritability of this disease, most likely as an autosomal recessive. In the cat, EPI is most commonly due to loss of exocrine tissue due to ongoing chronic pancreatitis, the end-point of chronic pancreatitis being fibrosis and scarring. Juvenile onset disease, similar to PAA in dogs, has not been described in the cat to date. Chronic pancreatitis as a cause of primary exocrine insufficiency has been described in dogs, and is the most common cause of late-onset exocrine insufficiency (i.e. in dogs >4 years of age).

Signalment and breed factors
Pancreatic acinar atrophy is usually diagnosed in young dogs, with a peak time of diagnosis at around 18 months of age. Development of clinical signs consistent with EPI in dogs older than three years should prompt the clinician to search for small intestinal disease. The German shepherd breed is most commonly recognized, as previously discussed this breed and the Rough-coated collie have a heritable predisposition for PAA in some family groups. PAA may be diagnosed in any breed of dog, although overall large breed dogs are diagnosed more commonly.

In the cat, EPI is usually diagnosed in middle-aged to older cats, reflecting the occurrence of EPI as an end result of chronic pancreatitis in this species. The time for development of EPI in cats with chronic pancreatitis is unknown, but given that this is a relatively rare (but increasingly recognized) diagnosis in the cat, and chronic pancreatitis appears to be remarkably common (See “Finicky feline: Pancreatitis in cats”), development of EPI is probably a relatively slow process in the cat.

Making the diagnosis of exocrine pancreatic insufficiency
Measurement of the serum concentration of trypsinogen (TLI) is the diagnostic test of choice to rule in/rule out exocrine pancreatic insufficiency due to a loss of pancreatic acinar tissue. As loss of acinar tissue is the most common cause of exocrine insufficiency, assessment of serum TLI should be carried out early in the diagnostic assessment of animals with compatible clinical signs.

In the dog, a serum TLI concentration of 2.5 μg/L or less is highly sensitive and specific for pancreatic acinar atrophy. In the cat, exocrine insufficiency is diagnosed when the serum TLI concentration is less than 8 μg/L. Detection of > 5 μg/L serum TLI in the
dog or > 12 μg/L serum TLI in the cat effectively rules out a loss or absence of pancreatic acinar tissue, and thus makes the diagnosis of primary pancreatic exocrine insufficiency much less likely.

The major differential diagnosis for EPI is small intestinal disease. A failure of the small intestinal mucosa to absorb digested nutrients will result in osmotic diarrhea and steatorrhea, with large volume diarrhea and weight loss. Animals with small intestinal disease may also present with a ravenous appetite and failure to thrive, as a result of the decreased efficiency of utilization of dietary nutrients. Empirically, many animals with small intestinal disease will show mild improvement in their clinical signs with digestive enzyme supplementation, but this is an expensive and usually only mildly beneficial therapy for these cases. For this reason, digestive enzyme supplementation (see therapy below) should typically be reserved for cases where EPI/PAA has been confirmed by measurement of serum TLI concentrations.

In the cat, small intestinal disease is much more common than EPI. Most cats in which serum TLI is measured due to a suspicion of EPI actually have normal or mildly elevated serum TLI concentrations. This finding rules out loss of pancreatic acinar tissue, and should prompt the clinician to investigate more thoroughly for small intestinal disease.

As small intestinal disease is a major differential for EPI, measurement of serum concentrations of cobalamin and folate is often helpful. In both cat and dog, but particularly in the cat, serum concentrations of cobalamin are often low in EPI patients due to lack of pancreatic intrinsic factor. The presence of low serum cobalamin with a normal TLI is a highly specific indicator of small intestinal disease. Even in patients with confirmed EPI, cobalamin malabsorption and subsequent deficiency may lead to poor response to therapy.10–11

Several other methods for assessing pancreatic exocrine function have been described. Before the development of the TLI assay, determination of fecal proteolytic activity, measurement of the fecal fat content and microscopic examination of fecal smears for undigested muscle fibers have both been used in the past. Recently, measurement of canine fecal elastase activity has been promoted as an alternative to the TLI assay, with the benefit of an ELISA methodology that can be run in-house (the canine TLI assay is a radioimmunoassay, limiting its availability to specialty laboratories). Without exception, these other tests show a lower sensitivity and specificity for diagnosis of EPI than the TLI assays. Fecal proteolytic activity assays are still occasionally used in exotic species (ferrets, meerkats), but their use is strongly deprecated in dogs and cats.

**Therapeutic considerations in the dog**

The mainstay of therapy for EPI in the dog is replacement of pancreatic enzymes with any of a variety of porcine-pancreas derived products. Powdered forms are generally preferred; enteric-coated tablet forms have poorer bioavailability in the dog and are often associated with treatment failure.

Using a powdered form, a typical starting dose is 2 teaspoons/20 kg of dog, given with every meal. There are no benefits to pre-incubation of the meal with the enzymes. A standard maintenance diet is usually adequate for initial treatment, although some dogs will show additional benefit from a lower fat diet to reduce the osmotic load from fatty acids. Higher fiber diets should be avoided, as these may bind to the digestive enzyme supplement and reduce its availability. Fat absorption is particularly problematic for dogs with EPI, and development of fat-soluble vitamin deficiencies has been documented.12 Parenteral supplementation with vitamin K should be provided in affected individuals. Serum cobalamin concentrations should be monitored every 3–6 months, and supplementation provided if the serum cobalamin concentration is decreased.

Two meals a day of a balanced canine maintenance diet are usually adequate for weight gain and normalization of the nutritional state. Diarrhea usually resolves within 4-5 days, however up to 20% of dogs in one study showed poor response to therapy.13

**Therapeutic considerations in the cat**

In common with the dog, effective treatment of exocrine pancreatic insufficiency in the cat relies on the effective replacement of digestive enzymes with powdered porcine pancreas extracts. A reasonable starting dose for the cat is approximately 1/4 teaspoon of extract per meal. Pre-incubation of the meal with the enzymes should be avoided as this may lead to food aversion in the cat. Compounding of the enzyme powder into gelatin capsules can be used in cats with severe food aversion, however this relies on the ability of the owner to administer the capsules to the cat. Gelatin-encapsulated enzyme powder capsules must be kept scrupulously dry or the capsule will be degraded.

Cats with EPI are almost invariably cobalamin deficient, the exocrine pancreas is the only source of intrinsic factor in the cat. Parenteral cobalamin supplementation (250 μg/cat by subcutaneous injection, once weekly to every second week) is necessary in most cats with EPI, response to treatment is often poor if cobalamin is not supplemented.

**“Subclinical” EPI**

Occasionally dogs are encountered with mild clinical signs of small intestinal malabsorption and serum concentrations of TLI that are lower than the bottom end of the reference range (5.7 μg/L), but not at or below 2.5 μg/L. If the dog is a young, large breed dog with a known predisposition for PAA, this may represent a subclinical state of PAA and warrants monitoring for progression to full-blown PAA and EPI. This “subclinical” state may persist for extended periods in some dogs, and if clinical signs are not seen, specific
therapy is not indicated. Dogs with this gray zone TLI concentration and mild or only sporadic clinical signs often respond well to diet change, preferably to a lower fat diet.14 Digestive enzyme supplements benefit some of the dogs in this group, but the efficacy of this treatment is usually no greater than that achieved with fat restriction, and enzyme therapy is significantly more expensive.

Comorbidities and complications
Lymphocytic/plasmacytic enteritis and intestinal dysbiosis are common complicating conditions in dogs with EPI, thus in those cases with poor responses to therapy the use of glucocorticoids (prednisone/prednisolone at ~1mg/kg SID) and broad-spectrum antibiotic therapy (the author’s preference is tylosin (Tylan Powder®, Elanco) at 25 mg/kg BID) may be indicated.

Gastric acid degradation is not usually a significant problem, but in some cases where appropriate doses of enzymes, antibiotics and glucocorticoids are being administered yet response to therapy is poor, additional benefit may be seen from treatment with a proton pump inhibitor such as omeprazole.

Both dogs and cats developing EPI as an end result of chronic pancreatitis may also be at increased risk for the development of insulin-dependent diabetes mellitus.15,16 Dogs developing EPI due to pancreatic acinar atrophy, however, are at no greater risk for development of diabetes as the islet tissue is spared.

Selective pancreatic enzyme deficiencies
A limited number of dogs have recently been described with a clinical syndrome that appears to reflect a selective deficiency in pancreatic enzyme synthesis, rather than a complete loss of acinar cellular mass.17,18 These dogs presented at a comparatively young age (4 months to 1.5 years) with ravenous appetites, long histories of small intestinal diarrhea, poor body condition and failure to thrive. All of but one of these dogs showed normal serum TLI concentrations, with only one dog having TLI below the reference range, but greater than 2.5µg/L. All other diagnostic testing on these dogs was relatively unremarkable. In several of these dogs Specific-PL values were below the lower limit of detection of the assay, but this is also commonly observed in normal dogs and is not considered diagnostic for exocrine insufficiency or pancreatic acinar atrophy.19

Interestingly, after failure of all other diagnostic tests to yield a diagnosis, and only limited response to dietary modification trials, all dogs showed marked clinical response to pancreatic enzyme supplementation, supporting the hypothesis that clinical signs in these dogs were due to absence of at least one of the pancreatic digestive enzymes.

While these recent case reports indicate that at least some dogs can present with a condition that requires pancreatic enzyme replacement therapy while serum TLI concentrations were within the normal range, it is important to note that these dogs had all undergone rigorous diagnostic work ups to exclude all other potential differential diagnoses. Small intestinal disease due to other etiologies, such as dietary intolerance or chronic parasitism, are far more likely causes for dogs to present with these clinical signs, and should be rigorously excluded before therapeutic trials of digestive enzymes are considered.

Prognosis
The prognosis for dogs with EPI due to PAA is fair to good for recovery of normal intestinal function and weight gain with appropriate therapy. While this is often a straightforward condition to manage, it can become expensive. Particularly in larger breed dogs, where this diagnosis is made most often, the cost of enzyme replacement therapy for the life of the dog can be substantial, and may represent a hardship for some owners. For this reason, accurate diagnosis and differentiation of PAA/EPI from other small intestinal diseases is very important.

Overall the prognosis for cats with EPI is more guarded than for the dog, due to the greater tendency to food aversion, more difficult administration of enzyme supplements and the existence of comorbid conditions such as chronic pancreatitis, enteritis and other age-related diseases.

References
Let’s Just Monitor It:
The Pitfalls and Problems with Serial Serum Chemistries
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It is well known that clinical chemistry analytes vary naturally over time, both as a result of disease processes and due to intrinsic biological variation within the individual. Variation occurs at the level of the individual, as a result of analytical imprecision, and within groups of individuals. The degree of within individual variation is itself quite variable, some analytes showing marked changes over time, while other analytes are under more rigid homeostatic regulation and thus vary less within an individual.

In both human and veterinary medicine the diagnosis and management of chronic disease conditions is becoming increasingly important. As a profession we promote the idea of “screening blood tests” performed on a regular basis. The American Animal Hospital Association (AAHA) Senior Care Guidelines for Dogs and Cats, for instance, recommend regular clinical chemistry panels for “senior” dogs, defined as dogs in the last 25% of their expected lifespan. Similarly, the American Association of Feline Practitioners-AAHA Feline Life Stage Guidelines recommend a panel of clinical chemistry parameters that are considered part of the “minimum database” for regular assessment of mature and elderly cats. An implicit assumption in these recommendations is that clinically meaningful changes will be detectable, and that early, beneficial interventions will be prompted by the detection of changes. In order for the clinician to accurately gauge the presence and importance of changes in these “screening” biochemistry panels, we need a reasonable understanding of just how much these tests change over time in an individual, and just how great a change needs to be documented to most likely reflect a change in the patient’s physiology.

Concepts and terminology of biological variation
When considering biological variability and how it impacts the use of serial blood work, there are two important concepts that need to be understood: the Index of Individuality and the Reference Change Value. The index of individuality of any particular test is derived from the ratio of variation over time in an individual patient to variation within the population as a whole. If a test has a high degree of individuality, results from a patient will tend to cluster together over time, and the results of tests from one patient will often not overlap with results from another patient. If a test has a high degree of individuality, important changes for an individual may be missed if comparing to a broader, population based reference range. This concept is illustrated in Figure 1 (right). In this figure, each dog’s results are tightly grouped within the individual, with little overlap between individuals. The broken lines represent a theoretical reference range based on the 95th percentile of all the data. Note that quite large deviations from Dog B’s “normal”, in either direction, would still fall within the reference range and thus meaningful change may be missed.

Tests with a high degree of individuality are best used by taking serial measurements over time and comparing the individual’s test results to prior values, rather than taking a single measurement and comparing it to a population based reference range.

Most diagnostic tests in veterinary medicine are traditionally compared to population-based reference ranges derived from large populations of “normal” individuals. This means we make an underlying assumption that most diagnostic tests we use have a low individuality and comparison to a reference range is appropriate. There is actually relatively little information regarding the individuality of tests commonly used in dogs and cats in the veterinary literature, but what is available would suggest that a substantial majority of the tests that we use regularly actually have quite high individuality, leading to the unsettling thought that we miss important changes in our patients in spite of regular biochemistry screenings.

If we are monitoring a value over time, we need to have some idea of the magnitude of change that most likely represents a change in the patient’s physiology (either a worsening or an improvement, depending on the context of the testing). This is the Reference Change Value (RCV), which is derived from measurements of the within patient variability and the variability of the measurement technique itself. In most cases, the reference change value is stated as a percentage change, statistically associated with a P value of <0.05; in other words a change of this size has a <1:20 chance of being random, and thus is more likely due to a change in the patient’s physiology. A change in a test result less than this value, regardless of whether it is “better” or “worse”, is statistically unlikely to represent a real change, and therapeutic decisions should be made with caution if less than this degree of change is seen.
Factors that influence biological variability

As previously indicated most chemistry parameters that we measure in our patients have high individuality, and many have high reference change values. Generally speaking analytes that are actively regulated by some form of physiological homeostatic process will have lower individualities and relatively low reference change values. Examples of substances with low individualities and comparatively low reference change values include serum electrolytes (particularly potassium and calcium) and blood glucose concentrations. This intuitively makes sense; these electrolytes are rigorously regulated by the renin-angiotensin-aldosterone system and parathyroid/calcitonin hormone production respectively, while under normal circumstances glucose is regulated via the insulin/glucagon system within a relatively tight range of values.

Release of “leakage” enzymes, such as alanine transaminase (ALT) and the specific pancreatic lipases is not under any form of homeostatic control, their release into the circulation varies with their rate of synthesis (which may vary with disease), rate of loss from the cells (which may also vary with disease), and may also vary with changes in the clearance mechanisms of these enzymes from the circulation. Consequently, these enzymes often feature a very high degree of within-individual variation, resulting in high reference change values. This has been reported for both pancreatic lipase immunoreactivity and liver enzyme activities in dogs, and for liver enzyme activities in cats.

Disease states can also influence the degree of biological variability, and thus the reference change values for individuals who are already diseased may actually be markedly different from healthy individuals. This has been reported for the cardiac biomarker NT-proBNP in dogs, where the reference change value for dogs with mitral regurgitation was estimated at approximately 50%, while the RCV for healthy dogs was nearly 100%, the lower RCV in the dogs with mitral regurgitation was mainly due to lower within-individual variation in that group.

Data on biological variability and reference change values for other enzymes and other disease states are currently lacking for many important diseases and for many enzymes that are routinely measured in practice. While data for biological variation in specific canine pancreatic lipase (Spec-cPL) has been reported for healthy dogs (where a very high RCV of approximately 450% was reported), data from dogs with chronic pancreatitis or on the feline specific pancreatic lipase assay (Spec-fPL) in any group of cats (healthy or diseased) are not available at the time of writing.

The effect of disease states on biological variability

Disease states can also influence the degree of biological variability, and thus the reference change values for individuals who are already diseased may actually be markedly different from healthy individuals. This has been reported for the cardiac biomarker NT-proBNP in dogs, where the reference change value for dogs with mitral regurgitation was estimated at approximately 50%, while the RCV for healthy dogs was nearly 100%, the lower RCV in the dogs with mitral regurgitation was mainly due to lower within-individual variation in that group.

The importance of biological variability depends upon magnitude of change with disease

While many analytes used in clinical practice have high individuality, suggesting that the application of population based reference ranges is of limited utility, the degree of deviation from normal is often sufficiently high that, when used as a screening test, diseased individuals are still readily distinguished from the normal range. An example would be cardiac troponin-I in individuals with myocardial ischemia, where several hundred-fold elevations in cardiac troponin-I concentrations are regularly documented, a vastly greater change than the estimated RCV (approximately 110% for healthy dogs) for this marker. Similarly, even though the RCV for canine specific pancreatic lipase is approximately 450% (4.5 fold), the cut off value considered consistent with pancreatic disease (> 400µg/L) is actually greater than 4.5-fold higher than the average healthy dog’s Spec-cPL value (which is about 63µg/L). Because of the very large deviations from normal seen with these tests, the implication of their high individual variability is mitigated when using these tests in a clinically appropriate manner to establish a diagnosis. The application of these tests to ongoing monitoring of the disease state post-diagnosis should still be approached with caution, however, until better data regarding RCV’s for these markers in animals with chronic disease is available.

For some tests, the analyzer is the limiting factor

To this point the discussion has mainly been about understanding why remaining aware of biological variation and reference change values are important, and less about how we actually go about getting the values that we are monitoring. This does not mean that how the sample is obtained and how the instruments doing the test are performing is not important, but in most cases we assume that samples are handled correctly and analyzed on machines that are well maintained and calibrated appropriately.

When we are interested in changes that are occurring in substances that show very little intra-individual variation, however, the performance of the analyzer doing the test can actually become very important. The criteria for acceptable analyzer variability when calculating and using reference change values are that the analyzer’s contribution to the variability seen must be less than half of the biological variation (in our case, this is the intra-individual variation).

In one study of biological variation carried out by the author, the performance of three different levels of clinical chemistry instruments were compared using the same set of samples. The instruments tested were a Beckman Coulter AU480 (a very high end-machine used in large clinical pathology practices), a Sirrus chemistry system (middle-range, would be used in a busy human urgent care facility) and the IDEXX VetTest 8008, a common system used in veterinary practices. All of the analytical systems used were precise enough that they could be used to derive reference change values and monitor for changes in all of the analytes measured. The AU 480, interestingly, was insufficiently precise to derive a reference change value for serum cholesterol in the dog, and none of the
three instruments showed sufficient precision to derive reference change values for total calcium. The implications of these findings are not entirely clear, but they do illustrate that even under the best of conditions and using rigorously maintained and calibrated instruments, our actual ability to actually detect meaningful changes in blood chemistry values is sometimes a lot lower than we would think.

References
In recent years, with greater availability of high-level diagnostic imaging and minimally invasive methods for the determination of pancreas-specific marker proteins in the serum, we have undergone a paradigm shift with respect to pancreatic disease in the cat. Once thought to be uncommon, we now know that a very large proportion of feline patients have chronic pancreatitis. In one remarkable study, the overall prevalence rate for chronic pancreatitis was 67% in ill cats, and even more remarkably, 45% in normal cats, based on histopathologic examination of 115 feline pancreata.1 Far from being uncommon, it is now apparent that pancreatic pathology, and particularly chronic pancreatitis, is common in the domestic cat. This disease likely represents a large proportion of feline cases presenting with reduced appetite, lethargy or chronic vomiting disorders, hopefully further large-scale epidemiologic studies will help to confirm or deny this hypothesis.

Chronic pancreatitis in the cat is distinctly different from chronic pancreatitis in most dogs, and shares more features with chronic pancreatitis in humans. In particular, marked lymphocytic infiltration and the presence of profound fibrosis are common in feline chronic pancreatitis.1

Clinical signs of pancreatitis in the cat

One of the great challenges in managing the cat with pancreatitis is the vague nature of clinical signs typically manifested in these cats. Based on the aggregation of data from three studies, involving a variety of underlying histological diagnoses and apparent disease severities, the most common clinical signs of pancreatitis in the cat are reduced appetite, lethargy, dehydration and vomiting (Table 1, below).

Table 1
Common historical and clinical signs of pancreatitis in cats aggregated from three separate studies.2-4 Cats from one study (Ferreri et al.3) are subdivided into acute necrotizing (ANP, n=30) and chronic nonsuppurative (CP, n=33) presentations. NS = Not Specified. Overall prevalence is rounded to the nearest whole percentage value.

<table>
<thead>
<tr>
<th>Study</th>
<th>Stockhaus2</th>
<th>Ferreri3 (ANP)</th>
<th>Ferreri3 (CP)</th>
<th>Hilt4</th>
<th>Total</th>
<th>Overall Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Cats</td>
<td>33</td>
<td>30</td>
<td>33</td>
<td>40</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>Inappetance</td>
<td>32 (97%)</td>
<td>19 (63%)</td>
<td>23 (70%)</td>
<td>39 (98%)</td>
<td>113</td>
<td>83%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>33 (100%)</td>
<td>15 (50%)</td>
<td>17 (52%)</td>
<td>40 (100%)</td>
<td>105</td>
<td>77%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>24 (73%)</td>
<td>10 (33%)</td>
<td>17 (51%)</td>
<td>37 (93%)</td>
<td>88</td>
<td>65%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (55%)</td>
<td>13 (43%)</td>
<td>13 (39%)</td>
<td>14 (35%)</td>
<td>58</td>
<td>43%</td>
</tr>
<tr>
<td>Icterus</td>
<td>6 (18%)</td>
<td>5 (16%)</td>
<td>8 (24%)</td>
<td>21 (53%)</td>
<td>40</td>
<td>29%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>3 (9%)</td>
<td>12 (40%)</td>
<td>7 (21%)</td>
<td>NS</td>
<td>22</td>
<td>16%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>17 (52%)</td>
<td>NS</td>
<td>NS</td>
<td>10 (25%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abdominal pain, a very common clinical sign of pancreatitis in the dog, is much less frequently recognized in the cat. Accurate assessment of abdominal pain in the cat can be quite difficult, and thus the true frequency of this problem in cats with pancreatitis may be underestimated,3 however the central observation that abdominal pain is rarely appreciated by clinicians assessing cats with pancreatitis remains true. Given the vague nature of clinical signs of pancreatitis in the cat, this disease should be considered in the differential diagnosis of any cat with vomiting, anorexia/hyporexia or lethargy where another, more proximate cause has not been identified.

An interesting observation from the aggregated retrospective studies is that these signs were the same regardless of underlying type of pancreatitis in the cats, with both severe necrotizing disease and more chronic, fibrotic disease having the same general signs. Based on these observations, it is not possible to distinguish acute from chronic pancreatitis in cats based on clinical presentation, duration of clinical signs or apparent severity of the disease.3,6,7 While chronic pancreatic disease is commonly thought to be less severe than acute pancreatitis in the cat,6 either disease can present with complications or comorbidities that are potentially life-threatening, and attempting to draw a distinction between these two conditions is not particularly clinically helpful.

Diagnostic approach to pancreatitis in the cat

In order to make the diagnosis of pancreatitis in the cat, obviously a clinical suspicion is necessary. Given the highly vague and variable nature of pancreatic disease signs in the cat, essentially any sick cat should have pancreatitis on their differential diagnosis list.
at first assessment. Routine chemistry panels are very useful for screening for other significant diseases that can cause lethargy and a poor appetite, such as renal insufficiency. Routine chemistry panels may also provide evidence of hepatobiliary disease, which is a common comorbidity with pancreatitis in the cat.

In many patients routine chemistry panels are unremarkable, reflecting the fact that there are no diagnostic tests on a typical screening chemistry panel that are sensitive and specific for pancreatic disease. This includes amylase and lipase activities, which are generally thought to have no diagnostic utility for detection of pancreatitis in the cat. Further assessment of these patients typically involves both abdominal ultrasound examination and the use of more specialized blood tests, particularly the feline specific pancreatic lipase assay (Spec-fPL).

At the time of writing Spec-fPL has the highest sensitivity and specificity for the diagnosis of pancreatitis of any diagnostic test in the cat, exceeding ultrasound, plain radiography and computed tomography scanning. This test also has the advantage of being minimally invasive and relatively inexpensive.

Spec-fPL values increase dramatically early in the development of pancreatic inflammatory disease, and then are cleared from the circulation relatively slowly, taking up to 14 days to return to the baseline value after the onset of acute pancreatitis. When the clinician suspects that chronic pancreatitis is present, determination of Spec-fPL concentrations repeatedly at 2-3 week intervals can bolster this diagnosis. The expectation is that serum Spec-fPL will remain elevated above the reference range throughout this period, even if the cat is showing few or no clinical signs.

The low sensitivity and specificity of traditional amylase and lipase activities for the diagnosis of pancreatitis, in all species, may be partly explained by low substrate specificity for most of the catalytic assays. The substrates used in these assays vary in terms of selectivity for pancreatic lipase, with some substrates showing much higher selectivity for pancreatic-origin lipases in the circulation. 1,2-di-O-Dilauryl-rac-glycero-3-glutaric acid-(6’-methylresorufin) ester (DGGR) is a lipase substrate with relatively high substrate specificity for pancreatic lipases. In a recently published study of 251 client owned cats with a clinical suspicion of pancreatitis, DGGR-lipase activity >26 U/L showed a sensitivity of 48% with a specificity of 63%, while Spec fPL >5.3 µg/L showed a sensitivity of 57% and specificity of 63%. This study suggests that DGGR-lipase activity may have some clinical utility in the assessment of cats, however this would be reliant on the use of this specific substrate in whichever analytical system is being used. Information regarding the actual substrates used by the various reference laboratories and in-house chemistry systems commonly found in veterinary practice is not readily available at this time.

Therapeutic approaches to the outpatient case
Given the very high frequency of dietary intolerance recognized in some studies of cats with chronic gastrointestinal disease, a rational initial step in the approach to a cat with a diagnosis of pancreatitis is an elimination trial using a hypoallergenic diet. The author’s preference is to use a novel protein source, selected based on a thorough dietary history, rather than the modified/partially hydrolyzed protein diets, however in some cases these modified diets are effective and well received. Dietary modification to a novel protein source often seems to be helpful in cats with chronic pancreatitis as well as in those with gastritis. Fat restriction, the mainstay of therapy for chronic pancreatitis in the dog, is less beneficial in most cats with chronic pancreatitis.

The patient is started on the elimination diet exclusively for a minimum period of 14 days. In most patients with diet-responsive disease a notable improvement in clinical signs will have occurred at 14 days, and those that have failed to show a good response are unlikely to show much benefit from a longer period on the diet. If the cat responds to the diet change, the diagnosis becomes one of food-responsive gastritis or dietary intolerance. “Dietary allergy” implies demonstration of a hypersensitivity response to a dietary component, as this is not achieved in most veterinary patients this term is not appropriate to most cases. Reintroduction of the previous diet or dietary components (protein sources etc) can be attempted, and if clinical signs recur the diagnosis of food intolerance is confirmed, subsequent therapy emphasizes the avoidance of the offending food component. In many cases owners are unwilling to reintroduce the original diet if clinical signs have abated and the new diet is continued empirically.

If the patient shows no response to the first diet change at 14 days, another new diet can be trialed. Most owners are unwilling to persist beyond two dietary trials, and additional therapy is needed. Failure to respond to dietary modification in a cat with infiltrative gastric mucosal disease allows the diagnosis of idiopathic chronic gastritis to be made. Therapy for this condition usually requires anti-inflammatory therapy, typically using glucocorticoids. Many cats with chronic pancreatitis also show satisfactory responses to glucocorticoid therapy, typically starting with prednisone/prednisolone at 1-1.5 mg/kg SID for approximately 14 days. There is no evidence to date that glucocorticoid therapy is associated with increased risk of worsening pancreatitis in the cat. If good control of clinical signs has been achieved, a gradual taper of the glucocorticoid to the minimum effective dose is started.

Pain control, maintenance of adequate nutritional intake in cats with inappetance, and maintenance of hydration are all critical to success. Most cats with pancreatitis presenting to companion animal practices are able to be managed on an outpatient basis, but the owner should be counseled on the need for close monitoring of food intake and the possibility of worsening of the disease which may require hospitalization for fluid therapy and assisted nutrition (see below).
A common empirical therapy is the use of pancreatic enzyme supplements to attempt to “down regulate” the pancreatic synthesis of digestive enzymes, the theory being that this will reduce ongoing pancreatic pathology. There is no evidence that this is efficacious. Given that the main pancreatic pathology in the cat is a chronic lymphocytic and fibrotic process, rather than an autocatalytic degradative/necrotic process, we now know that there is little physiological rationale for this therapy, and it is not recommended.

**Therapeutic approach to the cat with severe disease**

Cats with suspected pancreatitis presenting with marked abdominal pain, tachypnea, tachycardia, significant fever, collapse or other evidence of systemic inflammatory syndrome or circulatory shock are considered to have severe disease, and require immediate and aggressive, hospital-based care. The existence of multiple abnormalities in screening clinical chemistries, particularly hypoalbuminemia and hypocalcemia, is a strong indicator of severe and potentially life threatening disease. As with dogs, cats presenting with severe pancreatic inflammatory disease require aggressive therapy, including fluid therapy, effective analgesia, and early planning for nutritional support given the risk of hepatic lipidosis as a comorbidity. The aims of therapy are to replace circulating fluid volume, restore and maintain end organ perfusion (particularly of the pancreas, as pancreatic ischemia is a significant contributor to the development of necrotizing pancreatitis), restore and maintain plasma colloid oncotic pressure. Colloid fluids, such as synthetic hydroxyethyl starches, are often highly beneficial in the initial resuscitation of these cases. Fresh-frozen feline plasma can also be considered, and likely provides oncotic support while replenishing coagulation cascade proteins, however there is little information in the veterinary literature regarding use of plasma in severe feline pancreatitis cases. We typically use a combination of synthetic colloid and crystalloid fluids for initial resuscitation and volume maintenance in these cats in our clinic. Substantial electrolyte abnormalities, particularly hypokalemia and hypocalcemia, should be anticipated in these cats. Supplemental potassium is administered in combination with crystalloid fluids following routine guidelines for concentrations based on serial determination of serum potassium.

Effective analgesia and control of vomiting are important aspects of management of severe pancreatitis in all species, including the cat. Narcotic pain control is typically indicated in cats with sufficiently severe pancreatitis to warrant hospitalization. Transdermal fentanyl patches (25µg/hr) can be very effective for longer term (up to 72 hrs) analgesia without the need for frequent handling and injection in these patients, but initial therapy with an injectable or sublingual agent (commonly buprenorphine) is necessary as it can take up to 12 hours for therapeutic fentanyl concentrations to be reached. Maropitant, a neurokinin-1 receptor antagonist, is both an effective antiemetic and has antinociceptive effects in the viscera. The combination of maropitant with a 5-HT3-receptor antagonist, such as ondansetron or dolasetron, provides an effective control for vomiting and nausea in these patients with minimal need for repeated handling during the day.

**The special case of the diabetic cat**

Cats with diabetes mellitus and chronic pancreatitis represent a significant challenge, particularly if they are poorly or minimally improved by rigorous use of an elimination diet. The use of glucocorticoids in these cats risks the loss of glycemic regulation, increased insulin requirements or the development of insulin resistance. When faced with this particular quandary, the author’s personal preference is to emphasize dietary modification and weight loss to attempt to improve the glycemic state of the cat, rather than use of glucocorticoids to control gastric or pancreatic inflammation. Many cats will show an improvement in their chronic vomiting as they enter a euglycemic state, and anecdotally many cats with chronic pancreatitis show an improvement in their clinical signs and a normalization of serum fPLI concentrations after they are switched to the higher protein, low carbohydrate dietary regimes currently recommended for management of diabetic cats.

**References**

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