Approach to Gastrointestinal Bleeding
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Gastrointestinal (GI) hemorrhage is an important cause of blood loss that is more commonly encountered in dogs than cats. Sometimes GI bleeding is easy to detect as there are obvious clinical signs, such as hematemesis, melena or hematochezia (overt GI bleeding). Other times animals with GI blood loss do not have overt signs and may present because of anemia; these cases are more challenging to diagnose. If the cause of bleeding can be determined with conventional endoscopy these cases are said to have obscure GI bleeding. If the cause cannot be found during endoscopy these cases are said to have occult GI bleeding. This lecture mainly focuses on how to approach a case with GI bleeding but also discusses treatment for GI ulceration, which is its most common cause.

Causes of GI bleeding
In basic terms, there are three things that can cause GI bleeding (from most to least common): GI ulceration, abnormalities of the hemostatic system, and vascular disorders. Common causes of GI bleeding are listed below:

**Drugs**
- Non-steroidal anti-inflammatory drugs (especially ibuprofen)
- Glucocorticoids (especially dexamethasone)
- Anti-thrombotic drugs (aspirin, clopidogrel)
- Heparin

**Systemic/metabolic disease**
- Hepatic disease (portal hypertension, intrahepatic congenital portosystemic shunts)
- Uremia
- Pancreatitis
- Hypoadrenocorticism

**Neoplasia**
- Adenocarcinoma
- Lymphoma
- Mast cell tumor
- Gastrinoma

**Infectious**
- Parasitic e.g. hook worms
- Bacterial e.g. *Clostridium difficile*
- Viral e.g. parvovirus
- Fungal e.g. *Histoplasma sp*
- Algal e.g. *Prototheca sp*

**Hemostatic disorders**
- Coagulopathies e.g. coumarone toxicity
- Thrombocytopenia
- Platelet function disorders

**Other**
- Trauma e.g. foreign bodies
- Poor perfusion
- Stress
- Caustic agents
- Vascular ectasia

Approach to GI bleeding

**History and physical examination**

The client should carefully be questioned about potential access of the pet to NSAIDs and coumarone rodenticides. As previously mentioned the absence of hematemesis, melena, and hematochezia does not rule out GI bleeding. Dogs and cats with obscure/occult GI blood loss may present for non-specific signs such as anorexia, lethargy, behavioral changes, signs consistent with anemia, or they may not have any signs.

Note that hematemesis should be differentiated from hemoptysis (see below). Dogs and cats can swallow blood from epistaxis or hemoptysis and so respiratory and nasopharyngeal disease are possible differential diagnoses. Fresh blood in the feces tends to
Indicate large bowel disease whereas as melena indicates gastric or small intestinal bleeding. However, it is possible to have fresh blood in the feces in an animal bleeding from its small intestine if a large amount of blood passes quickly through the GI tract.

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<tr>
<th>Hemoptysis</th>
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<td>• Bright red blood</td>
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<td>• pH&gt;7</td>
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<tr>
<td>• No nausea or vomiting</td>
<td>• Nausea and vomiting</td>
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<td>• Respiratory difficulty</td>
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The patient’s vital parameters should be assessed first as occasionally patients with GI bleeding can present with hypovolemic shock, which may necessitate immediate intervention. A rectal examination should be carefully performed to look for blood (fresh or altered) and feel for masses and foreign bodies. The patient should be carefully examined for evidence of a generalized hemostatic disorder. Abdominal palpation is also essential. As mast cell tumors can cause GI bleeding the patient should be examined for cutaneous/subcutaneous masses, which if present should be aspirated.

**Laboratory testing**

Animals with GI bleeding are often anemic. However, with peracute hemorrhage their hematocrit and total solids may actually initially be normal. Obscure/occult GI bleeding may only be suspected after a CBC is performed. During the preregenerative stage, the anemia is normocytic normochromic with few reticulocytes. With time the bone marrow will mount a regenerative response but prolonged GI bleeding can lead to iron deficiency anemia. This is typically microcytic hypochromic with a variable reticulocyte count. Gastrointestinal bleeding may be accompanied by thrombocytopenia due to consumption or thrombocytosis, which is secondary to iron deficiency. Severe thrombocytopenia (<30,000/μL) is associated with spontaneous bleeding but automated counts must be confirmed with microscopic evaluation of a blood smear.

Hypoproteinemia and an increased BUN/creatinine ratio are characteristic of GI blood but loss. However, the absence of these changes does not rule out GI blood loss and neither is specific for this problem.

Fecal occult blood tests are often used in human medicine and can detect blood loss at levels of only 2-5% of those needed to result in melena. The problem in veterinary medicine is that false positive results due to various dietary constituents. I very rarely perform fecal occult blood tests because of this limitation. If an immunochemical test can be developed that is specific for canine hemoglobin it would allow the development of a more specific and useful assay.

Other laboratory tests can be useful when working up a case with known/suspected GI bleeding. Coagulation testing is helpful to rule out coagulopathies as a cause of bleeding. A fecal float and direct smear exam should be performed to rule out parasites. Depending on the index of suspicion further infectious disease testing may also be indicated. Hypoadrenocorticism should be considered and in the absence of a stress leukogram testing of this endocrinopathy should be performed. Gastrinomas are an uncommon tumor but measurement of serum gastrin concentrations is available from a number of laboratories and should be performed prior to starting antacid therapy.

**Diagnostic imaging**

Abdominal radiographs rarely lead to a definitive diagnosis in cases with GI bleeding but could lead of the detection free fluid in the abdomen, pneumoperitoneum, foreign bodies and masses. Barium swallow studies have largely been superseded by other techniques and are seldom performed where I practice.

Abdominal ultrasound can allow the diagnosis of GI ulceration in some cases but false negative studies are definitely possible. GI ulcers are characterized by thickening around their periphery, possible loss of wall layering, and a defect or crater. Ultrasound is useful for detecting abdominal masses and lesions of other organs and so is a valuable tool in the investigation of GI bleeding.

Conventional endoscopy is the definitive way to diagnose gastroduodenal ulceration and also allows assessment of the colon (and distal ileum). It is possible to biopsy any lesions that are detected, although the center of ulcers should not be biopsied due to the risk of perforation. However, it is not possible to reach the entire intestinal tract using this technique and so it is possible to miss important lesions.
Recently a capsule endoscopy system marketed for use in dogs >6 kg in weight (ALICAM, Infiniti Medical) has become available. Capsule endoscopy is indicated where endoscopy does not localize the source of GI bleeding or perhaps in practices where endoscopy is not available. Capsule endoscopy obviously does not allow biopsy.

**Surgery**
Sometimes exploratory laparotomy is employed to look for or address the cause of GI bleeding. However, it can be difficult to detect the site of hemorrhage as surgical exploration does not allow assessment of the mucosal surface of the GI tract. One technique that can occasionally be useful is to combine an exploratory laparotomy with endoscopy. The surgeon can than help guide the endoscope further into the intestinal tract by pulling intestine over it, thus allowing the entire GI tract to be visualized.

**Treatment of GI ulceration**

**Histamine-2 receptor antagonists**
Histamine-2 receptor antagonists (H2RAs) reversibly inhibit H₂-receptors thereby reducing gastric acid secretion. These drugs are generally well tolerated and cause few adverse reactions. The kidneys excrete them and so it may be wise to decrease the dose at which they are given in patients with renal failure. They can be ranked by their potency (highest to lowest): famotidine, ranitidine, nizatidine, cimetidine. Cimetidine is not routinely used in dogs and cats as it needs to be dosed every 6 hours and has limited efficacy while the dose of nizatidine is not well established in these species. Although ranitidine and famotidine are frequently administered to dogs and cats, recent studies have called their efficacy into question. In one study assessing the suppression of gastric acid production in dogs, ranitidine was not shown to be superior to a saline placebo. Famotidine is more effective than ranitidine but its ability to increase the gastric pH of dogs did not meet targets established in humans i.e. intragastric pH >3 for at least 75% of the day. Therefore, the use of famotidine and other H2RAs is not optimal in dogs and cats with known gastroduodenal ulceration. However, some patients do appear to respond to famotidine or even ranitidine, possibly because they have milder disease.

**Proton pump inhibitors**
Proton pump inhibitors (PPIs) irreversibly bind to active proton pumps, inhibiting gastric acid production. Omeprazole and pantoprazole are the most commonly used PPIs in small animal practice. Several studies demonstrated that they provide more profound suppression of gastric acid production than H2RAs. Therefore, they are recommended for the treatment of dogs and cats with known/suspected gastroduodenal ulceration or those at high risk of developing ulcers. Omeprazole is more effective when given at a dose of 1 mg/kg PO q12 hours rather q 24 hours. Pantoprazole can be given IV to dogs and cats that cannot tolerate oral medications. These drugs ideally should be given one hour before meals and take several days to reach maximal efficacy. Despite this, combined treatment with famotidine does not appear to be advantageous. Omeprazole capsules and tablets are enteric coated and therefore should not be split or crushed. It is possible to compound an oral suspension for smaller patients. Proton pump inhibitors appear to be well tolerated in dogs and cats, although diarrhea is occasionally reported as a side effect. Preliminary data suggests that cats treated with omeprazole for 60 days may show mild decreases in bone mineral density and that rebound hyperacidity can occur when this drug is stopped. Because of the potential for the development of rebound hyperacidity it is advisable to taper the dose of PPIs prior to stopping them. The optimal way in which to do this is not known but a two-week taper after long-term treatment seems reasonable. This drug has also been shown to alter the oropharyngeal and gastrointestinal microbiota of dogs. This in theory could predispose at risk patients to aspiration pneumonia. Therefore, the indiscriminate use of PPIs (and other antacids) is not advised. Proton pump inhibitors are metabolized by hepatic cytochrome P450 enzyme and so can potentially interfere with the metabolism of other drugs including benzodiazepines, clodipogrel, cyclosporine, azole antifungal drugs, and rifampin.

**Sucralfate**
Sucralfate is an ionic sulfated disaccharide part of which binds proteins in the stomach exposed by mucosal damage. This forms a physical barrier that protects the damaged mucosa from gastric acid, pepsin, and bile. Additionally, sucralfate stimulates the production of mucus, bicarbonate, epidermal growth factor, and prostaglandin E, all of which can have an additional cytoprotective effect. Sucralfate is indicated to patients with gastroesophageal reflux or gastroduodenal ulceration. The author usually uses sucralfate in conjunction with a PPI. Sucralfate is well tolerated, as it is not systemically absorbed. However, it can interfere with the absorption of concurrently administered medications and therefore other oral drugs should be given at least two hours before sucralfate.

**Disclosure**
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**References/further reading**


Canine Chronic Enteropathies: A Logical Approach
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Dogs are often presented to veterinarians for chronic (>3 weeks’ duration) gastrointestinal (GI) signs such as vomiting or diarrhea. While acute GI signs are often self-limiting and may not require extensive diagnostic evaluation, dogs with chronic GI signs require further assessment. There are many causes of chronic GI signs in dogs and therefore it is essential to have a logical approach to these cases. This session outlines an approach to dogs with chronic vomiting/diarrhea mainly focusing on diet responsive, antibiotic responsive, and immunosuppressive responsive enteropathy (sometimes called steroid responsive enteropathy). Protein losing enteropathy will be discussed in a separate session.

Terminology
The terminology used to describe chronic GI disease is important to understand but can be confusing:

Inflammatory bowel disease
This commonly used term has been borrowed from human medicine where its two main forms are Crohn’s disease and ulcerative colitis. The WSAVA GI Standardizations Group defined inflammatory bowel disease in dogs (and cats) as a group of idiopathic, chronic gastrointestinal disorders characterized by mucosal inflammation. The are some important differences between IBD in humans and dogs, e.g. IBD is mainly a colonic disease in people whereas it mainly affects the small intestine of dogs. In actual fact IBD may not be a helpful term for veterinarians to use.

Chronic enteropathy
Chronic enteropathy (CE) is defined as chronic GI signs e.g. vomiting, diarrhea, borborygmus, hyporexia, abdominal pains, nausea, and or weight loss) where extraintestinal, infectious, and intestinal disease of other etiology e.g. foreign bodies, intussusception, and tumors have been ruled out. This term is more helpful for veterinarians to use than IBD as it reflects how we work these cases up and the differences between IBD in humans and small animals. Dandrieux (2016) divided CE into diet responsive enteropathy (DRE), food responsive enteropathy (FRE), immunosuppressant responsive enteropathy (IRE), and non-responsive enteropathy (NRE).

Initial workup
The first priority is to rule out extraintestinal disease, infectious disease, foreign bodies, intussusception, and tumors. When initially presented with dogs with chronic GI signs often my initial action is to have a fecal sample sent for floatation and a direct smear exam to rule out parasitism, I will often treat with fenbendazole for 3-5 days regardless of the result in case of a false negative result. Often at this stage I will try the dog on an “intestinal” type diet (discussed below). If the dog fails to respond to these interventions my next step is to rule out metabolic disease by running a CBC, serum chemistry profile, and urinalysis. Remember that atypical hypoadrenocorticism can cause GI signs without electrolyte abnormalities. If the patient does not have a stress leukogram I will therefore measure their baseline serum cortisol concentration or perform an ACTH stimulation test. At this stage I will often do additional infectious disease such as antigen testing for Giardia. Abdominal imaging especially ultrasound is helpful to rule out obstructions or masses. In many cases the results of ultrasound do not directly contribute to making a diagnosis but this imaging modality appears to most useful in patients that are vomiting, have weight loss, or have a palpable abdominal mass. Pancreatitis and exocrine pancreatic insufficiency can be tested for using serum cPLI and cTLI tests, respectively. Measurement of serum cobalamin and folate concentrations may give an indication of small intestinal absorption. If the serum cobalamin concentration is low it may be beneficial to supplement it by the subcutaneous (or oral) route.

For stable dogs the next step is to perform dietary/therapeutic trials. These need to be performed in a logical way in order to get the best information from them. Ideally only one intervention at a time is made. If more than one change is made it can be difficult to determine which intervention was responsible. Of course, this is more of a guideline than a rule. For example, in a very sick patient it may be necessary to be aggressive and try several things at once. It is also important to perform the trial in a way in which they are likely to help the patient and to for a duration long enough for them to have an effect.

Diet responsive enteropathies
This is the most common form of CE in dogs, accounting for about two thirds of patients in some studies. Therefore, it is advisable to perform a diet trial before trying antibiotics or intestinal biopsy in most cases. These dogs tend to have a good long-term outcome compared to those with other kinds of CE. Dogs that respond to a diet trial don’t necessarily have a dietary allergy as dietary intolerance and intoxication are other potential types of adverse food reactions. Dogs with DRE more often have large bowel signs than those with other forms of CE and may also have dermatological signs. Additionally, properties of some of the diets used in diet trials themselves can have a beneficial effect on GI. The options for types of diet to feed are reviewed below:
“Intestinal” type diets are typically highly digestible, with moderate fat restriction (this varies). These diets may also be supplemented with fermentable fibers, which can help modulate the GI microbiota and omega 3 fatty acids that may reduce inflammation. I use them as first step early in the work up of chronic GI signs but novel protein and hydrolyzed antigen diets may be more effective.

**Novel protein diets** are commercially available and can also be home cooked. The idea is to provide a novel protein source e.g. venison, rabbit, duck, kangaroo. It is essential to take a through dietary history to feed a truly novel protein and the closer the taxonomic relationship between meat sources, the higher the risk of cross-reactivity e.g. if a dog has previously been exposed to chicken a turkey based diet would be less likely to be helpful.

**Hydrolyzed antigen diets** contain small peptides that are less likely to be immunogenic than proteins. In one study dogs with CE fed a hydrolyzed antigen diet had a more favorable response than those fed an easily digestible diet. It is not known whether novel protein or hydrolyzed antigen diets are more effective.

**Supplementation of fermentable fiber** is a reasonable option in dogs with large bowel signs. This can be added to another diet e.g. as Metamucil or canned pumpkin or there are gastrointestinal diets with added fiber (e.g. Royal Canin Gastrointestinal Fiber Response).

When conduction a feeding trial is it important that the trial diet is fed exclusively. This requires an informed and compliant client. Usually for GI disease a response can be seen within 2 weeks (animals can continue to improve beyond this point). If there is a response to fully document the presence of an adverse food reaction the original diet should ideally be reintroduced (I rarely do this). Interestingly, it has been reported that when dogs with FRE were fed an elimination diet for 12 weeks and then were switched back to their previous diet many of them remained in remission. If a dog fails to respond to a trial with one diet it does not mean that it will also fail to respond to others.

**Antibiotic responsive enteropathy**

There are various reasons why a dog my respond to antibiotics: specific enteric infections e.g. Campylobacter or Salmonella; granulomatous colitis (of Boxers); or because of dysbiosis. This session will not focus of specific enteric infections. Intestinal dysbiosis, an imbalance of the GI microbiota often occurs secondary to other GI diseases, but may also occur as primary entity, or could also contribute the development of IRE or IBD. Therefore, if a dog fails to respond to a diet trial it is reasonable to perform an antibiotic trial. Common choices include tylosin or metronidazole. My preference is tylosin (25 mg kg PO q12 hours) because it has few side effects, a wide therapeutic range, and is rarely used to treat other infections. Dogs with tylosin responsive diarrhea tend to be younger than those with other forms of CE and are often larger breeds, especially German Shepherds. Frequently, these dogs have large bowel diarrhea. Usually if there is a response to tylosin it happens quickly, often within the first few days of treatment. Therapy is usually continued for 6 to 8 weeks. Some dogs will remain in remission when the tylosin is discontinued but many others relapse and require intermittent or long-term treatment. For long term treatment, a dose reduction is often possible (taper gradually to 5-10 mg/kg PO q24 hours). Interestingly, when given to healthy dogs, tylosin appears to cause a dysbiosis which in some individuals does not resolve after several months of follow-up. This is another reason why a diet trials should be performed before antibiotics are started.

Prebiotics, probiotics, symbiotics, or even fecal microbial transplant also have the potential to help address primary or secondary dysbiosis and to modulate the immune system in dogs with CE. However, there is not enough evidence available to make definitive recommendations on when and how to use them and so they are currently used on an empirical basis. I tend to reserve these options for refractors case of CE but it may also be reasonable to try them at an earlier juncture.

**Immunosuppressive responsive enteropathy**

If stable patients if a diet trial(s) and antibiotics trial are unsuccessful ideally the next step is to perform intestinal biopsy. This allows a histomorphological diagnosis and sometimes a causative diagnosis to be made. In most dogs with CE, histological assessment allows the confirmation, classification, grading of enteritis. Additionally, neoplasia and intestinal lymphangiectasia can be ruled in or out. It is important to remember that lymphoplasmacytic enteritis can be caused be a number of different things and is not a useful clinical diagnosis. Once other causes of clinical signs have been ruled out, trial treatment with an immunosuppressive medication can begin. Prednisone/prednisolone (2 mg/kg PO per day) are the most frequently used initial drugs. In most studies, initial response rates are >60%, although long-term outcomes are less favorable. The addition of metronidazole in the IRE dogs treated with prednisone did not appear to be beneficial. Budesonide has fewer systemic side effects then other glucocorticoids as it undergoes extensive first pass metabolism. A study suggested that it is associated with a similar response rate to prednisolone. In animals that fail to respond to these medications second line treatments are indicated. These include cyclosporine, chlorambucil, azathioprine, and mycophenolate. My preference is cyclosporine (5 mg/kg PO q24 hours) as results of initial studies using this agent were encouraging. Chlorambucil (2-4 mg/m² PO q24 hours) was reported to be more effective than azathioprine when each drug was given with prednisolone for treatment of PLE. However, further studies are needs before definitive recommendations can be made.
Reasons for a more aggressive course of action

This step-wise system of trial treatments is very helpful for stable case but is not appropriate for very sick patients. For these dogs, being more aggressive and collecting intestinal biopsies at an earlier stage is indicated. Often multiple interventions are made simultaneously e.g. in a dog with severe enteritis starting prednisolone, a diet trial, and tylosin all together. If the patient responds the prednisolone could be tapered and possibly discontinued. After that it may be possible for the tylosin to be discontinued and them the dog might be maintained on a therapeutic diet alone. Possible indications for a more aggressive approach are listed below:

- Protein losing enteropathy (see other session)
- Anorexia
- Severe weight loss/other clinical signs
- An intestinal mass or diffuse thickening

Scoring systems

Assessing the dog’s response to various interventions is an essential part of working up CE. In order to make this a more subjective process two clinical scoring scheme have been developed; the canine inflammatory bowel disease activity index (CIBDAI) and the canine chronic enteropathy activity index (CCEACI). The former is bases of clinical findings alone that later is based on clinical findings and serum albumin concentration. I recommend the use of these scoring systems in dogs with CE.

References/further reading


The differentiation between acute pancreatitis (AP) and chronic pancreatitis (CP) is ideally made based on histological criteria. Acute pancreatitis is a completely reversible condition with no histological evidence of fibrosis or exocrine atrophy. Acute pancreatitis is histologically characterized by necrosis, edema, and a neutrophilic infiltrate. Chronic pancreatitis is defined as a continuing inflammatory disease of the pancreas with irreversible morphological changes. The typical histological changes of CP are fibrosis, atrophy, and a mononuclear cell infiltrate. These in time may lead to “pancreatic failure” with exocrine pancreatic insufficiency and/or diabetes mellitus. In reality, the antemortem distinction between AP and CP is rarely made based on histological findings as pancreatic biopsy is seldom performed. Unfortunately it is not possible to reliably make a differentiation between AP and CP based on the duration of signs alone because acute flare-ups of CP can occur, AP can develop into CP, AP can be recurrent, and CP can present with acute clinical signs.

In studies of dogs undergoing necropsy for a variety of reasons, histological changes of the pancreas were very common, in fact only 8% of pancreata examined did not have any histological changes. Lymphocytic inflammation and fibrosis suggestive of CP were present in about half of the pancreata examined. Neutrophilic inflammation consistent with AP was present in about a third of the pancreata. This is intriguing as it suggests that pancreatitis, especially CP, is more common than we previously thought and may often go undiagnosed. The importance of pancreatic lesions in dogs that have no clinical signs is not known.

Chronic pancreatitis is more challenging to diagnose than acute pancreatitis and evidence-based treatment protocols have not been established. This session discusses the diagnosis and management of this challenging disease.

Etiology and risk factors
The causes of CP in dogs are not well defined but progression from AP probably accounts for at least some cases. Known/suspected risk factors for AP in dogs that may also be relevant for CP are listed below. Cavalier King Charles Spaniels, English Cocker Spaniels, and Collies from the United Kingdom were shown to be at increased risk. English Cocker Spaniels have been reported to have a form of CP, characterized by perilobular fibrosis, duct destruction, and a T-cell-dominated lymphocytic infiltrate. Some affected dogs also had keratoconjunctivitis sicca and glomerulonephritis. There are similarities between CP in this breed and type 1 (IgG4+) autoimmune pancreatitis but lymphoplasmacytic infiltrates consistent with this etiology are not uncommonly observed on histological sections from dogs of various breeds. In some humans, genetic variations play a role in the development of pancreatitis and it is possible that this is the case in dogs. For example, some humans have a genotype that results in translation of non-functional PSTI peptide predisposing them to pancreatitis. Recently, variations of the SPIK1 gene that encodes the PSTI protein in Miniature Schnauzers were shown to be associated with pancreatitis in this breed. However, a subsequent study did not reproduce this result and further work needs to be done to determine if these variations result in synthesis of non-functional PSTI. Other breeds of dogs have not been evaluated for these variations. Pancreatic duct obstruction is a common cause of CP in humans but is only occasionally diagnosed in dogs.

**Known/suspected risk factors for AP that are relevant for CP**

- Hypertriglycerideremia
- Diet (ingestion of an unusual food item, getting into garbage, and possibly high fat diets)
- Endocrinopathies (possibly hypothyroidism, hyperadrenocorticism, and diabetes mellitus)
- Drugs (possibly azathioprine, L-asparaginase, potassium bromide, phenobarbital, antimonial drugs, and organophosphates)
- Obesity

Clinical signs
In a recent retrospective study of dogs with CP the most common clinical signs recorded were lethargy (80%), decreased appetite (70%), vomiting (63%), diarrhea (36%), abdominal pain (27%), and pyrexia (24%). From this data, it is evident that some dogs with CP will present with classic signs of pancreatitis but others have a vaguer presentation. For this reason, Watson (2012) recommended that CP should be considered as a diagnosis in dogs with low grade waxing and waning gastrointestinal (GI) signs, intermittent anorexia and apparent postprandial discomfort, recurrent acute signs of pancreatitis, dogs with diabetes, in older dogs that develop signs of exocrine pancreatic insufficiency (EPI), and dogs with extrahepatic bile duct obstruction.
Diagnostic testing
Chronic pancreatitis is more challenging to diagnose than AP for a number of reasons. Firstly, as previously mentioned the clinical signs of CP can be vague so this condition may not be considered to be a possible diagnosis in the first place. Chronic pancreatitis is harder to diagnose with abdominal ultrasound than AP. Furthermore, based on studies of dogs undergoing necropsy it is probable that the Spec cPL and SNAP cPL tests are not as sensitive for diagnosing CP as they are for AP. Having said this, I usually diagnose CP based on compatible clinical signs, ruling out other causes of these, abdominal ultrasound findings, and the results of a Spec cPL assay. I seldom perform pancreatic biopsy on dogs I suspect of having CP. However, I would consider pancreatic biopsy if a dog is undergoing laparotomy for another reason and I suspected CP. It can also be difficult to determine if a dog has CP or AP.

Diagnostic imaging
Abdominal radiographs are not adequately sensitive for the diagnosis of canine pancreatitis. However, this imaging modality does play an important role in ruling out other causes of vomiting in dogs and therefore is relevant in the work-up of dogs suspected to have pancreatitis.

Abdominal ultrasonography is the most commonly used imaging modality to diagnose pancreatitis in dogs. Findings consistent with AP include peripancreatic fluid, hyperechoic peripancreatic fat, and an enlarged hypoechoic pancreas. The diagnostic performance of this test for AP has not adequately been evaluated but one study reported a sensitivity of 68%. The changes associated with CP such as fibrosis and atrophy are harder to detect with the imaging modality resulting in a lower sensitivity. If stringent criteria for diagnosing pancreatitis are used ultrasound is probably quite specific for diagnosing AP but false positives results can occur (for CP this has not been reported). Furthermore, the accuracy of this technique is very operator-dependent. Abdominal ultrasound is useful for ruling out other causes of the patient’s clinical signs and for detecting complications of pancreatitis such as pancreatic fluid accumulations, extrahepatic bile duct obstruction, or pancreatic masses.

In humans, contrast enhanced computed tomography is often used to diagnose pancreatitis. Results of initial studies in dogs were not promising but a subsequent a study suggested that this technique is feasible for the diagnosis of AP. The utility of contrast enhanced ultrasound for diagnosing CP also warrants further evaluation.

Pancreas-specific lipase
Pancreas-specific lipase can be measured by either the Spec cPL test or the SNAP cPL test. Because the lipase that is measured is specific to the pancreas these tests are more accurate than the traditional serum lipase activity assay. However, lower sensitivities were reported in studies where histopathological evaluation of pancreata collected during necropsy was used as reference standard. In one such study, the sensitivity of Spec cPL, using a cutoff value of 400 μg/L, was 21% in dogs with histopathologically mild pancreatitis (n = 56) and 71% in dogs with moderate to severe pancreatitis (n = 7). Using a cutoff of >400 μg/L, the specificity for the Spec cPL based on seven normal pancreata was 100%. There was a stronger correlation between serum Spec cPL concentrations and the histological features of AP than CP. This suggests that Spec cPL is more sensitive for the diagnosis of acute pancreatitis than chronic pancreatitis, perhaps as Watson (2012) suggested because enzyme leakage is more likely to occur in an actively inflamed pancreas than in a fibrotic and/or atrophied pancreas.

Pancreatic biopsy
Histological examination of a pancreatic biopsy specimen is theoretically the gold-standard test for diagnosing pancreatitis in dogs. Pancreatic biopsy can carefully be performed without complication in healthy dogs and so it is technically possible. However, pancreatic biopsy is invasive and requires general anesthesia. Additionally, sampling error is a diagnostic limitation of this technique as the lesions associated with CP maybe focal.

Treatment
Supportive care
Fluid therapy is essential for acute episodes of pancreatitis but will not be reviewed here.

Anti-emetics are also an important part of treatment as they reduce fluid losses, improve patient comfort, and help allow early enteral nutrition to be provided. The NK-1 receptor antagonist maropitant is my first choice for dogs with pancreatitis. This drug is very effective and has both peripheral and central effects. Another advantage is that this drug inhibits the effect of substance P and therefore may have an analgesic effect. Ondansetron and dolasetron are serotonin receptor (5-HT3) antagonists that are also effective antiemetic agents and in severe cases of pancreatitis I often use one of these in conjunction with maropitant. Metoclopramide is a dopamine receptor antagonist that has antiemetic and prokinetic effects. It is not as effective as the agents discussed above but sometimes I will add it to the treatment regimen of dogs that are unresponsive to other antiemetics or those that have gastric stasis. I find it most effective when given IV as a constant rate infusion and so it has less relevance in a chronic setting.

Abdominal pain is likely to be under-recognized in dogs and so I often give patients with CP the benefit of the doubt by giving them an analgesic and seeing if they improve. There are several options for providing analgesia in the hospital setting but options for providing analgesia at home are more limited i.e. tramadol or butorphanol given orally. Butorphanol is not likely to be effective analgesic given this way and I don’t send patients home with fentanyl patches for a variety of reasons. Therefore, currently I use
tramadol, realizing that it may not be that efficacious. I don’t use NSAIDs in dogs with CP due to concerns about GI and renal side effects. There is a rationale being using gabapentin or pregabalin in these dogs but I have not personally had to do this. As previously mentioned, maropitant may have analgesic effects.

Nutrition
Nutritional considerations are very important in the management of dogs with pancreatitis. It is now recommended to provide nutrition to dogs early in the course of pancreatitis. The question of which is the optimal diet to feed dogs with pancreatitis has not been rigorously answered, but given the role of obesity and hypertriglyceridemia in causing pancreatitis, feeding an ultra-low-fat diet is recommended. Because patients with pancreatitis are in a catabolic state feeding high-fiber weight loss diets does not make sense. Because of this I advise feeding an ultra-low-fat highly digestible diet.

Eliminate risk factors
In dogs with CP it is important to look for any risk factors such as hyperlipidemia or drugs known to be associated with pancreatitis. If possible these risk factors should be addressed. For example, in persistently hyperlipidemic dogs, in addition to feeding an ultra-low-fat diet supplementing omega-3 fatty acids and/or initiating treatment with gemfibrozil (150-300 mg per dog PO q12 hours) may be helpful.

Other treatments
It is important to have an index of suspicion for complications of CP such as EPI and diabetes mellitus and these should be tested for and treated if necessary. The use of pancreatic enzyme replacement products to decrease post-prandial pain has been described in dogs and humans but there is little evidence to support this practice. As oxidative damage can play a role in the pathogenesis of pancreatitis there is a rationale for using antioxidants such as S-adenosylmethionine but there are currently no studies in dogs with pancreatitis to support this. Some dogs with CP have lymphoplasmacytic pancreatic infiltrates and this may indicate an autoimmune etiology. Therefore, in a dog with CP that is not responding to symptomatic therapy and dietary changes, a trial treatment with prednisone may be warranted. Again, there are no clinical trials to support this. There is however an ongoing clinical trial that is being coordinated by the Gastrointestinal Laboratory at Texas A&M University to evaluate the efficacy of cyclosporine for treating dogs with CP and diabetes.
Defining the cat’s problems
The first step in working up a cat with chronic diarrhea is to make an accurate list of the cat’s problems. Trying to determine if the diarrhea is small bowel, large bowel, or mixed in nature seems very obvious but clinicians often skip this step. Determining this helps when it comes to formulating a list of differential diagnoses and in making a diagnostic plan. Having said this, sometimes it is oversimplistic to say the diarrhea is from either the large or small bowel as occasionally both are affected. Aside from helping to localize the site of disease the character of the cat’s stool can give other important diagnostic clues. For example, steatorrhea is consistent with exocrine pancreatic insufficiency, and especially foul smelling large bowel diarrhea with *Tritrichomonas foetus* infection. It is important to take note of non-gastrointestinal clinical signs as they can indicate metabolic causes of diarrhea. For example, polyuria/polydipsia would be consistent with hyperthyroidism, hypercalcemia, or renal disease.

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

Causes of feline chronic diarrhea

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

**Staged diagnostic approach**
Probably the most important thing when approaching a cat (or dog) with chronic diarrhea is to have a logical staged approach to performing diagnostic testing. Initially, cheaper less invasive tests are performed in order to rule out metabolic and infectious diseases. As there are no reliable diagnostic tests for dietary allergy/intolerance or dysbiosis, diagnostic trials are an important part of this process. Ideally therapeutic trials are performed sequentially rather than in parallel, so if there is a positive response the clinician knows what it was due to. If there is no response to these therapeutic trials and no diagnosis is made after performing the initial diagnostic tests, more expensive and invasive tests are performed. In some cases intestinal biopsy is indicated later in the diagnostic process. Every case is different but general guidelines for this staged approach are detailed below:

**Stage 1: initial evaluation**
- Perform a fecal direct smear and flotation to rule out helminth infection
- Consider administering a broad spectrum anthelmintic, such as fenbendazole at a dose of 50 mg/kg by mouth once daily for three days, regardless of the fecal analysis results
Perform a diet trial with a highly digestible intestinal diet

Stage 2: non-invasive testing

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

Stage 3: therapeutic trials

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

Stage 4: intestinal biopsy

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

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

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

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

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

**When to be more aggressive**

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

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

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

**Nutritional support**

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

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

**Treatment tips**

In cats with idiopathic inflammatory bowel disease, if the response to prednisolone alone is not optimal, chlorambucil can be used as an adjunctive treatment. There are several dosing protocols that have been reported. For cats with that are relatively easy to pill a dose of 2 mg per cat PO three times a week can be used. In smaller cats or cats that don’t tolerate chlorambucil well the dose frequency can be reduced to twice weekly. For cats that are harder to pill, pulse dosing can be used. This entails giving a dose of 20 mg/m² once every 2 weeks. Generally this drug is very well tolerated in cats but it may cause myelosuppression so complete blood counts should be monitored periodically. Some cats with IBD or lymphoma also have comorbid conditions, such as diabetes, that mean the use of prednisolone is contraindicated. Budesonide is a corticosteroid, which is extensively metabolized on its first pass through the liver. This means it causes fewer systemic side effects than prednisolone. In these cases budesonide can be used instead of prednisolone. However, there may still be some systemic side effects associated with this drug. A dose of 1 mg per cat PO q24 hours has been recommended.
References/further reading
Although laboratory testing and diagnostic imaging are valuable during the diagnostic investigation of dogs and cats with hepatobiliary disease, liver biopsy is often required to make a definitive diagnosis. Microscopic evaluation of liver tissues allows a histomorphological and sometimes an etiological diagnosis to be made. It can also provide important prognostic information and help guide therapy. Furthermore, liver biopsy allows collection of samples for copper quantification and bacterial culture. In order to get the most out of this process, it is important to pay attention to detail at every step of the process; patient preparation, biopsy, samples handling, and histological assessment.

**Indications for liver biopsy**
An approach to dogs with increased liver enzyme activities is outlined in my previous lecture. While it is not possible to make a definitive set of criteria for when to perform liver biopsy because every case is different, I can offer the following suggested indications for liver biopsy:

- Persistently increased liver enzyme activities (ALT in dogs, ALT and ALP in cats) where extrahepatic disease has been ruled out
- Icterus/hyperbilirubinemia where hemolysis and extrahepatic bile duct obstruction have been ruled out
- Hepatic masses (avoid incisional, laparoscopic, and needle biopsy with suspected hemangiosarcoma)
- Patients with congenital portosystemic shunts or acquired portosystemic shunts (when pre-hepatic portal hypertension has been ruled out)

**Suggested contraindications for liver biopsy**

- Platelet count <80,000 /μL
- Prolonged buccal mucosal bleeding time
- Prolonged prothrombin time or activated partial thromboplastin time (>2 times the upper limit of the reference interval)
- Plasma fibrinogen concentration <50% of the lower limit of the reference interval
- Infectious disease that could be disseminated by biopsy
- Suspected hemangiosarcoma (excisional biopsy may be possible)
- Ascites (try to treat first)

**Risks of liver biopsy**
Liver biopsy is considered to be a relatively low risk procedure but it occasionally leads to morbidity and even mortality. The most common adverse event is excess hemorrhage. In a study of dogs and cats undergoing percutaneous needle biopsy (renal and hepatic), minor bleeding was found to occur in 22% of cases and major bleeding, requiring fluid therapy or a transfusion, occurred in 6% of cases. However, this study did not evaluate renal and hepatic biopsy separately and renal biopsy is generally more prone to excess hemorrhage. Other studies have shown the laparoscopic liver biopsy in dogs was associated with a low complication rate. One complication that is very important to mention is that in a fatal severe shock developed in 5 o 26 cats that underwent liver biopsy with an automated Tru-Cut biopsy device, possibly due to intense vagotonia. For this reason, automated Tru-Cut needles should never be used for liver biopsy in cats.

**Limitations of liver biopsy**
Liver biopsy has some important diagnostic limitations. No matter which biopsy technique is employed a relatively small amount of the liver a whole is sampled. Because many liver diseases are heterogeneously distributed throughout the hepatic parenchyma, liver biopsy is susceptible to sampling error. This can mean the histological findings reported do not represent the rest of the liver. Bigger specimens of liver are generally more representative and are easier for the pathologist to interpret. In a recent study, the mean number of portal triads obtained were 2.9 for needle samples (14 gauge), 3.4 for 5-mm laparoscopic cup forceps samples,12 for 8 mm punch samples, and 30.7 for wedge samples. Diagnoses were in agreement with those from large wedge samples in 66% of needle samples, 60% of cup samples, and 69% of punch samples, and these proportions were not significantly different from each other. The investigators concluded that the histopathologic interpretation of a liver biopsy specimen in the dog is unlikely to vary if it contains at least 3 to 12 portal triads. These values should be seen as a minimum and it has been recommended that pathologists should be presented with specimens containing at least 11 portal triads. In another study, the morphologic diagnosis assigned to 18 gauge needle biopsy specimens by individual examiners agreed with the morphologic diagnosis assigned to larger wedge biopsy specimens for 56%
and 67% of the specimens. Even when biopsies of adequate size are collected substantial variation in lesions between liver lobes has been reported. Therefore, it is essential to sample several liver lobes.

Sampling error is also important when it comes to quantification of hepatic copper (and other metals). For example, if copper is quantified from tissue collected from a regenerative nodule it is expected to be lower than that of adjacent liver. Therefore, it is important to both quantify copper and to histologically assess it.

Another limitation of histological assessment of liver tissue is the lack of inter-observer agreement. In one study 3 examiners agreed on the morphologic diagnosis assigned to needle and wedge biopsy specimens for 44 and 65% of the specimens, respectively. In another study, there was fair inter-observer agreement when 6 pathologists assigned fibrosis scores and poor agreement when they assigned necroinflammatory activity scores to sections of liver.

Patient preparation
Prior to performing liver biopsy, the patient’s general health should be established. This usually involves performing physical examination, CBC, platelet counts, serum chemistry panel, and urinalysis. The hemostatic system is also usually evaluated by measuring PT and PTT, where possible fibrinogen concentrations, and buccal mucosal bleeding time. However, the ability of PT and PTT to predict bleeding during liver biopsy is controversial. Supplementation of vitamin K (0.5 to 1.5 mg/kg q 12 hours for 3 doses) should be considered in patients with intra or extra-hepatic cholestasis and patients with overt bleeding may benefit from plasma or other blood products.

Biopsy techniques
Three liver biopsies techniques are used in small animal medicine; percutaneous needle biopsy, laparoscopic biopsy, and surgical biopsy. Each has its own set of advantages and disadvantages. Laparotomy allows collection of relatively large wedge biopsies, with direct visualization. This technique does not require specialized equipment or training, and excessive bleeding can be readily identified. However, laparotomy requires general anesthesia and is the most invasive biopsy technique. Percutaneous needle biopsy techniques have been described. These techniques may be possible under heavy sedation and are the least invasive method for collecting liver biopsies. Ultrasound guidance is often used, allowing biopsy of focal lesions. It is also possible to biopsy tissue that is deeper within the hepatic parenchyma than is possible with other techniques. However, the specimens that are collected are relatively small and may be inadequate for accurate assessment in some patients. Therefore, if needle biopsy is performed a 14 gauge rather than a smaller needle should be used, except for small dogs and cats where a 16 gauge needle should be used. Excessive hemorrhage after biopsy may not be identified immediately. Laparoscopy allows collection of biopsies using forceps with laparoscopic guidance. This technique requires general anesthesia, but is less invasive than laparotomy. The biopsies collected are larger than needle biopsies and excessive bleeding can be visualized. However, laparoscopy requires specialized equipment and training. Regardless of the technique used, a tiny proportion of the organ is sampled and, because liver disease can affect the hepatic parenchyma in a heterogeneous manner, sampling error is possible. To reduce the effect of sampling error, several biopsies from different areas of the liver should be collected and focal lesions should be specifically biopsied.

Sample handling
It is very important to collect an additional specimen of liver that is stored (placed in a plastic container then frozen) or submitted for copper quantification. The pathologist who evaluates the specimen should be provided with a detailed but concise patient history including results of laboratory testing and diagnostic imaging findings. There are several pathology services that offer evaluation by pathologists who have expertise in histological assessment of the liver, which can be very valuable, especially for unusual cases. I request that sections are stained for copper, iron, connective tissue, and lipofuscin in addition to routine staining with H&E. Liver should be submitted in an appropriate container for aerobic and anaerobic bacterial culture. As bile cultures are more frequently positive than liver culture, bile should be collected whenever possible.

Interpretation of the histology report
It is important to read the descriptive section of the report as well as the diagnosis and comments. The reason for this is that is often possible to obtain useful information about what the pathologist is seeing from this section. It is often helpful to talk directly to the pathologist especially for unusual or challenging cases.

It is beneficial for clinicians to have a basic understanding of the terminology used to describe hepatic histology. It is particular important for clinicians to understand the basic structure of the hepatic lobule an acinus because the localization of lesions can provide vital information. Some commonly used histological terms are defined below:

- Periportal- lesions centered on the portal triads of the hepatic lobule
- Centrilobular- lesions centered around the central vein of the hepatic lobule
- Zone 1 hepatocytes- hepatocytes closest to the hepatic artery and portal (inflow)
- Zone 2 hepatocytes- transitional zone between zones 1 and 3
• Zone 3 hepatocytes- hepatocytes nearest the hepatic venule (outflow)
• Bridging fibrosis- fibrosis connects that portal triads to each other (portal-portal bridging fibrosis) or to central veins (portal-central bridging fibrosis). This is an important step in the progression of chronic hepatitis
• Cirrhosis- Formation of regenerative nodules surrounded by fibrous septa accompanied by vascular disorders (some pathologists do not use this term in dogs or cats)

References/further reading
Hepatic Copper Accumulation: When to Chelate

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Etiopathogenesis
Copper is an essential trace element that amongst other roles acts as a cofactor for cytochrome c oxidase, an enzyme involved in ATP generation (oxidative phosphorylation). It can exist in a variety of oxidative states the most important of which are Cu$^{2+}$ and Cu$^{3+}$.

Hepatic copper accumulation is identified as the underlying cause in approximately one third of dogs with CH. The liver is the principal recipient of copper that is absorbed from the gastrointestinal tract. Copper in hepatocytes is immediately bound to proteins such as glutathione or metallothionein. When the capacity of the hepatocyte copper binding proteins is saturated, free copper ions are released. These are toxic and can lead to the formation of hydroxyl radicals which can subsequently cause oxidative damage to the liver. This results hepatocyte necrosis and a resultant infiltration of inflammatory cells which can be mononuclear or mixed. The inflammatory cells contribute to further tissue injury and with chronicity fibrosis occurs.

Copper can accumulate in the liver due to defects in copper metabolism, cholestasis, possibly increased dietary copper intake, or a combination of these factors. The following breeds of dogs are proven or suspected to be predisposed to primary copper accumulation: Bedlington terrier, West Highland white terrier, Scottish terrier, Skye terrier, Labrador retriever, Dalmatian, and Doberman pincher. It is also possible to see copper associated CH in other dog breeds and in mixed breed dogs.

In the Bedlington terrier, a mutation of the COMMD1 gene that encodes the cellular copper exporter ABCA12 has been identified. This condition is recessive and a genetic test has been developed. The incidence of copper associated CH in Bedlington terriers has been dramatically reduced by testing and selective breeding programs.

A genetic basis for copper associated CH has also been suspected in Labrador retrievers and a genome-wide association study showed an association between increased hepatic copper concentrations and a mutation of the Wilson’s disease gene (ATP7B), which encodes a copper transporter protein. A mutation of another copper transporting protein ATP7A, seemed to attenuate copper accumulation. These mutations only explained about 12% of the heritability of this disease so other genes and environmental factors are also likely to play a role. A genetic basis or contribution is also possible for the other predisposed breeds but further studies are needed to determine whether or not this is the case.

Excess dietary copper intake may also contribute to the development of hepatic copper accumulation. For most laboratories, the reference interval for the hepatic copper concentration of healthy dogs is 120 to 400 ppm dry weight. Nine healthy research dogs fed a standard commercial diet were shown to have a hepatic copper concentrations ranging from 199 to 997 ppm while feral dogs presumed to eat a diet of foraged food had concentrations ranging from 69 to 372 ppm. This might be because commercial dog food contains more copper than the foraged food.

Fanconi syndrome has been reported in dogs with copper associated CH. These dogs had glycosuria in the absence of hyperglycemia, low urine specific gravity, and proteinuria caused by proximal renal tubule injury.

Primary vs. secondary copper accumulation
It is important to try to differentiate between primary and secondary hepatic copper accumulation. Primary copper accumulation tends to occur in the centrilobular zones of the liver. In such cases the hepatic copper content is typically >1,000 ppm and many require chelation therapy. In advanced disease, lobular collapse can make it difficult or impossible to identify the different zones of the hepatic lobules. The breeds previously mentioned that are predisposed to copper associated CH, typically have this pattern of copper deposition. When copper accumulates secondary to cholestasis it tends be found in the perportal zones of the liver and the hepatic copper concentrations are usually <1,000 ppm. Chelation therapy is generally not needed and therapy is aimed at the underlying cause of cholestasis.

Diagnosis
The diagnosis of copper associated CH is made based upon a combination of histological evaluation of liver biopsy specimens and hepatic copper quantification. Copper may not be apparent on standard H&E stained histological sections and is detected most easily using rubecanic acid or rhodamine stains. I therefore request that sections of liver stained for copper are made in every case to make sure copper accumulation it is not overlooked. It is also helpful if the pathologist provides a semiquantitative score for copper.

Although it is possible to measure copper by deparaffinizing a histological block it is much better to collect an extra liver biopsy specimen and save it for copper quantification (freeze sample in a plain container). In all dogs where chronic hepatitis is even a possible differential I submit liver tissue for copper quantification. About 20-40 mg of liver is needed for this and copper is ideally quantified on a dry weight basis. When submitting liver tissue for copper quantification it is important not to sample regenerative nodules as they usually contain less copper than other areas of the parenchyma. Indeed, as copper can be heterogeneously distributed
throughout the hepatic parenchyma and because copper quantification is typically performed on only one specimen results can occasionally be discordant with histological assessment. Recently, computer-assisted image analysis has been used digitally estimate the hepatic copper content. Although this technique does not provide a direct measurement of copper it allows multiple pieces of liver to be evaluated without loss of paraffin embedded blocks.

When do I chelate?
Deciding which dogs with CH to start chelation therapy can be difficult and is the subject of some controversy. Hepatic copper concentrations between 120 and 400 ppm are considered normal and concentrations >1,500 ppm are considered diagnostic for hepatic copper retention. This cutoff of 1,500 ppm was established from early studies of Bedlington terriers and is probably too conservative for other breeds. I consider treating dogs with concentrations >750 ppm with copper chelating agents if there is centrilobular copper accumulation, especially in breeds thought to be predisposed to copper associated CH. If the hepatic copper content is >1,500 ppm I will chelate regardless of the distribution. My reasoning is that regardless of whether the copper accumulation is primary or secondary to cholestasis, at this high level it is likely to be detrimental to the liver. If I get a hepatic copper concentration >400 ppm but <750 ppm with a histology report that reads very much like copper-associated CH, I will consider chelation or at least a copper restricted diet.

Chelation
The idea of treatment with chelating agent is to remove copper from the liver by making it soluble so that it can be excreted in the urine. D-penicillamine is my first choice of chelating agent for dogs (10–15 mg/kg PO q12 hours before feeding). This drug commonly causes gastrointestinal side effects, such as vomiting, diarrhea, and anorexia (about a third of dogs will develop these signs!). If this does happen it may be necessary to give the drug with food and/or reduce the dose. Glomerulonephropathy and dermatological lesions are other reported side effects of this drug that are probably due to idiosyncratic immune reactions. If either of these complications develops, therapy should be promptly discontinued. In humans D-penicillamine can also cause depletion of vitamin B6 and although this has never been reported to occur in dogs, some clinicians supplement this vitamin during treatment.

Trientine (10–15 mg/kg PO q12 hours on an empty stomach) may be used if penicillamine is not tolerated. However, currently it is prohibitively expensive. Dogs with copper-associated CH should also be started on a copper restricted diet, such as one of the commercial liver support diets (these are also supplemented with zinc).

As the optimal duration of therapy has not been determined and is likely to vary between patients it is also challenging to decide how long to chelate for. Prolonged therapy can result in copper deficiency. This can be manifested by microcytic hypochromic anemia, anorexia, vomiting, and weight loss. There is currently no non-invasive method to assess hepatic copper content but monitoring the dog’s clinical signs and liver enzyme activities can provide some indirect information regarding the efficacy of treatment. A decreasing ALT activity during treatment is encouraging. Usually it takes several months for this to return to normal. A study in Labradors suggested that 6–10 months of chelation should be adequate for most dogs. Ideally at this point a second hepatic biopsy procedure and copper quantification is performed.

At this time, if hepatic copper concentrations, when measured, have returned to normal or are <500 ppm, treatment with zinc acetate at a dose of 5–10 mg/kg PO q12 hours of can be initiated. Zinc decreases the absorption of copper from the gastrointestinal tract. Plasma zinc concentrations should be measured during treatment to ensure that toxic concentrations are not reached. Normal plasma zinc concentrations for dogs are 70–200 μg/dL. Concentrations around 200 μg/dL seem to effectively reduce copper absorption but concentrations exceeding 800–1,000 μg/dL may cause hemolysis. The dog should also be continued on a copper restricted diet.

Some dogs require repeated intermittent therapy with D-penicillamine and Bedlington terriers often need lifelong therapy. The decision to restart therapy is usually made based on an increasing ALT activity or ideally repeat biopsy.

Supportive care
The most important aspect of treating copper-associated CH is to treat the underlying cause. However, many veterinarians also start other supportive treatment. Corticosteroids and other anti-inflammatory medications are not advised. As copper hepatic accumulation causes oxidative injury there is a therapeutic rationale for treating with antioxidants such as S-adenosylmethionine or vitamin E. However, it is important to state that neither has been proven to be beneficial in these patients. Therapy for complications of CH such as HE and ascites are discussed in the next session on idiopathic CH.

References/further reading


Idiopathic Chronic Hepatitis: Therapeutic Choices
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Etiology
A variety of factors can lead to liver injury and inflammation in dogs, including drugs (e.g. phenobarbital), toxins (e.g. cycads, aflatoxins, Amanita phalloides, and blue-green algae), infectious agents (e.g. Leptospira spp, canine adenovirus-1, Heterobilharzia americana, and Bartonella sp.), hepatic copper accumulation, and possibly autoimmune disease. However, some of these factors, such as Amanita phalloides intoxication and most drugs (with the exception of phenobarbital) are more likely to cause acute liver injury than CH. Copper accumulation is the cause of CH in about a third of dogs but in many (about 60%) by the time CH is diagnosed it is not possible to identify an underlying cause. For these dogs, the term idiopathic CH is used.

In a study of dogs from the UK, the following breeds were shown to be at increased risk of developing CH: American Cocker Spaniel, Cairn terrier, Dalmatian, Doberman pincher, English cocker spaniel, English springer spaniel, Great Dane, Labrador retriever, and Samoyed. However, this study did not differentiate between copper-associated CH and idiopathic CH and some of these breeds are also thought to be at increased risk of developing copper-associated CH. The median age of dogs in this study was 7 years with a range of 7 months to 16 years. Some breeds such as Doberman pinchers, Labrador retrievers and West Highland white terriers can develop either copper associated and idiopathic CH.

There are several other theories to explain the development of CH in dogs. An autoimmune etiology has been postulated but not confirmed in some breeds such as Doberman pinchers, English springer spaniels, and Cocker spaniels. Chronic hepatitis seems to be more common in female Doberman pinchers than males and studies from Scandinavia showed a strong association with dog leukocyte antigen class II alleles and haplotypes. Such an association has also been demonstrated in English springer spaniels. However, this does not necessarily imply an autoimmune etiology. Additionally, studies have demonstrated autoantibodies against various proteins found in the liver in dogs with CH. However, this does not determine whether these antibodies are a cause of CH or the result of tissue injury. It does not appear that the recently canine hepavivirus is a cause of CH and although enteric bacteria are a known cause of cholangitis and cholangiohepatitis in dogs they have not been proven to cause CH.

Pathogenesis
Regardless of the underlying cause CH is a syndrome that is histologically characterized by hepatocellular necrosis or apoptosis, a mononuclear or mixed inflammatory infiltrate, regeneration, and fibrosis. Chronic inflammation of the liver can lead to activation of myofibroblasts, including hepatic stellate cells and portal fibroblasts. This results in hepatic fibrosis, which can diminish liver function as hepatocytes are replaced by collagen and can contribute to the development of portal hypertension. As the liver has a large functional reserve capacity, loss of liver function is detected relatively late in the course of CH. Portal hypertension and decreased hepatic synthesis of albumin contribute to the development of ascites, which is a poor prognostic indicator in these dogs. This is probably because ascites occurs late in the course of CH and usually signifies that irreversible changes to the portal circulation have occurred. Hepatic portal hypertension can also lead to the development of acquired portosystemic collateral blood vessels. These allow ammonia rich blood from the splanchnic circulation to bypass the liver, which in turn may lead to hepatic encephalopathy (HE).

Clinical findings
Although certain breeds of dog seem to be predisposed to CH, dogs of any breed can develop this syndrome. It is important to remember that early in the course of CH, dogs may not show any clinical signs. Later in the course of disease, clinical signs may become apparent. The most common are anorexia, lethargy, vomiting, polyuria, and weight loss, which are not specific for CH or hepatobiliary disease. More liver specific signs such as icterus, ascites, or hepatic encephalopathy tend to occur later still in the in the end-stage of CH.

Diagnosis
The diagnostic approach for a dog with increased serum liver enzyme activities is discussed in a previous lecture. It is important to remember that dogs with CH can have normal results upon serum bile acid testing and may not have abnormalities of the liver upon abdominal ultrasound examination. Chronic hepatitis is definitely diagnosed by histological evaluation of a liver biopsy specimen. Sometimes this also allows an etiological diagnosis to be made. Idiopathic CH is diagnosed by excluding underlying causes of chronic inflammation. The clients should be carefully questioned to rule out hepatotoxins. It is important to rule out copper accumulation by histological staining for copper and copper quantification. Liver tissue and bile should be submitted for bacterial culture (in my experience bacterial growth is uncommon). If histology reveals granulomatous hepatitis, further testing for geographically relevant infectious agents is indicated (e.g. Bartonella sp, Heterobilharzia americana, systemic fungal diseases).
Anti-inflammatory drugs

There is limited information supporting the use of the anti-inflammatory drugs in the treatment of idiopathic CH. A retrospective study of 151 dogs with chronic hepatitis of various causes found that those treated with corticosteroids survived longer than those that were not. However, these results should be interpreted with caution as the retrospective design of this study meant that it was susceptible to bias as the clinicians may have decided to start corticosteroids in dogs that were more likely to have a favorable response. The results of a more recent retrospective uncontrolled study of 36 dogs with idiopathic chronic hepatitis found that hepatic inflammation decreased and coagulation parameters returned to normal after 6 weeks prednisolone treatment and in some dogs the stage of hepatic fibrosis remained the same or improved. However, the majority of these dogs had a recurrence of clinical signs or residual disease at the end of treatment. Randomized placebo controlled clinical trials are needed before definitive recommendations can be made. Currently, when there is histological evidence suggesting a significant component of inflammation I consider using anti-inflammatory drugs such as prednisolone. Typically, a dose of 1–2 mg/kg/day PO is initially started and is then gradually tapered. It should be noted that high dosages of prednisolone/prednisone often cause vacuolar hepatopathy and other signs, which can be detrimental to these dogs. Monitoring response to treatment is difficult because liver enzyme activities usually increase after starting treatment with prednisolone. Some authors recommend a second liver biopsy procedure 6 weeks after initiation of treatment. Other anti-inflammatory drugs that are sometimes used in place of prednisolone include azathioprine (2 mg/kg PO q48 hours) and cyclosporine (5–10 mg/kg/day PO). Neither has been proven to be beneficial and azathioprine can be hepatotoxic.

The use of “hepatoprotectants” in canine chronic hepatitis

Nutraceuticals and other hepatoprotectants are often used in the management of dogs with CH and other liver disease. Unfortunately, there are very few clinical trials in dogs that have assessed their efficacy. This can make it difficult for clinicians to know when their use is justified. By understanding how these agents work it is easier to make rational treatment decisions. It is important to state that these agents are not a substitute for treating the underlying cause of hepatic disease.

Because of its central role in metabolism the liver is very susceptible to oxidative damage. Oxidative damage is important in the pathogenesis of a range of hepatic diseases, including CH. S-adenosylmethionine (SAMe) is a precursor of the important hepatic antioxidant glutathione. The main rationale for using this agent is that it helps prevent oxidative damage by preventing depletion of hepatic glutathione. It has also been purported that SAMe may have anti-inflammatory properties, modulate apoptosis, and be anticarcinogenic. However, these effects have not been documented in dogs. At the recommended dose of 20 mg/kg PO q12 hours SAMe has rarely been reported to have side effects in dogs other than occasional vomiting after dosing. S-adenosylmethionine is indicated in a range of liver diseases where oxidative stress is believed to be a contributing factor, including CH. However, it is important to note that there is currently little evidence supporting the efficacy of SAMe in dogs. Oral administration of SAMe has been shown to reduce oxidative stress but not histological changes consistent with vacuolar hepatopathy in dogs receiving prednisone.

Silymarin is extracted from the milk thistle plant. Silibinin is the most biologically active component of silymarin. Silymarin is believed to have antioxidant effects by scavenging free radicals and reducing lipid peroxidation. It is also believed to have anti-inflammatory and antifibrotic properties. Additionally, silymarin may be a choleretic agent. At commonly used doses silymarin does not appear to cause side effects although its bioavailability is low. Potential indications for silymarin include acute liver injury and CH. Again, there is very limited evidence to support its efficacy in the veterinary literature. In one study of Beagles administered Amanita phalloides toxin, 11 dogs treated with intravenous silibinin survived whereas four out of twelve control dogs died. In a study of dogs being treated with the chemotherapy agent lamustine, dogs treated with a product containing silymarin, SAMe, and phosphatidylcholine (Denamarin) were shown to have smaller increases in serum ALT and ALP activities than those that were not, suggesting a hepatoprotective effect.

Ursodeoxycholic acid (UDCA) was found to be the active compound in the traditional Chinese remedy of dried black bear bile. Ursodeoxycholic acid is a hydrophilic bile acid that is believed to have multiple beneficial properties including: choleretic effects, displacement of other more toxic bile acids from the circulating pool, an antiapoptotic effect, and immunomodulatory effects. When used at a dose of 15 mg/kg/day PO this drug has few side effects other than causing occasional diarrhea. Because of its choleretic effect and the displacement of more toxic hydrophobic bile acids it makes sense to use this drug in dogs with intra or extrahepatic cholestasis. Due to its claimed immunomodulatory and antiapoptotic there is a theoretical reason to use UDCA in dogs with CH. However, evidence supporting the use of UDCA in dogs is limited to a few case reports.

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

Supportive care is also important for these dogs. Dogs with hepatic disease, especially those with portal hypertension are at increased risk of gastroduodenal ulceration. Consequently, treatment with omeprazole (1 mg/kg PO 12-24 hours) is indicated is GI bleeding is suspected. The development of ascites in dogs with CH is a poor prognostic indicator. Furosemide can lead to hypokalemia and metabolic acidosis both of which can precipitate HE in humans. The aldosterone receptor antagonist spironolactone (2 to 4 mg/kg PO q12 hours) is therefore a better initial choice. If this is ineffective furosemide can be added starting at a low dose (1 mg/kg PO q12 hours). Severe protein restriction is no longer recommended for dogs with hepatic encephalopathy (HE) as this can lead to protein malnutrition. It is important to also note that dogs with liver disease that do not have signs of HE likely do not benefit from dietary protein restriction. Non-meat protein based diets are sometimes recommended for dogs with HE. Once the signs of HE are controlled with a commercial hepatic support diet, it is recommended to add non-meat protein to the patient’s diet to help prevent protein malnutrition. Lactulose can be given orally to patients with chronic HE. It is usually started at a dose of 1 to 3 mL per PO per 10 kg of body weight every 6 to 8 hours. The dose is then adjusted until the patient passes three to four soft stools per day. Neomycin is a poorly absorbed aminoglycoside antibiotic that is sometimes used to treat HE in dogs. The gastrointestinal absorption of neomycin is very low, but can be increased in patients with decreased gastrointestinal motility or bowel wall damage. Substantial systemic absorption can cause ototoxicity and nephrotoxicity. Metronidazole is another antimicrobial that is sometimes used for the treatment of HE in dogs. Metronidazole is usually given at a dose of 7.5 mg/kg PO q8-12 hours in dogs with HE.

Anti-fibrotic medications

Colchicine impedes microtubule polymerization during mitosis and therefore is believed to inhibit fibrosis and inflammation. Colchicine is frequently associated with gastrointestinal side effects in dogs and aside from a few case reports from which it is very difficult to prove efficacy there is little evidence to support its use. I therefore do not recommend using this drug.

References/further reading

Increased Liver Enzymes in Dogs: What Do I Biopsy?
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Increased serum liver enzyme activities, especially alkaline phosphatase (ALP) activities, are commonly identified in dogs. These increases represent a diagnostic challenge to clinicians for a number of reasons. Firstly, sometimes increased serum liver enzymes activities occur due to primary hepatobiliary disease and other times they can occur secondary to extrahepatic disease. This may be because tissues other than the liver also produce these enzymes. Additionally, the liver plays a major role in the metabolism and the excretion of drugs, as well as exogenous and endogenous toxins. The liver is perfused by the portal circulation, whereby a large proportion of its blood supply comes from the splanchnic circulation via the portal vein. Consequently, the liver is susceptible to injury caused by a variety of toxins, diseases in other parts of the body, as well as ischemia. Thirdly, sometimes increased liver enzyme activities can occur due to benign processes, such as hepatic nodular hyperplasia or can be due to conditions that are progressive and require early intervention to have an optimal outcome, such as chronic hepatitis. This can make it difficult for clinicians to know how aggressive to be when working up these dogs. Performing extensive diagnostic evaluation, including invasive tests such as liver biopsy, is costly causing some clients to be reluctant or unable to proceed. Sometimes in depth evaluation of dogs with increased serum liver enzyme activities is not required. For example, when there are mild increases in ALP activity. Despite these obstacles and uncertainties, using a logical approach clinicians can prioritize which dogs require liver biopsy, which require investigation for extrahepatic disease, and which can be managed less aggressively.

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

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

Initial patient evaluation
There are many causes of increased liver enzymes activities, so it very important for clinicians to go from a list of all the possible causes to a list of all the causes that are “probable for that patient on that day”. Information collected during history taking and physical examination is often very helpful when doing this. The patient’s signalment can help refine the differential list. For example, very young dogs are more likely to suffer from congenital conditions, e.g., congenital portosystemic shunts (CPSS) or certain infectious diseases, e.g. infectious hepatitis than neonplasia or inflammatory conditions, e.g. chronic hepatitis. Some breeds, i.e. Bedlington terriers, Skye terriers, West Highland white terriers, Dalmatians, and Labradors are predisposed to copper associated chronic hepatitis. Doberman pinchers and Cocker spaniels are predisposed to idiopathic chronic hepatitis. The breeds of dog predisposed to CPSS include the Maltese terrier, Yorkshire terrier, Havanese terrier, pug, and miniature schnauzer. Increased serum liver enzyme activities are more concerning in these breeds. When taking a history, it is very important to ask specifically about exposure to hepatotoxins such as cycads, blue green algae, amanita mushrooms, aflatoxins, heavy metals, xylitol, or chlorinated compounds. A variety of drugs can also be hepatotoxic, these include: ketoconazole, various antimicrobial agents, azathioprine.
carprofen, lomustine, acetaminophen, ketoconazole, mitotane, and phenobarbital. It is important to specifically ask about any herbal remedies that the dog is receiving as many of these have been reported to be hepatotoxic, including: herbal teas, pennyroyal oil, and comfrey. Ascertaining the dog’s vaccination history is also worthwhile as leptospirosis and canine adenovirus-1 can cause hepatic injury. Early in the course of liver disease dogs may not have any clinical signs. The earliest clinical signs seen in dogs with liver disease are often non-specific and include: vomiting, diarrhea, weight-loss, polyuria/polydipsia, and hyporexia. More liver specific signs such as icterus, ascites, and encephalopathy occur in late in the progression of chronic hepatitis. When any of these clinical signs are present, they warrant further investigation in an attempt to determine their cause. Certain historical findings may be relevant because they are suggestive of an extrahepatic disease that can cause increased liver enzyme activities. For example, polyphagia is consistent with diabetes mellitus or hyperadrenocorticism. Physical examination findings consistent with hepatobiliary disease include: icterus, ascites, poor body condition, stunted growth, hepatomegaly, or signs of hepatic encephalopathy. It is important to emphasize that dogs with hepatobiliary disease do not always display clinical signs or have abnormal findings on physical examination. Physical examination may also reveal findings that are suggestive of extrahepatic disease. For example, bilateral symmetrical alopecia is consistent with hypothyroidism or hyperadrenocorticism.

Routine laboratory testing
Other changes on a serum biochemistry panel can provide important clues as to the cause of increased serum liver enzyme activities. When serum concentrations of albumin, cholesterol, glucose, and urea are below the lower limit of the reference interval or towards the lower limit of the reference interval, and/or when the serum bilirubin concentration is above the higher limit of the reference interval, this is consistent with decreased hepatic function. It is important to remember that these changes are not specific for hepatobiliary disease. For example, the serum bilirubin concentration may also be increased when there is hemolysis. Additionally, due to the large hepatic functional reserve capacity, liver disease must be severe before these changes are seen. Patterns of serum liver enzymes activities can be suggestive of certain pathologies. For example, during cholestasis the serum activity of ALP is dramatically increased and is higher relative to that of ALT. There may also be evidence of extrahepatic diseases. Analysis of a complete blood count can suggest inflammatory conditions, rule out hemolysis, and if microcytosis is present this is consistent with portosystemic shunting (or iron deficiency). Urine specific gravity can be decreased in patients with hepatic insufficiency or portosystemic shunts. Excessive bilirubinuria in dogs implies hemolytic or hepatobiliary disease. Urate urolithiasis seems to be more common in patients with portosystemic shunts than those with other types of hepatic dysfunction. However, it should be noted that urate crystalluria is not specific for hepatobiliary disease.

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

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

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

Measurement of plasma ammonia and paired preprandial and postprandial bile acids are sensitive tests for portosystemic shunting and one of these tests should be performed when this is suspected. However, because of the hepatic functional reserve capacity, these tests are not as sensitive for detecting hepatic insufficiency in the absence of shunting and normal results do not rule out severe liver disease. Therefore, performing these tests does not always alter the decision whether or not to perform hepatic biopsy.
In selected cases, hepatic cytology is useful as it can lead to a definitive diagnosis of certain diseases and can be highly suggestive for the presence of others. Indications for performing hepatic cytology are a suspicion that a round cell tumor is present, when infectious agents, for example *Histoplasma capsulatum* are suspected, and when hepatic masses are observed on abdominal ultrasound.

To make a definitive diagnosis of primary hepatic disease liver biopsy is often required. Prior to doing this the patient’s risk of hemorrhage should be assessed by measuring prothrombin and activated partial thromboplastin time, ideally measuring serum fibrinogen concentration, performing a platelet count, and performing a buccal mucosal bleeding time. Liver biopsy techniques in dogs include: percutaneous needle biopsy, laparoscopic biopsy, and surgical biopsy. Each technique has its own set of advantages and disadvantages. No matter which technique is chosen, it is important to collect multiple biopsies as well as to save a specimen for copper quantification and another for bacterial culture. Although, supportive treatment, such as the hepatoprotectant agents are important in the management of patients with hepatic disease they are not a replacement for the specific treatments, for example copper chelating agents, that may be indicated once a histological diagnosis has been made. When in doubt, if there is a suspicion of primary hepatic disease it is better to biopsy rather than to delay biopsy until the dog is in end-stage liver failure, at which point treatment is unlikely to be effective.

**When should I biopsy the liver?**

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

- Hepatic biopsy is indicated when a hepatic mass has been diagnosed and a diagnosis has not been made based on cytology
- Hepatic biopsy is indicated when the serum ALT activity has been greater than twice the upper limit of the reference interval for more than 3 to 4 weeks and extrahepatic disease is unlikely to be the cause.
- Hepatic biopsy should be considered when there are multiple acquired portosystemic shunts. Acquired shunts suggest that there is hepatic parenchymal disease e.g. chronic hepatitis, which requires biopsy to be definitively diagnosed. However, acquired portosystemic shunts occur late in the course of disease and are irreversible. Consequently, the prognosis for these dogs is poorer so some clients may not wish to proceed. They can also occur due to pre hepatic portal hypertension e.g. due to portal vein thrombosis.

**References/further reading**


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Protein Losing Enteropathy: Improving Outcomes
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Protein-losing enteropathy (PLE) is defined as the loss of protein from the intestines due to intestinal disease. Often, this results in hypoalbuminemia, and may be accompanied by hypoglobulinemia. Strictly, any condition leading to abnormal protein loss from the intestines is a PLE. However, if the patient’s serum albumin is not decreased, this protein loss often goes un-noticed. Any intestinal disease, if severe enough, can result in PLE. The underlying mechanisms for this are disruption of the intestinal the mucosal barrier and/or lymphatic dysfunction. Protein losing enteropathy is therefore classified as being a syndrome rather than a disease. Protein losing enteropathy is much more commonly diagnosed in dogs than cats. Diseases that have been found to cause PLE in dogs include: intestinal lymphangiectasia (IL), inflammatory bowel disease (IBD), intestinal neoplasia (especially lymphoma), fungal infections, intussusception, and gastrointestinal (GI) parasites. Protein losing enteropathy can lead to some important consequences in our patients, which can even be life threatening.

Clinical presentation
Due to the diverse range of underlying conditions that cause PLE, any age, breed, or sex of dog may develop PLE. However, some breeds have been demonstrated to be particularly at risk. These include Yorkshire Terriers, Rottweilers, German Shepherd Dogs, Soft Coated Wheaten Terriers, Norwegian Lundehunds, and Basenjis.

The most common clinical signs of PLE are diarrhea, vomiting, and weight loss. It is important to remember that some dogs with PLE may not vomit or have diarrhea, these dogs usually but not always present with weight loss. Other clinical signs may be due to the loss of serum proteins, especially albumin, including ascites, edema and pleural effusion. Occasionally, dogs suffering from PLE develop respiratory distress due pulmonary thromboembolism. During PLE, blood proteins including antithrombin is lost into the intestines potentially making them hypercoagulable. However, a study using thromboelastography showed that all 15 dogs with PLE enrolled were hypercoagulable but this was not entirely explained by decreases in antithrombin. Ionized hypocalcemia can occur secondary to hypovitaminosis D. This hypocalcemia may be manifested as muscle tremors or even seizures.

Physical examination may reveal weight loss and poor body condition due to mal-nutrition. Thoracic auscultation may reveal decreased lung sounds due to pleural fluid. Swelling of the legs and/or ventral parts of the body due to edema may be present. Abdominal palpation may reveal a fluid wave, abdominal masses, enlarged organs, enlarged lymph nodes, or thickened bowel loops.

Diagnostic approach
As discussed before, many animals with PLE have non-specific signs of gastrointestinal disease. However, some dogs will present with weight loss alone or decreased serum albumin may even be noticed as an incidental finding. A serum biochemistry panel will confirm hypoalbuminemia. Globulin concentration can be decreased, normal, or increased, so it is the albumin concentration that is more important to consider.

Once hypoalbuminemia has been documented it is tempting to diagnose PLE in any dog with gastrointestinal signs. However, there are other possible causes of hypoalbuminemia and these can be associated with clinical signs of diarrhea, vomiting, and weight loss. The possible causes of a serum albumin concentration below 2.0 g/dL are hepatic insufficiency, severe dermatological disease, protein losing nephropathy, and protein losing enteropathy. To diagnose PLE, the three other possible causes should be ruled out (or increased fecal protein loss should be demonstrated). The possibility of liver disease is investigated by interpretation of a serum chemistry panel and possibly measuring a pre- and postprandial bile acid concentrations. The presence of severe dermatological disease is easily determined during physical examination. Protein losing nephropathy is investigated by measuring the amount of protein in the urine. This can initially be done by urinalysis and if urinary protein loss cannot be ruled out this way, a urine protein to creatinine ratio should be performed. It is also very important to consider hypoadrenocorticism as a cause of low albumin. When PLE cannot be diagnosed by ruling other causes of severe hypoalbuminemia it may be helpful to document fecal protein loss using the fecal alpha-1 protease inhibitor test.

Once PLE has been confirmed, efforts should be made to find the underlying cause. Abdominal ultrasound is frequently the most useful imaging modality for assessing the gastrointestinal system of small animals. Changes on abdominal ultrasound, such as hyperechoic mucosal striations, can often be observed with PLE patients, but these seldom give us a definitive diagnosis. Microscopic evaluation of intestinal biopsy specimens is often the most informative test. Intestinal biopsies can be collected via endoscopy, via an open abdominal surgery, or via laparoscopy. Each technique has its advantages and disadvantages. At Texas A&M, endoscopy is often performed initially. It is very important to perform an upper and lower gastrointestinal tract endoscopy so that the stomach, duodenum, ileum, and colon can all be biopsied. In most cases when combined with the clinical presentation, laboratory tests and imaging
findings, histopathologic analysis of endoscopic intestinal biopsies can lead to at least a provisional diagnosis, and guide initial treatment. However, sometimes a final diagnosis is only made after assessing the patient’s response to treatment.

**Common causes**

Intestinal lymphangiectasia is characterized by dilation of the lymph vessels of the intestines. It is believed to be the most common cause of PLE in dogs. Intestinal lymphangiectasia occurs in both a congenital form (primary IL) and an acquired form (secondary IL). Primary IL is a developmental abnormality that leads to an insufficiency or malformation of the lymphatics. This condition may affect other parts of the body as well as the intestines. Secondary IL is due to obstruction of lymph flow. This develops either due to physical blockage of the lymphatics, or high venous pressure. The lacteals can be physically blocked by inflammation or cancer of the intestines. When the lymph flow is obstructed, high protein lymph leaks out into the intestinal wall. This leakage of protein contributes to the intestinal disease as it can cause inflammation and secondary granuloma formation, which can further impede lymph flow.

Because of the inflammation that develops secondary to IL, it can be very difficult/impossible to differentiate primary IL and IL secondary to chronic enteropathy. Yorkshire Terriers, Maltese Terriers, Rottweilers, and Norwegian Lundehunds are predisposed to IL (probably primary IL). During endoscopy, distended lacteals may be visible as multiple white spots on the intestinal mucosa.

Inflammatory bowel disease is defined as a group of idiopathic, chronic gastrointestinal disorders characterized by mucosal inflammation. It is diagnosed on the basis of observing inflammatory cell infiltrates in the bowel wall on intestinal biopsies and ruling out other causes for the inflammation. These other causes of chronic enteropathy in dogs include dietary intolerance or allergy, antibiotic responsive enteropathy (intestinal disease). In idiopathic IBD, inflammatory cells accumulate in the bowel wall for an unknown reason. The inflammation is often classified according to which cell types are most abundant. Lymphoplasmacytic inflammation is the most commonly identified variety of IBD in dogs and cats. IBD must be severe in order to result in intestinal protein loss.

Certain breeds of dog are predisposed to getting distinct forms of PLE. Soft Coated Wheaten Terriers often develop a hereditary PLE characterized by IL and inflammation of the intestinal wall with a concurrent protein losing nephropathy. Basenji’s can develop what is described as an immunoproliferative enteropathy. Lundehund syndrome is characterized by gastritis, IL, and IBD.

Lymphoma can affect many parts of the body, including the intestines. Roughly 75% of dogs with intestinal lymphoma will have hypalbuminemia. Lymphoma can be diagnosed based on intestinal biopsies, although endoscopic biopsies may not be deep enough to distinguish this cancer from intestinal inflammation. Laboratory tests such as immunophenotyping and PCR for antigen receptor rearrangements can help differentiate lymphoma from IBD. Adenocarcinoma and other tumors may also cause PLE due to blood loss and mucosal ulceration. These tumors may be confined to one section of the intestine. Because of this it may not be possible to reach them with an endoscope. Consequently, surgical biopsy or fine needle aspiration of any mass that is present may be required. Abdominal ultrasound can help in selecting which sampling technique is best to use.

*Histoplasma capsulatum* is a fungal organism that can cause gastrointestinal disease in dogs. It is unusual for Histoplasma to affect the gastrointestinal tract of cats, but it is reasonably common in dogs, although usually other organs are also affected. Diagnosis can often be made on cytological evaluation of rectal scrapings, lymph node aspirates, hepatic aspirates, or splenic aspirates, depending upon which organs are affected. Occasionally the diagnosis is made on intestinal biopsy, but this is not usually necessary. A urine/serum antigen test (*Histoplasma EIA, Mira Vista Laboratories*) is also available.

**Treatment**

As there are many underlying causes of PLE in our patients there is no single treatment protocol for this syndrome, every patient has different needs. The aims of therapy are to treat the underlying cause and to support the patient. Treatment of IL and IBD as well as supportive care are discussed below.

The mainstay of treatment for IL is feeding an ultra-low-fat, highly digestible diet. Reducing the dietary fat content decreases the amount of fat that needs to be transported in the intestinal lacteals, thereby to some extent reducing the problem of the lacteal obstruction. The commercial diets with the lowest fat contents are Royal Canin Gastrointestinal Low-Fat, Purina EN Low Fat, and Hill I/D Low-Fat. An alternative is to use an ultra-low-fat home cooked diet, for example, boiled turkey breast and rice. This diet can be used initially and if the patient responds after 2–3 weeks, it must be supplemented in order to make it nutritionally balanced. Commercial weight-loss diets are not suitable for dogs with PLE because although they have a fairly low fat content they are calorie restricted and usually these dogs are already severely malnourished. Some very sick PLE patients may benefit from being fed an elemental diet such as Vivonex T.E.N. Elemental diets very easy to digest, as they contain amino acids rather than proteins. If using an elemental diet, it is important to select one with a very low fat content. They are expensive and so are typically used to provide short-term nutrition. In many cases of IL there is a component of inflammation. The presence of inflammation is determined by evaluation of intestinal biopsy specimens. If this is the case, the patient may benefit from anti-inflammatory medications. Common choices are prednisone, chlorambucil, and cyclosporine (see below). The justification for these medication in cases of IL is to prevent the development of lymphatic granulomas, which can impede lymphatic drainage.
As previously discussed, IBD must be severe in order to cause PLE. Consequently, aggressive treatment is needed. Anti-inflammatory drugs are the main treatment for IBD. Common choices are prednisone (2 mg/kg PO per day), chlorambucil (2-4 mg/m² PO q24 hours) cyclosporine (5 mg/kg PO q24 hours), and azathioprine (2 mg/kg PO q48 hours). Prednisone and prednisolone are the most commonly used anti-inflammatory drugs for treating IBD, and are cheap and frequently effective. However, these drugs often have unwanted side effects when used at higher doses. Azathioprine is often used in conjunction with prednisone to provide additional immunosuppression, or so that a lower dose of prednisone can be used. This drug can have serious side effects (it can affect the liver and the bone marrow) and should NOT be used in cats. Furthermore, it takes up to 2-3 weeks of treatment before it is fully effective. This is an important consideration for a sick patient. Cyclosporine is a newer immunosuppressive drug that is generally well tolerated and acts quickly. It is expensive, especially for larger dogs, and there is currently not much data to support its use in IBD, although the preliminary data is encouraging. A recent retrospective study suggested that a combination of prednisolone and chlorambucil was more common than a combination of prednisolone and azathioprine for treating dogs with chronic enteropathy including those with PLE. Dietary management is also important in dogs with IBD. Often dogs with IBD and PLE have not undergone a diet trial prior to biopsy, so a diet trial with a novel antigen or hydrolyzed antigen diet is frequently worthwhile. However, if microscopic evaluation of the intestinal biopsies suggests or confirms a diagnosis of IL, I advise feeding an ultra-low-fat diet.

Supportive care
Because of their hypoalbuminemia, gastrointestinal disease, and their potential to develop spontaneous blood clots PLE patients are fragile. Supportive care is therefore extremely important.

Providing adequate nutrition is vital. Patients, who are vomiting or have severe gastrointestinal disease, may not willingly eat. Often, treatment of nausea with anti-emetics such as maropitant (Cerenia; 1 mg/kg SQ/IV q24 hours) is the first step to take. If this is not effective, tube feeding may be needed. In small to medium sized dogs an esophageal feeding tube is my preference, whereas I typically place gastrotomy tubes endoscopically in larger dogs, and in giant breeds or deep chested breeds surgical placement of a gastrotomy tube may be needed. Forced syringe feeding is not a practical solution. The dog’s resting energy requirement (RER) should be estimated. It is advisable to initially feed half or one third of the estimated RER during the first 24 hours before gradually increasing the amount. With emaciated dogs eventually it is important to feed more calories than the estimated RER so that they gain weight. One method is to estimate a target weight for the dog and feed the RER calculated based on this.

When necessary administration of intravenous fluids that provide oncotic support can help reduce fluid accumulation and therefore stabilize the dog’s circulation. This can be important prior to or during anesthesia. However, often these dogs have had chronic hypoalbuminemia and so they have compensated for their low blood oncotic pressure and do not require colloidal support. Synthetic colloids (e.g. Hetastarch or Vetastarch) are currently my preference for providing colloidal support to dogs with PLE. Human albumin solutions are available and are sometimes used in severely hypoalbuminemic dogs but can be associated with severe side effects due to immune reactions. Canine albumin has intermittently been available in the US and in theory should avoid these problems. Plasma transfusion is not a practical way to provide increase a dog’s serum albumin in most cases as relatively large amounts need to be given, which for all but very small dogs is cost prohibitive.

Measures to reduce the risk of thrombosis include giving ultra-low dose aspirin (0.5 mg/kg PO q24 hrs) or preferably clopidogrel (Plavix; 1–3 mg/kg PO q24 hours), meticulous care of IV catheters, not placing unnecessary IV catheters, and frequently encouraging the patients to move.

Dogs with PLE often have low serum vitamin B12 (cobalamin) concentrations as they cannot absorb this vitamin from their small intestine. Supplementing cobalamin by subcutaneous injection or orally can correct this, and may improve the patient’s gastrointestinal signs, as well as their appetite. It is important to use cyanocobalamin and not vitamin B mixtures, as these do not contain sufficient cobalamin. Supplementation with vitamin K (1 mg/kg SQ q24 hours for 3 to 5 days) is indicated in patients with prolonged clotting times. In dogs with symptomatic or severe ionized hypocalcemia, supplementation with calcium and calcitriol is indicated.

References/further reading