Beyond the Bloodwork: Diagnostics for Liver Disease
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The liver is a vital organ necessary for many functions in the body, including nutrient metabolism and detoxification of various substances. As a result, liver dysfunction due to many different etiologies can be potentially life threatening. The powerful regenerative capability of the liver, however, makes early disease detection critical when considering a favorable long term prognosis.

Liver diseases can be divided into two broad categories: hepatocellular injury and hepatocellular dysfunction / failure. Clinical signs may overlap between these two groupings, and in general will typically be non-specific with liver disease. These categories can frequently be differentiated based on initial laboratory work, including a serum chemistry panel, complete blood count, and urinalysis. More often, however, baseline blood work will be suggestive of generalized liver disease but more information will be required to make informed decisions on treatment and prognosis.

Serum biochemistry profile
ALT, AST, ALP, and GGT are all liver enzymes that can be elevated with liver injury or dysfunction. The pattern of elevation can be helpful in determining the source of the injury. For example, if ALT and AST are substantially higher than ALP then damage to hepatobiliary cells should be suspected. If, however, GGT and ALP are more elevated compared to ALT then biliary obstruction or cell membrane damage should be suspected. Elevated total bilirubin would also be expected with the latter (Center SA 2007). With severe liver disease (ie. chronic active hepatitis, fibrosis, cirrhosis, toxicity-induced failure, etc.) all four of the previously mentioned enzymes may be markedly elevated due to multifactorial cellular injury. Caution should be taken when evaluating a case where ALT and AST are the only elevated liver enzymes, as these enzymes are found in myocytes and muscle injury will cause their release.

In addition to liver injury and membrane damage, late-stage hepatocellular dysfunction may also be recognized on a biochemistry profile, characterized by a deficiency in products made by the liver. This may include hypoglycemia, hypocholesterolemia, and hypoalbuminemia. These results remain non-specific, as various gastrointestinal and endocrine diseases will have similar results. Normal concentrations of liver-specific enzymes cannot be used to rule out liver disease in these cases either, as with severe liver failure there may be a deficiency of hepatocytes to even synthesize and release the enzymes. An elevation in serum total bilirubin can also be non-specific, as this can be seen with hepatocellular dysfunction (intra-hepatic cholestasis), extrahepatic biliary obstruction, or even hemolysis unrelated to liver disease.

Complete blood count
Red blood cell microcytosis can be seen in some dogs with liver disease, most frequently being seen with a portosystemic shunt. With acute cholangiohepatitis, neutrophilia with or without a left shift may be present. Thrombocytopenia has been reported with late stage liver failure due to a diminished concentration of thrombopoetin (Webster CRL and Cooper JC 2014).

Urinalysis
Isosthenuria may be present due to medullary washout with liver failure secondary to decreased urea nitrogen production. Overflow of bilirubin will also be reflected in the urine, characterized by bilirubinuria. This can be a normal finding in low concentrations, especially in male dogs.

If initial blood work is suggestive of liver disease, additional diagnostics should be pursued in a logical and step-wise fashion.

Blood tests for liver function
When liver function is greatly diminished, many toxins that are ordinarily filtered remain in circulation. The most well documented and easily measured is ammonia. A portosystemic shunt is the most common cause of hyperammonemia, however this can be seen with other diseases that lead to diminished liver function including cirrhosis and fibrosis as well. Measurement of ammonia has historically been challenging due to instability in serum over time, however recent advancements in laboratory technology now allow in-house testing. This now makes serum ammonia concentration testing a reasonable non-invasive first step in the evaluation of liver function. Ammonia testing should be considered especially when the patient has clinical signs suggestive of hepatic encephalopathy.

When diagnosing a portosystemic shunt, fasting serum ammonia concentration has a sensitivity of 85% in dogs. Serum bile acid testing has even higher sensitivity at 93% (Ruland K et al 2010). These results from 2010 contrast a 2006 study where fasting ammonia concentration was found to be both more sensitive (100% vs. 92%) and specific (89% vs. 68%) than serum bile acids for detecting a portovascular anomaly (Gerritzen-Bruning MJ et al 2006). There are many cases where liver function is compromised but not to the extent of hepatic encephalopathy and resulting hyperammonemia, such as with mid-stage chronic active hepatitis. In these cases serum bile acid testing is the preferred first-choice. This test consists of a fasting blood sample followed by feeding the patient...
and then a 2-hour post-meal blood draw. Be aware that mild elevations may be considered normal, especially in some breeds (ie. Maltese) (Tisdall PL et al 1995).

**Other laboratory tests**

Most coagulation factors are synthesized in the liver, making the measurement of prothrombin time and partial thromboplastin time useful cage-side tests to evaluate liver function. Since clotting times are frequently elevated in dogs with liver dysfunction, this is useful information prior to obtaining liver aspirates or biopsies as well.

Plasma protein C can be used to help differentiate portosystemic shunts from microvascular dysplasia, when these are the top differentials for liver dysfunction (protein C was <70% in 88% of dogs with a portosystemic shunt) (Toulza O et al 2006).

**Diagnostic imaging**

Abdominal radiographs can be a sensitive test for evaluating liver size in dogs, with microhepatica being associated with a negative gastric axis on the right lateral view while hepatomegaly presents with a near horizontal gastric axis on the same view.

Abdominal ultrasonography by an experienced ultrasonographer is a useful test for evaluating liver shape and size and investigating echotexture. Size and number of visible intrahepatic vessels, intra- and extra-hepatic bile duct size and shape, presence of single or multifocal nodules or masses, etc. are just a few of the potential abnormalities that can be identified using ultrasound. Surgical planning can be accomplished using ultrasound, especially when finding a single mass versus identifying diffuse infiltrative disease. Mass location, however, can be challenging to definitively identify. A recent study showed only 52% success in correctly locating the lobe affected by a single hepatic mass (Wormser C et al 2016). This should be taken in to account when planning a surgery for a liver lobectomy. Ultrasound is the test of choice for some clinicians for identifying a portosystemic shunt, however sensitivity can be as low as 75% (Berent A and Weiss C 2010). If an anomalous vessel is not directly identified on ultrasound, ancillary findings including bilateral renomegaly and urolithiasis as well as microhepatica and inadequate intrahepatic vasculature can help increase the degree of suspicion for a shunt (d’Anjou MA et al 2004).

There are some liver diseases that have characteristic findings on ultrasound, including a confirmed anomalous vessel. Many diseases, however, have non-specific and sometimes even minimal to no abnormalities seen on ultrasound. A recent study found that 64% of livers that had no ultrasonographic abnormalities had some degree of pathology when biopsies were taken, including moderate to severe fibrosis (Kemp SD et al 2013).

Nuclear scintigraphy can be used as a highly sensitive test for portovascular anomalies, however availability is limited for most practitioners. Computed tomography (CT) is becoming more prevalent and is available in most specialty practices. This test is sensitive for even small liver masses (ie. primary or metastatic) and with angiography can be diagnostic for portosystemic shunts.

**Liver sampling**

A fine needle aspiration is the least invasive method of sampling the liver. This can frequently be done with an awake or lightly sedated patient. Use of a 22-gauge needle with a 6cc syringe is the author’s preference. Ultrasound-guidance can help target specific lesions and avoid important vasculature. Cytology results should be interpreted carefully, however, as diagnostic accuracy is marginal. Correlation between cytology and histopathology of the liver is reported to occur only 30% of the time (17/56 dogs) (Wang KY et al 2004). Vacular hepatopathy was the diagnosis with the highest degree of accuracy, however this was also the most commonly misdiagnosed disease with cytology. Hepatocellular inflammation was incorrectly identified 75% of the time.

While comparisons can be made, as above, to cytology and histopathology, not all biopsy samples are equal either. There are many ways to obtain a liver biopsy, including some of the following: ultrasound-guided tru-cut biopsy, laparoscopic biopsy, punch biopsy, guillotine method, liver lobectomy, etc. Clinician preference and confidence in various techniques plays a significant role in which method is used, as well as the suspected underlying disease. When a single mass lesion is detected a liver lobectomy accomplishing an excisional biopsy may be recommended, whereas a collection of laparoscopic or surgical punch biopsies may be indicated with diffuse infiltrative disease. Equipment availability will also play a role, as laparoscopic capabilities are not available in all practices.

When an abdominal ultrasound identifies diffuse liver disease it is preferable to biopsy multiple liver lobes if possible. Even though the external appearance of the liver may be similar diffusely the histopathology may vary between lobes; odds of obtaining the correct diagnosis increases with each additional liver lobe that is sampled (Kemp SD et al 2015). Method of biopsy has not correlated well with an increased odds of diagnosing the disease, provided at least 3 portal triads are sampled from each lobe (Kemp SD et al 2015).

**References**


Webster CRL, Cooper JC. Diagnostic approach to hepatobiliary disease. *Kirk’s Current Veterinary Therapy XV* 2014;139:569-575.


The large bowel is an uncommon site of disease in the dog, but when present the clinical signs can be severe and often challenging to manage. Constipation and even obstipation may be present with some forms of colonic disease (ie. megacolon), but large bowel diarrhea is more commonly found when the colon is affected. Clinical signs of large bowel diarrhea are often distinctive and include hematochezia, tenesmus, increased frequency of defecation, and pain during defecation. While these signs are characteristic of disease isolated to the colon, frequently colitis will be seen in conjunction with small bowel disease and clinical signs will be less specific, including weight loss, abdominal pain, large volume of stool, etc.

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<th>Clinical signs</th>
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<th>Large bowel</th>
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<td>Weight loss</td>
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<td>Frequency of stools</td>
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Diagnostics for colorectal disease
A detailed history and physical examination will often lead to a high suspicion of colon disease, especially when following the above table if diarrhea is present. Once the pathology has been isolated to the colon, diagnostics should be performed in a step-wise fashion to try and identify the underlying cause. A serum biochemistry profile and complete blood count should be performed but are rarely abnormal with primary colonic disease. One exception is chronic Histoplasmosis, which may present with hypoalbuminemia and hyperglobulinemia. Dogs with chronic colitis, especially older females, will be at an increased risk for an ascending urinary tract infection so a urinalysis should also be included.

A fecal flotation and Giardia ELISA should be tested on all dogs with suspected colitis. Giardia and Trichuris vulpis are two widespread parasitic diseases that can be associated with large bowel diarrhea. A fecal cytology can be helpful especially when trying to identify overgrowth of a single population of bacteria, particularly clostridium spores. If there is clinical suspicion for Histoplasma capsulatum, a rectal cytology should be performed. This is a simple test that can be performed in-house during the physical examination. It is important, however, to not mistake this test for a fecal cytology. Diagnostic accuracy of the rectal scrape depends on penetrating deep to the mucosal layer using either a finger or cytology brush; the organism is unlikely to appear in just mucus or stool. When examining a rectal scrape cytology, neutrophils or large mononuclear cells should be seen indicating that an adequate depth has been achieved. The organisms will be found in clusters within macrophages in most cases. If this test is unrewarding but Histoplasmosis is still suspected then a urine Histoplasma antigen titer can be tested.

Abdominal radiographs are often non-specific and are not sensitive for colonic disease; however mucosal irregularities may be present with a severe nodular colitis. Sublumbar lymphadenomegaly may be present with severe Histoplasmosis or neoplasia. Abdominal radiographs can be helpful identifying megacolon or severe obstipation.

Abdominal ultrasound is more sensitive for detecting colonic wall thickening as well as evaluating the wall layering of the colon, however this modality also has its limitations with the colon. There is a section of colon and rectum within the pelvic canal that cannot be imagined with ultrasound. Additionally, the colon is frequently stool or gas distended, both of which are obstacles to ultrasound penetration. An MRI or CT scan may be alternative methods of advanced imaging that can better evaluate the entire length of the colon and do not suffer from the effect of gas or fecal artifact.

If chronic large bowel diarrhea is present secondary to ulcerative colitis, inflammatory bowel disease, etc. then it is possible all of the above diagnostic tests are within normal limits. Surgical full thickness colon biopsies carry increased inherent risks due to the thin wall and high intraluminal bacterial load, making this a less desirable method of obtaining samples. As a result, colonoscopy is the preferred method of biopsy procurement in dogs with chronic large bowel diarrhea. Adequate colon preparation is vital for thorough investigation of the entire colonic mucosa. This can be accomplished using oral solutions such as GoLytely (50mL/kg PO once to twice the day prior to the procedure) and / or a series of warm water enemas given the day of the procedure. A 36 hour minimum fast is usually recommended. Colonoscopy allows thorough investigation of the entire colonic mucosa, including segments unavailable to ultrasound, as well as allowing a safe method of taking multiple representative biopsy samples. Entry in to the ileum and cecum may also be possible, depending on the level of experience of the endoscopist.
Chronic lymphoplasmacytic colitis
Commonly referred to as inflammatory bowel disease or steroid-responsive diarrhea, lymphoplasmacytic colitis may be an isolated disease or may be one component of diffuse gastrointestinal inflammation. This condition will often contribute to mixed-bowel diarrhea. An underlying cause is infrequently identified, however many theories exist including food allergies. If the patient is clinically stable besides the diarrhea, a diagnosis of exclusion should be initiated. A food trial using a hypoallergenic diet (novel protein, hydrolyzed protein, etc.) should be fed exclusively for a minimum of 2-3 weeks. If there is no clinical improvement then food allergy is considered less likely. An antibiotic trial should then be instituted (metronidazole or tylosin generally). If clinical signs persist, then biopsies should be obtained. In dogs with suspicion of mixed bowel disease, an upper GI endoscopy is often performed just prior to the colonoscopy in order to obtain a wide selection of biopsies. Diagnostic accuracy will be maximized with more good quality biopsy samples representing all aspect of the gastrointestinal tract (Willard MD et al 2001).

If histopathology confirms IBD, then localization of the disease will dictate the therapeutic plan. When inflammation is severe and widespread including small and large intestine, immunosuppression may be indicated. Prednisone is typically the first-line medication for this, with secondary drugs including Cyclosporine A, azathioprine, and more recently choramubicil. Sulfasalazine as monotherapy is indicated if inflammation is restricted to the colon.

Canine ulcerative colitis
The Boxer is the most common breed affected by this disease. It has been categorized as a form of aggressive IBD and occurs more often in young dogs. Unlike traditional IBD, or steroid-responsive diarrhea, ulcerative colitis is typically non-responsive to corticosteroid use. Since this disease affects the aforementioned breeds almost exclusively, there is a presumed genetic predisposition. Until 10-15 years ago this disease was considered to be a highly refractory form of severe IBD and patient morbidity and mortality were high. In recent years, however, a connection with intracellular E. coli has been identified (Mansfield CS et al 2009). Now that a bacterial component has been proven, both morbidity and mortality have decreased significantly. Oral enrofloxacin has been successful in treating many such cases, however recently fluoroquinolone resistance has been determined (Craven M et al 2010). In addition to the Boxer dog, a series of cases with a similar presentation including E. coli identification has been reported in the French Bulldog (Manchester AC et al 2013).

Colorectal neoplasia
Hematochezia, tenesmus, and constipation are some of the more commonly reported clinical signs associated with neoplasia in the colon. The most common tumors seen include adenocarcinoma, lymphoma, and GI stromal tumors (ie. leiomyosarcoma). Positive contrast enema with radiographs, abdominal ultrasound, digital palpation, and endoscopy are all ways that colon and rectal masses can be identified. Histopathology is the only way to definitively determine the diagnosis, which makes colonoscopy an essential tool to reduce morbidity and still make a diagnosis. Prognosis for benign adenomas and stromal tumors is favorable with surgical or endoscopic excision, while malignant neoplastic diseases including lymphosarcoma and adenocarcinoma carry a guarded prognosis even with excision.

Location of a focal mass will dictate the surgical approach and morbidity. A mass in the ascending or transverse colon, provided it is not immediately adjacent to the ileocolic junction, makes surgical excision more routine. A mass in the distal descending colon or the rectum may be much more challenging, especially if it is located within the pelvic canal. A distal rectal mass may be amenable to a rectal pull through surgical approach. This procedure carries a favorable outcome for benign rectal polyps, however there is a high complication rate (78%) with malignant rectal masses, with fecal incontinence being the most common (Nucci DJ et al 2014).

Constipation / obstruction
This is a clinical phenomenon that is more commonly seen in cats than dogs, secondary to colonic hypomotility. When a dog is presented with severe constipation or obstruction, a primary underlying disease should be investigated including outflow obstruction (rectal or colonic mass, prostatomegaly, etc.) or sources of pain while defecating (lumbosacral disease, perianal fistulas, etc.). Inflammatory disorders are more likely to contribute to decreased water absorption and subsequent diarrhea as opposed to constipation.

If idiopathic constipation is identified, one or more warm water enemas may be all that is needed to help relieve the obstruction. If this becomes a recurring problem then special attention should be paid to the patient’s metabolic status, level of hydration, and diet. A stool softener such as lactulose or a moderate fiber diet may help to control the problem. If colonic hypomotility is suspected, using a prokinetic agent such as cisapride may be beneficial.

Rectal prolapse
A rectal prolapse is an easily identifiable abnormality found on physical examination. In most cases there is a history of tenesmus or other large bowel signs that over time will weaken the anal sphincter making prolapse more likely. Rectal or colonic intussusception will look nearly identical to prolapse, and can be differentiated by probing the lateral aspect of the tissue. If the probe advances easily beyond the anal sphincter then an intussusception is present and not a rectal prolapse.
Identification and treatment of the underlying disease (frequently intestinal parasites) should be done prior to surgical correction. A purse string suture can be placed after reduction of the prolapse along with a stool softener, however if the dog continues to have tenesmus there is a high likelihood of prolapse recurrence. If the rectal prolapse persists once the underlying pathology has resolved surgical intervention may be indicated. A colopexy (securing the serosal surface of the colon to the left caudal aspect of the adomen, helps to provide tension to the descending colon and rectum and will help to prevent further prolapse.

References
Diagnosing and Treating Canine Pancreatitis
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Pancreatitis is a commonly diagnosed condition that affects dogs of all ages. Clinical signs can vary greatly depending on both the chronicity and severity of disease. While in some cases pancreatitis is a straight forward diagnosis, the presenting complaints are often vague or non-specific, diagnostic tests may be misleading, and concurrent illnesses may complicate the clinical picture. This is made even more difficult by the lack of a single gold standard test.

Diagnosing pancreatitis

- Clinical signs
  - Mild pancreatitis: Decreased appetite, lethargy, loose stools, etc.
  - Severe pancreatitis: Vomiting, diarrhea, abdominal pain, lethargy, fever, hypovolemic shock

- The initial diagnostic testing should help to begin ruling out other illnesses with similar presenting complaints, including gastroenteritis, acute renal failure, gastrointestinal obstruction, cholangiohepatitis, etc.
  - A thorough medical history may be the most important step in making a diagnosis. Questions should focus on whether there have been any changes in diet, has the dog eaten anything unusual lately, is he taking any medications, are there any concurrent illnesses, etc.
  - Physical examination: Is the patient clinically dehydrated, is there abdominal pain (focal vs. non-specific), is nausea present, how do stools look on rectal examination.
    - Will guide the clinician towards a working diagnosis as well as help to start formulating a treatment plan.
  - Baseline blood work: When a dog is presented for evaluation of vague, non-specific clinical signs initial lab work should include a minimum of a serum chemistry panel, complete blood count, and urinalysis.
    - Abnormalities that may be seen directly related to or secondary to pancreatitis may include:
      - Inflammatory leukogram (mild to marked)
      - Non-regenerative anemia
      - Thrombocytopenia (with severe necrotizing pancreatitis, leading to DIC)
      - Azotemia (pre-renal or renal)
      - Cholestasis (secondary to post-hepatic biliary obstruction from inflamed pancreas)
      - Hypoalbuminemia (negative acute phase protein)
      - Elevated amylase and lipase (variable)
      - Metabolic acidosis secondary to azotemia, poor perfusion, etc.
      - Isosthenuria
  - If vomiting and abdominal pain are presenting complaints, then 2-view abdominal radiographs should be included in the initial diagnostic testing. While radiographic changes are often non-specific for pancreatitis this can be a helpful measure to rule out other differentials including intestinal obstruction.

If the above test results remain suggestive of pancreatitis, then more specific testing should be pursued. Since amylase and lipase have poor sensitivity for canine pancreatitis (32-73% and 42-69%, respectively) (Hess RS et al 1998) as well as low specificity (~50%) (Steiner J 2008), additional testing is often necessary to confirm or to rule out the diagnosis. The SPEC cPL (pancreatic lipase assay) is the most accurate confirmatory test for pancreatitis, with a sensitivity of 87-94% and specificity of 81-88% (McCord K et al 2012). A newer test (Precision PSL) has similar accuracy to the SPEC cPL (Kook PH et al 2014). The SNAP cPL has similar sensitivity and specificity to the SPEC cPL and Precision PSL, but has the advantage of being cage-side. Specificity of the SPEC cPL will increase to as high as 88% when a more stringent cut-off of 400ug/L is used, which makes it a preferred test when clinical signs are suggestive of pancreatitis (McCord K et al 2012). When used in union, the SNAP cPL can be an effective and rapid screening tool, however for a more definitive diagnosis (and to obtain a quantitative result) the SPEC cPL should be the follow-up test.

Abdominal ultrasonography is a useful diagnostic test for pancreatitis in the hands of an experienced ultrasonographer. Possibly more so than with any other test for pancreatitis, this is a great deal of user variability with ultrasound which makes results difficult to interpret. Challenges in imaging the pancreas are multifactorial, including:

- Some animals can be challenging to image due to body shape (deep-chested dogs), making even identification of the pancreas.
- Patients with severe pancreatitis will frequently have severe abdominal pain which makes accurate imaging difficult without adequate pain management and/or sedation.
Ultrasound machines vary greatly in quality. Older machines will deliver grainy images and make detailed imaging nearly impossible, especially when trying to evaluate the pancreas.

User inexperience is the biggest roadblock to obtaining an image of the pancreas and being able to interpret the finding. Even in the hands of an experienced radiologist making a diagnosis of pancreatitis can be demanding. In some cases ultrasonographic changes lag behind clinical signs, and vice versa. Sensitivity of making a diagnosis with ultrasound has at best been shown to be 70% (Steiner J 2010).

The gold standard diagnostic test to confirm pancreatitis remains histopathology, but this is widely considered an unnecessary test that can lead to increased morbidity and mortality. Placing a hemodynamically compromised patient under general anesthesia and manipulating the pancreas may be indicated if there is acute bile duct obstruction or neoplasia is suspected, but a presumptive diagnosis can often be made prior to going to surgery and rarely does a patient benefit clinically from this procedure.

**Treatment of pancreatitis**

Fluid therapy is the most important management strategy in dogs with pancreatitis. Early and aggressive use of IV fluids can be the difference between a patient surviving or not; however, caution should be taken to avoid over-use of crystalloids leading to fluid overload. While dogs with mild pancreatitis may thrive on crystalloid therapy alone, patients with more severe pancreatitis often require a more diverse plan. Hypoalbuminemia, vasculitis, severe pain, and hypotension can all be components of pancreatitis requiring a tailored fluid plan including the following:

- **Colloid therapy** (ie. Vetstarch) in the form of boluses initially to raise BP as well as a continuous infusion.
- **Vasopressor therapy** such as a dopamine CRI, to help raise blood pressure (once rehydration has been completed).
- **Continuous infusion of pain management** (ie. fentanyl CRI) either administered separately through a syringe pump or combined in a bag of crystalloids.
- **Ongoing anti-emetic therapy** in the form of a CRI (ie. metoclopramide).
- **Other targeted colloids**, including human albumin and fresh frozen plasma. The success/failure of these products with acute pancreatitis has not been confirmed, and there are risks especially with albumin, but severely critical cases may require this level of aggressive management.

Additional medical therapy is dictated by the patient’s ongoing clinical signs and severity of clinical illness, including the use of other antiemetics, intravenous antacids, alternative pain control, supplemental oxygen therapy, etc.

Management of chronic pancreatitis can be frustrating, especially if the only abnormality is in the blood work. In asymptomatic dogs with persistently elevated cPL, for example, a low fat diet may be all that is indicated. If the dog is symptomatic (including inappetance, mild chronic abdominal pain, intermittent vomiting, etc.) then supportive care including antiemetics, appetite stimulants, antacid therapy, etc. may be necessary during supposed flare-ups. If these therapies are not effective, an alternative diagnosis should be suspected and more testing may be indicated (ie. intestinal or liver biopsies, gall bladder culture, etc.).

Pancreatitis can be a challenging condition to both diagnose and manage, especially when 24 hour care is not available. Learning how to interpret the available diagnostic tests (including having a solid understanding of their pitfalls and inaccuracies) and implementing early and, if necessary, aggressive therapy will help to improve the outcome of your patients with pancreatitis.

**References**


It’s Just a Gallbladder…What Could Go Wrong?

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The gallbladder is a storage vessel for bile, located between the right medial and quadrate lobes of the liver, and is a major component of the extrahepatic biliary tract (EHBT). Bile is synthesized in the hepatocytes before being secreted into the canaliculi. From there it flows through the interlobular ducts, lobar ducts, the left and right hepatic ducts, and then either into the cystic duct to the gallbladder or down the common bile duct to the duodenum. Bile enters the duodenum through the sphincter of Oddi after the common bile duct joins the minor pancreatic duct.

There are two broad categories of disease involving the gallbladder and the extrahepatic biliary tract: obstructive and non-obstructive. Obstructive diseases almost always will require corrective surgery, while non-obstructive diseases may be able to be managed medically.

Clinical signs and presenting complaints of dogs with gallbladder disease are often vague and non-specific. Vomiting, loss of appetite, diarrhea, and abdominal pain may be reported. Since there is a wide variation of severity of gallbladder disease, these signs can vary greatly. Clinical signs associated with obstructive gallbladder disease are often worse and may present more acutely, but this is not always the case.

Cholecystitis

Bacterial cholecystitis is a rarely reported condition in dogs that can cause a variety of clinical signs. Definitive diagnosis of this condition requires documentation of bactobilia, ideally with a subsequent positive bacterial culture. Gram-negative rods are the most common bacteria isolated from the gallbladder of dogs, with E. coli being the most commonly reported (Lawrence YA et al 2015).

Procurement of a bile sample for culture and cytology can be via a cholecystocentesis or at the time of surgery (typically performed at the time of a cholecystectomy). Indications for this testing may include laboratory abnormalities including elevated liver enzymes indicative of hepatocellular injury or cholestasis, ongoing inflammation, or ultrasonographic evidence of gallbladder disease including a thickened wall, static sludge, persistently dilated bile ducts, etc. (Lawrence YA et al 2015).

Bacterial contamination of the gallbladder and subsequently the biliary tree and liver is most commonly thought to occur due to pancreatic or intestinal disease causing an ascending infection. The bile duct anatomy of the cat makes this species more likely to have bacterial cholangitis. Hematogenous spread of bacteria via the portal vein is another possible avenue for infection.

If bile cytology and/or culture is indicated and surgery is not necessary, a cholecystocentesis may be performed ultrasonographically with the patient heavily sedated using either a 22 or 25 gauge needle, angling through the right medial liver lobe if possible to help prevent bile leakage. Even when clinically and clinicopathologically indicated, bile cytology and culture can be unrewarding. A recently published study evaluating 140 bile samples from dogs and cats with suspected bacterial cholecystitis found bactobilia in only 24% of cases, with bacterial culture yielding a positive result in only 21% (Peters LM et al 2016).

Treatment for mild to moderate bacterial cholangitis / cholangiohepatitis should include hepatic support medication (SAM-e, milk thistle), a choloretic agent such as ursodiol, and broad-spectrum antibiotics (a combination of metronidazole, amoxicillin, and enrofloxacin may be indicated unless a positive bacterial culture and sensitivity panel is available for review). In more severe cases, especially if the gallbladder wall appears compromised on ultrasound, a cholecystectomy should be performed. Special focus after removing the gallbladder should be on the common bile duct to ensure patency, and a stent placed if unsure (Richter KP and Pike FS 2014).

Cholelithiasis

The presence of choleliths in a dog may warrant immediate surgery for removal, however in most cases these are an incidental finding and are unlikely to be associated with the patient’s presenting clinical signs. Stones typically form in the gallbladder and this is where they are most often incidentally found. Due to their composition, they are frequently radiolucent and thus are found only on ultrasound (14/27) (Kippenstein J et al 1993). Despite the infrequency of extrahepatic biliary obstruction secondary to cholelithiasis, cholecystitis can be seen concurrently with stones and thus medical management may be indicated. In the above referenced study, 15/20 cases that were taken to surgery for cholecystectomy had a positive bacterial culture (primarily gram negative rods, as in cholecystitis). Additionally, many of these cases had histopathological evidence of cholecystitis and mucosal hyperplasia. Thus, while immediate obstruction may not be present and surgical removal not indicated if the stones are found incidentally, the patient should be monitored for evidence of bacterial cholecystitis and medical management pursued if clinical or clinicopathologic evidence arises.
Gallbladder mucocele
A gallbladder mucocele has been defined as an accumulation of a green-black, bile-laden, semisolid to immobile mucoid mass within the fundus of the gallbladder (Aguirre AL et al 2007). The mucocele is widely considered to be the most common cause of extrahepatic biliary obstruction in dogs. Mucoceles are being diagnosed with an increasing frequency, which is likely due to the increasing availability of ultrasound in clinical practice. As with any test, however, false positives are a possibility and over-interpretation of a gallbladder image can lead to unnecessary surgical intervention. The appearance of a gallbladder mucocele on ultrasound is frequently compared to that of a kiwi fruit, with the impression of spokes around the periphery. What this represents is non-gravity dependent thick sludge within the lumen that has adhered to the walls of the gallbladder. Gravity-dependent echogenic sludge that is non-obstructive, however, may be easy to mislabel as a mucocele, especially when only still images are being evaluated.

The underlying cause of gallbladder mucocele formation is still unknown, however there are some diseases and breeds that seem to predispose dogs. Shetland Sheepdogs, Miniature Schnauzers, and Cocker Spaniels are prone to gallbladder disease, particularly mucoceles (Aguirre AL et al 2007). Some endocrinopathies put dogs at an increased risk for mucoceles, in particular hyperadrenocorticism and hypothyroidism. Dogs with hyperadrenocorticism have a 29 times higher risk of developing a mucocele compared to dogs with normal cortisol (Mesich MLL et al 2009). Diabetes mellitus has not been associated with mucocele formation.

Dogs do not always present with clinical signs of cholecystitis or other gallbladder disease when a mucocele is identified; in fact 11/38 dogs in the Aguirre study referenced above had their mucoceles identified incidentally during an abdominal ultrasound. Another study showed 7/30 dogs with a confirmed gallbladder mucocele had no adverse clinical signs (Pike FS et al 2004).

The two most important questions when evaluating a dog for a possible mucocele are: is the dog clinical for gallbladder disease, and is there evidence of obstruction / post-hepatic cholestasis. An answer of “no” to each of these questions does not rule out a mucocele, but it should make the clinician at least consider medical management prior to going to surgery. Medical management of presumed mucoceles often involves hepatic support therapy (ie. Ursodiol, SAM-e, milk thistle) with or without antibiotics (ie. metronidazole, amoxicillin). Use of a choloretic in cases of suspected extrahepatic biliary obstruction should be discouraged; in these cases surgical intervention is indicated.

Perioperative mortality rate with cholecystectomy due to a mucocele has been reported as high as 21% (Pike FS et al 2004). This study included gall bladders that were both ruptured and intact, however there was no significant difference between these two types of cases. While this study did not show a higher mortality rate when the gallbladder was ruptured, from a clinical perspective post-operative management is more intense and hospitalization is often longer with a higher total bill if the gallbladder has ruptured prior to surgery. It is the author’s preference, therefore, to recommend cholecystectomy if a mature mucocele is identified. In the absence of clinical pathologic evidence of cholestasis in a patient with no clinical signs medical management may be pursued, but close observation of the patient along with routine follow-up visits including blood work are highly recommended.

References
Managing PLE in Dogs
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Protein losing enteropathy (PLE) is defined as greater than normal loss of protein through the gastrointestinal tract (GIT) (Hall EJ 2010, Moore LE 2009). As much as 10% of daily protein catabolism occurs in the GIT, therefore losses greater than this are considered pathologic (Greenwald DA 2006). Clinically apparent PLE, however, involves much greater protein loss, as the liver is capable of increasing albumin production by greater than 100% to compensate for the deficiency (Peterson PB 2003). Quiescent disease, therefore, may be present long before clinical detection of hypoalbuminemia is made. There is a short list of differentials for hypoalbuminemia, including severe protein losing nephropathy/nephrotic syndrome, liver dysfunction, and protein losing enteropathy (PLE). One key difference that separates the three is the panhypoproteinemia that is seen with PLE. The loss of proteins is non-selective and thus results in loss of small proteins (i.e., albumin) as well as larger protein (globulins).

In dogs, PLE is frequently associated with lymphoplasmacytic enteritis and lymphangiectasia (Kull PA 2001), but any disorder resulting in disruption of the intestinal mucosa or increased intestinal lymphatic hydrostatic pressure may result in protein loss. Additionally, protein loss may occur in the face of normal intestinal mucosa secondary to leakage through enterocyte tight junctions (Bode L et al 2008). Some of the less common causes of PLE include acute or chronic infectious diseases (Parvovirus, Histoplasmosis), neoplasia (diffuse round cell neoplasia such as lymphoma, discrete mass such as adenocarcinoma, etc.), acute or chronic GI bleeding (neoplasia, ulcerations), severe dysbiosis, etc.

When hypoalbuminemia is identified on initial blood work in a sick dog, even in the face of severe chronic diarrhea, certain additional laboratory tests should be performed to rule out liver and kidney involvement. At a minimum, a urinalysis and bile acids (pre- and post-prandial) should be checked; finding normal results in each of these tests will help to direct a diagnostic plan geared towards the gastrointestinal tract. A detailed medical history including patient signalment is equally as important to the aforementioned lab tests. There are a few well known breed-specific enteropathies that contribute to hypoalbuminemia, including the following:

- **Yorkshire Terrier**: Commonly seen with primary and secondary lymphangiectasia which can lead to severe PLE, hypomagnesemia, hypocalcemia, etc. (Kimmel SE et al 2000)
- **Soft Coated Wheaten Terrier**: Genetic predisposition to presumed severe food allergy that can contribute to PLE and protein losing nephropathy, with a poor long term prognosis (Litman MP et al 2000).
- **Norwegian Lundehund**: Nearly 100% of the breed is affected to some extent by a severe chronic enteropathy leading to PLE (Berghoff N 2007).
- **Many breeds seem more sensitive to the effects of chronic enteropathies, leading to PLE**, including Rottweiler, German Shepherd Dog, and Chinese Shar-Pei.

As previously mentioned, the most common causes of PLE in dogs are lymphoplasmacytic enteritis and lymphangiectasia. Diagnosis of these conditions can be made via intestinal biopsies, taken either endoscopically or surgically. The author’s preference in dogs with severe PLE is for endoscopic biopsies, as intestinal edema, ascites, and hypoalbuminemia can contribute to an increased risk of dehiscence secondary to prolonged healing time of the enterotomy site. An additional advantage is that immunosuppressive therapy, including corticosteroids, can be initiated immediately following an endoscopic procedure. If lymphangiectasia is a suspected differential diagnosis, administering 5-10mL of corn oil per os 2-4 hours prior to the endoscopy can make dilated lacteals more prominent, aiding in a visual diagnosis.

The quality and size of the endoscopic biopsies has been proven to be correlated to ability to make an accurate diagnosis, which makes experience of the endoscopist and quality of the equipment used of great importance when consider options for biopsies (Washabau RJ et al 2010). Additionally, endoscopy equipment is not readily available to all veterinarians, making surgery the only way to obtain tissue samples.

Once a cause has been identified treatment should begin as soon as possible, as acute decompensation can occur when hypoalbuminemia progresses. A combination of diet therapy, gastroprotectants, antibiotics, and immunosuppressive medications should be considered. If primary lymphangiectasia is suspected (or confirmed), an ultra low fat diet is indicated (Okanishi H et al 2014). In moderate cases a prescription low fat diet can be used.

Gastroprotectants can be used when gastric ulceration has been documented, or if vomiting is an accompanying clinical sign that may result in esophagitis. Omeprazole and famotidine are first-line antacids that should be used.

Antibiotics may be indicated in severe cases for treatment of bacterial translocation across the wall of the diseased intestines. Broad spectrum coverage with an antibiotic such as amoxicillin/clavulanic acid would be indicated in this instance. More commonly, however, there may be a component of dysbiosis, or bacterial overgrowth, which can contribute to a non-specific condition known as antibiotic-responsive diarrhea. While this is not generally the only pathology associated with PLE, it can often be one part of the disease process. Tylosin 10-20mg/kg PO BID is the drug of choice for this condition (Kilpinen S et al 2014).
Immunosuppressive therapy, first and foremost corticosteroids, will be indicated in most cases of chronic enteropathy that are severe enough to cause hypoalbuminemia. Prednisone is the most commonly used first line therapy, with starting doses up to 3mg/kg/day for severe cases. Larger dogs generally require a lower starting dose, in some cases only 1mg/kg/day. Alternatively, budesonide has been shown to be as effective (Dye TL et al 2013). In severe cases or if prednisone therapy has failed, additional immunosuppressive medications can be used. The use of chlorambucil (4.4mg/m²/day) has recently been shown to be more effective than prednisone alone in a subset of dogs with severe refractory PLE (Dandrieux JR et al 2013). Cyclosporine (Atopica) is another drug that has shown effectiveness in dogs with inflammatory bowel disease refractory to prednisone alone (Allenspach K et al 2006).

Long-term survival in dogs with chronic enteropathy is shorter in dogs with hypoalbuminemia compared to those with normal albumin at the time of presentation (Owens SL et al 2011). If an underlying diagnosis can be made and appropriate medical management started early, however, a favorable prognosis can be achieved. Recognizing breed predispositions, obtaining a thorough medical history, and ruling out other cause of hypoalbuminemia will help allow earlier medical intervention, contributing to an increased chance for survival.

References
Vomiting is a common yet non-specific presenting complaint in dogs, which can be defined as forceful, active expulsion of gastric contents from the body (Twedt D 2010). In some cases, vomiting is a necessary response to expel toxic contents from the body. In the majority of cases, however, a non-gastric disorder will stimulate the emesis center leading to the act of vomiting.

There are two central locations that respond to hormonal influence to inducing vomiting: the emetic center and the chemoreceptor trigger zone. Various factors are capable of stimulating these areas, which makes vomiting such a non-specific clinical finding. These include gastric over-distention, pancreatic inflammation, pain, intestinal stretch receptors, uremic toxins, vestibular imbalance, and other factors. Hormone receptors that are capable of inducing vomiting include serotonin (5-HT3), alpha adrenergic receptors, and neurokinergic (NK-1). This information is clinically important when considering anti-emetic therapy.

The single most important first step when evaluating a patient for vomiting is a detailed medical history. Differentiating vomiting from regurgitation is a vital first step, since the diagnostic approach for each is very different. Identification of the three stages of vomiting (nausea, retching, and actual emesis) is crucial to differentiating it from the more reflexive act of regurgitation. Once vomiting has been established, the rest of the patient’s history will help dictate what additional testing may be indicated to most quickly determine an underlying cause. The following are some pertinent questions to be asked during the history:

- What is the duration and frequency of vomiting
- Is the patient on any current medications
- Has there been a recent diet change or unusual food eaten/ table scraps, etc.
- Have any remedies been tried and failed
- What other clinical signs are the patient exhibiting (diarrhea, inappetance, chronic weight loss, etc.)
- Are there any known concurrent diseases
- Has there been recent travel or exposure to infectious diseases

Once the medical history is complete, a thorough physical examination is performed. Baseline lab work can then be completed (chemistry, CBC, urinalysis). Many underlying metabolic diseases that cause acute or chronic vomiting can be identified by reviewing these basic tests, including acute or chronic renal failure, pancreatitis, liver failure, chronic hepatitis, pyelonephritis, and others. In the absence of abnormalities on the initial lab work, further investigation will be needed:

- Abdominal radiographs
  - Evaluate the stomach for over-distention, foreign material, and marked thickness.
  - Inspect the small intestines for two separate populations (one normal, one markedly distended) indicating an obstruction.
  - Evaluate overall serosal detail for suggestion of peritoneal effusion.
  - If there is still suspicion of regurgitation, remember to take a right lateral thoracic radiograph to look for megaesophagus.

- Barium study
  - With increased availability of ultrasound, this is becoming a less desirable test. Barium in the GI tract prevents the ability to perform endoscopy until it has all passed, and if a bowel perforation has occurred barium peritonitis can aggravate the septic process further (Ko JJ 2014).
  - Interpretation can be difficult, especially when trying to determine gastric outflow and speed of transit through the gastrointestinal tract. Gastric and intestinal mobility may be delayed due to an underlying metabolic disease, hypoperfusion, or medications the patient is receiving, leading to a possible false positive for intestinal obstruction.

- Abdominal ultrasound
  - This can be a useful test to determine a cause of vomiting, however be cautious to avoid over-interpreting results. Severe intestinal ileus from pancreatitis, for example, can lead to dilated, fluid-filled loops of intestine. This finding can also be suggestive of an obstruction.
  - While abdominal ultrasound can be a sensitive and specific test when performed by an experienced ultrasonographer evaluating a case of acute vomiting for bowel obstruction, it has a lower utility for cases of chronic vomiting. A recent study showed that abdominal ultrasonography helped establish a diagnosis in only 23% of cases of chronic vomiting (Leib MS 2010). In the majority of cases the results did not change the clinical course.
• Additional lab work
  o Resting cortisol
    ▪ Atypical Addison’s disease is an uncommon cause of chronic vomiting, but should not be overlooked (Sadek D 1996). Failure to recognize this disease prior to anesthetizing a patient for more invasive diagnostics can lead to a possible crisis with increased risk of morbidity. A resting serum cortisol >2.0ug/dL should be sufficient to rule out this condition. Perform a full ACTH stimulation test if the resting cortisol is <2.0.
  o Bile acids
    ▪ Decreased liver function can be present in the absence of marked elevations in liver enzymes; conversely primary gastrointestinal disease can contribute to elevated liver enzymes. Bile acid testing will help to differentiate these disorders.
  o Leptospirosis antibody titer
  o GI Panel
    ▪ Cobalamin/folate
    ▪ SPEC cPL
    ▪ TLI

When a definitive diagnosis cannot be obtained using the above diagnostics, consider the clinical history to help dictate the course of action. When the vomiting is acute and gastritis / acute gastroenteritis are suspected, symptomatic therapy including supportive care and anti-emetics should be pursued. If abdominal pain is initially present and persists, or if it develops after a therapeutic trial has begun, repeat abdominal radiographs may be indicated to recheck intestinal gas distention.

Anti-emetic therapy:
• Serotonin antagonists (5-HT3 receptor inhibitor) (Plumb D 2015)
  o The 5-HT3 receptors are found both centrally and peripherally.
  o Receptors are stimulated by serotonin when intestinal mucosa is disturbed
  o Ondansetron
• Substituted benzamides (Plumb D 2015)
  o Dopamine antagonist (and 5-HT3 receptor blocker at higher doses)
  o 5-HT4 agonists
  o Also include prokinetic properties (caution if obstruction is suspected)
  o Metoclopramide, cisapride
• Neurokinin-1 antagonist (Benchmaoui HA 2007)
  o Acts as a ligand for Substance P in the brain (Substance P-Neurokinin receptor complex is thought to be the final pathway in the vomiting reflex).
  o Effective with both central and peripheral causes of vomiting.
  o Maropitant

Prior to more invasive diagnostics, and in a patient with chronic vomiting, consider prescribing a hypoallergenic diet as an elimination diet trial. If the patient continues to vomit after 3 weeks on an exclusion diet, a food allergy can be ruled out. If a novel protein diet is chosen instead of a hydrolyzed diet, two or three diet trials may be indicated if the patient’s complete diet history is not well known.

If vomiting continues in the face of symptomatic therapy, and a definitive diagnosis has yet to be reached, consider obtaining gastrointestinal biopsies. Gastroduodenoscopy is the least invasive method of obtaining samples for histopathology, with the ability to reach the stomach, duodenum, colon, and possibly ileum. Disadvantages of this technique include availability and experience of the endoscopist, ability to only take mucosal biopsies, and inability to visualize the entire gastrointestinal tract. Benefits include it being an outpatient procedure with minimal complications. Alternatively, a laparotomy with full thickness intestinal biopsies can be pursued. This approach allows for full evaluation of the gastrointestinal tract. If no foreign bodies or masses are identified, multiple full-thickness biopsies can be obtained representing various segments, including stomach, duodenum, jejunum, and ileum. A negative exploratory should not be looked upon as a waste of time or an inappropriate test, but an opportunity to obtain biopsies.

Once histopathology results have been evaluated, any further therapy that may be indicated should be started. If full thickness biopsies are taken surgically and corticosteroid therapy is warranted, I recommend waiting at least 5 days after surgery before starting, to allow adequate healing time.

References

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Dogs with chronic intestinal disease typically present for investigation of clinical signs such as diarrhea, weight loss or vomiting. Diarrhea that has lasted 3 weeks or more is usually considered chronic. The initial approach to chronic diarrhea is based on determining the nature and severity of the diarrhea and the presence of specific or localizing clinical findings. The presence of additional clinical signs often points to the underlying cause: e.g. tenesmus and dyschezia (large bowel disease), melena (upper GI bleeding/ulceration), abdominal pain (structural disorders, perforation, thrombosis), and abdominal distension, difficulty breathing and peripheral edema (enteric protein loss). This information is integrated to determine whether diarrhea is most likely due to large bowel disease (dyschezia, tenesmus, increased frequency of defecation, small volume of feces with mucus and blood) or a consequence of small intestinal disease or exocrine pancreatic insufficiency (large volume of diarrhea, weight loss, may also be vomiting). In patients with abdominal pain, dehydration, frequent vomiting, or localizing findings such as an abdominal mass, these problems are pursued ahead of an in-depth work up for chronic diarrhea. In patients with chronic diarrhea and no obvious cause it is best to adopt a systematic approach, determined by the localization of diarrhea to the small or large bowel. Patients with signs of large and small bowel involvement are usually evaluated for diffuse GI disease. This presentation will review the diagnosis and management of dogs with chronic enteropathies that are predominantly associated with small bowel diarrhea.

### Investigation of chronic small bowel diarrhea

<table>
<thead>
<tr>
<th>Table 1. Initial diagnostic approach to chronic small bowel diarrhea</th>
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<tbody>
<tr>
<td>Breed predisposition, environment, diet</td>
</tr>
<tr>
<td>other clinical signs, localizing findings</td>
</tr>
<tr>
<td>Fecal analysis (e.g. Giardia)</td>
</tr>
<tr>
<td>CBC, profile, UA</td>
</tr>
<tr>
<td>± TLI, ACTH stim, freeT&lt;sub&gt;4&lt;/sub&gt;/TSH, bile acids</td>
</tr>
<tr>
<td>hypoproteinemia, hypocalcemia, hypocholesterolemia, leukocytosis</td>
</tr>
<tr>
<td>Radiographs, ultrasound</td>
</tr>
<tr>
<td>(liver, spleen pancreas, lymph nodes, masses, effusions)</td>
</tr>
<tr>
<td>Radiographs, ultrasound</td>
</tr>
<tr>
<td>(obstruction, intussusception, focal masses, thickening, loss of layering, hyperechoic striations (Gaschen 2008))</td>
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The initial diagnostic approach to patients with chronic small bowel diarrhea is summarized in Table 1.

After the exclusion of infectious / parasitic agents, non-GI disorders, exocrine pancreatic insufficiency, and intestinal structural abnormalities requiring surgery, the most common group of intestinal diseases associated with chronic small bowel diarrhea are idiopathic inflammatory bowel disease, diet responsive enteropathy, antibiotic responsive enteropathy and lymphangectasia. The approach to this group of patients is usually determined by the severity of clinical signs (frequent severe diarrhea, excessive weight loss, decreased activity or appetite) and the presence of hypoalbuminemia, intestinal thickening, or mesenteric lymphadenopathy. In patients with these abnormalities intestinal biopsy is required to define the cause (e.g. IBD, lymphangectasia, lymphoma,) and to optimize therapy. Controlled studies have shown that hypoalbuminemia is associated with a poor outcome in dogs with chronic enteropathy (Craven 2004, Allenspach 2007). Serum concentrations of cobalamin and folate can be measured to determine if supplementation is required and low serum cobalamin concentration (<200ng/L) has also been associated with a negative prognosis (Allenspach 2007). Evaluation of hemostatic function is recommended to determine if hypo- or hyper- coagulability have arisen as a consequence of enteric protein loss.

The clinical severity of intestinal disease can be quantified by determining the clinical disease activity index (attitude activity, appetite, vomiting, stool consistency, stool frequency, weight loss) (Jergens 2003). Measurement of serum C-reactive protein (has been shown to correlate with clinical disease activity (CIBDAI) and implies that severe clinical disease is accompanied by a systemic
Inflammatory response (Jergens 2003). Measurement of clinical disease activity or CRP can also serve as a baseline for determining the response to treatment.

In stable patients with chronic diarrhea (i.e. good attitude, appetite, mild weight loss, normal serum proteins and no intestinal thickening or lymphadenopathy) measurement of serum cobalamin and folate can be performed to evaluate disease severity, aid localization of intestinal disease, and to determine if supplementation is required. Intestinal biopsy is indicated in dogs with low serum cobalamin to determine the nature of the intestinal disease.

In stable patients with chronic diarrhea and normal cobalamin concentrations the client can be given the option of empirical treatment trials with diet, followed by antibiotics if there is no response to diet (see below). Failure to respond to empirical therapy, or worsening of disease, is an indication for intestinal biopsy.

Intestinal biopsy
Intestinal biopsies can be acquired endoscopically or surgically. In patients without an indication for surgery e.g. intestinal masses, anatomic or structural disease, perforation, the authors prefer to perform diagnostic endoscopy to visually inspect the esophageal, gastric and intestinal mucosa and to procure endoscopic biopsies. Guidelines for biopsy acquisition have recently been published (Willard 2008). Operator experience, and biopsy quality and number are of key importance in enabling effective histopathological evaluation. Surgical biopsy is usually performed where intestinal disease is suspected to involve the submucosa or muscularis and where the results of endoscopic biopsies do not adequately explain the clinical picture.

Unfortunately the interpretation of gastrointestinal histopathology varies considerably among pathologists (Willard et al 2003). To try to correct this problem a working group established by the WSAVA has formulated a scheme to standardize the evaluation of intestinal histopathology (Day et al 2008). The ability of this scheme to increase agreement between pathologists, and the clinical relevance of the criteria it evaluates remain to be determined, but it is a step in the right direction.

The most common histopathological diagnoses in dogs with chronic diarrhea are inflammatory bowel disease, lymphangiectasia and lymphoma. The most commonly described histopathological lesion in the intestines of dogs is increased cellularity of the lamina propria that is usually referred to as inflammatory bowel disease (IBD). The extent of inflammation is variable and ranges from focal to diffuse involvement of the small and large intestine. The degree of cellular accumulation is also variable and is subjectively categorized as normal, mild, moderate and severe. Increased numbers of lymphocytes and plasma cells, so called lymphoplasmacytic enteritis is the most frequently reported form of IBD. Moderate to severe lymphoplasmacytic enteritis is often described in association with a protein losing enteropathy. Predisposed breeds include Basenji, Lundehund and Chinese Sharpei. However, recent studies have called into question the appropriateness and clinical relevance of the term lymphocytic plasmacytic enteritis. Dogs have similar numbers of CD3+T cells before and after clinical remission (Schreiner 2008), and cats with and without signs of intestinal disease have similar numbers of lymphocytes and plasma cells (Waly 2004).

The presence of moderate to large numbers of eosinophils in intestinal biopsies, which is often accompanied by circulating eosinophilia, suggests possible parasitic infestation or dietary intolerance. Moderate to high numbers of macrophages and neutrophils raise the possibility of an infectious process, and culture and special stains are indicated.

Changes in mucosal architecture such as mucosal atrophy and fusion are less frequently commented on than cellularity, but appear to be important indicators of disease severity. A recent study in cats with signs of gastrointestinal disease measured mucosal cytokine levels to identify histological correlates of mucosal inflammation. In this study villus atrophy and fusion correlated with severity of clinical signs and degree of proinflammatory cytokine upregulation in the duodenal mucosa (Janeczko 2008).

Dilatation of lymphatics and the presence of crypt abscesses and crypts cysts are most commonly encountered in dogs with protein losing enteropathies, and often are accompanied by lymphoplasmacytic inflammation of varying severity (Peterson 2003, Willard 2003).

Treatment
The therapeutic approach to chronic enteropathies is influenced by suspicion of a breed-related problem; severity of disease as characterized by clinical signs, albumin and cobalamin concentrations, and endoscopic appearance; type of cellular infiltrate; the presence of bacteria or fungi; and presence of architectural changes, such as atrophy, ulceration, lymphangiectasia/crypt cysts. Therapeutic intervention is directed at correcting nutritional deficiencies (e.g. cobalamin) and counteracting inflammation and dysbiosis. The clinical severity of disease, nature and severity of histopathological lesions, and the presence or absence of hypalbuminemia guides treatment.

Minimal change enteropathy
Low clinical disease activity, normal intestinal histopathology, normal serum cobalamin serum albumin>2.0g/l,
1. Empirical treatment for Giardia and endoparasites if not already performed (e.g. fenbendazole 50mg/kg PO x 5d)
2. Dietary trial (see Table 2). A positive response suggests diet responsive enteropathy. If a good response, continue diet, consider re-challenge, and defining basis of dietary intolerance.
3. Antibiotic trial: tylosin (10-15mg/kg TID PO), oxytetracycline (20mg/kg TID PO), or metronidazole (10mg/kg PO BID). A positive response suggests antibiotic responsive enteropathy, maintain on antibiotics for 28 days then discontinue. If a good response consider transition to probiotics? If signs recur after stopping antibiotics chronic therapy with tylosin at 5mg/kg PO SID can be used to maintain dogs that are tylosin responsive (Elias Westermarck 2010, personal communication).

4. If response is poor reappraise before considering other treatments.

**Inflammatory bowel disease**

Treatment of any disease is ideally directed at the underlying cause, which is problematic for IBD as the etiopathogenesis is unclear. IBD in people and animals is increasingly considered a consequence of uncontrolled intestinal inflammation in response to a combination of elusive environmental, enteric luminal constituents (principally microbial and dietary) and immunoregulatory factors in genetically susceptible individuals.

In people, genetic susceptibility is linked increasingly to defects in innate immunity exemplified by mutations in the innate immune receptor NOD2/CARD15, which in the presence of the enteric microflora may lead to up-regulated mucosal cytokine production, delayed bacterial clearance and increased bacterial translocation, thereby promoting and perpetuating intestinal inflammation (Packey 2008). While the mucosa-associated flora is implicated frequently as a pivotal factor in the development of IBD in people and animals, the specific bacterial characteristics that drive the inflammatory response have remained elusive. The clinical responses of some dogs with idiopathic chronic diarrhea to antibiotics such as tylosin or oxytetracycline, and the predisposition of certain breeds, e.g. German Shepherd, points to a similar interaction of host susceptibility and microflora in dogs (Batt 1988, Westermarck 2005, German 2003). As the numbers of cultivable aerobic and anaerobic bacteria in the duodenal juice of dogs that respond to antibiotics is similar to dogs that respond to food or immunosuppression it is plausible that dogs with antibiotic-responsive enteropathy are more susceptible to their resident microflora (German 2003, Simpson 1994), but this remains to be determined.

Recent advances in molecular microbiology have enabled the analysis of complex bacterial communities without bacterial culture. Culture-independent analyses of bacterial 16S rDNA libraries in people reveal that only 30% of the fecal flora appears cultivable, and there is significant variation in the flora in different gastrointestinal segments and luminal contents versus the mucosa of healthy individuals (Eckburg 2005). The application of these culture independent techniques to people, dogs and cats has revealed that intestinal inflammation is associated with a floral shift from Gram-positive Firmicutes to Gram-negative bacteria, predominantly Enterobacteriaceae (Baumgart, 2007, Janeczko 2008, Xenoulis 2008). It is noteworthy that increased numbers of Enterobacteriaceae have been found to correlate with mucosal inflammation and clinical signs in cats with signs of gastrointestinal disease (Janeczko 2008), and a novel group of adherent and invasive E. coli (AIEC) have been associated with intestinal inflammation in people and Boxer dogs with granulomatous/histiocytic ulcerative colitis (Baumgart 2007, Simpson 2006). While it remains to be determined if these floral alterations are a cause or a consequence of the inflammation, their discovery has provided new opportunities for therapeutic intervention.

There is also growing evidence to support an important role for diet in the development of canine IBD. In controlled studies of 65 dogs with diarrhea of at least six weeks duration, 39/65 dogs responded to dietary modification (10 days of Purina Veterinary Diets LA Salmon and Rice), and the remaining dogs were treated with corticosteroids (2mg/kg /24hrs for 10 days followed by a tapering dose over 10 wks (Luckschander 2006). The CIBDAI and histopathological scores were similar (> 70% moderate to severe in each group) in dogs that did and did not respond to diet. Dogs that responded to diet tended to be younger and have higher serum albumin than dogs that did not respond to diet. Dogs that did not respond to diet were treated with steroids. Interestingly intestinal histopathology did not differ in either diet responsive or steroid responsive dogs before and after treatment.

Taken as a whole the results of studies in dogs with chronic diarrhea to date provide reasonable evidence that various subsets of dogs will respond to treatment with antibiotics, diet or immunosuppressive therapy. At present there is no reliable means for predicting which dogs will respond to which treatment, and a treatment consists of a series of therapeutic trials.

**Lymphocyte and plasma cell predominant IBD**

Studies in dogs with chronic diarrhea diagnosed as lymphoplasmacytic enteritis provide reasonable evidence that various subsets of dogs will respond to treatment with diet, antibiotics, or immunosuppressive therapy. At present, because there is no reliable means for predicting which dogs will respond to which treatment, treatment consists of a series of therapeutic trials.

**Mild to moderate disease activity, mild to moderate histopathology (lymphocytes and plasma cells are predominant cell type), serum albumin >2.0g/L (inflammatory bowel disease):**

1. Empirical treatment for Giardia and helminths if not already performed
2. Dietary trial with a hydrolyzed diet for 2 weeks. If a good response then maintain on diet, consider re-challenge, and defining basis of dietary intolerance.
3. Poor response to diet perform antibiotic trial with tylosin for 2 weeks. If a good response maintain on antibiotics for 28 days then discontinue. Consider transition to probiotics? If signs recur after stopping antibiotics chronic therapy with
tylosin at 5mg/kg PO SID can be used to maintain dogs that are tylosin responsive (Elias Westermarck 2010, personal communication).

4. **Immunosuppression with glucocorticoids** (2mg/kg PO/d x 21d, 1.5mg/kg PO/d x 21d, 1mg/kg PO/d x 21d) and or azathioprine (2mg/kg PO /d x5d, then 2mg/kg PO EOD)

5. If poor response reappraise before considering escalating immunosuppression (e.g. add azathioprine, or substitute with cyclosporine (5mg/kg PO SID: Allenspach 2006, if already on azathioprine)

6. If good response taper immunosuppression, then stop antibiotics

**Moderate disease activity, moderate to severe intestinal histopathology (atrophy, fusion, lymphocytes and plasma cells are predominant cell type), serum albumin <2.0g/L (inflammatory bowel disease):**

1. Empirical treatment for Giardia and helminths if not already performed

2. Concurrent dietary modification (hydrolyzed diet), antibiotics (tylosin), and immunosuppression (glucocorticoids and/or azathioprine)

3. Reappraise if poor response before considering escalating immunosuppression (e.g. cyclosporine)

4. Consider failure to absorb oral prednisolone and switch to injectable corticosteroids
   a. Dexamethasone may be preferable to prednisolone in patients with ascites to avoid increased fluid retention
   b. Concurrent therapy with ultra low dose aspirin (0.5mg/kg) and judicious use of diuretics (lasix and spironolactone) are often used in patients considered at risk for thromboembolic disease, and those severely distended with tense ascites respectively.
   c. The use of elemental diets and PPN may be required in some dogs with severe PLE.

5. If good response taper immunosuppression, then stop antibiotics

This approach has been evaluated on 27 dogs with a histopathological diagnosis of IBD: 26/27 dogs have responded to standardized treatment: 16 dogs were diet responsive, 3 steroid responsive, 3 were partially responsive to a combination of food and antibiotics, and three to food steroids and antibiotics.

**Granulomatous or neutrophilic enteritis**

Enteropathies characterized by neutrophilic or granulomatous inflammation are described infrequently in dogs. Some may be associated either with bacterial infections, such as from *E. coli* (granulomatous colitis in boxers), *Streptococcus*, *Campylobacter*, *Yersinia*, and *Mycobacteria*, or fungal (e.g. *Histoplasma*) or algal (e.g. *Prototheca*) infections. Culture of mucosal biopsies, intestinal lymph nodes, and other abdominal organs; and imaging of chest and abdomen should be undertaken in cases of granulomatous or neutrophilic enteritis to detect infectious organisms and systemic involvement. Special stains such as GMS, PAS, Gram and Modified Steiner are traditional cytochemical methods used to search for infectious agents in fixed tissues. Fluorescence in situ hybridization (FISH) with a probe directed against eubacterial 16S rRNA is a more contemporary and sensitive method of detecting bacteria within formalin fixed tissues. It is imperative not to immunosuppress patients with granulomatous or neutrophilic infiltrates until infectious agents have been excluded.

Eradication of mucosally invasive *E. coli* in Boxers and French Bulldogs with granulomatous colitis is associated with clinical cure, but treatment failure associated with antibiotic resistance is increasing. The prognosis for idiopathic granulomatous or neutrophilic enteropathies is guarded to poor if an underlying cause is not identified.

**Lymphangiectasia and crypt cysts / abscesses**

Intestinal lymphangiectasia is characterized by abnormal distention of lymphatic vessels within the mucosa. Lymphangiectasia is a consequence of a localized or generalized lymphatic abnormality or increased portal pressure (e.g. right-sided heart failure, caval obstruction, hepatic disease). Lymphatic abnormalities are often associated with lipogranulomatous inflammation that is visible as small white granules on the intestinal mesentery. Tumor infiltration of lymphatics or lymph nodes can also cause lymphangiectasia. In some cases lymphangiography reveals a generalized lymphatic abnormality. Dilation of lymphatics is associated with the exudation of protein-rich lymph into the intestine and severe malabsorption of long-chain fats. Crypt cysts and abscesses may also be observed in intestinal biopsies.

The Yorkshire terrier (4.2-10-fold relative risk), soft-coated wheaten terrier (concurrent proteinuria), and Norwegian Lundehund seem to be overrepresented, supporting a familial cause in some dogs.

**Clinical findings**

Clinical findings are essentially a consequence of the intestinal loss of protein and range from weight loss to chronic diarrhea, vomiting, ascites, edema, and chylothorax. In a study of 12 Yorkshire terriers, hypoalbuminemia (<3.1g/dl) was present in all 12 dogs (median 1.6g/dl), and hypoglobulinemia (<1.9g/dl) in 7 dogs (median 1.7g/dl). Additional biochemical abnormalities included hypocalcemia (n=12), hypokalemia (n=11), hypomagnesemia (n=9), hypokalemia (n=5) and hypochloremia (n=5). Hypocalcemia and hypomagnesemia have been attributed to hypovitaminosis D. Hematological abnormalities in 12 Yorkshire terriers included mild anemia (n=5), thrombocytosis (n=8), mature neutrophilia (n=6), and neutrophilia with a left shift (n=3).

**Diagnosis**
Lymphangiectasia usually presents as a protein-losing enteropathy, with endoscopic appearance of white blebs on the mucosa (dilated lymphatics). Endoscopic biopsies are often adequate. Surgical biopsy should be undertaken carefully, with appropriate attention to potential for bleeding, exacerbation of hypoproteinaemia by fluid therapy, and potential for dehiscence.

**Treatment**

The cause of lymphangiectasia is usually not determined. Treatment is supportive and symptomatic. Dietary recommendations are similar to those for other causes of small bowel diarrhea (highly digestible, restricted antigen or hydrolysate). Fat restriction has been emphasized as a mainstay of treatment but there is little evidence to support this. Medium-chain triglyceride (MCT) oil usually in the form of coconut oil at 0.5 to 2 mL/kg body weight per day can be added to the diet, or a diet already containing MCT can be fed to provide a source of calories, that is in theory easy to assimilate. The use of MCT improves outcome in children with primary lymphanghiectasia (1) but there are no studies in dogs.

Prednisolone is often employed at 1 to 2 mg/kg PO Q 12 H and may work by decreasing lipogranulomatous inflammation or concurrent mucosal inflammation. Prednisolone is tapered to the lowest effective dose once remission has been achieved. In patients with severe malabsorption, parenteral glucocorticoids may be required, and a switch to dexamethasone may be made in patients with ascites or edema. Escalation of immunosuppression (eg, by administration of cyclosporine at 5 mg/kg PO Q 24 H) may be tried if the patient is unresponsive. However patients with lymphangiectasia appear more prone to sepsis than other forms of IBD so it is imperative not to over immuno suppress these patients and concurrent therapy with metronidazole or tylosin is frequently initiated to decrease the risk of bacterial translocation through the markedly impaired gut. Aspirin at 0.5 mg/kg PO Q 24 H is often given to dogs with low ATIII if they are considered at risk for thromboembolism. Diuretics are used if ascites is problematic (IBD with albumin < 2 g/L).

Response to therapy is variable, with some dogs staying in remission for several years and others pursuing a path toward fulminant hypoproteinaemia or thromboembolic disease. The prognosis is always guarded. In a recent study of 12 Yorkshire terriers (4) empirical therapy with corticosteroids (11/12), azathioprine (2/12), antibiotics (amoxicillin-clavulanate, n=6, metronidazole, n=6, tylosin n=5, enrofloxacn n=2), plasma and diuretics was associated with a poor outcome. 7/12 cases died or were euthanased within 3 months of diagnosis (thromboembolism was suspected in 3). Long-term survival was achieved in 3 dogs, (36, 24, and 8 months), and 2 are alive at 3 and 4 months after diagnosis.

**Acknowledgements**

We gratefully acknowledge the support of the Morris Animal Foundation and Nestle Purina for studies of inflammatory bowel disease in dogs.

**Disclosure**

K. Simpson is a member of the Nestle Purina Advisory Council

**References**


Diagnosing Pancreatitis in Dogs and Cats-
Tips and Traps
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Dogs
From a clinical perspective pancreatitis can be broadly categorized as acute, recurrent acute or chronic. It can be further classified according to its effect on the patient as mild or severe, non-fatal or fatal, and also by the presence of sequela such as abscess formation. Histologically, acute pancreatitis is characterized by findings that range from pancreatic edema to necrosis, variable infiltrates of mononuclear and polymorphonuclear cells, and local changes such as peri-pancreatic fat necrosis and thrombosis. Acute pancreatitis may resolve or persist and can be complicated by secondary infection and pseudocyst or abscess formation. It is tempting to equate mild acute pancreatitis with pancreatic edema, and severe or fatal pancreatitis with pancreatic necrosis, but this relationship has not been critically examined in patients with naturally occurring pancreatitis. Chronic pancreatitis is characterized by fibrosis and low grade mononuclear inflammation and may be a sequela of recurrent acute pancreatitis or a subclinical disease process that may present as diabetes mellitus or exocrine pancreatic insufficiency (EPI).

Etiology and pathogenesis
The etiology and pathogenesis of spontaneous pancreatitis is poorly understood. The major factors which have been implicated (by association) as causes of acute pancreatitis in the dog and the experimental evidence to support their involvement are summarized as follows:

<table>
<thead>
<tr>
<th>Potential aetiology</th>
<th>Clinical</th>
<th>Experimental</th>
</tr>
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<tbody>
<tr>
<td>Hyperlipidaemia</td>
<td>Lipemia</td>
<td>High fat diet</td>
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<tr>
<td>Abnormal lipid profiles</td>
<td>Lipodystrophy</td>
<td>IV Free Fatty Acids</td>
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<tr>
<td>Diet</td>
<td>Diet indiscretion</td>
<td>Fat &gt;&gt;protein diet</td>
</tr>
<tr>
<td>Obesity</td>
<td>Bile reflux</td>
<td>Ethionine supplementation</td>
</tr>
<tr>
<td>Concomitant biliary disease</td>
<td>Hyperlipidaemia</td>
<td>Ca infusion</td>
</tr>
<tr>
<td>Obesity (<em>cats</em>)</td>
<td>Bile reflux</td>
<td>Ca infusion</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Ca infusion</td>
<td>? Hyperparathyroidism</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>? Hyperadrenocorticin</td>
<td>Increased CCK sensitivity</td>
</tr>
<tr>
<td>? + Disc surgery?</td>
<td>Organophosphates</td>
<td>Pancreatic duct hyperplasia</td>
</tr>
<tr>
<td>Drug/toxin related</td>
<td>L-asparaginase</td>
<td>Organophosphates</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>Azathioprine, sulphonamides</td>
<td>Potassium bromide and Phenobarbital</td>
</tr>
<tr>
<td>Zinc</td>
<td>Post-GDV</td>
<td>Ex-vivo pancreas</td>
</tr>
<tr>
<td>Ischemia/reperfusion</td>
<td>Hereditary predisposition?</td>
<td>Miniature Schnauzer, Min. poodle,</td>
</tr>
<tr>
<td></td>
<td>Terriers, non-sporting dogs</td>
<td></td>
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<tr>
<td>Endocrinopathies</td>
<td>Hypothyroidism, diabetes mellitus</td>
<td></td>
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</table>

Irrespective of the initiating cause pancreatitis is generally believed to occur when digestive enzymes are activated prematurely within the pancreas. In the normal pancreas safeguards are present to ensure that harmful pancreatic enzymes are not activated until they reach the intestinal lumen. Enzymes are stored in zymogen granules within the acinar cell in the presence of pancreatic secretory trypsin inhibitor (PSTI) and are released at the apical surface directly into the duct system. They are only activated in the intestine, by trypsin, following the cleavage of trypsin activation peptide (TAP) from trypsigen by enterokinase. Potential sites for the intrapancreatic activation of pancreatic enzymes can therefore logically be divided into interstitial (within the duct system and interstitium) and intracellular (within the acinar cell). Experimental studies suggest that bile and enteric reflux, and intravenous free fatty acid (FFA) infusion initiate pancreatitis by an interstitial mechanism whereas hyperstimulation with caerulein or organophosphates, pancreatic duct obstruction and choline deficient ethionine supplemented diet (CDE diet) result in intracellular activation. Experimental pancreatic hyperstimulation with cholecystokinin (CCK: or its analogue cerulein), dietary supplementation with ethionine, and obstruction of the pancreatic duct lead to the formation of large intracellular vacuoles in acinar cells. Vacuole formation is thought to be a consequence of the uncoupling of exocytosis of zymogens and abnormal intracellular trafficking of digestive and lysosomal enzymes. These subcellular alterations are considered to precipitate the intracellular activation of digestive enzymes. Pancreatic hyperstimulation may be of direct relevance to naturally occurring pancreatitis in dogs. CCK is normally released by cells in the duodenum in response to intraluminal fat and amino acids and coordinates and stimulates pancreatic secretion and gallbladder contraction during digestion. It is possible that high fat diets exert their effects via the excessive release of cholecystokinin and that hypercalcemia, organophosphates and high levels of circulating glucocorticoids also facilitate (potentially by
changing pancreatic sensitivity to hyperstimulation), or cause pancreatic hyperstimulation; however, this is not proven. Edematous pancreatitis induced by CCK hyperstimulation in dogs is characterized by a rapid but self-limiting, burst of trypsinogen activation suggesting that the pancreas has a feedback mechanism to limiting trypsinogen synthesis and activation (see nutritional management). This concept of pancreatic down regulation is important when considering nutritional intervention in acute pancreatitis.

Often pancreatic inflammation is a self-limiting process, but in some animals reduced pancreatic blood flow and leukocyte and platelet migration into the inflamed pancreas may cause progression to pancreatic necrosis. Secondary infection may arise by bacterial translocation from the intestine. Release of active pancreatic enzymes and inflammatory mediators from the inflamed pancreas, such as Tumor Necrosis Factor-a (TNF-a), interleukin-1 (IL-1) and phospholipid platelet activating factor (PAF), amplifies the severity of pancreatic inflammation, and adversely affects the function of many organs (systemic inflammatory response), and cause derangement in fluid, electrolyte and acid-base balance. It is the development of multisystemic abnormalities that separates mild from severe, potentially fatal pancreatitis.

**Diagnosis**

There is currently no single specific test for pancreatitis in dogs and diagnosis is based on a combination of compatible clinical, clinicopathological and imaging findings. Surgical biopsies may be required to confirm a diagnosis, and to distinguish inflammation from neoplasia.

**Clinical findings**

**Signalment and history**

Middle aged to old dogs (>5yrs years old) who are overweight appear at higher risk. Miniature Schnauzers, Yorkshire and Silky Terriers, non-sporting breeds and perhaps miniature poodles may be at increased risk of developing pancreatitis. There is no clear sex predisposition. Endocrinopathies such as hypothyroidism, diabetes mellitus and hyperadrenocorticism may also be risk factors.

Thirteen percent of 221 dogs with diabetes mellitus had histological evidence of acute pancreatitis. Hyperlipidemia is another potential risk factor.

The history may reveal a recent episode of dietary indiscretion, toxin ingestion or drug administration. Common clinical signs include lethargy, anorexia, hunched stance, vomiting (± blood), diarrhea (± blood), increased respiratory rate and enlarged abdomen. Some dogs have a history of icterus preceded by vomiting. Polyuria and polydipsia may be present in dogs with diabetes mellitus and pancreatitis.

**Physical examination**

Physical findings in dogs with acute pancreatitis are variable and range from depression, to mild dehydration with signs of abdominal pain, to acute abdominal crisis with shock (tachycardia, prolonged capillary refill time, tacky mucous membranes, hypothermia), petechiation, icterus and ascites. An abdominal mass is palpated in some dogs.

**Diagnostic approach and differential diagnosis**

The differential diagnosis of acute pancreatitis in dogs is usually centered round the problems of vomiting and abdominal pain.

In vomiting dogs the initial approach is to distinguish self-limiting from more severe causes of vomiting on the basis of physical findings and a minimum database (e.g. packed cell volume, total protein, azostick, urinalysis, plasma concentrations of sodium and potassium). Where vomiting is associated with systemic signs of illness, or is persistent, the clinician has to differentiate metabolic, polysystemic infectious, toxic and neurologic causes from intra-abdominal causes. This is usually achieved on the basis of combined historical and clinical findings coupled with a minimum database and the evaluation of hematology and serum chemistry profile, urinalysis and abdominal radiography. Measurement of serum amylase or lipase is often reported on routine serum chemistry profile. Additional procedures such as ultrasonography, abdominal paracentesis or assay of trypsin-like immunoreactivity , TAP or immunoreactive canine pancreatic lipase (cPLI, spec cPL etc) are usually performed on the basis of these initial test results and help to distinguish pancreatitis from other intra-abdominal causes of vomiting.

Where abdominal pain is the major finding localizing abnormalities such as abdominal distension are rapidly pursued with radiography, ultrasonography and paracentesis while providing supportive treatment on the basis of physical findings and a minimum database base balance and awaiting the results of hematology, serum chemistry profile and urinalysis. Abdominal pain can arise from any intra-abdominal structure. Musculoskeletal disorders such as discospondylitis and prolapsed discs can be hard to distinguish from abdominal causes of pain.

Diarrhea, which was bloody in some cases, is reported as a more frequent sign than vomiting in dogs with experimental acute pancreatitis. Acute pancreatitis and its complications (infection, pseudocyst or abscess formation) should also be considered in the differential diagnosis of icterus and pyrexia. Some dogs with pancreatitis exhibit few localizing clinical signs. Diagnosis in these animals requires a high index of suspicion and use of versatile diagnostic tests such as ultrasonography.

**Clinicopathological findings**

**Hematology**

Extremely variable, ranging from mild neutrophilia and slightly increased haematocrit, through marked leukocytosis with or without a left shift, to thrombocytopenia, anemia and neutropenia with a degenerative left shift. Thrombocytopenia in dogs with pancreatitis is often associated with DIC and additional tests of hemostasis (OSPT, APTT, FDP or D-dimer, fibrinogen, antithrombin III) are performed to determine if DIC or other coagulopathies are present.

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Serum biochemical abnormalities include azotemia (pre-renal and renal), increased liver enzymes (ALT, AST, AP), hyperbilirubinemia, lipemia, hyperglycemia, hypoproteinemia, hypocalcemia, metabolic acidosis and variable abnormalities (usually decreased) in sodium, potassium and chloride.

Urinalysis
Enables azotemia to be characterized as renal or pre-renal. Proteinuria occurs in some dogs with acute pancreatitis and is usually transient. The presence of glucose or ketonuria should prompt consideration of diabetes mellitus.

Pancreas specific markers
Classically, elevations in serum amylase and lipase activity have been used as indicators of pancreatic inflammation in dogs. However these enzymes can be increased in non-pancreatic disease, and dogs with confirmed pancreatitis may also have normal amylase and lipase activity. For example, in dogs with histologically confirmed pancreatitis, lipase is normal in 28 to 61% of dogs, and amylase is normal in 31 to 47% of dogs.

These limitations have led to the development of assays for enzymes or markers considered pancreatic in origin such as trypsin-like immunoreactivity (TLI), trypsinogen activation peptide (TAP), pancreatic lipase immunoreactivity (PLI, cPL) and pancreatic elastase. Experimental studies have documented high concentrations of TLI, TAP, PLI and elastase in dogs with experimental acute pancreatitis. The utility of TLI, TAP, PLI and elastase for the diagnosis spontaneous pancreatitis in dogs has not been thoroughly evaluated. Normal, subnormal and increased concentrations of TLI have been observed in dogs with confirmed pancreatitis. Elevations of TAP have been observed in the serum and urine (TAP:creatinine) of dogs with severe pancreatitis, and TAP may be a better prognostic than a diagnostic indicator of pancreatic inflammation. Experience with PLI/cPL is increasing and it appears better than serum amylase, conventionally measured serum lipase, TLI and elastase in the diagnosis of pancreatitis.

1. A negative cPL (<200 µg/l) or SNAPcPL is better at predicting the absence of pancreatitis than a positive cPL (McCord et al)
2. In 40 dogs classified as having no pancreatic disease because of an absence of clinical signs and no inflammation on histology- Thirty-eight had a Spec-cPL value ≤ 200 µg/L, and 39 had values < 400 µg/L. This resulted in a specificity using the lower cutoff value of 95% (95% confidence interval 83.1-99.4), and using the higher cutoff value a specificity of 97.5% (95% confidence interval 86.8-99.9) (Neilson Corley ey al)
3. Spec-cPL more likely to be positive in severe than mild disease: A study of 70 dogs presented consecutively for post-mortem at a tertiary referral center (Trivedi et al): The estimated sensitivity of canine pancreatic lipase was 21% for mild disease and 71% for moderate disease. This was a lower sensitivity than for total lipase (54% and 71%, respectively) in the same cohort of dogs! Although only 7 dogs were classified as having normal pancreatic histology, there was a specificity of 86% for Spec-cPL as compared with 43% for total lipase reported.
4. Recent studies show dry chemistry serum lipase correlates with cPL: The results showed a good correlation (r = 0.91), and the normal and pancreatitis dogs identified based on the PLI values were correctly separated based on lipase activity. (Ishioka et al)

Radiography
Radiographic findings in dogs with acute pancreatitis are generally non-specific and include loss of serosal detail, increased opacity in the right cranial quadrant of the abdomen, displacement of the duodenum ventrally and/or to the right, dilated hypomotile duodenum and caudal displacement of the transverse large intestine. Punctate calcification may occasionally be identified in dogs with longstanding pancreatitis; it indicates saponification of mesenteric fat around the pancreas.

Thoracic radiographs may enable the detection of pleural fluid, edema or pneumonia which has been associated with pancreatitis in dogs and cats.

Ultrasonography
Ultrasonographic findings include enlarged, hypoechoic pancreas, cavitary lesions such as abscess or pseudocyst, dilated pancreatic duct, swollen hypomotile duodenum, biliary dilatation and peritoneal fluid. One study of dogs with fatal acute pancreatitis indicated that ultrason supported a diagnosis of pancreatitis in 23/34 dogs. Disorders other than pancreatitis e.g. pancreatic neoplasia, pancreatic edema (associated with hypoproteinemia or portal hypertension) and enlarged peri-pancreatic structures, can have identical ultrasonographic appearance to pancreatitis. Fine needle aspirates of cavitary lesions may be useful to distinguish abscess from pseudocyst.

Abdominal paracentesis
Examination of peritoneal fluid may aid the detection of various causes of acute abdominal signs such as pancreatitis, gastrointestinal perforation or ruptured bile duct.
Prognostic indicators

Stratifying the severity of pancreatitis is useful when deciding how aggressive to be with medical and nutritional support, and in offering a prognosis. Severe pancreatitis requires aggressive support and carries a guarded prognosis, whereas mild pancreatitis often responds to short term symptomatic therapy and has a good prognosis. Clinical and clinicopathological criteria can be used to predict the severity of acute pancreatitis. The presence of shock or abnormalities such as oliguria, azotaemia, icterus, markedly elevated transaminases, hypocalcaemia, hypoglycaemia, hypoproteinaemia, acidosis, leukocytosis, falling haematocrit, thrombocytopenia and DIC should be considered likely indicators of severe pancreatitis in the dog and cat.

The measurement of components of the systemic inflammatory response such as TNF-α, and C-reactive protein, and IL-6 may also yield information about the severity of pancreatitis that in the future might lead to the administration of specific antagonists of this response.

Potentially useful prognostic indicators that are pancreas specific include assay of trypsinogen activation peptide (TAP), trypsin complexed with inhibitors, and phospholipase A₂. Trypsinogen activation peptide has been shown to accurately predict severity in humans with pancreatitis. This peptide is released when trypsinogen, a pancreas-specific enzyme, is converted to its active form and rapidly accumulates in the urine and plasma of dogs with experimental acute pancreatitis. In spontaneous pancreatitis. Plasma and urinary TAP concentrations, as well as urinary TAP to creatinine ratio, were all increased in dogs that died with necrotising pancreatitis. Values were not increased in mild, interstitial pancreatitis. Increased plasma TAP concentrations were also present in dogs with severe renal disease. Phospholipase A₂ is elevated in dogs with severe pancreatitis.

A recent study determined that PE-1 had an overall sensitivity of 61% and specificity of 92%, comparable with published sensitivities for other pancreatic markers such as lipase and pancreatic lipase.

Morphologic assessment of severity is accomplished in humans by use of contrast enhanced computed tomography (CE-CT). Where lack of pancreatic perfusion is encountered i.e. necrosis, fine needle aspiration is used to distinguish infected from sterile necrosis. Substantially reduced mortality has been achieved by the detection and surgical treatment of people with infected necrosis. CE-CT has recently been reported in 2 dogs with pancreatitis. Contrast-enhanced computed tomography (CT) findings in both dogs were compatible with pancreatic necrosis. In one dog managed medically for 11 days the follow-up CT scan disclosed decreased pancreatic size and increased contrast enhancement compatible with partial resolution of pancreatitis.

Cats

Since its initial description in 1989 feline pancreatitis has emerged as an important and potentially life threatening disease. Despite increased awareness its etiology remains unknown, diagnosis is challenging, and surgical biopsy is often required to confirm a diagnosis, and facilitate detection of intercurrent disease. Treatment is generally symptomatic and typically involves aggressive nutritional support. This article reviews the current state of play in the diagnosis and treatment of acute pancreatitis in cats.

Clinical findings

Signalment and history

<table>
<thead>
<tr>
<th>KEY POINTS</th>
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<tbody>
<tr>
<td>• The most common clinical findings in cats with acute pancreatitis are lethargy, anorexia, and weight loss.</td>
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<tr>
<td>• A specific cause for pancreatitis is not apparent in the majority of cats</td>
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<tr>
<td>• There is no single test that will accurately diagnose pancreatitis in all affected cats</td>
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<tr>
<td>• Cats with pancreatitis often have inter-current disease involving the liver and small intestines</td>
</tr>
<tr>
<td>• Medical treatment is based on maintaining or restoring adequate tissue perfusion, limiting bacterial translocation, inhibiting inflammatory mediators and pancreatic enzymes and providing enteral nutritional support.</td>
</tr>
<tr>
<td>• Surgical treatment consists of restoring biliary outflow, removing infected necrotic pancreatic tissue, or coping with sequelae such as pseudocysts.</td>
</tr>
<tr>
<td>• The prognosis for acute pancreatitis in cats is always considered guarded, and is particularly poor for suppurative pancreatitis</td>
</tr>
<tr>
<td>• Feline EPI is typically due to end stage chronic pancreatitis</td>
</tr>
<tr>
<td>• Weight loss, subnormal fTLI and low serum cobalamin are very common in feline EPI</td>
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</tbody>
</table>

Acute pancreatitis has been reported in cats aged from 4wks to eighteen years old. Domestic Short- and Long-hair cats are most commonly affected. Siamese cats have been over-represented in some series. No sex bias has been demonstrated. A small number of cases have been associated with trauma, Toxoplasma gondii, pancreatic and liver flukes, FIP, calcivirus (virulent variant) and hypodystrophy. Usually there are no obvious associated factors.
Diagnostic approach and differential diagnosis

Lethargy anorexia and weight loss are the most common presenting complaints. Localizing signs or findings such as vomiting, icterus, diarrhea, abdominal pain, abdominal mass, polyuria or polydipsia should be pursued if present. The duration of clinical signs until presentation varies from less than 3 days to 12 wks.

Where a high index of suspicion for pancreatitis is present ultrasonography and determination of pancreatic markers (e.g. pancreas specific lipase) should initially be employed to help to detect pancreatic inflammation. However, given the spectrum of inter-current disease in cats with pancreatitis a well performed exploratory laparotomy with biopsy of the pancreas, liver, intestines and mesenteric lymph nodes is often required to generate an accurate diagnosis and enable feeding tube placement.

Laboratory findings

Hematology

A mild anemia that may be non-regenerative, and leukocytosis, often without a left-shift, are common in cats with pancreatitis. Leukopenia is present in some cats and carries a poorer prognosis.

Serum biochemistry

Increased ALT, SAP, bilirubin, cholesterol and glucose, and hypokalemia and hypocalemia (total and ionized) are most frequently observed. Azotemia is variably present.

A Hypokalemia, present in about 50% of cases, is perhaps the most helpful finding for raising the probability of a diagnosis of pancreatitis. Pancreatitis associated hypokalemia may be caused by a variety of reasons, such as saponification of fat, soft tissue accumulation and changes in PTH homeostasis. The presence of ionized hypocalemia (<1mmol/l) carries a poor prognosis. Hypocobalaminemia is present in some cats with pancreatitis and is thought to reflect concurrent intestinal disease, rather than exocrine pancreatic insufficiency.

Urinalysis

Enables azotemia to be characterized as renal or pre-renal. The presence of glucose or ketonuria should prompt consideration of diabetes mellitus.

Pancreas specific enzymes

Classically, elevations in serum amylase and lipase activity have been used as indicators of pancreatic inflammation in dogs. In cats it seems fair to state that total serum amylase and lipase are of no utility for diagnosing acute pancreatitis.

These limitations have stimulated the development of assays for enzymes or “markers” considered pancreatic in origin. Tests for trypsin-like immunoreactivity (TLI), trypsinogen activation peptide (TAP) and pancreas specific lipase have been evaluated in cats.

Feline Trypsin like immunoreactivity (fTLI). Immunoreactive trypsin has been shown to be a reliable indicator of pancreatic mass, enabling the reliable detection of feline and canine exocrine pancreatic insufficiency. It is much less useful as an indicator of pancreatic inflammation. It’s sensitivity has been reported to be as low as 28%, and cats with fatal acute pancreatitis frequently have values within the normal range. Specificity is better, 66-75%. The poor sensitivity, particularly in cats with severe acute pancreatitis strongly suggests down regulation of TLI in the inflamed pancreas, similar to that observed in dogs with pancreatitis. Altered renal clearance in cats with renal failure can impact the specificity, as can the finding of normal pancreatic histology in cats with high TLI and intestinal disease.

Pancreas specific lipase immunoreactivity (fPLI)

Given the limitations of fTLI tests to measure feline pancreas specific immunoreactive lipase have recently been developed. Clinical utility is still being ascertained. However the initial results for fPLI are a lot more promising than fTLI, with sensitivity for pancreatitis reported as 67%, and specificity at 91%. Preliminary evaluation of the the commercial version of the fPLI test, Spec fPL using 5.4 µg/L as the diagnostic cut off, yielded a sensitivity of 79% and the specificity of 82% (Forman et al unpublished observations).

Diagnostic imaging

How do I accurately diagnose pancreatitis?

- There is no single non-invasive test that accurately identifies all cats with pancreatitis
- Measurement of serum amylase, lipase and TLI is not reliable for confirming a diagnosis of acute pancreatitis
- Pancreas specific lipase shows promise with a sensitivity estimated at 67% sensitivity , 91% specificity for fPLI. For the Spec fPL assay (a commercialized version of fPLI) using 5.4 µg/L as the diagnostic cut off, yielded a sensitivity of 79% and the specificity of 82%
- Abdominal ultrasound has a sensitivity of 35-67% and specificity of @73%
- Cats with pancreatitis may have normal fPLI/SpecfPL and ultrasonographic findings
- Pancreatic biopsy enables confirmation and distinction between histological subtypes of pancreatitis, pancreatic hyperplasia and pancreatic cancer
- An exploratory laparotomy enables diagnosis of intercurrent disease in the liver and small intestine.
Radiographic findings in cats with acute pancreatitis may include loss of serosal detail, increased opacity in the right cranial quadrant of the abdomen, displacement of the duodenum ventrally and/or to the right, dilated hypomotile duodenum and caudal displacement of the transverse large intestine. Although radiographic signs often are absent and non-specific radiography is a logical first choice imaging modality for animals with gastrointestinal signs.

**Ultrasoundography**

Ultrasoundographic findings include enlarged, hypoechoic pancreas, cavitary lesions such as abscess or pseudocyst, dilated pancreatic duct, swollen hypomotile duodenum, biliary dilatation and peritoneal fluid. Findings in cats indicate that ultrasound will detect from 35 to 67% of cats with pancreatitis (confirmed with biopsy), with a specificity of @ 73%. A recent study using fPL as the gold standard for pancreatitis found that the single ultrasound characteristic with the highest sensitivity was hypechoic peripancreatic fat at 68%, indicating a moderate probability that cats with pancreatitis will have this abnormality on ultrasonographic examination. Specificity was >90% for each of increased pancreatic thickness, abnormal pancreatic margin, and hypechoic peripancreatic fat. The sensitivity and specificity of ultrasound were 84% and 75%, respectively, in cats with elevated serum fPL indicative of pancreatitis. These findings reveal that a normal ultrasound does not rule out pancreatitis, and that diseases other than pancreatitis (e.g. pancreatic hyperplasia, pancreatic neoplasia) should be considered when an abnormal pancreas is visualized.

**Computed tomography and MRI**

Studies in cats with CT have been disappointing, ranging from a failure to detect the pancreas to no differences visualized in cats with pancreatitis. A recent study using MRI detected pancreatic abnormalities in cats suspected of pancreatitis, including T1 pre-contrast hypointense and T2 hyperintense pancreatic parenchyma and a dilated pancreatic duct. The MRI findings of the liver were non-specific. Nine of 10 cats had biliary abnormalities, including gall bladder wall thickening, gall bladder wall moderate contrast enhancement and/or gall bladder debris. Eight of 10 cats had histologic evidence of pancreatitis, as well as hepatitis or cholangitis, with one cat diagnosed with hepatic lymphoma. The advantages of MRI/MRCP over sonography was operator independence and lack of interference from bowel gas.

**Prognostic indicators**

Severe pancreatitis requires aggressive support and carries a guarded prognosis, whereas mild pancreatitis may respond to short-term symptomatic therapy. The presence of shock or abnormalities such as oliguria, azotaemia, icterus, markedly elevated transaminases, ionized hypocalcaemia (<1mmol/l), hypoglycaemia, hypoproteinaemia, acidosis, leukopenia, falling haematocrit, thrombocytopenia and DIC should be considered likely indicators of severe pancreatitis in the cat.

**Pancreatic biopsy and histology**

The pancreas can be biopsied surgically or laparoscopically. Current recommendations, based on the patchy distribution of pancreatic inflammation, suggest taking biopsies from parts that look or feel abnormal and from the left and right limbs and the body. Histological findings are variable and there is not yet a consensus on their interpretation. In general histopathology is reported according to the predominant features as acute necrotizing (necrosis predominates), acute supplicative (lymphocytic/plasmacytic inflammation and fibrosis). Whether these histologic types indicate a distinct etiology or some form of progression is unclear. The diagnosis for suppurative pancreatitis is poor.

**Further reading**


Feline IBD or Lymphoma?  
How to Differentiate and Manage Those Diseases  
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Ithaca, NY

Feline inflammatory bowel disease  
Feline inflammatory bowel disease (IBD) is the term applied to a group of poorly understood intestinal disorders that are associated with vomiting, diarrhea and weight loss in cats. Diagnosis is usually based upon subjective analysis of intestinal mucosal biopsies and qualified according to the dominant mucosal infiltrate, typically lymphocytes and plasma cells. However, more objective studies have demonstrated increased expression of MHC class II antigen by leukocytes in the lamina propria and enterocytes, and upregulation of pro-inflammatory and immunoregulatory cytokines, rather than an increase in mucosal cellularity. Abnormalities in mucosal architecture, such as crypt distortion, villous blunting and fusion, and fibrosis have also been described, and have been associated with the severity of clinical signs, and the subjective histological grade of IBD. The cause of feline IBD has not been determined, but it is suspected that IBD in cats, like IBD in people, is a consequence of uncontrolled intestinal inflammation in response to a combination of elusive environmental, enteric microbial, and immunoregulatory factors in genetically susceptible individuals. Genetic susceptibility in people is linked increasingly to defects in innate immunity, exemplified by mutations in the innate immune receptor NOD2/CARD15, that in the presence of the enteric microflora may lead to up-regulated mucosal cytokine production, delayed bacterial clearance and increased bacterial translocation, thereby promoting and perpetuating intestinal inflammation. This possibility is supported by studies showing the pivotal importance of the enteric microflora in the development of IBD in rodents with engineered susceptibility and those demonstrating an abnormal mucosa-associated flora, considered to interact most closely with the innate immune system, in people with IBD. Knowledge of genetic susceptibility in cats with IBD is limited, with some studies reporting a predisposition for purebred cats such as Siamese. Culture based studies have shown fewer lumenal microaerophilic bacteria in the duodenal juice of cats with clinical signs of gastrointestinal disease than healthy cats. More recent studies have revealed changes in the intestinal microflora of cats with chronic gastrointestinal disease, termed dysbiosis. The number of mucosa-associated Enterobacteriaceae was higher in cats with signs of gastrointestinal disease than healthy cats (P<0.001). Total numbers of mucosal bacteria were strongly associated with changes in mucosal architecture (P<0.001) and the density of cellular infiltrates, particularly macrophages (P<0.002) and CD3⁺ lymphocytes (P<0.05). The number of Enterobacteriaceae, E. Coli, and Clostridium spp. correlated with abnormalities in mucosal architecture (principally atrophy and fusion), upregulation of cytokine mRNA (particularly IL-1, -8 and -12), and the number of clinical signs exhibited by the affected cats. These data establish that the density and composition of the mucosal flora is related to the presence and severity of intestinal inflammation in cats, and suggest that mucosal bacteria are involved in the etiopathogenesis of feline IBD.

A stepwise approach to treating feline inflammatory bowel disease

How confident am I the cat has IBD?

- Clinical findings
- Clinicopathological tests
- Diagnostic imaging
- Intestinal biopsy

Have I ruled out

- Systemic/ metabolic disease
- Dietary intolerance/ food allergy
- Infectious agents
- Protozoa
  - Giardia
  - Tritrichomonas
- Pathogenic bacteria
  - Campylobacter / Salmonella
  - Viral?
- Structural/anatomic abnormalities
- Does the cat have multiple problems or organ systems involved?
- Is the cat deficient in cobalamin or folate?
- Do I need a biopsy?

What and how should I biopsy?

- How do I interpret the biopsy results and integrate gastric and intestinal histopathology?
- Is it IBD or small cell lymphoma?
An overview of diagnosis and treatment

Clinical findings

Vomiting is the most common clinical sign in cats with IBD. Vomitus often contains bile. Other findings include diarrhea, changes in appetite, weight loss and less commonly excessive borborygmi and abdominal discomfort.

The severity of disease ranges from intermittent vomiting in mild cases to intractable small bowel diarrhea, inappetance and weight loss in severe ones. The severity of the disease correlates with the degree of intestinal damage, particularly villus atrophy and fusion.

Physical findings range from normal to thickened intestines, mesenteric lymphadenopathy and loss of muscle mass. Ascites or edema are extremely rare in cats with IBD.

Routine laboratory testing may reveal mild to moderately elevated liver enzymes as a result of GI barrier dysfunction. However, IBD can be associated with concurrent hepatobiliary disease and pancreatitis-“triaditis”-so the clinician must consider these disorders (Ultrasoundography and fPLI aid detection of intercurrent disease). The presence of hypocalcemia would ring alarm bells for pancreatitis. Hypoalbuminemia is rare. CBC is usually normal. Eosinophilia is encountered in some cats with LP enteritis, and should prompt consideration of parasites or food intolerance/allergy, as well as mastocytosis or hypereosinophilic syndrome. Measurement of serum cobalamin and folate can aid the detection of intestinal disease-low cobalamin concentrations are common in cats with IBD (EPI should be excluded by TLI assay). Cobalamin deficiency can produce identical signs to those associated with IBD. A combination of low folate and cobalamin tends to support a diagnosis of severe IBD or GI lymphoma.

Ultrasoundographic findings in cats with IBD overlap with those of cats with lymphoma i.e. muscularis hypertrophy and mesenteric lymphadenopathy

Diagnosis

A diagnosis of idiopathic IBD is made by excluding systemic, parasitic, infectious, pancreatic and structural causes of chronic vomiting, weight loss or diarrhea and demonstrating histopathological abnormalities in intestinal biopsies. Keep in mind that IBD may co-exist with hepatobiliary disease and/or pancreatitis.

Treatment

Treatment of IBD is usually a “best guess least harm” approach employing dietary modification, vitamin supplementation, antimicrobial agents and immunosuppression. Treatment is to some extent based on the severity of the disease.

Mild to moderate disease may be associated with dietary sensitivity/intolerance, cobalamin deficiency or antibiotic responsive enteropathy.

A therapeutic dietary trial can be performed with either: 1) a highly digestible diet which is gluten-free, 2) a diet limited to a single novel protein source or 3) a diet containing protein hydrolysate, to determine if dietary sensitivity or intolerance are present. A response is usually observed within one to two wks. Re-challenge with the original diet is required to demonstrate intolerance. Cobalamin deficiency is treated with parenteral cobalamin (0.5ml SC q 2-3wks). Folate should be given orally if serum concentrations are low.

A therapeutic trial (21 days) with Tylosin (10mg/kg PO TID), metronidazole (15mg/kg PO BID) or oxytetracycline (10-20mg/kg PO TID) can be undertaken to determine if an antibiotic responsive enteropathy is present.

In patients who fail these trials and in those with severe disease or hypoproteinaemia, immunosuppressive agents are usually added to achieve a response. Oral prednisolone (1-2mg/kg PO BID) is the initial drug of choice. It is usually administered at an immunosuppressive dose for 2-3 wks and then decreased by 50% every 2-3 wks, and continued on an alternate day basis for 2-3 months. If clinical response is poor, chlorambucil (6mg/m2 PO PO EOD (@2mg/5.3 kg cat) and prednisone (5mg PO /cat/day) are initiated. Metronidazole (15mg/kg PO BID 10-14d then SID 10-14d) is frequently used in conjunction with corticosteroids to modify the microflora. However metronidazole is a potential mutagen and the author avoids long-term therapy.

Successful treatment is accompanied by a decrease in clinical signs, and an increase in plasma proteins (though low albumin is uncommon in IBD). Once a patient has had 2-3 months remission from signs it may be possible to gradually withdraw immunosuppressive therapy. If signs recur daily medication is continued until signs resolve then gradually reduced. In patients who respond poorly to therapy or relapse after an initial response lymphoma should be ruled out.

Prognosis

The prognosis for lymphoplasmacytic enteritis is variable and depends on its severity and the presence of concurrent disease. Many patients require prolonged treatment with glucocorticoids and diet. As no accurate criteria exist for predicting response it is wise to give a guarded prognosis.

Alimentary lymphoma

The changing and variable phenotype of feline alimentary lymphoma
Lymphomas represent up to ninety percent of hematopoietic tumors in the cat and are one of the most frequently diagnosed tumors of domestic cats. During the feline leukemia virus (FeLV) era of the 1960s through the 1980s, FeLV was the most common cause of up to 70% of cases of lymphoma that were predominantly cranial mediastinal, multicentric, renal and central nervous forms, associated with FeLV antigenemia. However, despite a decline in FeLV-associated lymphoma and contrary to expectations the prevalence of lymphoma has increased in the post-FeLV era, and there has been a change in the frequency of affected anatomic sites and patient demographics. Alimentary lymphoma is now the most common anatomic form and predominantly affects middle age to older cats, in contrast to mediastinal or multicentric lymphoma that typically affect younger cats. This increase in alimentary lymphoma has also been accompanied by a change in immunophenotype, from predominantly high grade B cell to predominantly low grade T cell. In a study of 41 cats with low-grade lymphocytic lymphoma evaluated at the Cornell University Hospital for Animals and South Carolina Veterinary Internal Medicine between 1995-2005, the median age at diagnosis was 13 years (range, 6-17 years) and 40/41 were Domestic Shorthair (n = 33) or Domestic Longhair (n = 7). Lymphoma was confined to the gastrointestinal tract in 68% of cats and eighty-nine percent (32 of 36) of lymphomas were determined to be of T-cell origin by immunohistochemistry, while 8% (3 of 36) were of B-cell origin. A search of our pathology database for feline alimentary lymphoma during the years 2007 to 2011 yielded a total of 136 small cell lymphoma (SCL) and 16 cases of large cell lymphoma (LCL). The immunophenotype of a randomly chosen subset of 33 of the 136 cats with SCL indicated they were all T-cell. Surprisingly, we found that LCL were divided evenly between T-(8/16) and B-cell (7/16), with one tumor considered B&T-cell. This diversity in cell morphology and immunophenotype has potential implications for etiopathogenesis and treatment, and subsequent studies should be stratified on the basis of tumor immunophenotype and cell morphology.

The response to therapy has also changed, with overall median survival time reaching 704 days in low-grade lymphoma versus weeks to months in high-grade large cell lymphoma. Until recently the large B cell phenotype predominated in Australia and the UK, but small T-cell phenotype has recently emerged. The sequential temporal emergence of low-grade alimentary lymphoma in the USA, Great Britain and Australia echoes the appearance of feline hyperthyroidism and raises the possibility of an underlying environmental or infectious etiology. The factors responsible for the changes in prevalence, immunophenotype and biology of feline alimentary lymphoma are not known.

Clinical findings

Middle aged and older cats (median 13yrs), predominantly DSH cats are reported. Weight loss, vomiting, chronic small bowel diarrhea and progressive anapetappance are common features of GI lymphoma. Physical examination may reveal diffusely thickened or nodular intestines ± mesenteric lymphadenopathy. Hepatosplenomegaly, renomegaly, generalized lymphadenopathy and abdominal mass may also be detected. Acute abdominal pain and shock may be present if intestinal perforation has occurred.

Diagnosis

Routine biochemistry may reveal hypoalbuminemia. Anemia which is either normocytic normochromic non-regenerative or microcytic and hypochromic, and neutrophilia may also be present. Serum concentrations of cobalamin are often very low in cats with GI lymphoma and serum folate concentrations may also be reduced. High PLI concentrations are found in some cats and may indicate concurrent pancreatitis or pancreatic lymphoma. Ultrasound is useful for evaluating intestinal thickness / layering, presence or absence of mucularis hypertrophy, and detecting mesenteric lymphadenopathy and abnormalities in liver/kidney/spleen and pancreas. However it cannot distinguish lymphoma from IBD. Diagnosis can be made by demonstrating neoplastic lymphocytes in aspirates or biopsies from enlarged intestinal or peripheral lymph nodes, but is more often made by intestinal biopsy. The absence of lymphoma in a fine needle aspirate does not rule it out: there is a high degree of discordance between FNA and biopsy results of LN aspirates from cats with confirmed alimentary lymphoma. Endoscopic visualization and biopsy can enable the accurate diagnosis of GI lymphoma. However, endoscopy can also miss submucosal and serosal lesions or yield a diagnosis of “lymphoplasmacytic enteritis”. Many cats with signs of intestinal disease including GI lymphoma have concurrent evidence of hepatic and pancreatic disease and undergo exploratory laparotomy and circumvent the endoscopy surgery debate.

Treatment and prognosis

In a recent study of 41 cats with low-grade lymphoma, lymphoma was confined to the gastrointestinal tract in 68% of cats, while 32% had other organ systems affected with or without gastrointestinal involvement. Extra-gastrointestinal sites involved included mesenteric lymph nodes (n = 6), liver (n = 10), spleen (n = 1), and pancreas (n = 1). Some cats had more than 1 site affected. Eighty-nine percent (32 of 36) of lymphomas were determined to be of T-cell origin via immunohistochemistry, while 8% (3 of 36) were of B-cell origin.

Fifty-five per cent of cats achieved a complete response to therapy and 37% achieved a partial response. The majority of cats (n = 31; 76%) received prednisone at a dose of 5 mg, PO, q 12-24 hrs and most (n = 35; 85%) received chlorambucil at a dose of 2 mg, PO, every other day. Eight percent of the cats experienced no response. There was no association between any risk factors and response to therapy. Overall median remission duration was 948 days. Partial response to therapy was associated with shorter remission duration (P = 0.002). Overall median survival time was 704 days. No factors were significantly associated with survival time. Interestingly, 78% of cats tested in this study had hypocobalaminemia, which was associated with short remission duration, but only in the univariable analysis. Thus supplemental cobalamin (0.5ml SC q 2-3wks) and folate should be given as required. Lymphoblastic
lymphoma, is much more aggressive than lymphocytic lymphoma, is generally treated with combination chemotherapy, and carries a poor prognosis.

**Given the dramatic differences in outcome of lymphocytic vs. lymphoblastic lymphoma is there any way to distinguish these forms of the disease without a biopsy?**

In the study of Fonduccaro et al clinical signs, physical exam findings and endoscopic localization of disease overlapped in cats with lymphoblastic and lymphocytic lymphoma. Lethargy and the presence of an abdominal mass tended to be more frequent in cats with lymphoblastic lymphoma.

**Can I diagnose intestinal lymphoma with an endoscopic biopsy?**

Yes and No! Endoscopic visualization and biopsy can enable the accurate diagnosis of GI lymphoma. However, endoscopy can miss submucosal and serosal lesions or yield a diagnosis of “lymphoplasmacytic enteritis”. Many cats with signs of intestinal disease including GI lymphoma have concurrent evidence of hepatic and pancreatic disease and undergo exploratory laparotomy circumventing the endoscopy surgery debacle. Diagnosis also depends on the pathologist! Some pathologists are unwilling to diagnose lymphoma on endoscopic biopsies.

**How can I distinguish gastrointestinal lymphoma from inflammatory bowel disease?**

The signalment, clinical presentation, physical examination and results of clinical investigation are often very similar in cats with IBD and alimentary lymphoma. Hypoalbuminemia is a rare feature of IBD in cats and it’s presence makes me think of high grade IBD or lymphoma. Intestinal perforation should place lymphoma high up the list. Concurrent renalomegaly or splenomegaly should also prompt consideration of lymphoma and aspiration/biopsy. The presence of intestinal thickening, muscularis hypertrophy and mesenteric lymphadenopathy is consistent with IBD and lymphoma. Moreover, fine needle aspiration of enlarged lymph nodes can yield reactive hyperplasia in cats with GI lymphoma. Endoscopy may reveal marked thickening of the gastric mucosa and increased friability of the intestinal mucosa in cats with lymphoma, but there is an overlap between cats with IBD and alimentary lymphoma. At the present time the accurate distinction of GI lymphoma from IBD relies on histopathological evaluation. This can be relatively straightforward where biopsies are considered adequate in size and number, and unequivocal lymphoblastic cells or a monomorphic population of small lymphocytes are present. However, some biopsies display features of lymphoma and IBD, and others such as endoscopic biopsies do not allow thorough evaluation of all tissue compartments, and make it difficult to distinguish IBD from lymphoma. Immunophenotyping for T and B cell lineage, and PCR to detect clonal expansion of B (feline immunoglobulin heavy chain variable region genes) and T cells (T cell receptor gamma variable region genes) have been developed to aid this process.

**What is driving the development of feline alimentary lymphoma?**

Low-grade alimentary lymphoma in cats does not appear to be related to FeLV or FIV. There is strong evidence in people that low grade mucosa associated lymphomas develop as a consequence of a genetic predisposition (typically chromosomal translocations that impact mucosal inflammation or apoptosis) and a chronic infections with bacteria and viruses are increasingly associated with lymphoma. In people, infections with Helicobacter, Borrelia, Chlamydia and Campylobacter are associated with gastric, cutaneous, pericardial and intestinal B cell MALT-lymphomas, respectively. The observation that 8-13% of people with celiac disease develop non-Hodgkin’s enteropathy-associated T cell lymphoma is of high relevance to cats with alimentary lymphoma. Lymphomatous transformation in celiac disease is associated with unresolved chronic lymphocytic inflammation, villus blunting, an IL-6 and IL-8 rich cytokine environment, and global shifts in the enteric polymicrobial environment, towards proteobacteria and E.coli. We have established that cats with lymphoplasmyacytic enteritis have shifts in mucosal Enterobacteriaceae, E. coli, and Clostridium spp. that correlate with abnormalities in mucosal architecture (principally atrophy and fusion), proinflammatory cytokine upregulation (IL-1, -8 and -12), and clinical severity, that parallel human coeliac disease. In preliminary studies, we found that the mucosal cytokine environment in feline alimentary lymphoma is dominated by IL-6 upregulation, and have detected invasive bacteria in 14/17 large cell lymphomas (a mix of T and B cell lymphomas) and 6 of 33 small cell lymphomas (T cell) relative to 0/18 controls.

While it is well established that persistent viral infections can drive lymphoma in cats, the relationship of FeLV to alimentary lymphoma in cats is controversial, with discordance between antigenemia (0-38%) and PCR positivity of tissues for viral sequences. It is conceivable that latent FeLV infection drives feline alimentary lymphoma, but this possibility has to be weighed against the falling prevalence of FeLV in the cat population. In people a variety of viruses have been associated with lymphoma including: the γ-herpesvirus Epstein Barr Virus (EBV), which is associated with Hodgkin’s lymphoma and various non-Hodgkin’s lymphomas, including B-cell lymphoma in immunocompromised patients, Kaposi Sarcoma herpesvirus in individuals with immunosuppressive conditions, Human T-cell Leukemia Virus-I with Adult T-cell leukemia-lymphoma (ATLL), a peripheral T-cell malignancy and Kaposi Sarcoma herpesvirus (HCV), which has been implicated in the development of some cases of non-Hodgkin lymphoma (NHL). Recent studies have expanded our knowledge of the role that viruses may play in promoting chronic intestinal inflammation, which is a known risk factor for tumorigenesis. A new dimension in understanding the multifactorial basis of chronic inflammatory diseases such as Crohn’s disease has emerged from the discovery that a virus trigger (norovirus) is required to observe intestinal abnormalities in IBD susceptible Atg16l1/HM mice. Mucosal inflammation depended on the presence of the intestinal microbiome and pro-inflammatory cytokines. Thus, variations in a host autophagy gene, exposure to a specific virus and the microbiome can act together to trigger intestinal inflammation in mice that is similar to that in patients with Crohn’s disease.
Taken as a whole, the evidence to date supports the possibility that an underlying bacterial or viral infection could be involved in the etiopathogenesis of feline alimentary lymphoma

References and further reading


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What’s Causing this GI Bleeding?
Kenneth Simpson, BVM&S, PhD, DACVIM, DECVIM
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Bleeding into the gastrointestinal tract is usually manifest clinically as hematemesis, melena or hematochezia.

Hematemesis suggests bleeding into the stomach or upper small intestine. Rarely nasal or oral bleeding that is swallowed.

Melena suggests proximal GI bleeding typically stomach, small intestine.

Melena and hematemesis frequently occur together.

Hematochezia suggests loss of blood in the distal GI tract typically the colon.

The underlying disease processes that cause blood loss in the GI tract are erosions, ulcers, coagulopathies and rarely vascular hypertension or leakiness.

Causes of melena / hematemesis

Gastrointestinal erosion/ulceration

Metabolic uremia (?), severe liver disease, hypoadrenocorticism

Inflammatory gastritis, enteritis, HGE

Neoplastic leiomyoma, adenocarcinoma, lymphosarcoma

Paraneoplastic mastocytosis, hypergastrinaemia/ other APUDomas

Vascular A-V fistula, aneurysms

Ischaemia hypovolemic shock, hypoadrenocorticism, thrombosis / infarction, reperfusion

Foreign objects non-steroidal and steroidal anti-inflammatories

Drug induced

Coagulopathies thrombocytopenia, factor deficiencies, D.I.C.

Ingestion of blood oral, nasal, pharyngeal, pulmonary bleeding

Hematochezia is typically a sign of colonic disease

Colitis

- Parasitic (whipworms, giardia), bacterial (Campylobacter, Salmonella) and fungal (Histoplasma) colitis, algae (prototheca)
- Acute-non-specific
- Chronic non-specific usually called lymphoplasmacytic colitis
- Granulomatous colitis / Histiocytic Ulcerative Colitis (usually Boxer, French Bulldogs, Mastiff breeds)

Neoplasia polyps, adenocarcinoma, lymphoma

Cecal-inversion

Vascular ectasia

Diagnostic evaluation

A thorough history and physical examination provide valuable clues to the site and cause of bleeding.

- e.g. A Black Standard Poodle with melena, hematemesis and bradycardia should immediately trigger suspicion of hypoadrenocorticism. A Shitzu with sudden onset hematemesis, melena and injected mucus membranes would be a prime suspect for HGE. An eight week old puppy with melena and a painful abdomen and a thick segment of gut would rapidly raise suspicion of parvovirus and potential intussusception. Has the patient had access to NSAIDs, rodenticides? What food is fed - raw (salmonella)? Grain based (aflatoxin)? What treats are fed (jerky)? A patient with hematochezia that is accompanied by mucus and tenesmus is likely to have colitis, whereas focal streaking of fresh blood on a relatively normal stool suggests an ulcerated polyp or tumor.

Routine clinicopathological testing will help to determine cause

CBC/ProfileUA: e.g. PCV 75/ total protein 6.5 is suggestive of HGE.

Anemia - Microcytosis (MCV < 63fl), decreased red cell haemoglobin and thrombocytosis are common in dogs with iron deficiency secondary to GI blood loss from intestinal parasites or tumors (Ddx portosystemic vascular anomalies or fibrosing liver disease in young dogs with signs of gastrointestinal disease). Eosinophilia may suggest mastocytosis, hypoadrenocorticism, parasitism or food intolerance. Isothenuria and azotemia with renal disease. White cell count varies depending on degree of inflammation and dogs with low white cell counts and melena and hematemesis are suspects for Parvovirus, Salmonellosis, sepsis, pancreatitis, intestinal perforation etc.

Elevated liver enzymes and hyperbilirubinemia in the absence of anemia would be consistent with severe hepatic or biliary disease. Melena in association with clinicopathogical evidence of liver dysfunction, particularly low cholesterol should raise the suspicion of end stage liver disease or where acute in presentation aflaoxicosis.
Patients with hematochezia accompanied by tenesmus and mucus should undergo fecal evaluation for endoparasites (whipworms) and culture for campylobacter and Salmonella and rectal cytology for Histoplasma may be warranted.

**Screening for coagulopathies:**
Where no underlying disease is apparent to explain GI bleeding a thorough evaluation of coagulation status should be performed. However, many systemic diseases associated with GI bleeding can also have concurrent coagulopathies. Physical exam may show evidence of an underlying coagulopathy e.g. petechiae, acchymoses. Tests used to evaluate hemostasis include:

- Platelet count
- APTT, OSPT, Protein C, ATIII, D-dimer, fibrinogen, TEG
- Buccal mucosal bleeding time

**Diagnostic imaging**
Radiographs and ultrasound can help to localize the underlying disease associated with GI bleeding. Ultrasound may reveal gastric or intestinal masses or ulcers, or underlying hepatic disease associated with bleeding (usually acquired shunting). Contrast radiography is rarely performed to detect ulcers. Patients with focal masses in the intestines are typically taken to surgery. In the absence of a surgical condition endoscopy is often used to investigate the underlying cause and site of GI bleeding. Patients with undefined melena and hematemesis are frequently evaluated with an upper endoscopy and if this is negative a lower GI endoscopy to access the ileum can be performed. In patients with hematochezia endoscopic examination is typically restricted to the colon.

The approach outlined above should help to determine the cause and site of GI bleeding in most patients. However, what steps can be taken if we do all these tests and we still can’t find the site or cause of bleeding? Or the patient has significant GI bleeding and is too sick to undergo anaesthesia?

**Additional modalities include**

- Scintigraphy with labeled red cells
- Push-pull enteroscopy
- Surgical exploratory
- Capsule endoscopy

Of these techniques capsule endoscopy has shown the most promise in people for a test that is minimally invasive and accurate and has recently been applied to dogs. So keep your eyes open……..

**Further reading**
Samuel N Adler and Ingvar Bjarnason. What we have learned and what to expect from capsule endoscopy World J Gastrointest Endosc. 2012 October 16; 4(10): 448–452.
A thorough and systematic approach is required to determine the cause of chronic diarrhea. An integrated approach based on patient history, physical findings, clinicopathological and intestinal function testing, and diagnostic imaging will be presented.

**Pathophysiology of diarrhea**

The most frequent clinical sign of intestinal disease is diarrhea - the passage of feces containing excess water, resulting in an increase in the fluidity, volume or frequency of bowel movements. The pathomechanisms in the genesis of diarrhea can be categorised as osmotic, secretory, permeability and motility. Most intestinal disease in dogs and cats involves several patho-mechanisms so attempts to categorise animals presented for the investigation of diarrhea using these criteria are usually redundant. e.g. the accumulation of inflammatory cells within the intestine in response to antigenic challenge and other less well defined stimuli, can exert its effects both directly and indirectly by the production of inflammatory mediators such as prostaglandins and leukotrienes. The net result is abnormal mucosal absorption, secretion, permeability and intestinal motility.

**General approach**

Diarrhea which has lasted for 2 or more weeks is considered chronic. The approach to chronic diarrhea is based on the origin of diarrhea - large bowel or small bowel, and the presence of other specific or localising clinical findings. Differentiation is important as the diagnostic and therapeutic approaches to small and large bowel diarrhea are different. Differentiation is made on the basis of information furnished by the owner in response to questions about faecal characteristics, volume and frequency and related signs such as vomiting, weight loss, tenesmus and dyschezia.

Small bowel diarrhea is a consequence of diseases that affect the small intestine or related structures such as the exocrine pancreas.

**Causes of chronic diarrhea**

<table>
<thead>
<tr>
<th>infection</th>
<th>causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Salmonella, Campylobacter, Giardia, Tritrichomonas, Cryptosporidium, FIV/FIV,FIP</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hyperthyroidism, liver disease, kidney disease</td>
</tr>
<tr>
<td>Dietary</td>
<td>Intolerance / allergy</td>
</tr>
<tr>
<td>Exocrine pancreatic insufficiency</td>
<td></td>
</tr>
<tr>
<td>Small intestinal disease</td>
<td>Partial obstruction- intussusception, foreign object, neoplasia, congenital anomalies</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>lymphoplasmacytic, granulomatous (FIP), eosinophilic</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Lymphosarcoma, adenocarcinoma, leiomyoma, fibrosarcoma</td>
</tr>
<tr>
<td>Functional</td>
<td>Motility disorders, idiopathic</td>
</tr>
</tbody>
</table>

**Patient evaluation and diagnostic approach**

**Signalment and history**

Infectious and parasitic diseases are common in young animals, whereas neoplasia and metabolic disorders are more common in middle aged to older animals. Certain conditions appear more common in certain breeds e.g. IBD in Siamese. Small bowel diarrhea is generally associated with weight loss and large stool volume. Failure to thrive, changes in appetite, borborygmi, flatus, abdominal discomfort, ascites and oedema are also more common with small than large bowel diarrhea.

**Physical examination**

Particular attention should be paid to hydration status and examination and palpation of as much of the gastrointestinal tract and abdomen as possible. The thyroid gland should be palpated in cats >6yo. A thorough rectal examination should be performed.

**Investigation of chronic small bowel diarrhea**

The approach to patients with chronic small bowel diarrhea who are stable, have no specific localizing clinical findings and are negative for fecal parasites is usually to:

- Rule out endoparasites and pathogenic bacteria
- Screen for systemic disease
- Rule out exocrine pancreatic insufficiency
- Rule out partial obstruction
- Evaluate intestinal structure and function

- Fecal
  - CBC, profile, UA ± T4, FIV/FIV
  - TLI
  - Palpation, radiographs, ultrasound
  - Biopsy - endoscopic / surgical, cobalamin/folate
Laboratory evaluation of chronic small bowel diarrhea

**Fecal analysis**
Giardia (cysts-ZNSO4,IFA, ELISA), Cryptosporidium (IFA), Coccidia, Tritrichomonas fetus (In pouch, PCR), other endoparasites (fecal float). Analysis for Clostridial endospores and endotoxin is fraught with difficulty in interpretation. Culture for Campylobacter and Salmonella in animals with bloody stools, or fever, or chronic undefined diarrhea. Fecal culture cannot be used to diagnose small intestinal bacterial overgrowth which has not ben described in cats!

**Hematology**
Anemia - Microcytosis (MCV < 42fl cat) may occur secondary to GI blood loss. Macrocytosis (MCV> 53fl): ddx regenerative anemia, hyperthyroidism, FeLV or cbl/ folate deficiency. 
Eosinophilia - intestinal parasitism, mast cell tumors, eosinophilic enteritis or hypereosinophilic syndrome. 
Neutrophilia ± a left shift may be encountered in inflammatory or infectious conditions. Lymphopenia may be associated with protein losing enteropathies and immunodeficiency. 
Lymphocytosis is typical in stressed cats (adrenaline response).

**Serum biochemistry**
R/O non-intestinal diseases which cause signs such as weight loss, vomiting and diarrhea that overlap with primary GI disease i.e. hyperthyroidism, kidney disease, renal disease, diabetes mellitus. 
Metabolic consequences e.g. hypokalemia, hyponatremia. Mild to moderate increases in liver enzymes such as ALT (up to 500 IU/l) are common in cats with gastrointestinal and intestinal disease. Serum bile acids - liver dysfunction or shunting in patients with GI signs. 
Hypoglycemia with signs of gastrointestinal disease should arouse the suspicion of sepsis, liver disease, hypoadrenocorticism or pancreatic tumor. Hypoalbuminemia + hypoglycemia R/O protein losing enteropathies 
Hypoalbuminemia with normal or increased globulin concentration has to be distinguished from protein losing nephropathy and liver disease. 
Chronic diarrhea associated with hypoalbuminaemia usually requires intestinal biopsy to define the cause. Non-intestinal causes of protein losing enteropathy such as portal hypertension should also be considered. When globulin concentrations are normal or elevated renal and hepatic causes should also be pursued.

**Protein losing enteropathies**

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Panleucopenia, Salmonella,</th>
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</thead>
<tbody>
<tr>
<td>Structural</td>
<td>Intussusception</td>
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<tr>
<td>Neoplasia</td>
<td>Lymphosarcoma</td>
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<tr>
<td>Inflammation</td>
<td>Lymphoplasmacytic, eosinophilic, granulomatous</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>Neoplasia, ulceration</td>
</tr>
</tbody>
</table>

**Urinalysis**
Part of a baseline evaluation to detect or rule out urogenital disorders in patients with signs of intestinal disease. Urate crystalluria may prompt the investigation of hepatic dysfunction as a cause of clinical signs. Urine Prot:creatinine for determining if the kidney is involved in the development of hypoalbuminaemia in patients with intestinal signs.

**Serology and hormone assays**
T4, FIV and FeLV.

**Tests of pancreatic function**
Exocrine pancreatic insufficiency is uncommon in cats and is usually associated with chronic diarrhea and polyphagia and a poor haircoat fTLI ≤ 8µg/l. 
Pancreatitis can occur concurrently with chronic intestinal disease and cholangitis. Measurement of serum PLI (sensitivity 67%, and specificity at 91%) and ultrasonography (sensitivity 35 to 67 %, with a specificity of 73%) may help to determine the presence of pancreatitis.

**Radiography**
Survey abdominal radiographs are taken in patients with vomiting, but are low yield in patients with chronic diarrhea. Contrast radiography can be useful in evaluating partial obstruction and transit time/ gut length if ultrasonography is not available. Thoracic radiographs are often warranted in older cats with weight loss to screen for systemic disease.

**Ultrasonography**
Ultrason is useful for detecting intestinal lesions such as intussusceptions, masses and foreign bodies, and for assessing intestinal wall thickness. The results of radiography and ultrasound provide a rational basis for selecting endoscopic biopsy (duodenal juice analysis) or a laparotomy. Normal or diffusely thickened intestines can initially be evaluated endoscopically while focal lesions usually require guided aspiration or laparotomy. Muscularis hypertrophy and mesenteric lymphadenopathy are frequently associated with inflammatory bowel disease and alimentary lymphoma.

**Tests of intestinal function**
When a clinical problem cannot be adequately defined or localised to the small intestine a variety of tests can be used to assess small intestinal function. Intestinal function tests have the potential benefit of allowing an overall assessment of SI function, rather than the small snapshot provided by a biopsy. They should always be critically evaluated in the context of the whole patient.

**Cobalamin and folate**

The measurement of circulating concentrations of cobalamin and folate may give an indication of the site and cause of intestinal dysfunction. Plasma concentrations of cobalamin and folate are labile and reflect the balance between dietary intake, bacterial utilisation and production, and intestinal absorption and body losses. The interpretation of circulating cobalamin and folate concentrations with regard to small intestinal disease is only valid if exocrine pancreatic insufficiency, dietary supplementation, parenteral administration have been excluded and attention is paid to dietary vitamin content.

Subnormal concentrations of cobalamin are common in cats with EPI, intestinal, pancreatic or hepatic disease:

Forty-nine of 80 serum samples submitted from cats with signs of gastrointestinal disease during the period of January 1996-January 1998 had cobalamin concentrations below the reference range for healthy cats (range 900 - 2,800 pg/ml; mean ± SD = 1775 ± 535 pg/ml SD ; n=33). Cats with subnormal cobalamin concentrations (mean ± SD = 384 ± 272 pg/ml; range 3 - 883pg/ml) were middle aged or older and were presented for weight loss, diarrhea, vomiting, anorexia and thickened intestines. Definitive diagnoses in 22 cats included inflammatory bowel disease, intestinal lymphoma, cholangiohepatitis or cholangitis, and pancreatic inflammation. Serum concentrations of cobalamin were particularly low in cats with intestinal lymphoma, 3/5 of which also had subnormal serum concentrations of folate (<9ng/ml). The simultaneous presence of disease in the intestines, pancreas or hepato-biliary system in many cats made it difficult to determine the cause of subnormal cobalamin concentrations. The circulating half-life of parenteral cyanocobalamin was shorter in two cats with IBD (5 days) than in four healthy cats (12.75 days).

The presence of subnormal serum concentrations of cobalamin in 49 of 80 cats evaluated suggests that the measurement of serum cobalamin may be a useful indirect indicator of enteric or pancreatic disease in cats. The rapid depletion of circulating cobalamin in cats indicates that cats may be highly susceptible to cobalamin deficiency. From studies to date it appears that cats with a cobalamin below 200pg/ml consistently have increased MMA and require parenteral cobalamin.

**Intestinal biopsy**

Biopsy of the intestine is frequently required to achieve a diagnosis in patients with chronic diarrhea due to malabsorption. In diffuse intestinal diseases and in animals with hypoproteinaemia endoscopy provides a minimally invasive low risk way of obtaining a biopsy. At least seven to 10 endoscopic biopsies should be acquired

Endoscopic biopsies are restricted to the mucosa and are small, difficult to process and orientate, and can be obtained only from the proximal duodenum and occasionally the distal ileum. Thus surgical biopsies are necessary in patients with focal intestinal lesions and in those whom endoscopic biopsy has not yielded a result. Surgical biopsies should be taken from multiple sites along the small intestine even if the intestine looks grossly normal. A small dermatologic punch aids the surgeon in obtaining full thickness biopsies and biopsy sites are sutured in an appropriate fashion. Extreme care is required where the bowel looks grossly abnormal and in hypoproteinememic patients to ensure leakage does not occur. Precautionary measures such as serosal patch or omental wraps may be employed. Biopsies of mesenteric lymph nodes should also be obtained. Other abdominal organs such as the liver, and pancreas can be grossly examined and biopsied.

The information which can be obtained from intestinal biopsies depends on the expertise of the pathologist. Minimum evaluation should include routine microscopic examination of H&E stained sections. The pathologist should be able to give an indication of villus height and morphology, ratio of crypt to villus and the type and degree of cellular infiltrate and intraepithelial lymphocyte count. Recent studies suggest that changes in mucosal architecture are much more significant than subjective alterations in cellularity. Staining for different lymphocyte sub-types and clonality PCR may be useful in distinguishing IBD and low grade alimentary lymphoma.

**References**


Swallowing (a.k.a deglutition) is the transport of food and liquids from the oral cavity to the stomach. This process requires a coordinated effort between the oral cavity, pharynx, esophagus, and associated muscles and nerves. A comprehensive understanding of the mechanisms of swallowing is critical to identifying the underlying cause of dysphagia and dysmotility. In this presentation, we will review the phases of deglutition in preparation for a discussion about dysphagia and esophageal dysmotility.

Dysphagia refers to a difficulty in swallowing which can arise because of an abnormality in any of the structures that participate in deglutition including the oral cavity, pharynx, esophagus, or associated muscles and nerves. Dysphagia is generally divided broadly into two major categories based on location: oropharyngeal or esophageal disease.

**Oropharyngeal dysphagia**

**Initial assessment**

Oropharyngeal dysphagia encompasses any abnormality that causes disruption in the transport of a liquid or food bolus from the oral cavity to the upper esophageal sphincter (UES). A problem-oriented approach with consideration of the signalment, history, and physical examination findings is the only way to develop a successful diagnostic and therapeutic plan. The history should be tailored to obtain important information such as if regurgitation and/or coughing accompanies the signs of dysphagia and whether the animal has been exposed to any potentially caustic substances (e.g. household cleaners). Ptyalism and gagging are commonly observed in animals with oropharyngeal dysphagia. Other clinical signs can include reluctance to eat despite an interest in food, dysphonia, poor drinking ability, and dropping food. Immediate food ejection may be confused for regurgitation in animals with oropharyngeal dysphagia. Causes of oropharyngeal dysphagia can be divided into anatomic and functional causes. Anatomic abnormalities are much more common than functional disease and are often identified or suspected after physical examination. Unless concern for aspiration exists, the practitioner should observe the animal’s eating behavior. During the oropharyngeal exam, special attention should be paid to whether the animal has facial asymmetry and/or pain on opening its mouth. A thorough neurologic examination should also be performed in any animal that presents for dysphagia.

**Diagnostic testing**

Although it is generally low yield, a minimum database is recommended to evaluate the overall wellness of the patient prior to sedation or anesthesia. The minimum database may also provide information about inflammatory or immune-mediated causes of dysphagia. Survey cervical and thoracic radiography is performed to further evaluate for anatomic causes of dysphagia and to evaluate for aspiration pneumonia. A complete oropharyngeal exam should be performed under sedation or anesthesia if necessary prior to advanced imaging such as dental radiography or CT. Videofluoroscopy is the best diagnostic to evaluate for functional causes of dysphagia such as cricopharyngeal achalasia or asynchrony. Additional diagnostics that can be considered if initial evaluation is unrewarding include acetylcholine receptor auto-antibody and/or anti-nuclear antibody testing, thyroid function tests, ACTH stimulation, EMG, tissue biopsy, endoscopy, MRI and/or 2M auto-antibody testing.

**Esophageal dysphagia**

**Initial assessment**

Esophageal dysphagia encompasses any disease that causes disruption in the transport of a liquid or food bolus from the UES to the gastric cardia. The approach to esophageal dysphagia mirrors that discussed for oropharyngeal dysphagia. Often, clinical symptoms of dysphagia including multiple attempts to swallow and ptyalism will not be observed with esophageal dysphagia. However, symptoms of dysphagia may be appreciated with particularly painful esophageal lesions or proximal esophageal disease. Regurgitation is the hallmark of esophageal dysphagia. Dropping of food or poor drinking ability should not be observed in animals with esophageal dysphagia unless the oropharynx is concurrently affected. The practitioner should ensure that the client is truly reporting regurgitation and not vomiting or hemoptysis. Again, unless there is concern for aspiration, the practitioner should observe the animal’s eating behavior. I often do this with small meatballs or treats. Particular attention should be paid to palpation of the cervical esophagus and salivary glands. The animal’s body and muscle condition should be assessed and a full neurologic examination should be performed.

**Diagnostic testing**
As with oropharyngeal disease, the initial approach to an animal with esophageal disease is to start with a minimum database to evaluate for concurrent disease and/or inflammatory and metabolic causes of esophageal dysmotility. Survey thoracic radiography that includes the cranial esophagus should be performed to evaluate for the presence of structural disease, megaesophagus, and/or aspiration pneumonia. A barium swallow using videofluoroscopy should be performed if the cause of esophageal dysmotility is not identified on survey radiography. Additional diagnostics that can be considered if initial evaluation is unrewarding are similar to those listed for oropharyngeal disease.

Treatment of both oropharyngeal and esophageal dysmotility is mostly focused on medical management of the underlying disease and provision of supportive care (e.g. nutritional support, prokinetics). Surgery may be indicated for several of the less common causes of oropharyngeal or esophageal dysphagia (e.g. cricopharyngeal achalasia, esophageal tumor).
Evidence and Indications for Using Probiotics in Dogs and Cats

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There are approximately $10^{12}$-$10^{14}$ microbes in the dog and cat intestine, approximately 10 fold more bacteria than cells in the body. Intestinal bacteria provide a number of benefits to the host including synthesis of nutrients (e.g SCFAs) and vitamins (B vitamins), regulation of the intestinal epithelial barrier, promotion of digestion, crosstalk with the host immune system, and protection against pathogens. For this reason, manipulation of intestinal bacteria with probiotic administration represents a potential therapeutic target for a variety of diseases. Probiotics are live microorganisms, which when administered in appropriate concentrations, are intended to colonize and interact with the host intestinal epithelium and immune system and confer a physiological health benefit to the recipient (e.g. anti-inflammatory activity, antagonize enteric pathogens, etc). Probiotics, therefore, must survive not only processing and storage in vitro but also gastric and bile acid degradation in vivo. Most probiotics contain lactic acid-producing bacteria (i.e. *Bifidobacterium*, *Lactobacillus, Enterococcus spp*). Lactic acid-producing bacteria maintain anti-microbial properties as a result of secretion of bioactive compounds and induction of changes in environmental pH that may be unfavorable to certain pathogens. Although a variety of veterinary probiotics are now available, many animals are still treated with probiotics intended for human use as these are more widely available. Thus, practitioners should have a good understanding of the probiotics that are available, both those intended for human and animal use. Probiotic strains derived from dogs can adhere to the human and canine GI tract similarly. Moreover, the use of probiotics intended for humans can transit the canine and feline GI tract. Thus, despite differences in resident bacteria among species (e.g. cats have more anaerobic bacteria in their intestine compared to dogs and humans), probiotics do not necessarily need to be derived from the species being treated. However, they must be shown to survive GI transport and colonize the intestinal tract of the species of interest. Practitioners should also be aware of dosing guidelines for each probiotic as they vary greatly between products.

**Studies in healthy dogs and cats**

At this time, a global conclusion about the use of probiotics in dogs and cats is difficult because of the limited number of studies evaluating their use and the variability in both the methodology as well as the type and number of bacteria administered among studies. Most studies to date have evaluated the effect of probiotics or synbiotics (prebiotic + probiotic) on intestinal microbial composition and immune function in healthy dogs and cats.

A study performed in which Beagle dogs were orally administered *Lactobacillus rhamnosus* GG at 4 doses suggested that doses as high as $5 \times 10^{11}$ CFU/day were needed to allow for fecal colonization and recovery of the *L. rhamnosus* strain in fecal samples via fecal culture. Although the methodology used in early this study was far less sensitive than currently available high-throughput techniques, if these results are applied to our clinical patients, it would suggest that doses 5-10 fold higher than the suggested dose of *L. rhamnosus* for humans are needed for canine patients.

The effect of a multi-bacterial species symbiotic designed for use in companion animals was evaluated in 12 cats and 12 dogs using high-throughput technologies. The symbiotic was well tolerated. Administration of the symbiotic induced several changes in the abundance of specific bacterial species found in the probiotic (e.g. *Enterococcus faecium, Bifidobacterium longum, Lactobacillus spp*). The functional significance of these changes (e.g. alteration of bile acid metabolism, production of short-chained fatty acids) was not studied. These changes did not persist following discontinuation of the probiotic. Despite the change in bacterial species, there was no change at the phyla level in the most abundant fecal bacterial phyla (i.e. *Firmicutes, Actinobacteria, Bacteroidetes, Proteobacteria,* and *Fusobacteria*) nor were there any changes in specific markers of GI and immune function.

Administration of the probiotic strain *Lactobacillus acidophilus* DSM13241 to 15 healthy adult cats for 4.5 weeks resulted in increased numbers of the beneficial *Lactobacilli* and decreased numbers of *Clostridium spp* and *Enterococcus faecalis* in the cats’ feces. Changes supportive of positive systemic and immunomodulatory effects were also observed.

**Probiotics in intestinal diseases**

Evaluation of the effect of probiotics as adjunctive therapies for the treatment of animals with naturally occurring diseases is still in its infancy. Most work to date has been focused on the use of probiotics for the treatment of intestinal diseases with the treatment of acute idiopathic diarrhea showing the most promise. For example, administration of the probiotic *Enterococcus faecium* SF68 to shelter cats resulted in a significantly lower percentage of cats with diarrhea for $\geq$2 days compared to cats that received placebo. Administration of the canine-derived probiotic containing *Bifidobacterium animalis* AHC7 to dogs with acute idiopathic diarrhea resulted in significantly reduced time to resolution of diarrhea and reduced percentage of dogs administered metronidazole compared to dogs receiving placebo. Similar results were found in a study investigating the effects of a probiotic cocktail orally administered to dogs with acute vomiting and diarrhea. In this study, dogs who received the probiotic cocktail had a quicker resolution of diarrhea, but not vomiting, compared to dogs who received placebo. The beneficial effects of probiotics and microbial therapy for infectious diarrhea (e.g. *C. diff*-associated diarrhea) has been well established in people. However, the beneficial effects of probiotics for infectious diarrhea in dogs and cats have been underexplored. To the author’s knowledge, only one published report has described the use of...
probiotics for infectious diarrhea in dogs wherein treatment of dogs with giardiasis with the probiotic Enterococcus faecium SF68 did not reduce giardial cyst or fecal antigen shedding compared to dogs receiving placebo.6

It stands to reason the probiotics would also be helpful in the treatment of intestinal disorders where dysbiosis is thought to play a major role (i.e. antibiotic-responsive diarrhea, inflammatory bowel disease). Unfortunately, at the time of this writing, only one study has evaluated the use of probiotics in dogs with idiopathic IBD.7 Ten dogs each were treated with either a high-dose (1-2 x 1011 lyophilized bacteria per 10 kg per day) probiotic cocktail intended for human use which contains 8 different bacterial strains or metronidazole and prednisone for 60 days. Before therapy and 30 days following completion of the drug trial, the clinical disease activity index (CIBDAl) scores, duodenal histology scores as well as presence of inflammatory cells, and fecal bacteria were compared. All dogs regardless of treatment improved clinically. Moreover, the group treated with probiotics had an increase in T-regulatory cells as well as an increase in the potentially protective bacteria, Faecalibacterium prausnitzii, in fecal samples. Although more studies are needed, this early data suggests that certain probiotics might have a steroid-sparing effect in dogs with IBD. However, until additional studies with a larger sample size are performed, the author recommends probiotics as an adjunctive, but not sole, therapy in dogs with IBD.

The use of probiotics for the treatment of food-responsive diarrhea (FRD) has led to mixed results likely because dogs with FRD often respond quickly to diet alone making it difficult to evaluate for a potential beneficial effect of the probiotic. In one placebo-controlled study evaluating a synbiotic containing Enterococcus faecium for dogs with food-responsive diarrhea, no effect was observed compared to diet alone over a 6-week treatment period however the study only included 12 dogs (7=syncbiotic, 5=placebo) and thus was underpowered.8 In another placebo-controlled study evaluating the administration of an elimination diet and probiotic containing a combination of different Lactobacillus spp., the elimination diet (with or without concurrent probiotic administration) resulted in clinical improvement in dogs with FRD. Moreover, the effect of the administration of probiotics on intestinal mucosal cytokine profiles was highly variable.9

Probiotics in extra-intestinal diseases

The few studies that have investigated the effect of probiotics in extra-intestinal diseases in veterinary patient are as follows:

1. Early life exposure to a Lactobacillus-containing probiotic resulted in long-term decrease in clinical signs in dogs with experimentally-induced atopic dermatitis.10 Oral administration of Lactobacillus paracasei probiotic had a steroid-sparing effect in dogs with naturally occurring canine atopic dermatitis.11
2. The effect of probiotics for the treatment of feline herpes virus infection has also been studied in an investigator-blinded, prospective study. 12 shelter cats were treated with either Enterococcus faecium SF68 or placebo once daily for 140 days.12 Although the sample size was low and there was no crossover in this study, Enterococcus faecium was well-tolerated and seemed to have a benefit in decreasing conjunctivitis in some cats.
3. Probiotics have also been purported to provide benefit in the treatment of canine and feline lower urinary tract infections (UTIs). Vaginal colonization with lactic-acid producing bacteria is thought to reduce the risk of recurrent UTIs in human women. However, administration of an oral probiotic containing Lactobacillus, Bifidobacterium, and Bacillus spp. to 35 healthy, spayed female dogs for either 14 or 28 days failed to increase the prevalence of vaginal lactic acid-producing bacteria.13 Moreover, lactic acid-producing bacteria were not commonly isolated from the vaginal vault of healthy dogs13 and there were no significant differences in isolation of lactic-acid producing bacteria in healthy dogs compared to dogs with recurrent UTIs.14 Thus, more studies evaluating the role of specific bacteria in the development of UTIs in dogs and cats as well as the beneficial effect of probiotics, if any, in the treatment of UTIs in companion animals are warranted.
4. No studies have investigated the effectiveness of probiotics in reducing the incidence of uroliths in dogs. However, Lactobacillus spp. containing probiotics were able to decrease oxalate concentrations in vitro.15 Thus, further studies are warranted to determine if probiotics could play a role in reducing risk of calcium oxalate urolith formation.

Cautions with use

Probiotics are considered supplements and therefore are not under the purview of the FDA. Demonstration of effectiveness is not mandated. Moreover, probiotics might be inaccurately labeled, contain organisms at the incorrect concentration, or contain organisms that might be pathogenic or have not been demonstrated to possess probiotic properties.16 Clients should be notified of these concerns as well as the lack of efficacy data in veterinary medicine. Some probiotics intended for human use are manufactured in enteric-coated capsules to prevent premature acid degradation and to assist in delivery of bacteria to the distal intestine prior to activation. A study performed in cats with CKD demonstrated that opening an enteric-coated synbiotic capsule and sprinkling its contents on food or delivering as a slurry resulted in ineffectiveness of the synbiotic.17 Thus, this form of delivery, unless otherwise indicated by the manufacturer, is not recommended.

Conclusions
The culmination of this early work suggests that probiotics might have a place in the adjunctive treatment of a variety of diseases. However, much work is needed to determine which diseases will respond and which type and how much of the probiotic is needed to induce such a favorable response.

References
Feline Vomiting: New Tactics for Identifying the Cause and Treating It
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Vomiting is a common chief complaint reported by clients of cats presented to their veterinarian for evaluation. Vomiting can be caused by stimulation of at least four major areas including the abdominal viscera, chemoreceptor trigger zone, vestibular apparatus, and central nervous system. Thus, a systematic approach is required for the workup of vomiting since it can be a symptom of many gastrointestinal and systemic diseases.

History and physical exam
A problem-oriented approach to vomiting begins with consideration of the animal’s signalment. Evaluation of age-related and breed-predisposed diseases may dictate the selection of diagnostics in your first tier diagnostic plan which otherwise may have been second or third. For example, Siamese cats are overrepresented in feline patients with GI carcinoma.1 Thus, an abdominal ultrasound may be considered as a frontline diagnostic in a middle-aged Siamese cat with chronic vomiting. A comprehensive “GI history” is also critical to the workup of a vomiting cat. In this presentation, I will present a GI history form that can be used to obtain information from the client while the client is waiting in the reception area. This allows for more detailed information to be obtained than you might otherwise have time to secure in a 15-30 minute appointment slot. For example, how soon is the patient vomiting after eating? Do the two appear to be related? Does the client have a video or picture of the cat vomiting to ensure that the act is actually vomiting? The physical exam is focused initially on characterization of the animal’s demeanor and posture to help assess the severity of the problem. Particular attention will also be paid to the animal’s hydration status. Following performance of a thorough physical examination, a fundic examination is performed to evaluate for evidence of systemic causes of vomiting. The cause of vomiting is often identified or suspected following review of the history and performance of a physical exam. Moreover, the diagnostic and therapeutic plans are dependent on the problems identified in the history and physical exam. A more aggressive diagnostic plan is warranted when the cat is depressed, moribund, has moderate to severe abdominal pain, or has a history of hematemesis and/or intractable vomiting.

Diagnostic plan
The diagnostic and therapeutic plan is based on the chronicity and severity of the vomiting. For acute, mild gastroenteritis, I generally recommend fecal testing, subcutaneous fluids if needed, antihelminthic treatment, dietary restriction for 8-12 hours followed by introduction of a bland diet, and an anti-emetic if obstructive disease is ruled out. For cats with acute disease that does not respond to this initial therapy or those that have more severe disease or chronic disease, I recommend performing a complete blood count, serum chemistry, urinalysis, tT4 and FeLV/FIV (if appropriate), and abdominal imaging. If no abnormality can be identified and supportive care does not eliminate the symptoms, additional testing is recommended based on clinical signs and results of the first tier diagnostics. These may include but are not limited to evaluation of serum gastrin, bile acids, thoracic radiographs, urine and/or bile culture, infectious disease testing, heartworm serology, fPLI, cobalamin, folate, diet, antibiotic, or probiotic trial, and exploratory endoscopy or surgery with biopsies. If concern for GI lymphoma exists, surgical biopsies are preferred. The most common sites of GI lymphoma, the jejunum and ileum, are in places that may be hard to impossible to reach via endoscopy.2,3

Therapeutic plan
The most effective treatment for feline vomiting is identification and elimination of the offending agent. When the etiology of vomiting has not yet been determined, dietary modification (low fat, alteration of fiber source, novel protein or hypoallergenic) is often recommended as an empirical therapy for chronic vomiting.4 Dietary restriction, occasionally used for cats with acute vomiting, should be limited to 8-12 hours to reduce the risk of hepatic lipidosis. Anthelminthic treatment should also be recommended in the susceptible cat (outdoor and/or young) regardless of the results of fecal testing. Supportive treatment of vomiting should include rehydration and correction of electrolyte disturbances and anti-emetics if the vomiting is persistent and obstruction has been ruled out. The type of anti-emetic should be chosen to target the mechanism of vomiting. In this presentation, I will review the mechanisms of vomiting and the way that commonly used anti-emetics target these mechanisms. Recently published studies on the use and efficacy of anti-emetics in cats will also be discussed. Acid suppressant and prokinetic drugs should be used when appropriate for treatment of esophagitis and delayed gastric emptying, respectively.

In conclusion, feline vomiting is common and is caused by a wide range of diseases. Using a problem-oriented approach with
a specifically tailored GI history form will help narrow down the list of causes. The diagnostic and treatment plan should be based on the chronicity and severity of vomiting and the choice of supportive care should be based on careful consideration of the mechanism of vomiting.

Selected references (Additional references can be provided upon request)
New Evidence for Using Gastroprotectants in Cases for Ulcers and Other Pains in the Gut

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The gastric mucosa is repeatedly exposed to noxious substances including an acidic pH, mechanical and chemical irritants, and digestive enzymes. The gastric mucosal barrier (GMB) is comprised of defense mechanisms that protect the gastric mucosa against these noxious substances. The GMB includes a single layer of highly resistant epithelial cells that repel gastric acid and are capable of rapid repair, a double mucus layer that is rich in bicarbonate ions, the local production of prostaglandins that serve to regulate blood flow and stimulate the secretion of mucus and bicarbonate ions, and a rich mucosal blood supply. Gastric and proximal duodenal erosion and ulceration develops when there is an imbalance of increased injurious agents and/or a decrease in these protective mechanisms.

The most common cause of gastrointestinal (GI) ulceration in the dog is NSAID administration whilst the most common cause in the cat is GI neoplasia (i.e. mast cell tumor, gastrinoma, lymphoma, adenocarcinoma). Thus, the diagnostic approach and direct treatment of the underlying cause of ulceration often differs between species. However, the approach to the treatment of ulcerative and erosive disease with mucosal gastroprotectants is very similar. A summary of gastroprotectant drugs used for the treatment of GUE can be found below. Additional details and less commonly used drugs (e.g. nutraceuticals, conventional antacids, etc) will be provided in the presentation.

Acid suppressants

The development of gastric erosion and ulceration (GUE) is multifactorial, however excessive gastric acidity is closely associated with ulcer development. Thus, the clinical goal for the medical treatment of ulcerative disease in people is to reduce gastric acidity and maintain the intragastric pH at or above 3 for at least 18 hours per day. Although no goals have been established for the treatment of GUE in companion animals, it is widely accepted that increasing gastric pH aids in healing of GUE in dogs and cats. For this reason, acid suppressant drugs are used as a first line treatment for dogs and cats with GUE. There are 2 major classes of acid suppressant drugs used in veterinary medicine, the histamine-2 receptor antagonists (H2RAs) and the proton pump inhibitors (PPIs). The H2RAs, which target the histamine-2 receptor on the acid-producing gastric parietal cells, have some advantages. The H2RAs are maximally effective within hours of administration, have a good safety profile, and, unlike the PPIs, has a bioavailability that is unaffected by food. However, the PPIs, which target the final pathway for acid production, are significantly more effective at acid suppression than the H2RAs. Although PPIs can take up to 4 days to reach peak effect, evidence suggests they are likely as effective as H2RAs on day 1 of administration. The disadvantages of PPIs are that the majority of them are cytochrome P450 (CYP) inhibitors and thus can result in interactions with other drugs dependent on CYP metabolism. The PPIs are also associated with some serious adverse effects when given chronically to humans. These adverse effects are covered in more detail in the proceedings on acid suppressants. Dogs and cats with documented or suspected GUE should be treated with a PPI (e.g. omeprazole, esomeprazole, pantoprazole) at 1 mg/kg q 12 hr.1-3 A variety of omeprazole formulations (tablet, capsule, reformulated paste, suspension) have been evaluated and demonstrated to be effective in raising the intragastric pH in healthy dogs and cats. With the exception of self-limiting diarrhea, PPIs appear to be well-tolerated during short-term administration in dogs and cats. However, based on the evidence for adverse effects in humans, I would advise avoiding long-term administration of PPIs when possible.

Coating agents

Coating agents include sucralfate, barium, and alginate-antacids (e.g. Gaviscon). Sucralfate, a polyaluminum sucrose sulfate, forms a protective layer on the esophageal and gastric mucosa. Sucralfate is activated in the presence of an acid to form a gel-like substance that covers areas of denuded epithelium. Sucralfate may also stimulate the production of protective prostaglandins. There are very few studies which have evaluated the efficacy of sucralfate in the treatment of GUE in dogs and cats. However, studies investigating the use of sucralfate in the polypharmacy treatment of GUE and muscositis in humans suggest there is a benefit to this practice. Moreover, sucralfate is associated with very few adverse effects aside from constipation. Sucralfate does change the pH of the stomach and therefore may interfere with the metabolism of drugs that are dependent on an acidic gastric pH (e.g. PPIs). It also may interfere with drugs affected by the aluminum component of sucralfate (e.g. tetracyclines, ciprofloxacin). Therefore, these drugs should be administered at least two hours before or after sucralfate administration.4

Barium, like sucralfate, is proposed to have mucosal protecting effects. It has also been proposed to have hemostatic properties although neither of these mechanisms have been proven in the treatment of dogs and cats with GUE. I do not use barium in my practice but many of my colleagues use it often for the treatment of GI hemorrhage. Barium should be withheld at least 24 hours prior to gastrointestinal endoscopy and should not be used in animals where GI perforation is suspected.
Alginate-antacid drugs are acid-neutralizing drugs that also contain sodium bicarbonate and alginic acid. The alginic acid and bicarbonate combine to target acid-pockets in the stomach to prevent reflux of gastric acid into the esophagus. In humans with gastroesophageal reflux disease, alginate-antacids significantly decreased reflux and symptoms of dyspepsia compared to placebo.5 No studies have evaluated the use of this mediation for the treatment of reflux esophagitis or GUE in dogs and cats. Alginate-antacids are likely inferior to acid suppressant therapy and should not be used as the sole treatment for GUE. Moreover, they may lead to rebound gastric acid hypersecretion if not administered frequently and in the absence of an acid suppressant.

Prostaglandin agonists
The most commonly used prostaglandin agonist in veterinary medicine is misoprostal, a PGE1 analog. By simulating endogenous eicosanoids, misoprostal increases mucosal blood flow and epithelial repair and stimulates mucus and bicarbonate secretion. Despite its mechanism of action, misoprostal is only effective for NSAID-induced injury and has no effect with steroid-associated ulceration. Misoprostal may increase GI and urogenital smooth muscle contractions leading to side effects of cramping, diarrhea, and abortions.6

Selected references (additional references provided on request)
Acid-related tissue injury arises from multifactorial and often overlapping mechanisms related to an impaired mucosal barrier and/or overproduction of injurious substances (e.g. gastric acid, pepsin, bile salts). Gastroesophageal ulceration and reflux esophagitis are two of the more commonly recognized causes of acid-related tissue injury in dogs and cats. As in people, it is widely accepted that intragastric pH is closely associated with the healing of gastroesophageal ulceration and reflux esophagitis in dogs and cats. Clinical pH goals have been established that suggest that the gastric pH should be at or above 3 for at least 18 hours per day to promote healing of gastroesophageal ulceration in humans. Although there are no goals for the treatment of acid-related tissue injury in dogs and cats, acid suppression is generally recommended.

Two major classes of drugs, antacids and acid suppressants, can be used to increase the gastric pH. Antacids are acid-neutralizing drugs that are significantly less effective in sustaining a high intragastric pH. Moreover, they need to be administered frequently, which can be problematic in vomiting patients, to prevent rebound gastric acid hypersecretion. Thus, acid suppressants are the preferred drug for raising intragastric pH. Acid suppressants can be divided into at least two categories of drugs, the histamine-2 receptor antagonists (H2RAs) and the proton pump inhibitors (PPIs).

Histamine-2 receptor antagonists target the histamine-2 receptor on the acid producing cell of the stomach, the parietal cell. Peak serum concentration and effect occur within hours of H2RA administration. The H2RA drugs may also have effects independent of their action on gastric pH including stimulation of bicarbonate and mucus secretion. The potency of the H2RA drugs varies with famotidine being more effective than ranitidine. Cimetidine is not an effective H2RA in dogs and is associated with acute liver injury in people. Unlike the PPIs, the bioavailability of H2RAs is not affected by food. Because H2RAs target only one pathway of acid secretion, they are significantly inferior to PPIs in raising intragastric pH. However, they may be a good choice for nocturnal acid secretion as these drugs are more effective against basal acid secretion compared to food-stimulated acid secretion.2

The PPI drugs target H+/K+ ATPase, the enzyme responsible for the final production and secretion of gastric acid. These drugs inhibit gastric acid secretion irrespective of the secretagogue. Because there is a delay to peak effect because of recruitment of newly synthesized H+/K+ ATPase enzymes, maximal effect of the PPI drugs may take up to 4 days. However, studies in healthy dogs suggest that PPIs have acid suppressant activity comparable to H2RAs on day 1. Additionally, there is no evidence in dogs to suggest that combined therapy (H2RA + PPI) results in better acid suppressant activity even in the first few days of PPI administration. Studies in healthy dogs and cats as well as clinical experience suggest that PPIs should be dosed twice-daily when concern for acid-related tissue injury exists.3-6 Many formulations (e.g. capsule, tablet, reformulated paste, suspension) of PPIs are effective in raising intragastric pH in dogs and cats. I also recommend short-term administration of PPIs in combination with a prokinetic drug prophylactically for animals at risk for or with documented anesthesia-induced reflux.7 During this presentation, I will discuss potential risk factors that can be used to determine which dogs and cats may be considered “high risk” and therefore may benefit from prophylactic, transient acid suppressant therapy.

Acid suppressants are efficacious for the treatment of acid-related tissue injury but the rationale for and efficacy of acid suppressant administration in metabolic (e.g. chronic kidney disease (CKD), liver failure) and inflammatory (e.g. pancreatitis) disease are less clear.

Hypergastrinemia, gastritis, and gastric ulceration are common complications of end-stage renal disease (ESRD) in humans. Thus, human patients with ESRD are monitored for and often treated for gastric ulceration. Recent studies suggest that hypergastrinemia and mineralization, but not gastric ulceration are commonly identified in companion animals with CKD.8 Despite this, famotidine is one of the top medications administered to cats with CKD. Animals with CKD often suffer from an enormous pill burden, therefore more studies are needed to evaluate the benefit of this practice. Furthermore, administration of PPIs to animals with CKD may not be benign. Recently published studies suggest that PPIs are associated with an increased risk of development of CKD in humans.9 If acid suppressant therapy is initiated, prolonged use should be avoided and objective indicators of benefit should be closely monitored.

Liver disease is one of the most common predisposing factors for GI ulceration in dogs. The pathophysiology of ulcer development is likely multifactorial (e.g. compromised hemodynamics, gastric hyperacidity secondary to hypergastrinemia). Thus, the efficacy of acid suppressant therapy in dogs with ulcers resulting from liver disease is unknown. The liver is responsible for the metabolism of serum gastrin, one of the secretagogues of gastric acid production. Thus, liver dysfunction would be expected to result in gastric hyperacidity from reduced serum gastrin clearance. However, a recently published study evaluating serum gastrin in dogs with congenital portosystemic shunt (PSS) and hepatocellular disease showed no difference between dogs with hepatocellular disease and normal dogs. Surprisingly, dogs with PSS had significantly lower serum gastrin compared to healthy dogs.10 However, this study did not evaluate the dogs for the presence of gastroesophageal ulceration and did
not assess the impact of acid suppressant therapy. The PPI drugs have been associated with an increased risk of infection in humans with decompensated liver cirrhosis. Thus, further study is needed to determine if acid suppressant are warranted or contraindicated for dogs and cats with liver disease. For now, I reserve the use of the drugs until there is evidence of GI bleeding (e.g. melena, iron-deficiency anemia, regenerative anemia in the absence of hemolysis).

The use of acid suppressants for the treatment of inflammatory diseases such as pancreatitis is controversial. Some reports describe a causal association of PPIs with pancreatitis in humans whilst other suggest that PPIs, especially pantoprazole, may ameliorate inflammation. In a recent placebo-controlled study, no benefit could be detected secondary to PPI administration in humans with acute pancreatitis. Thus, larger studies are needed to evaluate the benefit of acid suppressant drugs in the treatment of pancreatitis. For now, I do not use acid suppressants as an adjunctive treatment for pancreatitis unless concurrent GI erosion, ulceration, and/or esophagitis is appreciated.

Chronic administration of acid suppressant drugs should be avoided when possible. The prolonged use of H2RAs likely leads to tolerance whereas the chronic use of PPIs is associated with serious adverse effects including development of CKD, altered bone metabolism and pathologic fractures, and increased risk of community-acquired pneumonia and Clostridium infections. Moreover, a recent pilot study performed in healthy cats suggest that PPIs may have an effect on bone mineral content and may be associated with rebound acid hypersecretion following abrupt drug withdrawal. Thus, judicious use of acid suppressant drugs is warranted.

Selected references (Additional references available on request)