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 (i.e. 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). Vascular 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**

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Colorectal Disease in Dogs
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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.

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Small bowel</th>
<th>Large bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Possible</td>
<td>Rarely</td>
</tr>
<tr>
<td>Frequency of stools</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>Rare</td>
<td>Possible</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>Rare</td>
<td>Likely</td>
</tr>
<tr>
<td>Volume of stool</td>
<td>Large</td>
<td>Typically small</td>
</tr>
<tr>
<td>Melena</td>
<td>Possible</td>
<td>Rare</td>
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</tbody>
</table>

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 distented, 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.

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**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 chorambucil. 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 / obstipation**

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 obstipation, 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 abdomen, helps to provide tension to the descending colon and rectum and will help to prevent further prolapse.

References
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 straightforward 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 road block 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**


Diagnostic Approach to Canine Chronic Enteropathy
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A “chronic” enteropathy (CE) is typically defined as gastrointestinal disease that has been present for at least two weeks. This may be in the form of two solid weeks of persistent diarrhea, or intermittent loose stools for many months that fluctuates between normal and liquid. A chronic enteropathy is a description of a symptom, and as such there are many underlying illnesses that can be responsible for these clinical signs. The diagnostic approach will have some fundamental differences compared to a dog who is presented with more acute clinical signs.

A detailed history is a crucial first step towards trying to identify an underlying disease process. In many cases a great deal of information can be gathered simply by taking a complete medical history. The differential list can be narrowed and appropriate tests can be pursued, while other tests may be considered unnecessary, following a thorough history on a patient and getting a better understanding of how long the signs have been occurring and to what degree the patient is affected (vomiting, regurgitation, diarrhea, weight loss, inappetance, etc.).

The value of a thorough physical examination cannot be overstated in dogs with CE. While most causes of CE will have non-specific changes seen on the physical examination (including normal to decreased body condition score, possible abdominal pain, nausea, etc.), there are some exam findings more suggestive of certain GI diseases. Dogs with weight loss and a thickened colonic mucosa may be more likely to have an infectious cause of diarrhea such as Histoplasmosis. Thickened small intestines on abdominal palpation, or suspected mesenteric lymphadenomegaly, may be indicative of GI lymphoma. While rare, a sliding intussusception can occur as a consequence of a severe CE; this can also be detected on PE. While these specific changes are less common, there is still a substantial amount of information that can be gathered from a physical examination. Urgency of diagnostic tests is another important take-away from the physical examination. A dog with a protein losing enteropathy that has muffled lung sounds and ascites and is dehydrated is going to need more intensive medical management and more aggressive diagnostic testing to find an underlying cause compared to a dog with mild intermittent diarrhea and no other clinical signs.

Baseline blood work will generally follow the history and physical examination. Many underlying metabolic diseases that can cause chronic gastrointestinal disease can be identified by reviewing these basic tests, including 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.

If the signalment and history are suggestive of an infectious cause (young dog, history of shelter experience, extensive travel history) then infectious disease testing should be prioritized. While an uncommon cause of chronic diarrhea, a viral disease such as Parvovirus is easy to rule out with ELISA testing. PCR testing is available for other viral diseases such as canine coronavirus and distemper virus. In addition to these viral diseases, PCR testing is also available for other infectious diseases that may be more likely to be associated with chronic gastrointestinal diseases, such as Salmonella, Clostridium, Giardia, and Campylobacter. A routine fecal evaluation for ova and parasites should also not be forgotten in the initial work-up for all dogs with chronic diarrhea. Depending on the geographical location of the patient, Histoplasmosis should also be considered for dogs with chronic enteropathy, especially with predominantly lower GI clinical signs. A rectal scrape for cytology can be performed (different from a fecal cytology) to look for organisms, as can a fine needle aspirate of enlarged lymph nodes or other abnormal abdominal organs. If these tests are negative and Histoplasmosis is still suspected, confirmation can be made via an antigen detection test on urine.

There are many common non-infectious causes of CE in dogs, and thus a diagnostic plan should developed beyond the investigation for infectious diseases. In dogs with waxing and waning GI signs including vomiting, diarrhea, and inappetance, signalment and disease severity should help dictate the prioritization of tests. In young to middle aged dogs, I suggest ruling out hypoadrenocorticism (even with normal electrolytes) by checking the dog’s resting cortisol. A value of >2.0ug/dL has a 100% sensitivity of detecting Addison’s disease, thus making this a rapid and highly sensitive screening test for this disease. If liver disease is suggested on base line blood work, now is the time that pre- and post- prandial bile acid testing should be pursued to test liver function. If chronic small intestinal diarrhea is present as well as weight loss, serum TLI should be tested to rule out exocrine pancreatic insufficiency. While a rare disease outside of the German Shepherd Dog breed, making this diagnosis prior to more invasive testing will save the owner a great deal of expense and the patient decreased morbidity associated with general anesthesia.

Abdominal imaging should next be pursued, with or without abnormalities detected on abdominal palpation. It is generally advised to take abdominal radiographs prior to performing an ultrasound, as complementary information can be obtained with both tests. Radiographs will give a good overall impression of the abdominal organs including gas distention of the intestines. Intestinal wall thickness is often over-interpreted on radiographs and caution should taken when making this determination. Fluid in the bowels can easily be misinterpreted as a thickened wall. Following radiographs, a wealth of information may be gathered from an abdominal ultrasound performed by an experienced ultrasonographer. Most importantly in cases of presumptive primary GI disease, the integrity
of intestinal wall layering and overall wall thickness of the entire visualized GI tract (from stomach to colon) should be evaluated. Mucosa, submucoosa, muscularis, and serosal layers should all be discretely identified in all segments of the intestinal tract. The colon is the thinnest layer, measuring up to 0.2cm on average. The small intestine can range up to 0.3-0.4cm, while the normal stomach may be as thick as 0.4-0.5cm. These figures are averages, so there may be some normal variation in some dogs, but subtle changes can also represent diffuse infiltrative disease. It is important to keep in mind that normal wall layering and thickness does not rule out inflammatory disease. Complete loss of layering in the intestinal wall, especially if focally observed, is highly suggestive of neoplasia.

If the clinical signs and initial diagnostic testing suggests chronic intestinal disease, a malabsorptive blood panel should next be considered. Serum folate and especially cobalamin concentration are commonly decreased with inflammatory bowel disease as well as other causes of chronic malabsorption. Similar to intestinal wall thickening, the presence of normal serum cobalamin does not rule out a chronic enteropathy including inflammatory bowel disease (ie. the test is not as sensitive as it is specific for IBD).

In dogs with mild clinical signs or diarrhea with no other systemic signs of illness, a hypoallergenic diet trial should be pursued prior to more advanced testing. There are two options to consider with a diet trial; a novel protein or a hydrolyzed protein. I will frequently make my decision dependent on the patient’s diet history; if the dog has been exposed to many dietary proteins in the past I will generally choose either a hydrolyzed diet or an anallergenic diet such as Royal Canin Ultamino. The owner must be made aware that this is a strict exclusive diet trial that should last a minimum of three weeks with no treats or other food made available to the dog.

If the patient has had chronic diarrhea and the diet trial is unsuccessful (ruling out food-responsive diarrhea), an antibiotic trial should next be pursued. Tylosin dosed at 20mg/kg by mouth every 12 hours is my antibiotic of choice. In many cases, if antibiotic-responsive diarrhea is present there will be a resolution of clinical signs within a few days when starting this new medication. If diet and antibiotics are unsuccessful at resolving clinical signs and no primary disease has been identified, intestinal biopsies should be taken. Endoscopy 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 equipment availability and experience of the endoscopist, ability to only take mucosal/submucosal biopsies, and inability to visualize the entire gastrointestinal tract. Benefits include it being an out-patient 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.

Histopathology of the GI tract should help to better define the underlying disease process. The diagnostic approach to chronic enteropathies must be methodical and step-wise, as biopsy results showing lymphoplasmacytic enteritis is not diagnostic for inflammatory bowel disease, which is a diagnosis of exclusion. For example, a patient with food-responsive diarrhea may also have similar pathology results.

Dogs being presented for clinical signs consistent with a chronic enteropathy can be a diagnostic challenged, but if a standard approach is taken, including using therapeutic trials at some stages, an definitive diagnosis can often be made allowing for targeted therapy.

References available upon request
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 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) (Kirpensteijn J et al 1993). Despite the infrequency of extrahepatic biliary obstruction secondary to cholelithiasis, choleliths 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 gallbladders 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
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-discriminatory 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 help 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 (Littman MP et al 2000).
- Norwegian Lundehun: 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

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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). Imunosuppressive 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

The pancreas consists of both an exocrine and an endocrine component, each with its own very different purpose in normal daily homeostasis. The endocrine pancreas consists of alpha, beta, and delta cells that produce glucagon, insulin, and somatostatin, respectively. The most common disease involving the endocrine pancreas is under-production of insulin by the Beta cells, leading to diabetes mellitus. The much larger (anatomically) portion of the pancreas, the exocrine pancreas, is responsible for producing and secreting digestive zymogens that, when mixed with proteases in the intestinal lumen, become digestive enzymes such as amylase and lipase. Pancreatitis is the most commonly diagnosed disease affecting the exocrine pancreas; however other diseases including exocrine pancreatic insufficiency and pancreatic neoplasia are also reported.

Unlike in dogs, most cats that develop diabetes mellitus retain some normal functioning ability of the beta cells in the pancreas. This equivalent to “Type 2” diabetes in humans more often occurs due to insulin resistance systemically (due to obesity, systemic inflammation, etc.) and less often due primary pancreatic dysfunction. Since the remaining beta cells retain their ability to produce and secrete insulin, early management should be focused on trying to diagnose and eliminate the underlying cause of insulin resistance, and an attempt should be made to achieve diabetic remission. In some studies the ability to achieve remission is as high as 40-50%.

A connection between exocrine and endocrine pancreatic disease has been suspected, with the belief that cats with pancreatitis are at higher risk for diabetes mellitus. A recent study, however, has shown that there was no significant difference in pancreatic histopathology between cats with diabetes mellitus and healthy control cats. Additionally, the presence of ketoacidosis did not increase the risk of inflammation. In a separate study in dogs, up to 40% of diabetic cases were associated with pancreatitis.

The primary focus of this talk will be on diseases of the exocrine pancreas. Pancreatitis is by far the most common of these diseases, with neoplasia and EPI being seen much less frequently. Literature has shown that pancreatitis is a highly under-diagnosed disease, as necropsy studies have shown up to 67% of cats have evidence of pancreatic inflammation, including 45% of cats with no clinical signs of GI disease. Relevance of this finding, however, should be questioned, as many of these cats had no prior clinical signs associated with pancreatic disease. While histopathology is considered the gold standard for diagnosis, this is also an impractical test for most cats. This lack of a highly available gold standard test makes the definitive diagnosis even more challenging, and makes a thorough physical examination and history even more important when determining the cause of illness and how to develop a treatment plan.

There is a wide range of disease severity when discussing pancreatitis in cats, from very mild to life-threatening. There are also many suspected triggers for this disease, although in most cases the underlying cause goes unidentified. Recent dietary fat intake and obesity / hypertriglyceridemia is not a common cause of pancreatitis in cats, unlike what is seen in dogs. In up to 2/3 of cases of cats with pancreatitis, however, a concurrent disease is present including inflammatory bowel disease, cholangiohepatitis, diabetes mellitus, etc. Ultimately the most important reason to identify this trigger is to be able to avoid it in the future, as case management will be similar regardless of cause. The most common clinical signs in cats with pancreatitis are lethargy and anorexia, with vomiting only seen in ~40% of cats and diarrhea even less commonly occurring at 11-38%. Other physical examination findings are often vague and non-specific, including depression, dehydration, and cranial abdominal pain.

When a cat is presented with clinical signs consistent with gastrointestinal disease, baseline blood work including chemistry, complete blood count, and urinalysis should be performed. Unfortunately the standard lab variables on these tests (specifically amylase and lipase) are highly insensitive and non-specific for pancreatitis. As a result, interpretation of these two tests should only be done as one component of all other lab and clinical abnormalities. There are, however, many other diseases that will present with similar clinical signs and history that will have detectable abnormalities on these tests. These might include acute cholangiohepatitis, acute renal failure, pyelonephritis, etc. Cats are even less likely to have changes seen with the leukogram compared to dogs.

When pancreatitis is suspected based on clinical history, physical examination, and baseline blood work, additional testing should involve testing pancreatic lipase (SNAP test or SPEC IPL) and an abdominal ultrasound. While pancreatic lipase testing is more sensitive and results are more accurate compared to serum lipase, there are still great deficiencies with these tests. The cage-side SNAP IPL is designed to be highly sensitive and acts as a screening test for pancreatitis; sensitivity ranges up to 92% depending on the severity of the pancreatitis. The SPEC IPL lacks the sensitivity of the SNAP test (54% for mild pancreatitis), but is a more specific test (82%) for pancreatitis. The interpretation of ultrasonographic changes is dependent upon skill and experience of the ultrasonographer. There are no specific guidelines for the diagnosis of pancreatitis, but typical changes seen with the disease include pancreatic enlargement, peri-pancreatic inflammation or edema, cystic changes, hyperechoic echotexture, and a dilated pancreatic duct.

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Ultimately the diagnosis of pancreatitis in cats is made based on a combination of clinical history, physical examination findings, laboratory abnormalities, and ultrasound results. The gold-standard diagnosis is made via histopathology, although this is rarely necessary to make the diagnosis and this is not without a high risk of morbidity.

Treatment of pancreatitis should be dictated based on the severity of the patient’s clinical presentation. Regardless of severity, fluid therapy is the most important component of treatment. Rehydration with crystalloid fluids followed by correction of ongoing losses (if vomiting and diarrhea is present) will help maintain adequate blood flow to the pancreas and aid in healing. Further supportive care is dictated by the patient’s clinical signs (anti-emetics, anti-diarrheal medication, etc.). Pain management can be a very important aspect of therapy as well. Overt abdominal pain is not always clearly evident, but is frequently present. As such, pain management should always be considered in the treatment plan. My top recommendations for the abdominal pain associated with pancreatitis include intermittent buprenorphine injections or, preferably, a CRI of fentanyl. Fentanyl is very fast acting and has a short half-life, which means the dose can easily be manipulated to meet the patient’s needs. Abdominal pain associated with pancreatitis can often be deceiving and lead to lethargy, depression, inappetance, and vomiting, even in cats that don’t outwardly object to abdominal palpation. In these cats a trial of pain management should be instituted to see if clinical signs begin to resolve.

Exocrine pancreatic insufficiency (EPI) is an uncommon pancreatic disease in cats. The presumed cause of this condition is severe end-stage chronic pancreatitis, resulting in loss of the acinar cells; however there are many cats that have no clinical history of chronic pancreatitis that are diagnosed with this disease. Regardless of the cause, clinical disease is typically not detectable until ~95% of pancreatic function is lost. Unlike in dogs with EPI who are frequently presented with chronic history of a ravenous appetite and voluminous soft stools, the most common presenting complaint in cats is weight loss. Diagnosis of EPI in cats is made by confirming a low serum TLI (trypsin like immunoreactivity). Management of this disease is simple in most cats, as they will frequently respond quickly to supplemental pancreatic enzymes added to the diet. When adding the enzyme, it is suggested to moisten the food (if feeding kibble), sprinkle the powder over the food, and then allow it to sit for 10-15 minutes prior to feeding.

Hypocobalaminemia is a common concurrent finding in cats with EPI, so serum cobalamin should be measured with subsequent supplementation if necessary. If weight gain and clinical improvement are not noticed within a few weeks of starting the pancreatic enzyme then evaluation for other underlying diseases such as inflammatory bowel disease should be considered.

Pancreatic adenocarcinoma is the most common neoplasia found in the cat pancreas. In the largest case series available, 34 cats were reviewed. Of these 34 cats, 11 had evidence of metastatic disease at the time of presentation. Prognosis is guarded with pancreatic adenocarcinoma, especially if the tumor has already metastasized at the time of diagnosis. 10% of cats survived over 1 year, but overall median survival was just 97 days. Median survival was slightly longer if surgery or chemotherapy was pursued (165 days).

There are other less common pancreatic diseases in cats, including pancreatic abscesses (which can be an adverse effect of severe pancreatitis), pancreatic cysts, and parasitic pancreatic disease.

References
Diarrhea is one of the most common reasons for presentation of a cat to their veterinarian. There are many underlying causes of diarrhea in cats, including both acute and chronic disease. Acute gastroenteritis characterized by diarrhea seems to occur less frequently in cats compared to dogs, possibly because cats are less likely to experience dietary indiscretion after getting into the trash, eating human food, etc. Chronic diarrhea is a more common occurrence, however this can be difficult to detect for some cat owners as certain types of cat litter can help the stool clump and appear more solid than it actually is. Additionally, many pet owners have more than one cat and defecation is rarely observed so it may take longer to make the diagnosis.

Characterize the diarrhea
There are some distinct differences between large and small bowel diarrhea that must be determined prior to pursuing appropriate diagnostic tests. Classic signs of large bowel diarrhea include tenesmus, production of excessive mucous, frequent defecation (up to 5-6 times per day), and frank blood in the stools. In cats exclusively large bowel diarrhea is rare and usually accompanies an infectious disease such as Tritrichomonas or Giardia. Small bowel diarrhea includes weight loss, normal frequency of defecation, large voluminous stool, and normal urgency. In many cases there is some degree of overlap between these two types of diarrhea, however certain diseases are more likely to be associated with either large or small bowel diarrhea so localization can be helpful especially if considering histopathology.

Determining the cause
Most cases of feline diarrhea can be characterized as either infectious or non-infectious. Infectious diarrhea is more common in younger cats, especially cats who have originated from a cattery or a shelter environment. Differentials for infectious diarrhea include feline panleukopenia, Giardia, Tritrichomonas, Campylobacter, multiple intestinal parasites, Histoplasmosis, and Salmonella. Non-infectious causes of diarrhea include food allergy, antibiotic-responsive diarrhea, inflammatory bowel disease (IBD), hyperthyroidism, intestinal neoplasia, pancreatitis, and idiopathic gastroenteritis.

Clinical history is crucial to helping to differentiate infectious versus non-infectious causes of diarrhea. In many cases a detailed medical history will help to prioritize the differential diagnosis list which will help guide further diagnostic tests. Important questions to ask include the following:

- Has the cat spent any time recently in a cattery or cat shelter, or been exposed to other cats that have?
- Does the cat spend any time outside, or indoors only?
- Has there been any change in diet recently?
- Is the diarrhea acute and progressive, or chronic?
- If chronic, has the cat been losing weight?
- Are there any concurrent clinical signs, such as vomiting, loss of appetite, lethargy, etc.?

Knowing the answers to these few questions will go a long way towards determining the first tests that need to be performed. A thorough physical examination should also be performed and can be helpful for similar reasons. While most physical examination findings are unlikely to be pathognomonic for any one disease, there are some classic findings that will help shape your diagnostic plan. Diffusely thickened, or “ropey” intestines is more likely to be associated with chronic infiltrative disease. This finding in addition to enlarged mesenteric lymph nodes is more suggestive of GI lymphoma (although there are other causes including severe IBD and Histoplasmosis). Muffled lung sounds and labored breathing accompanying diarrhea is suggestive of either a protein losing enteropathy (less common in cats compared to dogs) or a diffuse systemic disease such as lymphoma.

Initial diagnostic testing should be prioritized based on the history and physical examination. In all cases of feline diarrhea a routine fecal ova and parasite test should be completed, as even older cats with chronic diarrhea may have a compromised GI immune system making them more at risk for intestinal parasites. I will routinely add Giardia testing on to that as well. If the cat is young and very ill with acute and severe diarrhea, a canine Parvovirus SNAP test can be performed to quickly rule out Feline Panleukopenia. If the cat is young and otherwise healthy with a negative ova and parasite test, and if infectious diarrhea is still considered likely due to the history, then a fecal PCR panel should be considered. This test is available through outside reference laboratories and will test for the following infectious causes of feline diarrhea:

- Campylobacter
- Clostridium
- Salmonella
- Giardia
Results from this test should be regarded with some skepticism depending on the patient’s clinical signs. For example, many cats may be Clostridium perfringens positive but have diarrhea due to another cause that has compromised the normal flora of the GI tract. In this case using targeted therapy against the Clostridium may help in the short term but would be unlikely to cure the patient’s diarrhea entirely, and it may come back just as bad once treatment is completed. Regardless of the results of fecal testing, there are some intestinal parasites that are not shed regularly and thus may not be seen on routine testing, so a trial treatment with a broad spectrum de-wormer such as fenbendazole should be considered.

Routine chemistry, complete blood count, and urinalysis should be tested primarily to rule out non-intestinal causes of diarrhea. In older cats a T4 should also be checked, especially if weight loss is also occurring. Causes of diarrhea that may be found on routine lab work include kidney disease (acute vs. chronic), pancreatitis (may be suspicious for based on these tests but serum amylase and lipase are highly inaccurate for diagnosis pancreatitis in cats), liver disease (bacterial cholangiohepatitis, liver failure, etc.), and hyperthyroidism.

Advanced testing

If the above diagnostics do not provide a diagnosis for the patient’s diarrhea, there are many options on how to proceed. If the diarrhea is chronic, non-life threatening, and no other clinical signs are present, then a diet trial is suggested. For cats my first option is a hydrolyzed diet such as Hill’s z/d, followed by a novel protein diet. The new food should be transitioned slowly over the course of a few days, and then fed exclusively for a minimum of 3 weeks.

If the food trial is unsuccessful but the patient remains stable with only diarrhea (and/or mild vomiting) then an antibiotic trial may next be pursued to rule out antibiotic-responsive diarrhea, such as metronidazole or tylosin. If the patient’s clinical signs are too severe to warrant 4-5 weeks of therapeutic trials, or these both fail, then an abdominal ultrasound should be considered. This test is unlikely to provide a definitive diagnosis for the diarrhea, but can provide valuable information to help determine additional testing. The most common abnormalities seen when investigating chronic diarrhea include overall intestinal wall thickness, loss of normal wall layering, and thickening of the muscularis layer of the small intestine. Additional findings may include enlarged and irregular mesenteric lymph nodes, and enlarged or irregular pancreas, dilated common bile duct, etc. Thickening of the muscularis layer, when coupled with enlarged mesenteric lymph nodes and clinical signs consistent with GI disease, is highly suggestive (although not pathognomonic for) GI small cell lymphoma. Inflammatory bowel disease (most commonly associated with lymphoplasmacytic enteritis / colitis) with no documented underlying etiology has no consistent, reliable changes seen on ultrasound.

Measurement of serum cobalamin and folate should be performed especially in cases of weight loss accompanying the diarrhea. These B vitamins help determine the presence of malabsorption with chronic intestinal disease. The value of this test is low in acute cases and should only be considered if a chronic enteropathy is suspected. Serum TLI should be tested especially if weight loss is present along with the diarrhea, as this is the most common presenting complaint in cats with exocrine pancreatic insufficiency.

If the diagnosis remains elusive with all of the above testing completed, intestinal biopsies should be taken. With presumed diffuse infiltrative disease, gastrointestinal endoscopy is an appropriate option to obtain biopsies. Evidence has shown a difference in histopathologic diagnosis (especially with severity of inflammation) in different segments of the bowel so when possible the stomach, duodenum, colon, and ileum should be sampled. Alternatively, full-thickness surgical biopsies can be taken of these same areas (although full thickness colon biopsies are not typically recommended unless a mass must be removed).

If results of the biopsies do not correspond with the clinical picture, or if neoplasia is suspected but not confirmed, additional testing may be performed. Immunohistochemistry and PARR are two different tests that can be performed on formalin-fixed tissue that will help to confirm or deny monoclonal lymphocyte populations, suggestive of lymphoma.

Treatment of feline diarrhea is entirely dependent on the underlying cause. Some pharmaceuticals such as metronidazole or even prednisolone will be effective for multiple underlying etiologies but will be simply masking the disease and not curing it. Alternative therapies including probiotics may be helpful in conjunction with more targeted therapy.

References available upon request
Your Guide to the Vomiting Dog
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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 ePL
    - 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 (Benchaoui 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 out-patient 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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The conclusive diagnosis of inflammatory disease of the pancreas in dogs and cats is difficult. While the presence of compatible clinical signs such as vomiting, abdominal pain, dehydration, and pyrexia increase our index of suspicion for the disease, no specific findings on clinical examination are pathognomonic for pancreatitis.

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

Markers of pancreatic disease

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

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

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

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

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

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

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

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

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

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

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

Test selection and interpretation in animals with suspected pancreatic disease

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

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

Do TLI or PLI concentrations have prognostic value?

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

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

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

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

**‘Feeding through’ bouts of acute pancreatitis, multimodal antiemetics**

The idea that the pancreas should be “rested” during the treatment and recovery period from acute pancreatitis has long been held in the veterinary world. The theoretical basis for this recommendation was to decrease pancreatic enzyme synthesis and secretion, under the assumption that release of enzymes into the pancreatic interstitium and circulation was responsible for many of the clinical signs and complications of pancreatitis. While this approach still has some currency in the veterinary community, it flies in the face of our current understanding of the best management of critically ill patients. Animals with acute abdomen presentations are typically in a catabolic state, have additional metabolic demands due to the inflammatory process, and the development of functional ileus can result in substantial additional morbidity.5

One of the main reasons for the nil per os approach to treatment of acute pancreatitis was in an attempt to reduce frequency and severity of vomiting in these patients. In recent years we have had a dramatic increase in the number of effective antiemetic medications available to us, most notably the neurokinin-1 receptor antagonist maropitant citrate (Cernia®, 1 mg/kg q24 hr), and the 5-HT3 receptor antagonists such as dolasteron (Anzemet®) or ondansetron (Zofran®), 0.3-0.5 mg/kg IV q24 hr). These medications are highly effective at controlling vomiting and nausea in our patients, and have the advantage that they can be administered by injection or orally, and need only once daily dosing. They act via different mechanisms, and there does not appear to be any meaningful interaction between these drug classes. Maropitant also has some benefit as a visceral analgesic,6 which is of significant benefit in acute pancreatitis cases.

With the use of a multimodal antiemetic regime, vomiting and nausea are controlled rapidly in most cases of acute pancreatitis. This allows consideration of an early return to feeding. While controlled studies of early enteral nutrition in severe pancreatitis in veterinary species are relatively few, the data available so far suggest that early enteral nutrition in dogs with acute pancreatitis is associated with less incidents of vomiting, lower incidences of complications than parenteral nutrition, and no difference in outcomes.7 The author’s approach to dogs with pancreatitis is to reintroduce feeding as soon as possible, often within hours of ICU admission. Early enteral nutrition of cats with pancreatitis is arguably even more important, due to the risk of hepatic lipidosis in this species.

**Dietary manipulations in the management of chronic pancreatitis**

In the dog, use of a fat-restricted diet in the post-recovery period from a bout of acute pancreatitis is commonly accepted, and most authors will recommend fat restriction in dogs with chronic pancreatitis. The use of fat restricted diets is not recommended in cats, however, as this species has an obligate requirement for relatively high intake of essential fatty acids. Additionally, most fat-restricted commercial diets substitute carbohydrates for fat to maintain an iso-caloric formulation, this represents a problem for cats as their obligate carnivore nature means that they are less able to adapt to carbohydrate rich diets, and have a tendency towards protein catabolism if dietary fat is restricted. In many cats pancreatitis accompanies enteritis and cholangitis or cholangiohepatitis, so-called “triaditis” or “feline inflammatory syndrome”.8,9 While the underlying pathology of triaditis is not fully understood, overall it appears that the presence of inflammatory disease in the small intestine may be a common precipitating factor. Given the relatively low sensitivity of non-invasive tests for small intestinal disease in cats, and the low frequency with which biopsies are obtained, it is reasonable to assume that many cats with chronic pancreatitis will actually also have intestinal inflammatory disease that goes undiagnosed. Many cats with these diseases respond to dietary protein-source modification, using either a novel protein source or a modified antigen type diet. The author’s typical approach to a cat with a diagnosis of chronic pancreatitis is identical to the approach for inflammatory disease of the intestine, with carefully managed dietary elimination trials and screening for comorbid deficiencies in
water soluble vitamins such as cobalamin and folate. The protein type of the diet, rather than dietary fat content, has a much greater influence on diet selection in feline chronic pancreatitis cases.

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

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

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

Pancreatic acinar atrophy vs. chronic pancreatitis
In the dog, the most common cause of primary pancreatic exocrine insufficiency is pancreatic acinar atrophy (PAA). This condition is associated with progressive loss of pancreatic acinar tissue, in at least some groups of dogs PAA appears to be associated with or preceded by a lymphocytic/plasmacytic pancreatic infiltrate. In both German Shepherd dogs and the Rough-coated Collie there is evidence for heritability of this disease, most likely as an autosomal recessive.

In the cat, EPI is most commonly due to loss of exocrine tissue due to ongoing chronic pancreatitis, the end-point of chronic pancreatitis being fibrosis and scarring. Juvenile onset disease, similar to PAA in dogs, has not been described in the cat to date. Chronic pancreatitis as a cause of primary exocrine insufficiency has been described in dogs and is the most common cause of late-onset exocrine insufficiency (i.e. in dogs >4 years of age).

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

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

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

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

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

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

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

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

**Therapeutic considerations in the dog**

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

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

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

**Therapeutic considerations in the cat**

In common with the dog, effective treatment of exocrine pancreatic insufficiency in the cat relies on the effective replacement of digestive enzymes with powdered porcine pancreas extracts. A reasonable starting dose for the cat is approximately 1/4 teaspoon of extract per meal. Pre-incubation of the meal with the enzymes should be avoided as this may lead to food aversion in the cat.

Compounding of the enzyme powder into gelatin capsules can be used in cats with severe food aversion, however this relies on the ability of the owner to administer the capsules to the cat. Gelatin-encapsulated enzyme powder capsules must be kept scrupulously dry or the capsule will be degraded.

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

**“Subclinical” EPI**

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

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

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

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

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

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

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

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

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

References

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

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

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

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

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>Study Stockhaus2</th>
<th>Ferreri3 (ANP)</th>
<th>Ferreri3 (CP)</th>
<th>Hill4</th>
<th>Total</th>
<th>Overall Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Cats</td>
<td>33</td>
<td>30</td>
<td>33</td>
<td>40</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>Inappetance</td>
<td>32 (97%)</td>
<td>19 (63%)</td>
<td>23 (70%)</td>
<td>39 (98%)</td>
<td>113</td>
<td>83%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>33 (100%)</td>
<td>15 (50%)</td>
<td>17 (52%)</td>
<td>40 (100%)</td>
<td>105</td>
<td>77%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>24 (73%)</td>
<td>10 (33%)</td>
<td>17 (51%)</td>
<td>37 (93%)</td>
<td>88</td>
<td>65%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (55%)</td>
<td>13 (43%)</td>
<td>13 (39%)</td>
<td>14 (35%)</td>
<td>58</td>
<td>43%</td>
</tr>
<tr>
<td>Icterus</td>
<td>6 (18%)</td>
<td>5 (16%)</td>
<td>8 (24%)</td>
<td>21 (53%)</td>
<td>40</td>
<td>29%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>3 (9%)</td>
<td>12 (40%)</td>
<td>7 (21%)</td>
<td>NS</td>
<td>22</td>
<td>16%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>17 (52%)</td>
<td>NS</td>
<td>NS</td>
<td>10 (25%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abdominal pain, a very common clinical sign of pancreatitis in the dog, is much less frequently recognized in the cat. Accurate assessment of abdominal pain in the cat can be quite difficult, and thus the true frequency of this problem in cats with pancreatitis may be underestimated,5 however the central observation that abdominal pain is rarely appreciated by clinicians assessing cats with pancreatitis remains true. Given the vague nature of clinical signs of pancreatitis in the cat, this disease should be considered in the differential diagnosis of any cat with vomiting, anorexia/hyporexia or lethargy where another, more proximate cause has not been identified.

An interesting observation from the aggregated retrospective studies is that these signs were the same regardless of underlying type of pancreatitis in the cats, with both severe necrotizing disease and more chronic, fibrotic disease having the same general signs. Based on these observations, it is not possible to distinguish acute from chronic pancreatitis in cats based on clinical presentation, duration of clinical signs or apparent severity of the disease.6,7 While chronic pancreatic disease is commonly thought to be less severe than acute pancreatitis in the cat,8 either disease can present with complications or comorbidities that are potentially life-threatening, and attempting to draw a distinction between these two conditions is not particularly clinically helpful.

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

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

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

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

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

**Therapeutic approaches to the outpatient case**

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

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

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

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

Therapeutic approach to the cat with severe disease

Cats with suspected pancreatitis presenting with marked abdominal pain, tachypnea, tachycardia, significant fever, collapse or other evidence of systemic inflammatory syndrome or circulatory failure are considered to have severe disease, and require immediate and aggressive, hospital-based care. The existence of multiple abnormalities in screening clinical chemistries, particularly hypoalbuminemia and hypocalcemia, is a strong indicator of severe and potentially life threatening disease.5

As with dogs, cats presenting with severe pancreatic inflammatory disease require aggressive therapy, including fluid therapy, effective analgesia, and early planning for nutritional support given the risk of hepatic lipidosis as a comorbidity. The aims of therapy are to replace circulating fluid volume, restore and maintain end organ perfusion (particularly of the pancreas, as pancreatic ischemia is a significant contributor to the development of necrotizing pancreatitis6), restore and maintain plasma colloid oncotic pressure. Colloid fluids, such as synthetic hydroxyethyl starches, are often highly beneficial in the initial resuscitation of these cases. Fresh-frozen feline plasma can also be considered, and likely provides oncotic support while replenishing coagulation cascade proteins, however there is little information in the veterinary literature regarding use of plasma in severe feline pancreatitis cases. We typically use a combination of synthetic colloid and crystalloid fluids for initial resuscitation and volume maintenance in these cats in our clinic. Substantial electrolyte abnormalities, particularly hypokalemia and hypocalcemia, should be anticipated in these cats.5,7 Supplemental potassium is administered in combination with crystalloid fluids following routine guidelines for concentrations based on serial determination of serum potassium.

Effective analgesia and control of vomiting are important aspects of management of severe pancreatitis in all species, including the cat. Narcotic pain control is typically indicated in cats with sufficiently severe pancreatitis to warrant hospitalization. Transdermal fentanyl patches (25µg/hr) can be very effective for longer term (up to 72 hrs) analgesia without the need for frequent handling and injection in these patients, but initial therapy with an injectable or sublingual agent (commonly buprenorphine) is necessary as it can take up to 12 hours for therapeutic fentanyl concentrations to be reached.7 Maropitant, a neurokinin-1 receptor antagonist, is both an effective antiemetic and has antinoceptive effects in the viscera.11 The combination of maropitant with a 5-HT3-receptor antagonist, such as ondansetron or dolasetron, provides an effective control for vomiting and nausea in these patients with minimal need for repeated handling during the day.

The special case of the diabetic cat

Cats with diabetes mellitus and chronic pancreatitis represent a significant challenge, particularly if they are poorly or minimally improved by rigorous use of an elimination diet. The use of glucocorticoids in these cats risks the loss of glycemic regulation, increased insulin requirements or the development of insulin resistance. When faced with this particular quandary, the author’s personal preference is to emphasize dietary modification and weight loss to attempt to improve the glycemic state of the cat, rather than use of glucocorticoids to control gastric or pancreatic inflammation. Many cats will show an improvement in their chronic vomiting as they enter a euglycemic state, and anecdotally many cats with chronic pancreatitis show an improvement in their clinical signs and a normalization of serum fPLI concentrations after they are switched to the higher protein, low carbohydrate dietary regimes currently recommended for management of diabetic cats.12

References


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

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

### Historical and clinical findings

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

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

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

### Approach to the assessment of a chronic enteropathy patient

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

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

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

“Inflammatory bowel disease”

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

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

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

**Therapeutic planning in patients with chronic enteropathies**

On diagnosis of an inflammatory entero-pathy, therapeutic planning can take place. A remarkably large proportion of dogs with a diagnosis of lymphocytic/plasmacytic enteritis will show at least partial food responsiveness. A dietary exclusion trial is indicated in most cases, the author’s preference is for use of a novel protein source diet selected on the basis of a thorough dietary history. Partially hydrolyzed and modified antigen diets may also be beneficial. The patient is started on the elimination diet exclusively for a minimum period of 14 days. In most patients with diet-responsive disease a notable improvement in clinical signs will have occurred at 14 days, and those that have failed to show a good response are unlikely to show much benefit from a longer period on the diet. If the dog responds to the diet change, the diagnosis becomes one of food-responsive diarrhea or dietary intolerance. “Dietary allergy” implies
demonstration of a hypersensitivity response to a dietary component, as this is not achieved in most veterinary patients this term is not appropriate to most cases.

Dogs failing to respond to dietary modification, particularly when a rigorously controlled elimination diet trial has been carried, out are diagnosed with idiopathic inflammatory bowel disease. The mainstay of therapy for idiopathic inflammatory bowel disease is anti-inflammatory to immune suppressive drug therapy, typically with glucocorticoids. Prednisone or prednisolone is started at doses of approximately 2mg/kg per os SID, typically in the morning, for at least 14 days. If clinical signs are well controlled at this time, a gradual taper to the minimum effective dose is begun, with dose reductions of approximately 25% per week. In some animals, more aggressive immune suppressive therapy may be required. Azathioprine (2mg/kg SID to every other day) has traditionally been the next step for immune suppression, this drug requires several weeks to manifest full effect. Recent publications have examined the utility of cyclosporine-A in therapy of dogs with refractory IBD and saw benefit in many patients, however expense may limit the use of this drug in some patients. Drugs such as mycophenolate mofetil and leflunomide have been investigated for use in these patients, but to date limited information is available regarding their efficacy.

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

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

The small intestine is home to a large, diverse population of bacteria and other microflora. The microflora is essential to the normal anatomy and physiological function of the gastrointestinal tract, and abnormalities in this microflora are commonly associated with clinical signs of disease. The total number of organisms present in the canine GI tract has been a point of controversy. The term “Small Intestinal Bacterial Overgrowth” (SIBO) was originally defined in the context of culture studies that defined the upper limit of normal for the bacterial population of the duodenum as 10^5 colony-forming units/ml. We now know from more recent culture-based and genetic diversity studies of the canine intestinal microflora that these original culture studies likely underestimated the numbers and diversity of bacteria present. The term “antibiotic-responsive diarrhea” is gaining currency in the recent literature, recognizing the antibiotic responsive nature of this condition without applying arbitrary criteria regarding expected bacterial numbers.

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

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

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

**References**


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

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

Concepts and terminology of biological variation

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

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

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

If we are monitoring a value over time, we need to have some idea of the magnitude of change that most likely represents a change in the patient’s physiology (either a worsening or an improvement, depending on the context of the testing). This is the Reference Change Value (RCV), which is derived from measurements of the within patient variability and the variability of the measurement technique itself. In most cases, the reference change value is stated as a percentage change, statistically associated with a P value of <0.05; in other words a change of this size has a <1:20 chance of being random, and thus is more likely due to a change in the patient’s physiology. A change in a test result less than this value, regardless of whether it is “better” or “worse”, is statistically unlikely to represent a real change, and therapeutic decisions should be made with caution if less than this degree of change is seen.
Factors that influence biological variability
As previously indicated most chemistry parameters that we measure in our patients have high individuality, and many have high reference change values. Generally speaking analytes that are actively regulated by some form of physiological homeostatic process will have lower individualities and relatively low reference change values. Examples of substances with low individualities and comparatively low reference change values include serum electrolytes (particularly potassium and calcium) and blood glucose concentrations. This intuitively makes sense; these electrolytes are rigorously regulated by the renin-angiotensin-aldosterone system and parathyroid/calcitonin hormone production respectively, while under normal circumstances glucose is regulated via the insulin/glucagon system within a relatively tight range of values.

Release of “leakage” enzymes, such as alanine transaminase (ALT) and the specific pancreatic lipases is not under any form of homeostatic control, their release into the circulation varies with their rate of synthesis (which may vary with disease), rate of loss from the cells (which may also vary with disease), and may also vary with changes in the clearance mechanisms of these enzymes from the circulation. Consequently, these enzymes often feature a very high degree of within-individual variation, resulting in high reference change values. This has been reported for both pancreatic lipase immunoreactivity and liver enzyme activities in dogs,5,6 and for liver enzyme activities in cats.4

The effect of disease states on biological variability
Disease states can also influence the degree of biological variability, and thus the reference change values for individuals who are already diseased may actually be markedly different from healthy individuals. This has been reported for the cardiac biomarker NT-proBNP in dogs,7 where the reference change value for dogs with mitral regurgitation was estimated at approximately 50%, while the RCV for healthy dogs was nearly 100%, the lower RCV in the dogs with mitral regurgitation was mainly due to lower within-individual variation in that group.

Data on biological variability and reference change values for other enzymes and other disease states are currently lacking for many important diseases and for many enzymes that are routinely measured in practice. While data for biological variation in specific canine pancreatic lipase (Spec-cPL) has been reported for healthy dogs (where a very high RCV of approximately 450% was reported),8 data from dogs with chronic pancreatitis or on the feline specific pancreatic lipase assay (Spec-fPL) in any group of cats (healthy or diseased) are not available at the time of writing.

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

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

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

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

References
Protein-Losing Enteropathies: The Black Diamond Cases
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Protein loss through the GI tract (protein-losing enteropathy, PLE) presents in a spectrum of severities, ranging from cases with insidious weight loss and mild diarrhea through to highly challenging cases complicated by the development of ascites, peripheral edema and coagulopathies. Recognition of PLE can be quite challenging, particularly in cases where overt hypoproteinemia is not yet present. The presence of PLE in dogs with chronic inflammatory enteropathies has been shown to be a negative prognostic factor in these cases, and warrants more aggressive therapy.1 While cases with PLE secondary to inflammatory enteropathies tend to be the most challenging to manage, a variety of other mechanisms can result in significant intestinal protein losses. Selection of the appropriate therapy for a PLE case depends upon accurate identification of the pathology present, as differing modes of therapy are indicated for some of the non-inflammatory, structural diseases.

Clinical signs in PLE
Depending on the degree of severity and duration of the disease, clinical signs of PLE can range from the development of ascites, peripheral edema or acute severe respiratory distress due to pulmonary thromboembolism, through to vague signs such as weight loss and poor appetite.2,3 If an inflammatory enteropathy is present diarrhea may be noted, but many cases with PLE present with normal stools.2 Consequently, PLE should be considered as a differential diagnosis for any dog presenting with hypoalbuminemia, even if gastrointestinal signs as lacking.3

Mechanisms of protein loss in PLE cases
With some specific breed-related exceptions, the major mechanisms of protein loss in most cases of PLE in dogs (and cats, but this condition is recognized infrequently in that species4) can be divided into two major groups: primary lymphatic drainage abnormalities such as lymphangectasia, lipogranulomas or mesenteric lymphatic obstructions, and secondary to mucosal inflammatory disease. While these major categories account for the majority of PLE cases encountered in clinical practice, gastrointestinal ulcers, significant gastrointestinal parasitism and gastrointestinal neoplasms (both lymphosarcom and carcinomaa) can also result in marked GI protein loss. Intestinal motility accidents, such as intussusception, partially obstructing foreign bodies, and diverticulae can also result in quite marked protein loss, however their clinical signs and initial examination findings are usually sufficiently distinct from the more typical PLE cases to allow rapid identification.

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

Lymphatic drainage abnormalities such as lymphangectasia have been reported in the Rottweiler, Yorkshire terrier, Shar-pei and the Maltese terrier.2,3,6 In the Rottweiler lymphangectasia commonly accompanies eosinophilic inflammatory disease of the intestine, but a direct relationship between these two conditions has not been established and both diseases are commonly diagnosed in this breed in isolation.

As well as primary lymphangectasia, the Yorkshire Terrier is commonly diagnosed with significant inflammatory lesions of the intestinal crypts.2,7 These crypt lesions are commonly associated with severe gastrointestinal protein loss. The mechanism of crypt abscess formation in these dogs has not been well defined, but there does not appear to be any association with bacterial invasion.3

The Norwegian Lundehund, a relatively rare dog breed in the USA, has been reported to have 50% or more of individuals affected with intestinal lymphangectasia, with associated PLE.8

The Soft-coated Wheaten terrier presents with a breed specific PLE and protein-losing nephropathy that can be quite challenging to manage.9 This disease has been linked to food hypersensitivities in this breed,10 and is apparently worsened by high level exposure to gluten and other dietary allergens, but does not appear to be a true gluten hypersensitivity.11 Soft-coated Wheaten terriers may present with protein-losing enteropathy alone, protein-losing nephropathy alone, or may have both conditions simultaneously.9

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

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

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

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

In a suspected PLE case with hypoalbuminemia, where skin disease and protein-losing nephropathy have been ruled out and pre-/post-prandial bile acid tests are normal, the diagnosis of PLE can be made with a high degree of certainty through simple exclusion.

The diagnosis of PLE in dogs that have not reached a state of overt hypoalbuminemia is more challenging. This can be quite important in dogs from the breeds previously listed with predispositions for PLE, as some of the adverse outcomes of PLE such as hypercoagulability and thromboembolic potential can manifest before the albumin is markedly low, and thus in these breeds early diagnosis and management is important.

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

**Diagnosis imaging findings with lymphangectasia of the intestine.**

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

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

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

The author’s first choice of diet for management of relatively uncomplicated PLE cases is typically one of the commercially manufactured, ultra-low fat diets such as Royal-Canin’s LF or Hill’s I/D-LF (NB: the I/D low fat formulations. I/D GI health is too high in fat). Alternatively, home cooked diets have been described for dogs that are also extremely low in fat, and with careful attention to vitamin and mineral supplementation can be used long-term.2

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

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

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

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

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

Animals with this degree of PLE are usually assumed to be hypercoagulable. This hypercoagulable state persists in many dogs after therapy that increases albumin, and thus these dogs should be considered at long-term risk for thromboembolic complications.

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

**References**


Recognizing, Testing, and Treating Protozoal GI Tract Infections
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Recognition and management of gastrointestinal protozoal infection can be challenging for the companion animal practitioner. These organisms are often present in relatively low numbers, may show episodic shedding, asymptomatic carrier states are quite common, and the organisms are quite fragile and may be damaged or destroyed when using routine fecal flotation solutions. Clinical signs of disease with these organisms are also remarkably variable, and may depend upon the presence of other comorbidities or immune compromise in the host. To add to the difficulty of managing these cases, the enteric protozoa are eukaryotes and often depend upon the host to supply nutrients, thus they are resistant to many commonly used antimicrobials. Marked strain and geographical variances in apparent pathogenicity are seen. In animals with symptomatic infections an integrated approach to treatment of the affected animal, other in-contact animals and the housing environment are necessary to achieve the best chance at eradication, but even with diligent treatment of both animal and environment reinfection is common. The purpose of this presentation is to review the diagnostic and clinical approach to two common and important gastrointestinal protozoal groups, the Trichomonads and Giardia. Additionally, this presentation will discuss evidence for emerging protozoan infection in humans, Blastocystis, as either a pathogen or zoonotic threat in companion animals.

Feline intestinal trichomonosis
Trichomonosis is a rapidly emerging feline disease in cats that is caused by the protozoal pathogen, Tritrichomonas foetus. T. foetus was definitively identified as a cause of waxing and waning large bowel diarrhea in cats in 2003 and since then its prevalence has been recognized worldwide. The prevalence of T. foetus can be quite high (>30%) especially in young purebred cats that are maintained in high density housing environments (e.g. shelters, catteries).1 However, older, mixed breed cats have also been identified with the infection. No breed of cat is known to be resistant to infection. The pathophysiology of feline trichomonosis is largely unknown. The route of infection is presumed to be fecal-oral (e.g. sharing of litter boxes and mutual grooming). Following transmission, the trichomonads can be cleared by the feline host or can persist in the ileum and large intestine. Infected cats can be subclinical carriers or can develop signs of large bowel diarrhea.

Clinical presentation
The most characteristic clinical sign of feline trichomonosis is chronic waxing and waning large bowel diarrhea that is frequently malodorous with the consistency of cow patty feces. Occasionally, frank blood and/or mucus may be observed in the diarrheic feces. Young, severely affected cats may also have signs of proctitis, fecal incontinence and/or rectal prolapse. 2, 3 Although exclusively large bowel diarrhea is a more common finding, infected cats may also exhibit small bowel signs including weight loss, anorexia and/or vomiting. 4 T. foetus-induced diarrhea may resolve with antibiotic administration but returns following discontinuation of antimicrobial therapy. Untreated cats may develop new onset signs (or demonstrate relapse) following stressful events (diet change, new cat introduced into household, etc). Infected cats generally present in good body condition unless they are immunocompromised (young, FELV/FIV, etc) or have a comorbidity.

Testing for T. foetus is recommended for any cat with large bowel diarrhea, particularly young purebred cats, cats raised in a high-density housing facility, and/or cats that have developed diarrhea following introduction of a new cat into the household. There are several diagnostic tests that are useful in detection of T. foetus infection. The best sample to evaluate for the presence of T. foetus is one obtained by a colonic flush (video available at: http://www.youtube.com/watch?v=JMfZ9M80V8E) however, fresh fecal samples obtained by fecal loop or immediately after voiding are acceptable. Feces should be diarrheic and antibiotics should be discontinued a minimum of 14 days prior to testing.

Cats can be evaluated for T. foetus in several ways. Direct smear examinations of freshly voided, diarrheic feces may reveal mobile trophozoites. The motility of the trophozoites may be used to distinguish T. foetus from Giardia (T. foetus has a “tumbling” motion, Giardia looks like a falling leaf). Fecal culture in a pouch system, originally developed for diagnosis of venereal trichomonosis in bulls, can increase the sensitivity of diagnosis, but may take several days to a week for clear results, and are susceptible to bacterial overgrowth that results in loss of the trichomonads and a false negative finding. PCR examination of fecal samples is the current gold-standard test for this parasite. Samples are stable for prolonged periods in at room temperature when preserved with isopropyl alcohol at 1:1 volume.

No diagnostic test has 100% sensitivity. Negative test results should be interpreted with caution. Repeated testing is advised if a strong clinical suspicion exists in the face of a negative result test. Giardia is often confused for T. foetus and vice versa. Cats that do not respond to appropriate anti-giardial therapy or that have exclusively large bowel signs should be tested for T. foetus. Co-infections are common in T. foetus-infected cats. 5 Thus, additional enteric infectious disease testing (e.g. Giardia spp, coccidia) is recommended in cats testing positive for T. foetus. Other chronic causes of large bowel diarrhea (antibiotic-responsive diarrhea, inflammatory bowel
disease, enteric parasitic and fungal infections such as histoplasmosis if appropriate differential for the area, colonic neoplasia, etc.) should also be included among the differentials.

**Therapeutic plan**

Infected cats can often be successfully treated with ronidazole (30mg/kg PO q24hr for 14 days). Neurotoxicity can be a side effect of treatment however most reported cases of ronidazole toxicity occurred when cats were given higher than recommended daily doses of drug. Nevertheless, cats should be carefully monitored during treatment for signs of neurotoxicity. Doses above 30mg/kg SID are not recommended.

If diarrhea continues well-beyond ronidazole treatment, cats should be retested for *T. foetus* infection. A positive result may be attributed to resistant infection, poor owner compliance, re-infection and/or improper drug compounding or ineffective dose. Untreated cats may experience resolution of clinical signs however they often remain infected and can spread the organism to previously uninfected cats. Therefore, if concern for transmission to uninfected cats exists, the author recommends that infected cats be treated or be isolated from uninfected cats until shedding ceases (based on multiple negative PCR results).

**Giardiasis**

*Giardia duodenalis* infections are highly prevalent in dogs and cats. Reported prevalence rates are dependent on the sampling method used but are likely around 12-15% in cats and dogs. The route of *Giardia* transmission is fecal-oral usually via ingestion of environmentally stable cysts present in contaminated water and/or food. Once transmitted, trophozoites colonize the small intestine. Infected animals can become subclinical carriers or can develop small intestinal diarrhea. The prolonged survival of the cyst form in the environment represents a particular challenge for long-term management, as many patients will be living in highly contaminated environments, or may be exposed to reinfection by visiting community parks and other public spaces.

**Clinical presentation**

Clinical signs of *Giardia* spp. infection vary widely among infected animals. Many animals are subclinical carriers and do not exhibit signs of disease. Susceptible animals (e.g. young, immunocompromised, shelter-housed) may develop severe and/or chronic signs of disease. Clinical signs may include abdominal pain, acute self-limiting diarrhea, chronic diarrhea and/or weight loss. In human beings a “post-*Giardia*” irritable bowel syndrome has been recognized. This syndrome is associated with increased intestinal motility, functional dyspepsia, gassiness and abdominal pain and may persist for several months beyond the original diagnosis of giardiasis.

**Diagnostic plan**

There are a variety of *Giardia* diagnostic tests available. The most widely available diagnostic tests for the private practitioner are direct fecal smear, fecal flotation, *Giardia* SNAP ELISA and IFA.

As mentioned with the intestinal trichomonads, co-infection with *Giardia* is common. In animals with “resistant infection”, underlying diseases such as inflammatory bowel disease may be present. Thus, infected animals should be evaluated for the presence of mixed infection and/or concurrent intestinal disease.

**Treatment**

Many animals will have self-limiting diarrhea, which may not necessitate treatment. If treatment is required, fenbendazole (50 mg/kg q 24 h for 5 days) may be effective especially when concurrent infection with nematodes or cestodes is present. In patients with documented recurrent, a second course of fenbendazole 14-21 days after initial treatment and diligent attention to environmental control are crucial. Metronidazole (15-25 mg/kg q 12 h for 5-7 days) may also be used unless concern for neurotoxicity exists. Bathing the animal and changing the animal’s environment on the last day of each round of treatment should be performed if possible.

**Blastocystis**

*Blastocystis* spp. is a highly diverse group of enteric protozoa. These organisms are the most common enteric parasite identified in human stool samples within the USA, with marked regional and seasonal variations in prevalence noted. The pathogenicity of *Blastocystis* is an area of some controversy in the human literature, however infection with this organism is commonly noted in human patients with IBS symptoms. Initial descriptions of *Blastocystis* gave species names to the organisms reflecting the species from which they were isolated (i.e. *B. hominis*, *B. ratti*), however it is now recognized that genetic diversity within these species is very high, and thus consensus has developed around categorization of these organisms via numbered subtype (analogous to the concept of infectious assemblages in *Giardia*). At the time of writing at least 14 distinct subtypes have been reported, with new additional new subtypes being regularly identified.

**Diagnosis**

In human beings the most commonly used method for diagnosis of *Blastocystis* carriage is via direct light microscopy of either unstained, wet mount or stained fecal preparations. Enrichment culture and fecal PCR are also commonly used, with fecal PCR methods having the additional advantage of allowing subtype identification via sequencing of the small subunit ribosomal RNA gene. Fecal PCR has greater sensitivity than direct light microscopy.
Prevalence of blastocystis in companion animals, zoonotic potential?

Within the veterinary and parasitology literature there is a remarkable dearth of data regarding any link between Blastocystis carriage and clinical signs of disease in companion animals. A solitary case report describes a significant parasite burden in a mixed-breed dog with vomiting, diarrhea, and weight loss. This animal was definitively diagnosed with exocrine pancreatic insufficiency and marked hypocobalaminemia, which is sufficient to explain the observed clinical signs.13

The true prevalence of Blastocystis carriage in companion animals is unclear at this time, with most of the parasitology literature in this area focused on the domestic dog. Early data from subtropical and tropical environments suggested quite high carriage rates for Blastocystis in dogs, with rates as high as 70% reported for carriage in shelter-resident dogs in a subtropical environment, although this finding has been thrown into some doubt by recent PCR-based studies from the same environment. In a study of asymptomatic individuals and pet animals living in the same household as humans symptomatic for Blastocystosis (n=11), 8/8 in-contact animals (5 dogs, 3 cats) were positive for Blastocystis via fecal PCR, with 7/8 of the in-contact animals carrying the same strain as the symptomatic in-contact human. Interestingly, none of the in-contact animals or in-contact humans (n=17) in this, admittedly small, study showed clinical signs consistent with Blastocystosis. These data suggest that transmission between humans and companion animals is possible, however this is most likely a transient phenomenon and it appears unlikely that domestic dogs and cats represent a significant risk for zoonotic transmission.

Selected references (additional references provided on request)

The components of the “GI panel”

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

Trypsin-like immunoreactivity (cTLI, fTLI)

The serum concentration of trypsin-like immunoreactivity represents the presence of (mainly) trypsinogen and (rarely) active trypsin in the circulation. Trypsinogen, the zymogen precursor to active trypsin, is essentially exclusively synthesized in the pancreatic acinar cells, where it is packaged in secretory granules before excretion in to the pancreatic duct system. Pancreatic acinar cellular damage, for instance with pancreatitis, can result in the loss of trypsinogen into the pancreatic interstitium and circulation, resulting in a higher than normal concentration. Loss of acinar cell mass, as occurs in both pancreatic acinar atrophy in dogs and as an end stage of chronic pancreatitis in dogs and cats, can result in subnormal concentrations of TLI. Detection of a serum TLI concentration ≤0.8 µg/L is suggestive of exocrine insufficiency. Values within the reference range, even if “low normal”, rule out exocrine insufficiency due to reduced functional acinar cell mass.

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

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

Specific pancreatic lipase (Spec-cPL™, Spec-fPL™)

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

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

While pancreatic lipases are highly specific for the exocrine pancreas, the normal range of these assays in both dogs and cats includes values close to or equal to zero. Consequently, the Spec-c/fPL assays cannot be used to diagnose exocrine pancreatic
insufficiency. The main utility of the pancreatic lipase concentrations lies in the detection of exocrine pancreatic inflammation in both species, this is particularly valuable in the cat as clinical signs of pancreatitis in this species are often subtle or vague.

Serum folate

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

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

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

Serum cobalamin

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

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

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

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

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

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

**Common patterns of results and interpretation for cobalamin and folate**

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

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

### Indications for supplementation

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

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

### References


