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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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>
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</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Possible</td>
<td>Rare</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>
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<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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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 see indicating that an adequate depth has been achieved. The organisms will be found in clusters within macrophages in most cases. If this test is unrewarding but Histoplasmosis is still suspected then a urine Histoplasma antigen titer can be tested.

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

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

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

If histopathology confirms IBD, then localization of the disease will dictate the therapeutic plan. When inflammation is severe and widespread including small and large intestine, immunosuppression may be indicated. Prednisone is typically the first-line medication for this, with secondary drugs including Cyclosporine A, azathioprine, and more recently chlorambucil. 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 abomen, helps to provide tension to the descending colon and rectum and will help to prevent further prolapse.

References
Diagnosing and Treating Canine Pancreatitis

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Pancreatitis is a commonly diagnosed condition that affects dogs of all ages. Clinical signs can vary greatly depending on both the chronicity and severity of disease. While in some cases pancreatitis is a 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**


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

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

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

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

Perioperative mortality rate with cholecystectomy due to a mucocele has been reported as high as 21% (Pike FS et al 2004). This study included 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 the equipment used of great importance when consider options for biopsies (Washabau RJ et al 2010). Additionally, endoscopy equipment is not readily available to all veterinarians, making surgery the only way to obtain tissue samples.

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

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

Antibiotics may be indicated in severe cases for treatment of bacterial translocation across the wall of the diseased intestines. Broad spectrum coverage with an antibiotic such as amoxicillin/clavulanic acid would be indicated in this instance. More commonly, however, there may be a component of dysbiosis, or bacterial overgrowth, which can contribute to a non-specific condition known as...
antibiotic-responsive diarrhea. While this is not generally the only pathology associated with PLE, it can often be one part of the disease process. Tylosin 10-20mg/kg PO BID) is the drug of choice for this condition (Kilpinen S et al 2014).

Immunosuppressive therapy, first and foremost corticosteroids, will be indicated in most cases of chronic enteropathy that are severe enough to cause hypoalbuminemia. Prednisone is the most commonly used first line therapy, with starting doses up to 3mg/kg/day for severe cases. Larger dogs generally require a lower starting dose, in some cases only 1mg/kg/day. Alternatively, budesonide has been shown to be as effective (Dye TL et al 2013). In severe cases or if prednisone therapy has failed, additional immunosuppressive medications can be used. The use of chlorambucil (4.4mg/m²/day) has recently been shown to be more effective than prednisone alone in a subset of dogs with severe refractory PLE (Dandrieux JR et al 2013). Cyclosporine (Atopica) is another drug that has shown effectiveness in dogs with inflammatory bowel disease refractory to prednisone alone (Allenspach K et al 2006).

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

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

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

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

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

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

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

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

- Abdominal ultrasound
  - This can be a useful test to determine a cause of vomiting, however be cautious to avoid over-interpreting results. Severe intestinal ileus from pancreatitis, for example, can lead to dilated, fluid-filled loops of intestine. This finding can also be suggestive of an obstruction.
  - While abdominal ultrasound can be a sensitive and specific test when performed by an experienced ultrasonographer evaluating a case of acute vomiting for bowel obstruction, it has a lower utility for cases of chronic vomiting. A recent study showed that abdominal ultrasonography helped establish a diagnosis in only 23% of cases of chronic vomiting(Leib MS 2010). In the majority of cases the results did not change the clinical course.
Additional lab work
  - 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.
  - 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.
  - Leptospirosis antibody titer
  - GI Panel
    - Cobalamin/folate
    - SPEC cPL
    - TLI

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

Anti-emetic therapy
  - Serotonin antagonists (5-HT3 receptor inhibitor) (Plumb D 2015)
    - The 5-HT3 receptors are found both centrally and peripherally.
    - Receptors are stimulated by serotonin when intestinal mucosa is disturbed
      - Ondansetron
  - Substituted benzamides (Plumb D 2015)
    - Dopamine antagonist (and 5-HT3 receptor blocker at higher doses)
    - 5-HT4 agonists
    - Also include prokinetic properties (caution if obstruction is suspected)
      - Metoclopramide, cisapride
  - Neurokinin-1 antagonist (Benchaaoui HA 2007)
    - 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).
    - Effective with both central and peripheral causes of vomiting.
      - 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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Dysphagia and Dysmotility: Recognizing it Early and Correctly
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Swallowing (a.k.a deglutition) is the transport of food and liquids from the oral cavity to the stomach. This process requires a coordinated effort between the oral cavity, pharynx, esophagus, and associated muscles and nerves. A comprehensive understanding of the mechanisms of swallowing is critical to identifying the underlying cause of dysphagia and dysmotility. In this presentation, we will review the phases of deglutition in preparation for a discussion about dysphagia and esophageal dysmotility.

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

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

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

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

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

Treatment of both oropharyngeal and esophageal dysmotility is mostly focused on medical management of the underlying disease and provision of supportive care (e.g. nutritional support, prokinetics). Surgery may be indicated for several of the less common causes of oropharyngeal or esophageal dysphagia (e.g. cricopharyngeal achalasia, esophageal tumor).
Feline Constipation:
Novel Treatment Strategies
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Feline constipation (FC), defined by infrequent bowel movements, tenesmus, hard stools, and abdominal pain, is a common gastrointestinal disorder in cats. FC can occur secondary to a wide range of diseases and/or be a side effect of medical therapy. Several risk factors have been identified or proposed for FC including season, age, hydration status, inactivity and/or hospitalization, metabolic disease, orthopedic or neurologic disease, colonic neoplasia or structural disease, idiopathic megacolon, and/or µ-opioid receptor agonists) administration. Additional risk factors for constipation that have been identified in humans but may be difficult to appreciate in cats include anxiety, depression, and stress. A variety of other drugs including NSAIDs, antihypertensives, anticholinergics, and antiemetics are also associated with chronic constipation in humans, however, the role of these drugs in the development of FC are unknown.

Severe FC can negatively affect the cat’s quality of life and lead to life-threatening complications. Identification and removal, if possible, of the underlying cause is the most effective remedy for FC. Thus, a thorough diagnostic workup to evaluate for risk factors of FC is recommended in addition to initiation of medical management. A careful history should be taken to rule out acute causes of constipation (e.g. immobility, dehydration). To the extent possible, medications associated with constipation should be discontinued.

Coinciding with removal of the offending agent, management of FC should begin with maintaining adequate hydration and encouraging activity.

Conventional therapies
Pharmacologic management of FC can be difficult especially with drug shortages and aversion of some cats to dietary modification and oral therapies. The majority of FC pharmacologic treatments are given orally and work by acting as bulking agents, laxatives, or colonic motility stimulants.

Dietary fiber is one path towards ameliorating or preventing FC and should be considered as a frontline treatment for FC in combination with laxative therapy. Fiber can be divided into two major categories, insoluble and soluble. Insoluble (e.g. cellulose) fiber is bulk-forming and improves intestinal motility by distending the intestinal lumen. However, insoluble fiber is characterized by a lower nutrient digestibility and reduced fecal moisture content which may lead to excessively dry stool. Soluble (e.g. pectins from carrots or fruits, canned pumpkin, guar gum; psyllium) fiber often undergoes bacterial fermentation resulting in short-chain fatty acid (SCFA) production. These fatty acids have prokinetic effects on colonic smooth muscle. Too much SCFA production can lead to very liquid stools and lower nutrient digestibility, thus the addition of soluble fiber should be titrated carefully. In one uncontrolled study of 66 cats, addition of a psyllium-enriched diet improved stool consistency in 56 cats receiving laxative therapy.

Laxatives aid in the prevention or treatment of constipation by increasing fecal water content and promoting movement of feces through osmotic, lubricant, or stimulatory mechanisms.

Polyethylene glycol 3350 (PEG 3350; e.g. Miralax), a bulking and fecal hydration agent, contains large molecules that cannot be absorbed by the gastrointestinal tract. Therefore, it works as an osmotic laxative, pulling water into the colonic lumen. In an uncontrolled, open-label study of six healthy cats with no history of gastrointestinal disease, PEG3350, given at a median daily dose of 3.0±1.1g, resulted in the desired fecal consistency in all six cats within 1 month of therapy. Mild hyperkalemia was the only side effect noted in some of the cats. No other adverse effects were noted as a result of PEG 3350 administration. Although there are no published reports on the use of PEG3350 in cats with FC, I use it often and find it to be an effective prophylactic treatment for cats at risk for FC and may be a more palatable option as it can be added to the cat’s food without imparting a major taste change.

Lactulose is a semi-synthetic disaccharide that, like PEG 3350, acts as an osmotic laxative and draws water into the colonic lumen in addition to stimulation of colonic motility Lactulose may also have a prebiotic effect. There are a paucity of studies evaluating the efficacy of lactulose in the treatment of FC. However, lactulose is inexpensive, is a very effective laxative and is often used as a first-choice laxative for FC. The major disadvantage to lactulose is that it must be administered orally which may not be an option for some cats.

Liquid paraffin (mineral oil): Mineral oil, like white petroleum, acts as a lubricant laxative. In my opinion, it is not effective for severe cases of FC. Mineral oil should only be administered per rectum as oral administration is associated with a risk of aspiration pneumonia.

Promotility drugs may aid in the treatment of FC through stimulation of colonic motility and via increased fecal water content due to decreased amount of time for water absorption. Cisapride, a serotonin 5-HT₄ agonist, stimulates motility of the
entire GI tract. Unfortunately, because of its association with cardiac arrhythmias in people, sources of cisapride can be difficult to obtain. A newer drug, mosapride, is not associated with cardiac arrhythmias in people, however it does not stimulate motility in the large intestine and therefore it is not as effective for treatment of FC compared to cisapride. Metoclopramide, a dopaminergic drug, stimulates GI motility but it is far less potent than cisapride as a promotility drug. Misoprostal, a prostaglandin analog, may increase fluid secretion and improve colonic transit time. Based on these mechanisms, it would seem to be a rational consideration for a multi-drug approach to FC.

**Novel therapies**

**Probiotics**
The GI microbiota play an enormous role in the regulation of GI motility and secretion and therefore are a potential target for the treatment of FC. Studies evaluating the GI microbiota in human patients with chronic idiopathic constipation (CIC) demonstrate a reduced *Lactobacillus* and *Bifidobacterium* spp. compared to individuals without the disease. Administration of probiotics containing these bacterial spp. has resulted in improvement of clinical signs in some patients with constipation. However, the dose and appropriate bacterial composition of probiotics for the treatment of CIC remains underinvestigation. Dysbiosis in cats with FC is likely but has not been established. I do administer probiotics containing both *Lactobacillus* and *Bifidobacterium* to cats with FC, however there is currently a lack of evidence for this practice. Clinical studies of the microbiome in cats with FC as well as clinical trials investigating the use of probiotics as an adjunctive therapy for FC are needed.

**Stimulant laxatives**
Used in human medicine but have not been studied for the treatment of FC. Stimulant laxatives are often combined with osmotic laxatives for advanced cases of constipation in humans. Senna (e.g. Senacot) is a stimulant laxative that like PEG 3350 is available over-the-counter. It is harvested from the leaves and fruit of the Senna plant and irritates the inner lining of the intestine resulting in fluid secretion. Biscodyl (e.g. Dulcolax) is a stimulant laxative that is available in oral and rectal suppository form. Biscodyl increases fluid secretion and colonic motility via promotion of colonic secretion and stimulation of the myenteric plexus. The safety of prolonged administration of stimulant laxatives has not been investigated in cats, therefore these drugs should only be used as a last alternative and should be used in combination with other therapies. Prolonged administration should be avoided when possible.

**Novel promotility drugs**
Prucalopride and tegaserod are serotonin 5-HT4 agonists that have shown promise as promotility drugs in cats and/or dogs. No studies have evaluated these drugs in the treatment of FC, however some studies in human medicine suggest that these drugs may be comparable to the effects of commonly used laxatives (e.g. PEG 3350). Tegaserod, like cisapride, has been associated with cardiac arrhythmias, and therefore may be difficult to obtain. Prucalopride is marketed in the European Union and Canada.

**Intestinal secretagogues**
Lubiprostone and linaclotide are intestinal secretagogues that stimulate the release of Cl- and H2O into the intestinal lumen resulting in fecal hydration These drugs are approved for the use of chronic idiopathic and opioid-induced constipation in humans but have not been investigated for use in the treatment of FC.

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

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

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

Therapeutic plan
The most effective treatment for feline vomiting is identification and elimination of the offending agent. When the etiology of vomiting has not yet been determined, dietary modification (low fat, alteration of fiber source, novel protein or hypoallergenic) is often recommended as an empirical therapy for chronic vomiting.\(^4\) Dietary restriction, occasionally used for cats with acute vomiting, should be limited to 8-12 hours to reduce the risk of hepatic lipidosis. Anthelmintic treatment should also be recommended in the susceptible cat (outdoor and/or young) regardless of the results of fecal testing. Supportive treatment of vomiting should include rehydration and correction of electrolyte disturbances and anti-emetics if the vomiting is persistent and obstruction has been ruled out. The type of anti-emetic should be chosen to target the mechanism of vomiting. In this presentation, I will review the mechanisms of vomiting and the way that commonly used anti-emetics target these mechanisms. Recently published studies on the use and efficacy of anti-emetics in cats will also be discussed. Acid suppressant and prokinetic drugs should be used when appropriate for treatment of esophagitis and delayed gastric emptying, respectively.
In conclusion, feline vomiting is common and is caused by a wide range of diseases. Using a problem-oriented approach with a specifically tailored GI history form will help narrow down the list of causes. The diagnostic and treatment plan should be based on the chronicity and severity of vomiting and the choice of supportive care should be based on careful consideration of the mechanism of vomiting.

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

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

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

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

Coating agents
Coating agents include sucralfate, barium, and alginate-antacids (e.g. Gaviscon). Sucralfate, a polyaluminum sucrose sulfate, forms a protective layer on the esophageal and gastric mucosa. Sucralfate is activated in the presence of an acid to form a gel-like substance that covers areas of denuded epithelium. Sucralfate may also stimulate the production of protective prostaglandins. There are very few studies which have evaluated the efficacy of sucralfate in the treatment of GUE in dogs and cats. However, studies investigating the use of sucralfate in the polypharmacy treatment of GUE and mucositis in humans suggest there is a benefit to this practice. Moreover, sucralfate is associated with very few adverse effects aside from constipation. Sucralfate does change the pH of the stomach and therefore may interfere with the metabolism of drugs that are dependent on an acidic gastric pH (e.g. PPIs). It also may interfere with drugs affected by the aluminum component of sucralfate (e.g. tetracyclines, ciprofloxacin). Therefore, these drugs should be administered at least two hours before or after sucralfate. 316
Barium, like sucralfate, is proposed to have mucosal protecting effects. It has also been proposed to have hemostatic properties although neither of these mechanisms have been proven in the treatment of dogs and cats with GUE. I do not use barium in my practice but many of my colleagues use it often for the treatment of GI hemorrhage. Barium should be withheld at least 24 hours prior to gastrointestinal endoscopy and should not be used in animals where GI perforation is suspected.

Alginate-antacid drugs are acid-neutralizing drugs that also contain sodium bicarbonate and alginic acid. The alginic acid and bicarbonate combine to target acid-pockets in the stomach to prevent reflux of gastric acid into the esophagus. In humans with gastroesophageal reflux disease, alginate-antacids significantly decreased reflux and symptoms of dyspepsia compared to placebo. No studies have evaluated the use of this mediation for the treatment of reflux esophagitis or GUE in dogs and cats. Alginate-antacids are likely inferior to acid suppressant therapy and should not be used as the sole treatment for GUE. Moreover, they may lead to rebound gastric acid hypersecretion if not administered frequently and in the absence of an acid suppressant.

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

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

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

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

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

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

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

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

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

Selected references (Additional references available on request)