Acute Pancreatitis in Dogs
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It is generally believed that pancreatitis develops when there is activation of digestive enzymes within the gland and subsequent autodigestion. The location of the initiation of enzyme activation is thought to begin at the intercellular level, but the exact mechanism is unclear at this time. Experimental studies have shown that excessive acinar stimulation may be involved. Other observations suggest that the depletion of acinar glutathione in the pancreas may stimulate oxidative stress and that contributes to tissue injury. Certain drugs are also associated with development of pancreatitis.

Pancreatitis and subsequent autodigestion may be mild associated with an edematous pancreatitis or may become more severe associated with pancreatic acinar necrosis. It is the more severe pancreatic necrosis that tends to have the severe clinical signs and a poorer prognosis associated with systemic disease, such as systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction (MODS).

Clinical conditions
In most cases the etiology of pancreatitis is never determined. In many over nutrition is a common factor likely causing excessive acinar enzyme secretion. The ingestion of high-fat diets especially in the obese patient is a well-accepted risk factor. Animals getting into the trash also have a higher risk of developing pancreatitis. Hyperlipoproteinemia is common with pancreatitis and whether this is a result of fat necrosis secondary to the pancreatitis or possibly the hyperlipidemia resulting in pancreatic ischemia is unknown. It is postulated that high concentrations of triglycerides may become activated by pancreatic lipase and produce pancreatitis. Pancreatitis is common in Schnauzers and other dogs that have a primary hyperlipidemia. A number of drugs are also shown to cause pancreatitis including thiazides, furosemide, tetracycline, L-asparaginase, and azathioprine. I personally believe azathioprine is by far the most common drug causing pancreatitis. The role of corticosteroids as a cause of pancreatitis has been suggested but as yet is unproved and is still controversial. In a study of 70 dogs with confirmed pancreatitis certain risk factors were identified (note that the animals included in this study were all necropsy cases and thus likely had severe disease). It was concluded that the breed, overweight body condition, small breed size, prior gastrointestinal diseases, diabetes mellitus, hyperadrenocorticism, and hypothyroidism were risk factors for developing acute pancreatitis. It is thought that around one fourth of the dogs presented with acute diabetes mellitus also have concurrent pancreatitis. No concurrent medications, glucocorticoid therapy, anesthesia, or trauma were associated with increased risk. Dogs having surgery (within 2 weeks before onset of signs) is also a risk factor. The breeds most commonly involved include Yorkshire terriers, toy poodles, and miniature Schnauzers.

Acute or chronic vomiting is a major clinical sign associated with pancreatitis. The clinical spectrum can vary dramatically from case to case. In the above study of 70 dogs with severe pancreatitis, vomiting (90%), weakness (79%), abdominal pain (58%), dehydration (46%), and diarrhea (33%) were reported. In experimental pancreatitis, colitis signs (often a bloody mucoid stool) were common presumably due to the extension of inflammation from the inflamed pancreas to the transverse colon that lies in close proximity to the pancreas. Severe cases also have systemic clinical signs such as fever or even cardiovascular shock.

Diagnosis
Laboratory findings are quite variable and to some extent parallel the severity of the clinical disease. Leukocytosis is usually present and biochemistry profile will show variable changes. Azotemia, elevated liver enzymes, increases in total bilirubin, hyperglycemia and hypokalemia may also be present. When disseminated intravascular coagulopathy (DIC) and coagulopathies occur, it generally reflects a poor prognosis.

Amylase and lipase have been used for years to diagnose pancreatitis in the dog but unfortunately they are not consistently reliable. The specificity of amylase and lipase is approximately 50%. Factors such as azotemia increases serum amylase and lipase due to decreased renal removal and dexamethasone will increase serum lipase levels. More recently cPLI or Spec cPL was found to be more diagnostic. In a prospective study of cases with clinical evidence of pancreatitis found the test had a 93% sensitivity and a 78% specificity using the IDEXX cutoff value of <200 µg/L as normal. The conclusion was if the Spec cPL was < 200 µg/L (normal) it was likely that the patient did not have pancreatitis. If the value was above the normal reference range pancreatitis should be included in the differential diagnosis and other tests are required to support the diagnosis.

Traditional lipase is measured using a catalytic assay. More recently newer lipase assays including a DGGR lipase and a Fuji dry chemistry assay appear to have better correlation with PLI activity. Antech now offers a Precision Pancreatic Specific Lipase (Precision PSL) on their profiles. Further studies are required to support these initial observations.

Abdominal radiographs may reveal increased density, diminished contrast and granularity in the right cranial abdomen with displacement of the stomach to the left, and widening of the angle between the stomach and the duodenum. A non-homogenous mass and loss of echodensity in the area of the pancreas is often noted on ultrasonographic examination. Occasionally dogs having
pancreatitis may also have thoracic effusion as well, probably due to extension of inflammation through the diaphragm. One study found the sensitivity of ultrasound to be 68% but this varies based on operator skill. We will frequently perform a fine needle aspiration of suspected areas of pancreatitis; cytology showing suppurative inflammation also supports the diagnosis. We consider cytology to be safe as a diagnostic tool. Abdominocentesis and cytology is also very helpful if effusion is present. Suppurative nonseptic inflammation is the typical finding and is rarely septic.

**Treatment**

For humans suffering from acute pancreatitis there is an important short therapeutic window for successful management. It is considered to be the first 36–48 hours after hospital admission. Survival rate decrease and complication rates increase if treatment is delayed. The importance of rapid fluid therapy to maintaining adequate microcirculation within the pancreas and to prevent inflammatory cytokine release improves survival. These principles can also be extrapolated to the management of canine acute pancreatitis, rapid recognition and appropriate therapy.

**Fluid and electrolyte** therapy is given in virtually every case of pancreatitis for improving pancreatic perfusion and correcting the effects of fluid loss into the peritoneal cavity, and vomiting losses coupled with the vasoactive factors released from the pancreas producing a hypovolemic or possibly endotoxic shock. Fluid losses through vomiting may also result in a hypochloremic metabolic alkalosis. Most cases, however, usually have a metabolic acidosis with depletion of total potassium stores. A balanced crystalloid electrolyte solution often supplemented with additional potassium is indicated in almost all cases. Careful monitoring of electrolyte concentrations and patient hydration and renal output is essential in the severe pancreatitis case. Colloids such as Hetastarch have been recommended in the past but recent information suggests it is associated with acute kidney injury and consequently we do not use this product. Experimental studies of pancreatitis found aggressive fluid replacement prevented progression of edematous to the more severe necrotizing pancreatitis.

When protein levels decline plasma therapy has been suggested for improving oncotic pressure, pancreatic perfusion, and replacing protease inhibitors. More recently there have been questions on the benefit of fresh frozen plasma for protease replacement and one study failed to demonstrate the benefit in patients given plasma compared with those only given crystalloids. Probably the most important use of plasma is for factor replacement associated with coagulopathies or DIC.

**Analgesics** should be considered in all patients with pancreatitis, even if there is no outward evidence of abdominal pain. For mild pain buprenorphine (0.1–0.2 mg/kg intravenously [IV], intramuscularly [IM] q 4-6 has needed) is suggested. Moderate to more severe pain morphine (0.1–0.5 mg/kg IV, subcutaneously [SC], or IM as needed) fentanyl is given as a continuous rate infusion (CRI, 2–5 µg/kg/hour) or 4–10 µg/kg SC, IM not to exceed 500 µg/dog. With severe pain we increase the dose of fentanyl (5–10 µg/kg/hour) and may add either ketamine (0.2–0.4 mg/kg/hour CRI) or lidocaine (5–30 µg/kg/min CRI). The animals should be monitored for side effects, particularly respiratory depression. Narcotics do decrease gastrointestinal motility that is in theory are a potential downside for their use. In some cases there is severe wind-up pain and alternative measures may be required to block the pain before traditional analgesics are effective. Spinal blocks and local analgesia should be considered in this case. We have treated some patients having severe abdominal pain with some success using intrathoracic or intra-abdominal placement of local anesthesia. Either bupivacaine (1-2 mg/kg) or Ropivacaine (1-2 mg/kg) can be used. Ropivacaine has less side effects (CAN and cardiovascular) is my preference. We generally use a butterfly catheter or over-the-needle-catheter placed in the 8th mid-intercostal space or peritoneal cavity near the pancreas. Following injections the dog is rolled around and placed on its back so the anesthesia will drain into the area of the vagal nerves.

**Antiemetics** usually are given routinely if the patient has nausea and vomiting to help prevent fluid loss and make the patient more comfortable and possibly enhance return to early nutrition. The ideal antiemetic for pancreatitis should work both centrally and peripherally. Metoclopramide is suggested by some for their antiemetic effects and to improve gastrointestinal tone (0.2–0.4 mg/kg four times daily [QID] PO or SC, or 0.01–0.02 mg/kg/hr CRI). Metoclopramide, a dopamine antagonist, has poor prokinetic effects and is limited as an antiemetic in that it only works centrally. The dopamine antagonists may also decrease pancreatic perfusion. Anticholinergic agents are contraindicated because of profound effects on decreasing GI motility and little if any effects in decreasing pancreatic secretion. The serotonin antagonists such as ondansetron is a broad spectrum antiemetic but may have some effects in decreasing GI motility as well. My antiemetic of choice is maropitant (Cerenia, 1 mg/kg every 24 hours given SC or IV slowly or 2 mg/kg every 24 hours given PO). It is a broad-spectrum antiemetic that works both centrally and peripherally. Recent evidence by us has shown that maropitant also blocks visceral pain – at least in a visceral pain model given at the dose 1 mg/kg. There is also evidence that maropitant also helps with nausea as well although this is a subjective concept. Maropitant is a neuropeptide-1 antagonist that blocks receptors found in the emetic center, CRTZ, and in peripheral afferent nerves. At higher doses it is effective blocking vestibular input from motion sickness.

**Antibiotics** should be considered for prophylactic therapy in the severe case or whenever there is evidence of sepsis or pancreatic infection. Infectious etiology of pancreatitis is rare in dogs but an experimental pancreatitis study in dogs suggests antibiotic therapy improves survival. Broad-spectrum antibiotics effective against aerobes and anaerobes should be given. I generally
place my severe pancreatitis cases on a second-generation cephalosporin or a combination of amoxicillin and enterofloxacin for this purpose.

**Nutritional supplementation** in severe pancreatitis cases very important. Enteral nutrition is favored over parenteral nutrition. Pancreatic rest in the form of fasting has been the traditional recommendation for any patient with pancreatitis by giving nothing per os (NPO) for several days. The belief is that feeding results in the release of pancreatic secretory stimuli that will stimulate pancreatic secretions and exacerbate the pancreatitis. Studies have shown, however, that adequate nutrition improves survival in experimental and human pancreatitis pancreatitis. We now believe that severe vomiting and/or pain associated with eating would be the only reasons to fast patients. If the patient is not expected to be eating on its own within 3 days nutritional support is indicated. Nutrition not only improves patient survival but improved gut integrity. Parenteral nutrition is expensive and fraught with complications. It appears that enteral feeding does not significantly increase pancreatic secretions and actually improves gut integrity, with clinical improvement in the patients being fed. Free choice feeding or tube feeding (nasoesophageal, esophageal, gastrostomy or jejunal feeding) should be considered in moderate to severe cases. Some prefer low fat liquid nutrition that requires use of human products (Vivonex TEN™ (powder) 3% fat 1 Kcal/ml). Others feed ClinCare™ Canine/Feline Liquid Diet (45% fat, Abbott Animal Health) through a small-diameter feeding tube. During recovery I generally feed a low-fat diet given in small frequent meal.

**Surgery** for pancreatitis is controversial and indications would include septic peritonitis, to lavage the abdomen, treatment of pancreatic abscesses, feeding tube placement, or possibly for treatment of a biliary obstruction. Surgery for pancreatitis or obstructive biliary tract disease generally has a guarded prognosis. However we have a small series of cases that underwent laparoscopic exploration, lavage and jejunostomy tube placement that did well. Most obstructive biliary complications will resolve as the pancreatic inflammation obstructing the common bile duct resolves. In some cases we will place a temporary biliary stent if there is significant cholestasis.

**Other therapy** should be considered only after careful evaluation of the individual case. Because oxidative damage is thought to be the result of cellular membrane death antioxidants may be of benefit in the acute management of cases. Studies show that perfusion of the pancreas with free radical scavengers ameliorates the severity of pancreatitis in experimental canine models. Vitamin E is a potent membrane antioxidant and S-adenosyl L-methionine (SAMe) replaces glutathione stores that may have some benefit in pancreatitis. Pancreatic enzyme supplementation has been reported to decrease the pain that accompanies chronic pancreatitis in humans by the feedback inhibition by endogenous pancreatic enzyme secretion. It is not known if enzymes are helpful in acute cases. NSAID therapy is contraindicated and there is yet no evidence that corticosteroids are indicated or beneficial for acute pancreatitis. Hypertriglyceridemia is common in the Schnauzer and contributes to secondary pancreatitis. Triglycerides >500 mg/dL present after a 12- to 18-hour fasted sample should be treated first with a low fat diet (RC Low Fat or Hills I/D Low fat). If they persist omega-3 dose (70–100 mg/kg body weight) should be added and increased as needed up to the National Research Council safe upper limit (200 mg/kg body weight). Lastly I would consider gemfibrozil (dogs, 7.5 mg/kg body weight PO q12h; cats, 10 mg/kg body weight PO q12h). Gemfibrozil does have side effects and should only be considered only when diet cannot maintain serum triglyceride <500 mg/dL.

**Complications** of pancreatitis include diabetes mellitus, septic peritonitis and pancreatic abscess formation. Diabetes is treated with insulin therapy. Septic peritonitis or pancreatic abscess formation requires surgery. In both conditions the prognosis is guarded to poor.

### Drugs commonly used in pancreatitis therapy

<table>
<thead>
<tr>
<th>Action</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic</td>
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<td>2-10 µg/kg/h</td>
<td>IV</td>
<td>CRI</td>
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<td>IV, IM</td>
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<tr>
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<tr>
<td>Analgesic</td>
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<td>CRI</td>
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<td>Antiemetic</td>
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<td>0.2-0.5 mg/kg</td>
<td>IV, IM,SQ</td>
<td>q8h</td>
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<tr>
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<td>1-2 mg/kg 0.1-0.4 mg/kg</td>
<td>IV, IM,SQ</td>
<td>CRI q24h q8h</td>
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<td>1 mg/kg</td>
<td>SQ, IV</td>
<td>q24h</td>
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Selected references
Disorders of the esophagus in the dog are relative uncommon but may be "missed" in the general workup of a case. The clinical sign most often associated with esophageal disease is regurgitation however more subtle signs may exist. The problem in determining if it is regurgitation based on the history may be difficult as regurgitation is frequently mistaken for vomiting, dysphagia or respiratory disease.

Once an esophageal disorder has been identified the evaluation of the esophagus becomes relatively straightforward using either specialized diagnostic testing, imaging techniques and or endoscopy. It is often also helpful to watch the animal eat during the physical examination as this may aid in localizing the problem. Because motility is the major function of the esophagus dynamic imaging studies using video-fluoroscopic examination may be required to make a definitive diagnosis. Key point to remember is if the diagnostic work-up of an animal suspected of having gastrointestinal disease is not readily identified one should then always go back and evaluate for the possibility of esophageal disease. Esophageal disorders can be divided into one of three major categories: 1) motility disorders, 2) obstructions and/or 3) inflammatory disorders. In our hospital population esophageal motility disorders make up a majority of the cases we see. However, inflammatory disorders may in fact be more common but often go unrecognized unless endoscopy is performed.

**Diagnostic evaluation**

Radiology is possibly the most important tool for evaluating the esophagus. Routine survey radiographs (including cervical esophagus and pharynx) may easily demonstrate esophageal abnormalities or foreign bodies. In most situations a barium contrast study using a combination of liquid followed by a barium meal is required using video-fluoroscopic examination. Esophageal manometry and pH probes are specialized studies that have given a more complete assessment of the esophagus but are often limited to institutions capable of studying esophageal disease. Endoscopy is used for the visualization and or biopsy of mucosal disorders, obstructions and for foreign body removal.

**Inflammatory esophageal disease**

Mucosal damage most often results either from mechanical trauma (foreign bodies), ingestion of caustic material or from gastroesophageal reflux. Gastroesophageal reflux disease (GERD as referred to in human medicine) is the result of esophageal mucosal having abnormal contact with refluxed gastric or duodenal fluid and or ingesta resulting in esophageal mucosal inflammation. The incidence of GERD is unknown but is thought to occur much more frequently than is clinically recognized. The diagnosis of GERD is difficult and often requires endoscopy to demonstrate esophageal ulceration located in the distal esophagus. Using pH probes and identifying distal pH drop supports reflux.

Factors responsible for damage to the esophagus include the character of the refluxed material, the competency of the esophageal clearing mechanism, the volume and frequency of the reflux, the time the refluxed material remains in the esophagus and the integrity of the esophageal mucosal barrier. Common etiologies associated with reflux esophagitis in small animals include general anesthesia, hiatal hernia disorders and persistent vomiting. Disorders of gastric motility or increased abdominal pressure may be also associated with GERDs. Gastroesophageal reflux and hiatal hernias may occur from upper airway obstructions due to increased negative intrathoracic pressure. It appears to be quite common in brachycephalic breeds presumably secondary to their respiratory disease and signs often resolve following surgical correction of their upper airway disease. Esophagitis from gastric reflux is also common in animals with laryngeal paralysis.

Signs of GERDs include salivation, licking of the lips, anorexia, and regurgitation or vomiting. The owners may also report halitosis, salivation and or anorexia. Star gazing was also a reported sign of esophageal inflammation. If the reflux extends to the larynx and laryngeal irritation the patient may have coughing or hoarse voice change. Survey radiographs and contrast studies are often inconclusive however when reflux is suspected by apply pressure over the stomach filled with contrast may induce reflux that might be demonstrated on radiographs or with fluoroscopy. Endoscopy showing distal mucosal ulceration with a large open LES is consistent with GERDs.

Rational therapy for GERD involves first treating the inciting etiology (correct brachycephalic syndrome or laryngeal paralysis). Specific therapy is then directed at increase LES pressure and protecting the mucosa from acid damage. Therapy should begin with diet by feeding small, frequent meals low in fat to maximize LES pressure and minimize gastric volume. Topical liquid sucralfate binds to ulcers protecting the mucosa and promotes esophageal healing. Reducing gastric acid production is important because the esophagus has significant lack of tolerance to acid and a proton pump inhibitor (PPI) such as omeprazole (1 mg/kg q12h) is suggested. Gastric prokinetic agents such as cisapride (compounded 0.1-0.5 mg/kg BID to TID) or erythromycin (0.1-0.5 mg/kg BID to TID) will...
increase the LES pressure and gastric motility. Cisapride is available from compounding pharmacies and is my preference. Recent information suggests that metoclopramide (Reglan™, 0.2-0.4 mg/kg TID to QID) has poor prokinetic properties and does little if anything on improving distal esophageal sphincter tone.

**Motility disorders**

Motility disorders of the esophagus can be segmental or generalized. Megaesophagus is a descriptive term referring to generalized esophageal dilation from an aperistaltic esophagus. Megaesophagus is rare in cats. In most cases the prognosis for megaeosophagus is guarded. There are many etiologies causing a megaesophagus in the dog. Congenital megaesophagus occurs in young dogs though to likely be an inherited or developmental abnormality from abnormal esophageal innervations. It is inherited in the wirehaired terrier and schnauzer and there is a high incidence in the Irish setters, German shepherds, golden retrievers, Shar peis, and Great Danes. The prognosis is conflicting but some may have spontaneous improvement but this is generally the exception in my experience. If there is no evidence of improvement by 3-4 months it is unlikely they will improve. Adult onset idiopathic megaesophagus, occurs spontaneously in dogs generally from 7 to 15 years of age with no specific sex or breed predisposition; though more frequent in larger breed dogs. The etiology is unknown and the treatment is only symptomatic. It is thought to be a defect in the afferent arm of vagal or neurons in the swallowing center located in the medulla. I recommend upright feeding and this can be accomplished using a Bailey chair (websites provide specific information). The key to the Bailey chair is keeping the dog in an upright position for 15-30 minutes following eating letting gravity deliver the food to the stomach. Dietary consistency is variable and different diets should be tried to see what is best tolerated. There is no known drug therapy that will increase esophageal contractions. One report suggests sildenafil improved outcome of congenital megaesophagus by relaxing the lower esophageal sphincter. Severe debilitation requires tube feeding. Prognosis is variable and poor with aspiration pneumonia. Esophageal aspiration using an esophageal feeding tube to aspirate the esophagus lessened aspiration. In a review of 49 cases, 73% were dead or euthanized within several months of the diagnosis. There is a very small population of dogs that seem to tolerate their megaesophagus with minimal complications. A great client resource is www.tech.groups.yahoo.com/group/megaesophagus.

Secondary megaesophagus results from etiologies that directly affect neuromuscular function (nerve, neuromuscular junction or muscle) including myasthenia gravis (MG), adrenocortical insufficiency, SLE, polymyositis, hypothyroidism, dysautonomia and immune mediated polyneuritis. Focal myasthenia gravis is associated with generalized weakness of only the esophagus. Both young as well as older dogs are reported to have focal MG and the German shepherd and golden retriever were most frequently affected. The clinical presentation and initial diagnostic findings are similar to primary idiopathic megaesophagus. The diagnosis of MG is confirmed by identifying positive ACh receptor antibodies. Approximately half of the dogs with focal myasthenia improve or eventually have remission of clinical signs. Anticholinesterase therapy with pyridostigmine bromide (Mestinon™ 0.5-1.0 mg/kg tid to bid) and or immunosuppression is the suggested. Refer to therapy at (http://medicine.ucsd.edu/vet_neuromuscular).

Hypoadrenocorticism has been reported as a cause of reversible megaesophagus in the dog. Animals may present as typical Addison’s or may be atypical only with a megaesophagus. Measurement of cortisol levels pre and post ACTH stimulation confirms the diagnosis. We frequently measure a baseline cortisol and if elevated (> 2 µg/dl) it tends to rule out the disease. Adequate glucocorticoid and or mineralocorticoid (if typical Addison’s) replacement results in rapid resolution of the esophageal disease.

Polymyositis is possible but difficult to diagnose. Systemic involvement of skeletal muscles and or elevated CK concentrations tends to support a diagnosis. If all other conditions are ruled out I will sometimes try a course of steroids if aspiration is not evident. I have been pleasantly surprised having some dogs improve. Muscular dystrophy is also sometimes associated with megaesophagus.

Dysautonomia is a disorder identified in the dog as the result of degenerative changes involving neurons of the autonomic nervous system. The signs of disease are associated with dysfunction of the autonomic nervous system. In addition to megaesophagus and regurgitation other autonomic disorders include dilated pupils, dry eyes, nictitans protrusion, dilated anal sphincter, distended urinary bladder, fecal and urinary incontinence and delayed gastric emptying. Dogs with this disorder are usually young large breed dogs from ranching or farm environment. The prognosis for most cases is very guarded.

**Esophageal strictures**

Esophageal strictures result following deep submucosal ulceration with subsequent fibrosis. In a review of 23 cases anesthesia related gastric reflux occurred in 65% while 9% of the cases were associated with foreign bodies and the remainder were due to other causes such as pill-associated, trauma, or esophageal tube placement. The association of anesthesia and gastroesophageal reflux occurs in about 10-15% of dogs having anesthesia. If stricture formation occurs it is approximately 1-2 weeks following the anesthesia episode. Animals regurgitate solid food but often are able to hold down liquids. The regurgitation is usually immediately following eating. We first reported a series cats developing esophageal strictures secondary to doxycycline tablets. Most strictures were in the cervical esophagus. Doxycycline and NSAIDs are the most common drugs to result in stricture formation in humans. Studies in our laboratory showed cats given pills on a dry swallow have delayed in passage through the esophagus but if the pill is given with 3-6 ml
of water it will pass rapidly into the stomach. It is suspected doxycycline tablets failed to pass into the stomach and then the caustic nature of the drug causes inflammation and stricture formation.

The treatment of esophageal strictures involves either feeding a liquid diet or therapy using balloon dilation. Balloons of increasing size are placed in the stricture to mechanically dilate the lumen of the esophagus. Therapy is then directed at management of reflux esophagitis (see below) and steroids to lessen re-stricture formation (triamcinolone injection in the stricture citrix). In a review of 23 cases 84% were considered to have a good outcome following a mean of 3 separate balloon dilations performed at weekly intervals.

**Esophageal foreign body**

The most common esophageal foreign bodies are bones but stones, chews, wood and toys are also common. Terrier dogs are over represented with bone foreign bodies and most obstruct at the level of the distal esophagus followed then at the base of the heart and least common at the thoracic inlet. Signs of acute regurgitation should make an esophageal foreign body high on the differential list. Following diagnosis, routine and or contrast radiographs, prompt removal is required. The longer the foreign body remains in the esophagus the greater the mucosal damage with secondary complications such as strictures or perforation. Attempts should first be directed at conservative removal by either passing a gastric tube to dislodge the foreign body, a Foley™ catheter-assisted removal or esophagoscopy. We will use either a rigid or flexible fiberoptic endoscope to remove most foreign bodies. The disadvantage of flexible GI endoscopic removal is the small size of the foreign body grasping instruments. Removal of large foreign bodies such as bones often require a heavier rigid pronged grasping forceps (Storz Veterinary Endoscopy™). These can be adjacent to the flexible endoscope or through a rigid hollow esophageal scope. The advantage of using a rigid hollow endoscope is that it will both mechanically dilate the esophagus and allows one to pass large grasping forceps through the center of endoscope tube to retrieve the foreign body. The foreign body once grasped can be pulled into the scope for easy removal. One can also make their own esophageal scope by purchasing plastic (PVC) plumbing pipe of various sizes and lengths. A strong light is then used to illuminate the esophagus through the tube. Pronged grasping forceps can also be purchased from most hardware or auto stores. These are used for picking up small objects in difficult to reach areas and these will work for grabbing bones and other foreign bodies. When large distal esophageal bones can’t be retrieved orally, one should attempt to push them into the stomach where there will be eventually digested. Single barbed fish hooks attached to a line are easily removed by simply stringing the line through a rigid esophageal scope. The scope is then advanced through the line to the hook next the hook is pushed out of the esophageal wall with the end of the scope and then the line is tugged gently to pull the hook into the scope and then everything is removed – "hook, line and sinker".

**Selected references**

Vomiting is the most common gastrointestinal sign reported in cats. The sign however extends beyond problems associated only with the gastrointestinal system but includes a variety of disorders of many body systems. One should remember that vomiting is only a clinical sign and not a specific disease. Investigation of the vomiting cat should include a complete evaluation to determine the etiology and if identified the appropriate therapy is initiated. Of most importance for chronic vomiting in cats includes primary gastrointestinal disease, pancreatitis, and liver disease. Frequently the combination of all three systems is referred to as feline triaditis.

Pathophysiology
The primary reason for vomiting is to protect the animal from ingested noxious substances removing them before they become absorbed. The vomiting act is the result of a complex reflex pattern of responses that is centrally coordinated. The reflex act is initiated in the brain stem and referred to conceptually to a specific area of activation through multiple nuclei referred to as the vomiting or emetic center. Activation of the vomiting center results from either humoral or neural stimuli. Pathways to the vomiting center arise from receptors found throughout the body (including GI, pancreas, liver), from vestibular system, from higher CNS centers and through specialized chemoreceptors in the area postrema that are sensitive to blood-borne substances (chemoreceptor trigger zone [CRTZ]).

Antiemetics in cats
 Certain drugs or chemicals provoke vomiting through action on the chemoreceptor trigger zone (CRTZ) located on the floor of the fourth ventricle but outside the blood brain barrier that makes it responsive to substances in the circulation as well as in the cerebral spinal fluid. Apomorphine is a dopamine receptor agonist and is a potent emetic of the CRTZ in the dog but not in the cat suggesting cats lack dopamine receptors. Consequently metoclopramide, a dopamine receptor antagonist, may not be useful as an antiemetic in cats as it is in dogs. The emetic agent used in cats is xylazine.

Vestibular receptors in the labyrinth, upon stimulation, reach the vomiting center by way of the vestibulochochlear (VIII) cranial nerve. Motion sickness, inflammation of the semicircular canals or lesions in the cerebellum result in vomiting via this pathway. Idiopathic feline vestibular syndrome is also associated with vomiting through this pathway. Antihistamines (H1 histaminergic antagonists) are reported to be poorly effective in blocking stimuli from vestibular receptor input.

A newer NK1 antagonist maropitant (Cerenia™) has been approved for cats and is very effective as an antiemetic blocking receptors found in emetic center, CRTZ and vagal afferents. Published study in cats found it to be very effective at 1 mg/kg SQ or IV or 2 mg/kg PO q 24 hours. Research we have performed using a visceral pain model found maropitant to block visceral pain similar to that of some narcotic agents. It can be given safely IV and can be given longer than 5 days. Published study showed no side effects in cats treated for 4 weeks. At CSU we found cats having chronic kidney disease was successful in management of anorexia, nausea, and vomiting in cats compared to placebo. Maropitant is metabolized in the liver and with significant liver disease a lower dose should be used (suggesting 0.5 mg/kg).

The 5HT3 antagonists such as ondansetron or dolasetron, works on 5HT3 receptors found in the emetic center, CRTZs and peripheral vagal afferents. It is not approved for use in cats and has poor bioavailability given orally and parenterally. Another drug that is a 5HT3 antagonist is a tetracyclic antidepressant Mirtazapine (Remaron™). It also is an excellent appetite stimulate in cats. It is dosed at 1.4-1.8 mg/cat daily. Cats with chronic kidney disease or liver disease are generally dosed q 48h.

Differentials for vomiting
Non-GI causes of vomiting
The vomiting patient should be approached in a logical manner. Careful evaluation is essential to exclude all potential non-gastric causes of vomiting. Virtually all types of abdominal disorders are capable of eliciting vomiting by activation of local receptors. Enteric, colonic disorders, peritonitis, pancreatitis, liver disease, and urogenital disease are but a few non-gastric causes. A number of systemic or metabolic disorders are also responsible for vomiting. Included are ketoacidosis, hepatic encephalopathy, uremia, systemic infections and hyperthyroidism. Oral and pharyngeal disorders may cause vomiting and thus a complete oral examination should be performed in all cats.

GI causes of vomiting
One of the more common causes of chronic vomiting includes inflammatory bowel disease (IBD), chronic pancreatitis and chronic cholangitis. The syndrome associated with all three organs is often referred to as feline triaditis. In one report of IBD vomiting was the most common clinical sign of that condition then followed by anorexia and finally diarrhea. This may be because IBD almost always involves the duodenum in cats rich in vomiting receptors. Most cats respond well to diet and prednisolone therapy. Another
syndrome identified in cats associated with chronic vomiting is chronic pancreatitis. The incidence of chronic pancreatitis is high in older cats based on necropsy findings. However, many cats are likely subclinical. The diagnosis is problematic. Ultrasound may detect pancreatic changes that would support the diagnosis. The best test for pancreatitis is a feline PLI (spec fPL, IDEXX) is reported to be quite sensitive and fairly specific. Recently lipase determined by DDRG analysis is considered to be comparable to the PLI analysis (feline Precision PL, Antech™). If the PLI is abnormal then pancreatitis must be in the differential, if normal it is unlikely that pancreatitis is present. Cats having chronic pancreatitis are traditionally treated with steroids. However, in light of a recent study performed by the author found bacteria may actually play a role in the more moderate to severe cases having pancreatitis. I currently treat cats with chronic pancreatitis initially with antibiotics and antioxidants. Liver disease specifically cholangitis or cholecystitis is often associated with vomiting. Liver enzymes and or ultrasound may be abnormal. Bacteria or immune mechanisms are likely causes of neutrophilic cholangitis. The triad of organ inflammation involving the liver, pancreas and intestine is referred to astiaditis. Since the common bile duct and pancreatic ducts join a common channel before they enter the duodenum extension of inflammation and luminal contents in both directions is common however GI translocation of bacteria is also likely. Chronic fibrosing pancreatitis with ductal inflammation and nodular hyperplasia is reported commonly associated with inflammatory biliary tract disease in the cat. We have also identified that some of these cats to also have lymphocytic-plasmacytic infiltrates within the duodenum (IBD) as well. During surgical exploratory or laparoscopy the pancreatic and hepatic portion of the disease is diagnosed. One should always examine all three organs if surgery is performed to evaluate for the possibility of the triaditis syndrome. A course of antibiotic therapy is generally administered with the possibility a bacterial component causing pancreatitis or cholangitis or small intestinal bacterial overgrowth. E coli is the most common organism cultured followed by enterococcus. Since high concentrations of hydrophobic bile acids are toxic to hepatocytes and biliary and intestinal epithelium reducing there concentration seems reasonable. Ursodeoxycholic acid is a hydrophilic bile acid when administered changes the bile acid milieu to favor the less toxic hydrophilic bile acid. Ursodeoxycholic acid (ursodiol) dosed at 10-15 mg/kg/day. This drug will increase bile flow, change bile acid concentrations to less toxic concentrations, reduce inflammation and fibrosis and improve liver enzymes. In general the prognosis for feline triaditis is good following therapy however some cats will require prolonged treatment with periodic exacerbation of the disease. A failure to improve with antibiotic therapy then I will consider steroids. It is likely the steroids may be benefiting the IBD portion of the triad and likely less so for the liver and pancreas.

Both acute and chronic gastritis (or gastroenteritis) can be a cause of vomiting. With damage to the gastric wall there is a disruption in the normal gastric mucosal barrier and a resultant back diffusion of hydrochloric acid into the mucosal wall. Following damage to the gastric mucosa local receptors are stimulated which subsequently initiate vomiting. Primary motility disorders result in gastric retention with distention and becomes a factor in stimulating vomiting. These patients often respond to therapy using promotility drugs. Other gastric causes of vomiting include infiltrative, inflammatory or neoplastic disease or lesions that obstruct gastric emptying such as gastric intraluminal foreign bodies. Only following careful physical examination and appropriate laboratory testing to rule out non-gastric causes of vomiting should the cat be evaluated for gastric disease. Chronic vomiting from gastrointestinal disorders is common and when presented with the cat suspected of having gastric disease one should first attempt to categorize the patient as to the severity of the disease. Cats vomiting from gastric disease with mild signs and no debilitation are first treated using dietary manipulation using food trials and therapy for gastrointestinal parasites. Animals with significant gastric disease and debilitation or those that fail to respond to symptomatic therapy will require an in-depth gastrointestinal evaluation.

**Diagnostic work up**
The cat with chronic vomiting should have a complete diagnostic work up including a CBC, complete biochemistry, urinalysis, fecal examination, total T4, and if indicated FeLV, FIV and heartworm testing. This will rule out major systemic conditions prior to the directed work up. I then classify my patients to either ones having mild disease and minimal debilitation or those that have significant disease requiring an aggressive and in-depth work up. For those classified as having mild disease therapeutic trial therapy is indicated including anthelminthic therapy and dietary food trials.

Adverse food reactions are common in the cat and consists of either: 1) food allergies, 2) food intolerances or 3) food consistency or bulk effect of the diet. Intolerances refer to direct reactions to a specific substance in the diet such as a food preservative, food additive or dye as examples while an allergy is a specific immune mediated reaction to a specific protein antigen. Both can result in variable inflammatory gastric mucosal changes and vomiting. Dietary food intolerances are probably the more common in the cat. Generally, most are healthy and have only intermittent vomiting, primarily food, shortly following eating. Removal of the agent often results in prompt improvement. Food allergies are the result of a reaction to a specific protein antigen, usually the major antigen in the diet. Adverse reactions to food may require several weeks of therapy before resolution of signs occur. One study in cats with gastrointestinal disease (vomiting and or diarrhea) using dietary trials found approximately 50% improved with dietary manipulation, most within 4 days after the new diet. Clues to food intolerances might be an eosinophilia, concurrent diarrhea and possibly weight loss.

There is no ideal diet to use. Novel protein, GI, hydrolyzed or home-made diets could be used. Animals suspected of having food allergies or intolerances should be placed on a hypoallergenic diet for at least a two-week trial. My dietary trial of choice is a
hydrolyzed diet. Alternatively, I will prescribe a single protein diet such as turkey or chicken. The home diet will not be a permanent but rather it is fed for a short period (usually 1-2 weeks). If the patient is dietary responsive that confirms the diagnosis of a dietary food intolerance. Next one must then try multiple diets to identify one that would work for long-term management such as a balanced home diet, specialized diet, novel antigen containing diet, or a different commercial diet that works for the individual patient.

Dietary consistency may also be a factor responsible for vomiting and regurgitation in cats. We have observed cats vomit or regurgitate when fed a large volume of dry food but find signs resolve when feed small volumes of canned meat based diet. In these cats vomiting and regurgitation occurs shortly after eating, consists of undigested food and often presented in tubular formation suggesting esophageal involvement. It is speculated that marked gastric distention may be responsible for these signs. Experimental gastric distention in the cat caused reduced esophageal motility, esophageal dilation and reflux of gastric material into the esophagus. Cats with this suspected problem often have the tendency to be gluttonous in nature. Simply increasing the frequency of feeding, giving a smaller volume and perhaps in a semi-liquid consistency usually resolves the signs.

Parasites must always be considered when dealing with chronic vomiting in cats having minimal debilitation. Giardia and ascarids are usually diagnosed using proper fecal examination techniques and are a cause of vomiting. Ollulanus tricuspis, a feline gastric parasite, may be more common than previously thought and is a cause of chronic vomiting and unthriftiness in cats. Intermittent vomiting of mucus, bile or food is described. Multiple cats in a household may be affected. The parasite has a direct life cycle with oral-oral transmission consequently eggs are not passed into the feces or observed in the fecal examination. The diagnosis of Ollulanus tricuspis is made by examining the vomitus using the microscope on low power looking for a "heartworm microfilaria like" nematode parasites that is approximately 0.75 mm in length. Gastric fluid samples can be obtained through either endoscopy or by inducing vomiting to collection gastric fluid by administering the emetic xylazine (0.44 mg/kg IM). The parasite appears to be eliminated with pyrantel pamoate or febendazole (50 mg/kg/day for 3 to 5 days). Ollulanus tricuspis is reported to be associated with variable chronic inflammatory mucosal infiltrates. When the cause of vomiting is unknown and since gastric parasites are a possible etiology, anthelmintic therapy should be considered. I usually prescribe febendazole (50 mg/kg daily for 3 days) as my broad-spectrum anthelmintic therapy in both dogs and cats. We often use the liquid formulation for cats.

Advanced diagnostic investigation

In depth gastric evaluation should be considered in the vomiting animal suspected to have significant or severe gastric disease or in the patient that has failed to respond to adequate dietary and anthelmintic therapy. Persistent vomiting, hematemesis, weight loss and debilitation signify further diagnostic evaluation. Investigation of the stomach and intestine involves radiology, ultrasound, endoscopy and/or surgery. Radiology should be performed when a gastric lesion, foreign body or outflow obstruction is suspected. Ultrasound is preferred to evaluate GI mucosal disease and approximately half the cats in one study having IBD had ultrasound changes. Without ultrasound one can evaluate the stomach radiographically by performing a double contrast gastrogram. The technique involves sedating the cat with ketamine (1 mg/kg IV) and administering barium sulfate suspension (1-2 ml/kg) via stomach tube and then rolling the patient to coat the mucosa and then replace the stomach tube and distending the gastric lumen with air. This technique gives good mucosal delineation and identifies intraluminal foreign bodies or lesions.

Endoscopy offers the best means of examining the gastric mucosal surface and lumen and to obtain a gastric mucosal biopsy. When evaluating the vomiting cat I always obtain duodenal biopsies to rule out inflammatory bowel disease, collect gastric fluid for detection of Ollulanus, gastric mucosal brush cytology for Helicobacter organisms and obtain a gastric mucosal biopsy sample to culture for Helicobacter urea production (see below). If endoscopy is not possible then surgical exploratory and full thickness biopsy may be indicated. One should evaluate the entire abdomen taking careful note of the liver, pancreas and bowel. Full thickness biopsy of the duodenum, jejunum and ileum in addition to the stomach is indicated in patients with gastrointestinal signs.

Helicobacter

Helicobacter has been implicated as a cause of chronic gastritis in cats and dogs. It is a spiral shaped gram-negative urease producing bacteria that appears to be resistant to the effects of low gastric pH. Helicobacter was first identified in man (Helicobacter pylori) and subsequently identified in cats and named Helicobacter felis. A similar larger spiral gastric organism Gastrospirillum, has been noted for years in the stomach of dogs and cats and now using molecular identification is found to be similar to Helicobacter felis and has been given the name Helicobacter heilmannii. Cats clinical for Helicobacter are usually older (>6yrs) and have chronic vomiting as part of their history. They tend to vomit gastric fluid and occasionally food. Weight loss, unthriftiness and rarely diarrhea have been noted. I have only seen one cat having hematemesis and a gastric ulcer with helicobacter. Failure to respond to symptomatic therapy would warrant a helicobacter work up. Helicobacter is found as a normal inhabitant in 70% of cats causing no evidence of disease. There are however a few cases with gastric signs and high concentrations of the organisms associated with lymphocytic gastritis (lymphoid aggregates and gastric lymphoid elements). The clinical diagnosis is based on identification of the organism on gastric biopsy a silver or modified Giesma stain. A provisional diagnosis involves either gastric mucosal brush cytology showing many
small spiral organisms in the mucus or demonstrating presence of the organism in a gastric biopsy by incubating a small biopsy sample in a urea broth containing a pH indicator that demonstrates bacterial urease production by means of a color change.

Specific antibiotic therapy appears to eradicate the organism and resolve clinical signs in affected patients. Studies treating cats report a two-week course of "triple" therapy using amoxicillin, metronidazole and omeprazole have been suggested. The use of several antibiotics is indicated because it is difficult to get adequate concentrations of a single antibiotic in the lumen, gastric mucous and gastric epithelium. Recent studies suggest that acid blocking may not be required because ulceration is uncommon and preliminary studies using amoxicillin and clarithromycin (7.5 mg/kg bid) for two weeks appears also to be effective as. The amoxicillin-clarithromycin combination is the treatment I now use in cats. It may be reasonable to perform a trial helicobacter therapy before beginning an in-depth work up.

Other causes
Vomiting can result from obstructive lesions in the upper GI tract, neoplasia (lymphoma) or from motility disorders. These are very uncommon findings in the cat. One common clinical syndrome with associated vomiting is hairballs. I believe hairballs are a common clinical condition associated with the physiological consequence of different motility patterns in cats. To understand this phenomenon one must understand normal motility of the upper GI tract. The proximal stomach consists of the fundus and upper body and serves as a reservoir for the storage of food and controls the emptying of liquids. The distal half of the stomach including a portion of the body, the antrum and the pylorus functions as a gastric grinder breaking down solid food into particles of 2 mm in size or less. Lastly emptying of indigestible solids that remain in the stomach occurs during the fasted state by strong peristaltic activity that begins in the stomach and migrates through the small intestine. These contractions are called the migrating motor complex (MMC) or interdigestive housekeeper contractions and function to clear the digestive tract of mucus, bacteria and non-digestible substances. These cycles occur approximately every two hours in the fasted state. These electrical cycles correspond with increased motilin concentrations and appear to be responsible for this motility. As will be pointed out later the drug erythromycin has similar motilin-like effects on the gastrointestinal tract and the MMCs. MMCs do not appear to occur in the stomach of cats that may explain problems in removing non-digestible substances (i.e. hair) from the stomach. Vomiting of hair is suspected to be a normal physiological process but may also occur with other diseases as well. Hairballs are managed with frequent grooming, hairball diets (soluble fibers) and petrolatum laxatives.

Selected references
Chronic diarrhea is a common complaint, and the potential etiologies are extensive. Parasites, dietary intolerances, metabolic disease, pancreatic disease, bacterial causes, and inflammatory bowel disease are but a few etiologies of chronic diarrhea. Inflammatory bowel disease (IBD) is a common condition diagnosed in dogs and cats; however, it is not a specific disease but rather a term that describes animals having gastrointestinal (GI) signs with histologic evidence of inflammation within the intestine. IBD does not however describe the etiology, nor does the extent of inflammatory cells parallel the severity of clinical signs. Before beginning extensive diagnostics or obtaining an intestinal biopsy specimen from a patient with chronic diarrhea, there are a few diagnostic tests or trial therapies to consider. Obviously the course of action is predicated in part on a good clinical evaluation and based on the severity of the clinical disease.

Every patient with chronic GI signs should have a thorough history, physical examination, complete blood count, biochemical profile, urinalysis, and fecal examination. In many cases, this initial evaluation will determine if the etiology of the diarrhea is primary GI disease or secondary to other systemic or metabolic disease or if the diarrhea is predominately of small bowel or large bowel origin. For example, Addison’s disease, liver disease, and renal disease can all be associated with secondary GI involvement. If the initial workup fails to provide a clue as to the etiology, then begin a specific GI evaluation. The fecal examination should include standard fecal flotation, wet mount preparation, and stained cytology. A stained Diff-Quick cytology may reveal such things as neutrophils, eosinophils, fungal organisms, or clostridial spores and may provide clues about the etiology. This is also the time to classify the patient based on the severity of disease: minimal signs and debilitation or those cases having severe disease obviously requiring an in-depth GI workup. For the animal with relatively mild diarrhea without weight loss or debilitation, I prefer to use trial therapy as part of the clinical evaluation. Trial therapy involves antiparasitic therapy, dietary food trials, and antibiotic therapy. If these trial therapies fail to resolve the diarrhea, further GI evaluation is indicated. Additional diagnostic testing may include imaging studies (ultrasonography is preferred as barium studies are rarely helpful), serology trypsin-like immunoreactivity, folate, cobalamin), and endoscopy or surgery for intestinal biopsies.

Always rule out parasites
Parasites must always be considered in any dog experiencing chronic GI signs.1 Giardia and common nematodes are usually diagnosed using proper fecal examination techniques. Often it is difficult to find Giardia cysts on flotation, hence a more accurate way to diagnose Giardia is through fecal ELISA, which is highly sensitive and specific. It is important to know that Giardia also have antimicrobial sensitivity patterns like bacteria. Therefore, it is currently impossible to predict which anti-Giardia drug will be effective in an individual dog or cat. The treatment of choice for years has been metronidazole. Currently, metronidazole at a dose of 25 mg/kg orally twice daily for seven days is preferred; however, there are many different doses and durations of therapy reported (Table). Neurologic signs associated with toxicity occur at higher doses.

Other suggested Giardia therapies include febendazole or febantel for five days.1 High-fiber diets may help lessen re-infection when given during the therapy. With treatment failure, one should make sure that Giardia is truly the problem and also that subsequent recontamination is not occurring. Infection with Giardia does not confer immunity. In resistant cases, combined febendazole and metronidazole therapy has been suggested. In difficult cases, bathing the animal before therapy and decontaminating the environment using quaternary ammonium compounds is also recommended. It is controversial whether to treat healthy dogs and cats that test positive for Giardia because Giardia is generally not considered a significant human health risk. I recommend treating the asymptomatic, positive dog and if on recheck evaluation the patient is still positive but subclinical, I will repeat therapy using a different agent. If the animal remains positive after two therapies, I simply recheck the patient again at the next yearly health evaluation. Some animals are chronic asymptomatic carriers and are very difficult to clear. It is a more significant concern when infected dogs live with immunocompromised individuals or young children.

Young cats with diarrhea
The organism Tritrichomonas foetus (TTF) has been identified as a cause of chronic diarrhea in young cats.2 This organism appears to be genetically similar to that associated with bovine venereal disease. Most of the affected cats are under 1 year of age and are

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357
reported to have a watery to sometimes mucoid diarrhea. It is most often observed in cats from humane shelters or catteries, and Abyssinians and Bengal cats appear to be over-represented or to have a more resistant disease. There are several ways to diagnose TTF. In some cases, a diagnosis can be made by performing a wet mount fecal prep and identifying the organism. A small amount of stool is thinned with warm saline solution, a coverslip applied, and the feces examined at 40X. It is important that the stool is fresh for examination. A colonic flush of saline can also be used to obtain fecal material for cytology and culture. TTF is identified by its progressive forward motion. (In contrast, Giardia has a falling leaf motion.) Feces can also be cultured in your practice using the bovine TTF culture technique employing an In Pouch TF™ culture method (Biomed Diagnostic Labs) (Figure 3). With these pouches, a very small amount of stool is placed in the broth and cultured at room temperature. The bag is then examined under a microscope 24 to 72 hours later for evidence of motile organisms. Fecal PCR for TTF is offered by many commercial labs and is considered the test of choice for confirming the infection. Ronidazole is the only antimicrobial shown to have efficacy in treating TTF infection. Ronidazole is given at 30 mg/kg q24h PO for up to 14 days. Ronidazole has a very narrow therapeutic range; higher doses or a longer duration can result in neurotoxicity. Ronidazole is not approved for use in the United States and must be obtained through a reliable compounding pharmacy. It is very bitter and therefore should be given via capsule; liquid solutions are not recommended. Treatment failure can occur, and a fecal PCR should be performed if a cat fails to respond to therapy because a negative PCR result means TTF is a less likely cause of the diarrhea. When left untreated many cats eventually become normal, especially young cats under 1 year of age. In one study, 88% of cats with TTF infection were reported to undergo spontaneous resolution of diarrhea within two years of a diagnosis; however, most remained infected based on PCR results when retested as long as two to five years after the initial diagnosis. The role of these asymptomatic carriers in disease transmission remains unclear.

**When the diet works**

Over the years, I have become more and more impressed to see GI signs resolve simply by changing a patient’s diet. It is my impression, which is supported by a number of clinical studies, that possibly 30% to 50% of dogs and cats with nonspecific GI disease may respond to diet alone. A positive response to a diet trial is referred to as a food-responsive diarrhea (FRD). FRD’s include both true dietary allergies and dietary intolerances. Allergies result from a reaction with a protein antigen, whereas intolerances occur in response to some substance in the diet, such as a preservative or food coloring. Dietary trials using a test diet generally require two weeks or less to appreciate a response; the GI signs seem to respond much faster than dermatologic signs, which may take eight weeks or more to improve. There is no ideal diet that will consistently resolve diarrhea. My personal favorite is the use of a hydrolyzed diet, such as Purina HA®. Hydrolyzed diets are single-protein sources (usually soy-, rice-, or potato-based) and have undergone digestion, producing low-molecular-weight protein derivatives that are thought to be highly digestible with low antigenic potential. Their benefit might actually be because they are pure and contain little else that might contribute to a dietary intolerance. These diets have now become the ideal initial trial diet. If a positive response is observed, then the patient’s GI signs can be controlled with a diet. The patient can either continue on the test diet or you can attempt to find another long-term diet that works well for both the client and patient. Some clinicians recommend if there is a diet response that the patient to be fed that diet exclusively for at least three months, at which time the diet can be changed or even the original diet reintroduced. Only a small percentage of dogs with GI signs (∼8%) relapse on challenge and are thus truly food allergic. Feeding novel-protein diets with a single protein antigen would be an alternative approach. If using the novel antigen diets, one should prescribe only veterinary diets because many over-the-counter novel-protein diets are not all that novel and have not been shown to contain many other antigens not listed on the label. Highly digestible gastrointestinal diets such as Purina EN® may improve assimilation, promote gastrointestinal health, and modify the microbiota. Diets containing highly fermentable fibers such as those containing fructooligosaccharides (also referred to as prebiotics diets) are often useful for colonic disease because fermentation products are shown to benefit mucosal function and modify enteric microbiota, promoting “good” bacteria and inhibiting certain pathogenic bacteria. If a diet trial is unsuccessful, with no improvement in clinical signs after 10 to 14 days, the next step is to institute an antibiotic trial.

**GI drugs and bugs**

There are many dogs with chronic large or small bowel disease that have an antibiotic-responsive diarrhea (ARD). An old term for ARD is *small intestinal bacterial overgrowth (SIBO)*. However, SIBO is a poorly defined syndrome in dogs, and we currently have no way to adequately and convincingly diagnose bacterial overgrowth or to know in which cases antibiotics would be beneficial short of a therapeutic trial. More recently the term *gastrointestinal dysbiosis* has been given to conditions associated with an abnormal GI bacterial ecosystem. In simple terms, GI dysbiosis refers to an imbalance in GI bacteria with the loss of the “good bacteria” coupled with an increase in the so-called “bad bacteria.” For chronic diarrhea cases that do respond to antibiotic therapy, it is likely the antibiotics are not eliminating a specific pathogen but rather changing the overall bacterial ecosystem, promoting a more normal bacterial makeup. Some cats and dogs with gastrointestinal dysbiosis have decreased serum cobalamin (vitamin B₁₂) concentrations. The cobalamin deficiency can be due to lack of intrinsic factor production, abnormal increased intestinal bacterial utilization, or ileal disease causing inadequate cobalamin absorption. Serum folate concentrations are usually variable in cases having dysbiosis.

358
Metronidazole is frequently used in GI cases but long-term administration and potential side effects make it less desirable than other options. Metronidazole has been shown to cause DNA damage to feline lymphocytes in vitro. There is also evidence in laboratory animals that it has some carcinogenic potential. A suggested GI dosage for metronidazole in cats and dogs is 7.5 to 10 mg/kg given orally twice daily. A commonly used alternative, and my first choice, is tylosin. Tylosin was first reported to be useful for chronic diarrhea in the early 1970s and there has been a recent resurgence in interest and use of the antibiotic. Tylosin is a macroclide, bacteriostatic antibiotic that is currently marketed over the counter for the treatment of respiratory disease in chickens. Tylosin has activity against most gram-positive and gram-negative cocci, gram-positive rods, and Mycoplasma; however, the gram-negative bacteria Escherichia coli and Salmonella species are intrinsically tylosin-resistant. Tylosin works by transiently changing the GI enteric bacterial population, probably by promoting the growth of beneficial commensal bacteria while suppressing deleterious bacteria. Once tylosin is discontinued, the original bacterial population often returns to its pretreatment state. There is also a suggestion that tylosin may have anti-inflammatory properties. Tylosin appears to have almost no systemic or toxic side effects. The initial dose recommendation for tylosin in both dogs and cats is 15 mg/kg orally, twice a day, mixed with the food (has a bitter taste) or given via gelatin capsule. (Note: it comes as a powder and a #3 gelatin capsule holds 130 mg, a #1 capsule holds 240 mg, a #0 capsule holds 345 mg, and a #00 capsules hold 430 mg.) For cases that respond, the long-term dose can be reduced to as low as 5 mg/kg/day. Tylosin is effective for most Clostridium perfringes and is considered by many to be the treatment of choice for suspected clostridial diarrhea.

**Probiotics**

To date, there have been very few controlled clinical studies evaluating probiotic success. However, a large double-blinded placebo control study of shelter dogs and cats developing diarrhea found significantly fewer cats that received Enterococcus faecium (FortiFlora®; 2.1 x 10^11 cfu/day) developed diarrhea for greater than a two-day duration. Probiotics exert their effects as long as they are being given but once stopped the GI flora generally returns to the pretreatment state. It may seem counterintuitive to give antibiotics with probiotics, but clinical improvement is often seen when they are given in combination. Probiotics are considered a safe adjunctive therapy and are commonly used for both acute and chronic diarrhea in dogs and cats as well as for the prevention of stress-induced diarrhea. Recommendations for the ideal probiotic, containing an adequate type and number of viable organisms for specific GI disorders, become difficult to make. Some over-the-counter preparations have been found not to contain the label claims. My recommendation is to use a product produced by a reputable veterinary company that has done research on their product.

**German shepherds with chronic diarrhea**

A clinical syndrome frequently encountered in German shepherd dogs is chronic GI signs and weight loss. Exocrine pancreatic insufficiency is common in the breed, requiring pancreatic enzyme supplementation, and it must first be ruled out. The diagnosis is made by documenting a subnormal trypsin-like immunoreactivity (TLI) concentration followed by improvement with pancreatic enzyme replacement. A second group of German shepherd dogs with similar clinical signs have normal TLI concentrations. Many of these dogs turn out to have an antibiotic-responsive diarrhea due to GI dysbiosis. Testing should include measurement of folate and cobalamin (serum B12) concentrations. Low cobalamin and high folate levels are characteristic of both exocrine pancreatic insufficiency and GI dysbiosis. Dogs with subnormal cobalamin concentrations will require parenteral supplementation (initially, about 500 µg subcutaneously weekly) as part of the therapy. The cause of the GI dysbiosis in German shepherds is unknown. Researchers have investigated IgA concentrations, suggesting the possibility of an inherent deficiency leading to altered GI immunity. More recently researchers have measured toll-like receptors (TLR) in the GI tract of these dogs with a documented abnormal expression of the receptors. Using candidate gene analysis, polymorphisms in TLR4 and TLR5 were recently shown to be significantly associated with IBD in German shepherds. Furthermore, the same polymorphisms in TLR5 were also associated with IBD in a heterogeneous population of dogs consisting of 38 different breeds. These mutations could well play an important role in the pathogenesis of IBD in dogs, as a mutated receptor will lead to misrepresentation of commensal bacteria as pathogens, therefore signaling “danger” to the host and initiating the characteristic inflammatory response seen in this disease. Management of affected German shepherds involves diet, antibiotics, and cobalamin supplementation. Prebiotics and probiotics are also often given as additional adjunctive therapy. This condition tends to require life-long management.

**When is it inflammatory bowel disease?**

A diagnosis of IBD requires a complete laboratory evaluation to rule out other diseases. A complete blood count, biochemical profile, urinalysis, fecal cytology, and parasite evaluation are required in all cases. An eosinophilia or hypoproteinemia may provide clues to IBD. Abdominal radiographs or ultrasonography may be helpful. However, ultrasound images showing increased wall thickness are neither specific nor sensitive for the diagnosis of IBD. Specific testing may include measurement of serum folate and cobalamin concentrations. Cobalamin deficiency is a common complication of feline GI disorders, and complete improvement in GI function is not possible until cobalamin deficiency is corrected.
An overall impression is that most cases of IBD can be managed; however, unless the underlying etiology can be identified and removed, it can become a long-term proposition. A retrospective study demonstrated that only 26% of canine IBD cases progressed to complete remission, with intermittent clinical signs remaining in about half of the cases, 4% being completely uncontrolled, and 13% resulting in euthanasia because of poor response to treatment. Another study found 18% of the dogs were euthanized because of their disease. Poor prognostic indicators are hypoalbuminemia and hypocobalaminemia.

**Treatment of IBD**

Patients that do not respond to a diet or an antibiotic trial are usually administered glucocorticoids. It is estimated that about 30% of the dogs that fail to respond to a change of diet and antibiotics will respond to corticosteroids. Generally oral prednisolone is given to dogs and cats once daily at a starting dose of 1 to 2 mg/kg, and then the dose is tapered over an eight-week period. However, the side effects of glucocorticoids can be marked, and I try never to exceed a total of 40 mg per day in large-breed dogs. Budesonide is a novel glucocorticoid that is reported to have high first-pass hepatic metabolism and exerts a “local effect” on the intestine with minimal systemic effects. An enteric-coated formulation is used for people with IBD but a non-enteric coated formulation made by a compounding pharmacy should be used. Despite apparent efficacy of budesonide in dogs and cats, the systemic steroid effects are present and consequently, its use may have no benefit over traditional corticosteroid therapy in most cases. The recommended dose is 1 mg once daily in cats and toy breeds and up to 2 mg once daily for large-breed dogs.

If there is poor response to glucocorticoids in dogs after the first three to four weeks or if the side effects are severe, then I recommend oral cyclosporine at 5 to 10 mg/kg once daily for at least two months. Many dogs with IBD that are steroid refractive are reported to respond to cyclosporine. In cats, the use of chlorambucil (2 to 6 mg/m², q24h, PO, or 2 mg/cat three times a week) with prednisolone is preferable, if there is inadequate response to glucocorticoid treatment alone. If chlorambucil is used, hematologic parameters should be monitored regularly. Cyclosporine blood concentrations do not need to be monitored regularly, unless side effects induced by the cyclosporine treatment are suspected or an inadequate response to treatment is observed. If measuring cyclosporine serum concentrations, it is recommended to take blood samples one to two hours after giving the medication to ensure that peak concentrations are measured. If the cyclosporine serum concentration is above 700 ng/ml at peak level, then halving the dosage for the first two weeks can reduce the side effects. If the patient responds to cyclosporine, then the medication can either be tapered slowly or stopped after 10 weeks. Sulfasalazine (20 to 50 mg/kg orally three times daily for three to six weeks) and related drugs are often used in dogs when IBD is limited to the large intestine. However, side effects include keratoconjunctivitis sicca, so tear production should be monitored regularly when using these drugs. I rarely prescribe sulfasalazine for large bowel disease because, in my experience, most patients get better with diet and antibiotics. Other novel or adjunctive therapies could include omega 3 fatty acids for anti-inflammatory effects and various antioxidants. Probiotics have also been suggested to be beneficial for treating IBD due to the multiple mechanisms described above.

References upon request
Laboratory testing
A sick cat may become icteric (jaundice) without having primary liver disease. This is because of the complexities of bilirubin metabolism combined with cat’s weak ability to conjugate compounds. Normal hepatic bilirubin metabolism must go through several steps in the hepatocyte before excretion into the bile. This metabolism can be affected by inflammatory cytokines or endotoxins and from nutritional alterations due to mobilization of free fatty acids delivered to the liver or from protein deficiencies resulting from catabolic conditions. Cats also have inherent low concentrations of glucuronyl transferase, an enzyme required to convert bilirubin to water-soluble form prior to hepatic excretion. It is this complex pathway that can result in icterus without evidence of significant structural liver disease. We recently reviewed 180 cats having elevated bilirubin concentrations and cases were grouped them into those clinically icteric (bilirubin > 3.0 mg/dl) or those with biochemical icterus (having only icteric serum with bilirubin ranging from 0.5 to 2.9 mg/dl). Cats with clinically icteric (bilirubin > 3.0 mg/dl) most often have primary hepatobiliary disease when hemolytic disease is ruled out. Cats having biochemical icterus (bilirubin < 3.0 mg/dl) do not always have primary hepatobiliary disease and many have other non-hepatic disorders with the liver being secondarily affected with what I refer to as a reactive hepatopathy.

A study evaluating the utility of liver biochemistries in the diagnosis of feline liver disease found the best predictive tests for primary liver disease includes ALP, GGT, total bilirubin and bile acids. ALP increases with hepatic cholestatis. ALP is unique in cats in that the half-life of the enzyme is short (6 hours compared to 72 hours in the dog) and the feline liver is reported to contain only one-third the concentrations found in dogs. Consequently, increases in serum ALP with cholestasis are not expected to increase with the same magnitude as observed in dogs with similar diseases. ALP is also not induced by corticosteroids nor do they cause a steroid hepatopathy. Gamma-glutamyl transpeptidase (GGT) is a similar enzyme to ALP that increases with cholestasis and is more sensitive for feline inflammatory liver disease than ALP. Presumably this is because GGT is found in higher concentrations in the bile ducts than the hepatocyte where ALP predominates. Uniquely cats with idiopathic hepatic lipidosis usually have marked increases in ALP while GGT concentrations show only mild increases. Cats with cholangitis usually have higher elevations in GGT than ALP. Bile acids in the cat are most useful in screening for portosystemic shunts.

Liver disease in cats
In an unpublished review of 175 consecutive liver biopsies performed on cats at Colorado State University several large categories were observed. Making up 87% of the liver biopsies were 4 groups: Lipidosis (both idiopathic and secondary, 26%), Cholangitis (25%), Neoplasia (20%) and Reactive hepatopathies (16%). Hepatic cysts are also an occasional finding in some cats but rarely cause problems. Lipidosis and cholangitis were the most common conditions and will be discussed below. Reactive hepatopathies refer to changes in the liver that occur secondary to a primary non-hepatic disorder such as inflammatory bowel disease, hyperthyroidism and cardiac disease as a few examples.

Hepatic lipidosis
Hepatic lipidosis can occur as either a primary idiopathic disease syndrome or secondary to a number of other primary disease conditions. Lipid accumulation in the liver is simply the result of nutritional, metabolic or toxic insults to the liver and the degree of lipid accumulation can be quite variable and the process is reversible. For example, a common secondary disease associated with significant hepatic triglyceride accumulation is diabetes mellitus. This diagnosis is generally obvious (hyperglycemia and glycosuria) and the lipidosis resolves with appropriate therapy. Hepatic lipid accumulation can also result secondary to a number of other disease syndromes associated with anorexia and weight loss such as pancreatitis, inflammatory bowel disease or other major organ dysfunction. These secondary conditions generally have less severe lipidosis than the clinical syndrome associated with idiopathic hepatic lipidosis in which there is no identifiable etiologic factor. Lipid accumulation is more unique to cats than dogs, in other words cats get lipidosis easily from many conditions.

The etiology of idiopathic hepatic lipidosis is unknown and many theories have been put forward without substantial documentation. One proposal is that there is a defect in hepatic lipid mobilization and decreased ability for hepatic fat oxidation, decreased synthesis of apoproteins and decreased lipoprotein removal from the liver. The cause for the rapid mobilization of peripheral fat however is as yet unknown. A second novel theory speculated by some is that the disease is a primary central anorexia disorder with resultant lipidosis. In any event it is important to investigate all possible secondary conditions leading to anorexia and initiating the typical cascade of hepatic lipidosis. One study reported on a number of cats with acute pancreatitis resembling the idiopathic form of hepatic lipidosis.

In the idiopathic form affected animals generally are older and obese cats that have undergone a stressful episode in the recent history followed by a period of complete anorexia. There does not appear to be a breed or sex predisposition. Cats will present with
an acute history of rapid weight loss (up to 40-60% body weight over 1-2 weeks), depression and icterus. The weight loss is significant with loss of muscle mass while abdominal and inguinal fat stores are often spared. Typical neurological signs commonly associated with hepatic encephalopathy in the dog are uncommon. Complete anorexia, lethargy and depression may however be in part the result of hepatic encephalopathy. These cats generally have a total aversion to any type of food.

The diagnosis of idiopathic hepatic lipidosis is supported by the clinical history and laboratory findings. Icterus and marked elevations in ALP are consistent findings. ALT (SGPT) levels are generally abnormal and quite variable in magnitude of elevation. GGT concentrations are only moderately increased in these cats. Icterus with a very high ALP and normal GGT should be a clue to probable idiopathic lipidosis given with appropriate clinical features. Hypercholesterolemia, hyperammoniemia and abnormal bile acid levels are characteristic. About 1/3 of the cats have a nonregenerative anemia, hypokalemia and clotting abnormalities and about 1/2 the cats demonstrate poikilocytes in the RBC’s. Finding severe hypokalemia, anemia or other concurrent disease (ie pancreatitis) in lipidosis cats has a poor survival rate. The liver size may be normal or enlarged on palpation or radiographically. A definitive diagnosis requires a liver biopsy or hepatic cytology. A fine needle aspirate of the liver with cytological evidence of many vacuolated hepatocytes helps support a diagnosis. Be aware that cytological diagnosis does not always correlate with histology. A needle aspirate can be performed with the cat in dorsal recumbency and a 22 g needle on a syringe directed slightly cranial and lateral to the left from the left xyphoid space. The aspirate can be stained with Diff-quick or Sudan stain. A hepatic tissue biopsy confirms the diagnosis of lipidosis. Care should be taken when obtaining a liver biopsy as some cats may have coagulation abnormalities.

The therapy for idiopathic hepatic lipidosis requires aggressive management. I believe up to an 80% or higher survival rate should be expected in cats given appropriate therapy and no underlying disease is present. Initial therapy requires rehydration with balanced electrolyte solutions. Replacement of potassium deficits is imperative as normokalemia improves survival. Some cats may also require magnesium supplementation as well. Administration of glucose containing solutions may actually cause marked hyperglycemia in these patients and result in a refeeding syndrome (see below). Cats also have a tendency to develop lactic acidosis and therefore lactate-containing fluids (i.e. Lactated Ringers) should be avoided. The practice of adding B-vitamins to the fluids should also be avoided because their prolonged exposure to light in the fluid bag will inactivate them. Parenteral administration is a better option.

Adequate nutrition then becomes the most important part of the therapy for hepatic lipidosis. Force-feeding or appetite stimulation is generally not adequate to meet caloric needs and tube feeding is the best way to administer adequate calories. Nasogastric tubes can be used but due to the small size feeding is limited to liquid diets and they are less tolerated than larger tubes. I suggests placement of either an esophageal or gastrostomy feeding tube. In our practice we find that esophageal tubes to be well tolerated and having less complications than gastric tubes. One should refer to specific articles on tube placement techniques. We find the 20 French red rubber feeding tubes ideal for the esophagus.

The nutritional recommendations for idiopathic hepatic lipidosis are completely empirical and poorly documented. There is some evidence that L-carnitine supplementation in cats may protect against hepatic lipid accumulation (at least in weight reduction studies in cats) and consequently may be an appropriate dietary adjunct for cats with lipidosis. Carnitine is required for transport of long chain fatty acids into the mitochondria for subsequent oxidation and energy production. A deficiency of carnitine may lead to impaired mitochondrial function. It appears that carnitine deficiency could result in chronic liver disease and that supplementation may help protect against encephalopathy, hypoglycemia, and subcellular damage. Studies have however have failed to show carnitine deficiency in cats with hepatic lipidosis. Suggested dose is 250-300 mg/day. Supplementation is reported to be associated with better survival rates, however this is not well documented.

There is also new evidence to suggest many cats with hepatic lipidosis have or will develop cobalamin deficiency. Experimental cobalamin deficiency results in lethargy, anorexia and weight loss – the signs observed with lipidosis. Anecdotal reports suggest cats improve faster with high doses of cobalamin given 250 µg SQ weekly. Serum cobalamin levels should first be determined to document the presence of a deficiency.

Other therapies suggested include S-adenosylmethionine (SAMe) a nutraceutical that is a naturally occurring molecule found in all living organisms and is involved in the metabolism of glutathione (GSH). GSH participates in many metabolic processes and plays a critical role in detoxification mechanisms of the cell. SAMe is also important in hepatocyte membrane integrity and function. The suggested dose is 100 mg/day. Another antioxidant hepatoprotectant is milk thistle or its extract silybin (available as a silybin-phosphatidylcholine combination, Marin™), is a safe hepatic support therapy.

The prognosis must be guarded however with aggressive nutritional therapy many if not most cats recover. Several complications that can occur with therapy include a re-feeding syndrome and vomiting. The re-feeding syndrome is associated with the development of an often life-threatening electrolyte disturbances that occurs within 24 to 48 hours of enteral feeding. If vomiting occurs I will sometimes use maropitant (Cerenia™) or other antiemetics. Maropitant is metabolized by the liver and the dose I use in cats with hepatic lipidosis is lower (0.25- 0.5 mg/kg SQ q 24 h) with my normal cat dose being 1.0 mg/kg SQ q 24 h. We have also used...
mirtazapine (Remaron™) a tetracyclic antidepressant that has both antiemetic and appetite stimulant effects (approximate dose is 1/8 of a 15 mg tablet every 3 days) with encouraging preliminary success.

When the cat is consuming adequate calories without the need for tube supplementation the feeding tube can be removed. Tube feeding may extend for up to 4-6 weeks. A failure to respond to traditional hepatic lipidosis therapy should signal the need to investigate the likelihood of an underlying condition in the patient.

Inflammatory liver disease
Cholangitis is an inflammatory disorder of the hepatobiliary system. It is a disease complex that may be concurrently associated with duodenitis, pancreatitis, cholecystitis and/or cholelithiasis. The terminology is somewhat confusing and pathologists describe the condition differently. Based on the histological classification of the WSAVA Liver Standardization Group this complex has been separated into three histological groups; neutrophilic cholangitis, lymphocytic cholangitis and cholangitis associated with liver flukes.

Neutrophilic cholangitis
This classification has previously been referred to as suppurative or exudative cholangitis /cholangiohepatitis and is the most common type of biliary tract disease observed in cats in North America. Neutrophilic cholangitis is thought to be the result of biliary tract infection ascending from the gastrointestinal tract. In the acute neutrophilic form (ANF), the lesions are exclusively neutrophilic or suppurative but over time it is thought that cases may progress to a chronic neutrophilic form (CNF) having a mixed inflammatory pattern containing variable numbers of neutrophils, lymphocytes and plasma cells.

The ANF is thought to be the result of an ascending bacterial infection. Usually coliforms (E. coli) are cultured from the liver or bile. Inflammation can also extend into the hepatic parenchyma causing a cholangiohepatitis. Cats with this syndrome are usually young (~3-5 years) and present with acute illness usually a week or less in duration. They may have evidence of a fever, anorexia, vomiting or lethargy. A leukocytosis is generally identified on the CBC. The ALT and ALP are increased but variable and these cats are frequently icteric. Ultrasound should be performed to rule out pancreatitis and biliary obstruction. In some cases we will perform an ultrasound-guided cholecystocentesis for cytology and culture. An elevated feline PLI would support concurrent pancreatitis. A liver biopsy is required for histology and will confirm the diagnosis. The liver should always be cultured because of the relationship of bacteria and cholangitis. If obstruction is identified surgery becomes indicated to decompress and flush the biliary system. However, I always try to avoid surgical diversion surgery of the biliary system unless it becomes the last resort.

Therapy for these cats first includes fluid and electrolyte therapy if needed. Antibiotics are a critical part of the therapy as well. Ampicillin, ampicillin-clavulanic acid, cephalosporins and metronidazole have been suggested as effective antibiotics. Unless a culture and sensitivity says otherwise ampicillin or ampicillin-clavulanic acid are my choice because of the likelihood of E. coli and the fact that both are concentrated in the bile. It is recommended that cats be treated for at least 1 month or even longer with antibiotics. Short duration of therapy may result in reoccurrence of clinical signs. Ursodeoxycholic acid (Actigall 10-15 mg/kg/day) should be used as well. Abdominal discomfort and vomiting may be associated with hepatobiliary pain and buprenorphine (Buprenex™) should be administered.

There is also a direct relationship between chronic cholangitis and inflammatory bowel disease and chronic pancreatitis. One study found 83% of affected cats had inflammatory bowel disease and 50% had concurrent chronic pancreatitis. The association of the three together has been referred to as “feline triaditis”. Possibly the common channel theory where the pancreatic ducts and bile ducts join before entering the duodenum explain this triad of clinical signs. Ascending bacteria initiate the acute disease and then over time it becomes chronic. In a yet published study we have identified over 50% of affected cats to have evidence of bacteria in and around bile ducts of these cats suggesting that resident bacteria may be responsible for the chronic inflammation.

Affected cats are usually middle aged or older and have a long duration of signs being weeks to months. Presenting complaints are often vomiting, lethargy and anorexia. Signs may wax and wane and weight loss may be present. Physical findings identify jaundice in most, possibly hepatomegaly and rarely abdominal effusion.

The laboratory findings are variable. Most cats are icteric and there are variable increases in ALP/GGT or ALT/AST. Hyperglobulinemia is observed in over 50% if the cases. Ultrasound may reveal pancreatic, bile duct or gallbladder changes. The liver generally has a mixed echoegnicity pattern with prominent portal areas. Cats with concurrent pancreatitis may have increases feline pancreatic lipase immunoreactivity (PPLI). A liver biopsy confirms the diagnosis.

The primary treatment involves immunosuppressive therapy using prednisolone at 2-4 mg/kg daily and then slowly tapering over 6 to 8 weeks to 0.5-1 mg/kg given once or every other day. This therapy does not appear to resolve this chronic disease but generally slows the progression and may minimizes the clinical signs. A course of antibiotic therapy for several weeks is administered for the possibility of a bacterial component and in light of our yet unpublished study more aggressive antibiotic therapy may be indicated. Ursodeoxycholic acid is a nontoxic hydrophilic bile acid that when administered changes the bile acid milieu. Ursodeoxycholic acid (10-15 mg/kg/day) is nontoxic and suggested for these cats and in fact may be even more beneficial than corticosteroids. This drug is reported to increase bile flow (cholerisis), change bile acid concentrations to less toxic concentrations, reduce inflammation and...
fibrosis and improve liver enzymes. Liver support therapy such as SAMe, Silybin or other antioxidants may be of benefit in the long term management.

The disease is slow and progressive often scattered with periodic flairs. Approximately 50% of the cases will have a prolonged survival. The final stage of this disease complex is biliary cirrhosis having extensive fibrosis and bile duct proliferation that may end with liver failure associated with ascites and hepatic encephalopathy.

**Lymphocytic cholangitis**

This is a condition (severe lymphocytic portal hepatitis, progressive lymphocytic cholangitis or nonsuppurative cholangitis) is described as a very chronic inflammatory biliary tract condition that is progressive over months and years. Some describe it as being acute or chronic in nature. This disorder appears to be more common in European cats than in cats in North America. The pathology of the liver is characterized by a consistent moderate to marked infiltration of small lymphocytes predominately restricted to the portal areas, often associated with variable portal fibrosis and biliary proliferation. The later stages result in considerable distortion of liver architecture. The bile ducts can also become irregular with dilation and fibrosis. In some cases lymphocytic infiltrates in the portal areas may be confused with well-differentiated lymphocytic lymphoma. It is postulated that lymphocytic cholangitis could be the result of immune mediated mechanisms based on preliminary immunologic studies while others have found DNA fragments of Helicobacter pylori in the bile of some cats suggesting bacterial involvement in the pathogenesis of the disease. We have found bacteria to be less commonly associated with this condition using special fluorescent stains for enteric bacteria.

This syndrome as a slowly progressive chronic disease continuing over months and years. It is often first identified in cats under 4 years of age and Persian cats appear to be over-represented, suggesting a possible genetic predisposition. The most common clinical features observed late in the disease include ascites, jaundice, and hypergammaglobulinemia (in almost all cases). In advanced cases, ultrasonographic examination often demonstrates dramatic changes intra and extra-hepatic bile ducts with marked segmental dilations and areas of stenosis that may lead the observer to believe there is an obstruction. Ascites and hepatic encephalopathy occur late in the disease as a result of acquired portal hypertension and hepatic dysfunction.

The treatment for the chronic lymphocytic cholangitis involves using anti-inflammatory or immunosuppressive therapy in addition to supportive therapy as described with neutrophilic cholangitis. Some report lymphocytic cholangitis had a better response when treated with ursodeoxycholic acid than with corticosteroids. This finding may not be completely unexpected because ursodeoxycholic acid has been shown to have a positive treatment effect in humans having chronic primary biliary cirrhosis having a very similar histologic pattern to these chronic cases.

**References**

Several hepatobiliary disorders have in the last few years come under increased recognition and interest in dogs. Understanding these specific conditions is essential in the diagnosis and management of canine liver disease.

Copper associated liver disease

It appears that elevated hepatic copper concentrations and inflammatory liver disease is very common. When we recently reviewed 5 years of liver histology that also had copper quantitation (>2000 cases) 50% of these had elevated hepatic copper (>499µg/g DW) and there was also a significant relationship to concurrent inflammatory changes. Abnormal hepatic copper accumulation may result from increased dietary copper intake, from defects in copper metabolism (copper located in zone 3 location) or secondary to cholestasis (zone 1 location and usually mild elevations). The Bedlington terrier has an inherited disorder of copper homeostasis as the result of a deletion of the COMMD1 gene involved in abnormal hepatic copper excretion. Some other breeds associated with abnormal copper accumulation include the Doberman pinscher, Dalmatian, West Highland white terrier and the Labrador retriever are also suspected to have a genetic component. The mechanism of copper accumulation in these and other breeds is yet to be elucidated but possibly high copper dietary intake may unmask these cases.

We now speculate that a number of other dogs (different breed and mixed breeds) that have the inability to handle dietary copper resulting in hepatic copper accumulation. This theory comes about because the normal hepatic copper concentration for dogs has been increasing over the years and the fact that canine commercial diets are over supplementation with copper (if you compare that to copper requirements for humans). Further, in a study investigating feral dogs that were unlikely to have ever eaten commercial dog food were found to have significantly lower hepatic copper concentrations compared with normal control dogs eating a commercial diet. Consequently, we believe some dogs taking in excessive copper may have the inability to handle the high copper will develop copper associated hepatitis.

The definitive diagnosis of abnormal hepatic copper requires a quantitative analysis of liver tissue Cu. A semi-quantitative estimation involves histochemical staining for hepatic Cu. Reliable tissue bound copper stains include used rhodanine and rubenacid acid. A grading system estimating the quantity of Cu granules correlates roughly with quantitative determination of hepatic Cu. It is also possible to retrospectively determine hepatic copper if there is enough tissue remaining in the paraffin block. That sample can be sent to Colorado State University Diagnostic Laboratory for analysis.

If the liver biopsy of a dog with hepatitis and significant abnormal hepatic copper accumulation, a low copper diet and copper chelation should be started. I believe hepatic copper levels of greater than 1000 µg/g dry weight (dw) liver (normal <400 µg/g dw) requires therapy to reduce copper concentrations. I tend to be less aggressive with chelation if the biopsy shows primary cholestasis with impression the copper is secondary to cholestasis.

Chelation treatment using penicillamine is the primary therapy for copper associated liver disease. Penicillamine binds with copper and then promotes copper removal through the kidneys. Penicillamine is the most frequent copper chelator recommended for use in dogs. The human product is very expensive and I use compounded penicillamine or DePen from pharmacies out of Canada. The dose is 10-15 mg/kg bid given on an empty stomach. Side effects include anorexia and vomiting but can be managed by starting at a lower dose and then increasing the dose over time or by giving it with a small amount of food or using maropitant as needed. Penicillamine therapy takes months to cause a substantial reduction in hepatic copper concentrations. The length of chelation therapy is variable but based on past experience some general recommendations can be made. Ideally repeat liver biopsies should be obtained to determine success of the chelation and to direct duration of therapy. The following is only a general recommendations. Bedlington terriers and Dalmatians will likely require lifetime Cu chelation therapy to achieve normal Cu concentrations. Other breeds including the Doberman and Labrador usually only require short-term therapy. I believe chelation therapy should be instituted in dogs when hepatic Cu concentrations approach or greater than 1000 µg/g dry weight liver. In one 4-month study giving penicillamine to 5 Doberman pinchers with sub-clinical hepatitis and abnormal hepatic Cu concentrations (mean concentration of 1036 µg/g dry weight liver) had a significant decrease in mean hepatic Cu concentration by 407 µg/g dry weight with a significant improvement in liver pathology. In another larger placebo controlled study of forty affected Labrador retrievers with Cu associated hepatitis treated for 3 months with either penicillamine or placebo resulted in a mean reduction of 863 µg/g dry weight copper in the treated group (mean pretreatment Cu concentration was 1511 µg/g) while the placebo treated group had no significant change in Cu concentrations. Chelation for 4 to 6 months may be adequate to decopper the liver of other breeds such as the Labrador retriever and Doberman pincher but the length of therapy can only be determined following a repeat biopsy and Cu
quantitation. The table above shows my rough guidelines on duration of chelation therapy. Following clinical improvement either intermittent chelation therapy, oral zinc therapy and or low copper diets are required to prevent further intestinal absorption of Cu. Ideally the patient should be re-biopsied after 4-6 months of treatment. Often that is not possible to rebiopsy and so below are rough guidelines on chelation therapy I use. I also monitor serum ALT concentrations and when levels return to normal would be a time I would discontinue penicillamine therapy but continue low copper diets. Ideally repeat liver biopsies with copper quantitation is the gold standard to direct therapy. I supplement antioxidants such as vitamin E (10 IU/kg/day) and or other liver support therapy.

Zinc therapy has been shown to decrease copper absorption but is a slow process and may take years to deplete copper, therefore I do not recommend zinc treatment. Dogs should be on a lifelong low copper diet using the liver diets (RC Hepatic or Hills l/d or homemade with out additional copper supplementation.

**Gallbladder mucocele**

To date greater than 130 cases of gallbladder mucocele have been recently documented in the literature. 15-20 years ago a mucocele was a very rare pathological finding. A gallbladder mucocele is a condition that is described as an enlarged gallbladder with immobile stellate or finely striated patterns of mucoid material within the gallbladder lumen detected with ultrasound. The changes described can result in biliary obstruction or gallbladder perforation and peritonitis. Smaller breeds and older dogs are overrepresented. Shetland sheepdogs and Cocker Spaniels are most commonly affected. Most dogs are presented for nonspecific clinical signs such as vomiting, anorexia and lethargy. Abdominal pain, icterus and hyperthermia are common findings on physical examination in advanced cases. Most have serum elevations in bilirubin, ALP, GGT and variable ALT although some dogs are asymptomatic and a mucocele is diagnosed as an incidental finding on abdominal ultrasound. The Shetland sheepdogs tend to have hyperlipidemia and were first thought to have a genetic defect in the ABCB, hepatobiliary transporter gene involved phosphocholine transport into the bile. That theory is now questioned in a reported second larger study. Risk factors identified in mucocele cases include endocrine disease (hypothyroidism, Cushing’s disease) and idiopathic vascular hepatopathy, hyperlipidemia and dogs on high fat diets. Researchers have also reported abnormal gallbladder mucous production and another studied reported abnormal bile acid composition. It is possible that abnormal bile composition causes gallbladder irritation leading to cystic mucinous hyperplasia and subsequent mucocele formation.

Gallbladder mucoceles appear ultrasonographically as an immobile accumulation of anechoic-to-hyperechoic material characterized by the appearance of stellate or finely striated bile patterns (wagon wheel or kiwi fruit appearance). This should be differentiated from biliary sludge (bile sludge can be found in normal animals), by the absence of gravity dependent bile movement while the mucocele is non-movable. The gallbladder wall thickness and wall appearance are variable and nonspecific. The cystic, hepatic or common bile duct may be normal size or dilated suggesting biliary obstruction. Gallbladder wall discontinuity on ultrasound indicates rupture whereas neither of the bile patterns predicted the likelihood of gallbladder rupture. A mucocele is reported the most common cause of a gallbladder perforation.

Cholecystectomy is the treatment of choice for biliary mucoceles. Following cholecystectomy and recovery of postoperative period the prognosis is good especially when the liver enzymes are normal. Mortality rates have been reported to be in the 20% range and some may persist in having liver disease with elevated liver enzymes. It appears profound surgical hypotension occurs and is likely the result of elevated bile acids altering vascular function. There are reports of resolution of some mucoceles using ursodeoxycholic acid (ursodiol) and a low-fat diet but this should only be attempted in the healthy patient and with careful monitoring. Ursodeoxycholic acid is thought to up-regulate biliary excretion of phospholipids, improved bile solubility and increase bile salt dependent flow.

**Portal vein hypoplasia (microvascular dysplasia)**

Portal vein hypoplasia (PVH), also referred to as microvascular dysplasia (MVD), is a common syndrome in the dog associated with abnormal microscopic hepatic portal circulation. It is thought that PVH is 15 to 30 times more common that a congenital portosystemic shunt (PSS). Hepatic PVH has been suggested as the terminology by the WSAVA Liver Standardization Group that may better reflect the etiology of this condition although MVD is ingrained in the veterinary literature. It is believed that the primary defect in affected dogs is the result of hypoplastic or small intrahepatic portal veins. This condition is thought likely to be a defect in embryologic development of the portal veins. Genes for PVH are closely related to genes for PSS. With paucity in size or number of portal veins there is a resultant increased arterial blood flow in attempt to maintain hepatic sinusoidal blood flow. The hepatic arteries become tortuous and abundant in the triad. Sinusoidal hypertension occurs under this high-pressure system. Lymphatic dilation results and it is thought that this opens embryologic sinusoidal vessels to reduce pressure and thus acquired shunts develop to transport some (but not all) of the blood to the central vein thus by-passing the sinusoidal hepatocytes. This results in abnormal hepatic parenchymal perfusion and lack of normal trophic factors bathing the sinusoids causing mild hepatic atrophy. With portal shunting of blood increased iron uptake also occurs that results in hepatic iron granuloma formation. Ascites or portal hypertension generally do not occur in this condition.
Because similar histological changes occur in dogs having PVH and PSS (i.e., hepatic hypoperfusion) the diagnosis can be confusing. If an intrahepatic or extrahepatic macroscopic shunt is not observed then PVH becomes the probable diagnosis. Angiography or transcolonic portal scintigraphy fails to demonstrate macroscopic shunting in this condition. Often a needle biopsy is not sufficient to provide enough portal areas to make the diagnosis, and consequently a wedge or laparoscopic biopsy may be necessary. The lesion may be patchy or involving different liver lobes so multiple biopsies should be taken from different lobes.

The condition that was first described in Cairn terriers and now is felt to occur in other many other breeds of dogs. Yorkshire Terriers and Maltese may be over represented. Animals show no outward clinical signs and are usually identified because of elevated liver enzymes (ALT). All patients have abnormal serum bile acid concentrations (usually moderate elevations) but generally they are less than 100 µmole/L. It is reported PVH dogs have normal protein c concentrations while PSS dogs have concentrations less than 70% normal. Protein c is an anticoagulant and can be measured in specialized labs. There is no specific therapy. Low protein diets are not necessary. Some suggest antioxidants (i.e., SAMe, milk thistle etc.). The long-term prognosis is uncertain because of lack of experience with this relative new disease. There may be a small number of dogs developing portal hypertension over time (likely less than 5%) but most dogs have no evidence of clinical disease and live a normal life without therapy.

**Ductal plate malformation**

A ductal plate malformation is a congenital abnormality occurring from the primitive sleeve of epithelial cells that encircle the portal vein during early embriological maturation. This sleeve of epithelial tissue transform into bile ducts. Two basic types of ductal plate anomalies can occur; either cystic dilation of the bile ducts or marked bile duct proliferation with extensive fibrosis in the portal triad area. Cystic dilation generally causes little problems in the dog and cat but the proliferative form with extensive fibrosis does. Those affected patients develop portal hypertension and ascites and secondary acquired portosystemic shunts result in hepatic encephalopathy. This condition has also been referred as congenital hepatic fibrosis because there is significant fibrosis in the portal areas.

The hepatic histology demonstrates portal tracts associated with multiple arterioles, small or absent portal veins with extensive portal fibrosis, lymphatic distention and usually marked bile duct proliferation. The pathology is void of inflammatory infiltrates. There are also increased amounts of hepatic iron deposited in the liver.

The fibrosis variant is generally observed in dogs under 3 years of age and there is no breed prevalence however Doberman Pinschers, Cocker Spaniels and Rottweilers may be over represented. There was also a more recent paper reporting on a series of Boxer dogs with this condition. The clinical presentation is similar to dogs having advanced cirrhosis of the liver however they are generally much younger than the chronic hepatitis cirrhosis patients. The liver enzymes are generally increased with a hypoalbuminemia and very high bile acid concentrations (>100 µmol/L). The ALT and ALP are usually elevated. Work up of these patients fails to identify a single shunting vessel, but rather these cases have marked portal hypertension associated with multiple acquired portosystemic shunts. These dogs often present with signs of hepatic encephalopathy. Ultrasound is often helpful showing microhepatic, hepatofugal portal blood flow and multiple abnormal extrahepatic collateral shunts. Portal contrast studies demonstrate acquired portal shunts and pressure measurements document portal hypertension. The prognosis for this condition is generally guarded but some dogs are reported to have a prolonged survival using anti-fibrotic agents, hepatic support medications, ascites management and hepatic encephalopathy therapy. We generally believe colchicine is a poor antifibrotic agent and we prefer using angiotensinogen receptor blocker antagonist such as losartan or telmisartan. Spironolactone is thought to be the best first line diuretic in these cases and other cases of liver disease.

As a side note it is important to remember that congenital portosystemic shunts (ones you might recommend surgery on) do not have portal hypertension or ascites. A patient thought to be a shunt with ascites is not surgical and most likely a ductal plate anomaly.

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The identification of abnormal liver enzymes usually indicates liver damage but rarely provides a diagnosis or etiology. Abnormal liver enzymes are common and in a study of 1,022 blood samples taken from both healthy and sick dogs and cats, one diagnostic laboratory found 39% had ALP increases and 17% had ALT increases. When presented with a patient having abnormal liver enzymes it is important to recognize that the patient could have primary liver disease but more likely the patient has other primary non-hepatic condition resulting in secondary liver involvement. It is therefore important to perform a complete review of all other body systems.

It is also important to understand the reason for increased liver enzyme activity and the following sections will deal with liver specific tests.

**Tests of hepatocellular necrosis or degeneration**

Increases in either alanine aminotransferase (ALT) or aspartate aminotransferase activity (AST) indicate hepatocellular membrane damage and leakage of the enzymes. This could be due to death of the hepatocyte or from hepatocyte degeneration where the membrane just has increased permeability. Conceptually ALT and AST should be thought of as hepatocellular “leakage” enzymes. Subsequent to an acute and diffuse injury, the magnitude of increase crudely reflects the number of affected hepatocytes. The plasma half-life of ALT activity is about 2.5 days (60 hours) in dogs however concentrations may take days to weeks to decrease following an acute insult based on models of acute hepatic injury. Persistent increased ALT and AST enzyme activity over weeks is characteristic of chronic hepatitis in the dog. As a general rule, ALT increases should be investigated when they are greater than twice normal or persistently abnormal over weeks to months. Hepatic AST is located predominately in hepatocyte mitochondria (80%) but is also soluble in the cytoplasm. Because of the mitochondrial location, AST elevations are more sensitive for liver disease than ALT and reflect more significant cell damage. On the other hand, AST is less specific than ALT because of the presence in other tissues (i.e., muscle so always check CK). Following an acute injury resulting in a moderate to marked increase in the serum ALT and AST concentrations, due to their difference in plasma half-life, the serum AST will return to normal more rapidly (hours to days) than the serum ALT (days).

**Tests of cholestasis and drug-induction**

Alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) show minimal activity in normal hepatic tissue but can become increased in the serum subsequent to increased enzyme production stimulated by either impaired bile flow or drug-induction. These enzymes have a membrane bound location at the canicular surface; ALP associated more with the canalicular membrane and GGT associated more with epithelial cells comprising the bile ductular system. With cholestasis, surface tension in the canaliculi and bile ductules increases and production of these surface enzymes is then up-regulated. An increase in the serum ALP and GGT activity can be the result of induction by endogenous, topical or systemic glucocorticoids, anticonvulsant medications (ALP only) and possibly other drugs or herbs. The plasma half-life for hepatic ALP in the dog is 66 hours in contrast to 6 hours for the cat and the magnitude of enzyme increase (presumably a reflection of the synthetic capacity) is greater for the dog than the cat. Bone source arises from osteoblastic activity and is elevated in young growing dogs before their epiphysial plates close or in some dogs with bone tumors or lytic lesions. One study identified that increased ALP concentrations in some dogs with osteogenic bone tumors tended to indicate a poorer prognosis, probably from diffuse bone metastasis. In the adult without bone disease, an increased serum ALP activity is usually of hepatobiliary origin. Hepatic GGT is located predominately on the canalicular membrane and bile ducts. Chronic elevations in GGT tend to better reflect hepatobiliary tract disease, with the most marked elevations resulting from diseases of the biliary epithelium such as bile duct obstruction, cholangiohepatitis, cholecystitis or neoplasia. In dogs, GGT has a lower sensitivity (50%) but higher specificity (87%) for hepatobiliary disease than total ALP. If ALP is elevated with a concurrent increase in serum GGT, specificity for liver disease increases to 94%. Bone does not contain GGT and the administration of anticonvulsant medications to dogs does not cause an increase in the serum GGT activity.

**Evaluation of liver function**

On a routine biochemical profile it is important to note the liver function tests (or tests that involve liver function) including bilirubin, albumin, glucose, BUN, and cholesterol. Bilirubin elevations can occur from hemolysis, hepatic dysfunction or extrahepatic cholestasis. Measuring the percent conjugated to unconjugated bilirubin to determine location is not useful in the dog. Albumin is exclusively made in the liver and if albumin is not lost, sequestered or diluted, a low concentration would suggest significant hepatic dysfunction. It may take greater than 60% hepatic dysfunction for albumin concentrations to decline. Cholesterol can be variable and
increased in cholestatic conditions and decreased in portosystemic shunts. When glucose and BUN activity is low from liver dysfunction suggests significant hepatic disease and a guarded prognosis.

**Bile acids**

Measurement of serum bile acids is thought to be the most sensitive function test that is readily available in small animal practice. Bile acids are synthesized from cholesterol in the liver and then conjugated and excreted into the bile. Bile acids are transported to the gallbladder and following a meal are excreted into the intestine where they emulsify fat for absorption. In the distal small intestine bile acids are actively resorbed and return to the liver where they are efficiently extracted by the hepatocytes and then re-circulated back into the bile. Only a small fraction of the total bile acid pool ever escapes into the systemic circulation. Thus, the enterohepatic circulation of bile acids occurs with a 95-98% rate of efficiency. The current suggestion for performing bile acid levels is to differentiate between congenital portal vascular anomalies and liver insufficiency, prior to the development of jaundice. The determination of total bile acids can contribute to the decision to obtain histological support for a definitive diagnosis. The fasting total serum bile acid concentration (FSBA) is a reflection of the efficiency and integrity of enterohepatic circulation. Pathology of the hepatobiliary system or the portal circulation results in an increased FSBA prior to the development of hyperbilirubinemia, therefore, bile acid measurement is not useful in the icteric patient. An increase is not specific for a particular type of pathologic process but is associated with a variety of hepatic insults or abnormalities of the portal circulation. Bile acids should be used to screen patients with persistently abnormal liver enzymes, to determine if there could be loss of hepatic function, which adds further diagnostic support during investigation of the case. It is also helpful to measure bile acids to determine level of hepatic dysfunction in animals with PSS or portal vein hypoplasia (PVH), also known as microvascular dysplasia. When the fasting value is greater than 25 µmol/L for the dog and cat, there is a high probability that the histology findings will define a lesion.

When the total fasted bile acid concentration is normal or in the “gray zone” the FSBA should be followed by a 2-hour postprandial serum total bile acid (PPSBA) looking for an increase of greater than 25 µmol/L. The diagnostic value of determining PPSBA concentration is increased sensitivity for the detection of hepatic disease and congenital portal vascular anomalies. In dogs, the specificity of fasting and postprandial bile acids for hepatobiliary disease is 95% and 100% when cutoff values greater than 15 µmol/L and 25 µmol/L are used, respectively. When using these guidelines it is prudent to recognize that a small number of apparently healthy dogs have been reported with PPSBA values above 25 umol/L or these may actually represent dogs that have PVH. Occasionally the FSBA value is greater than the PPSBA value. The reason for this non sequitur is probably multifactorial. It has been shown that (1) the peak PPSBA concentration for individual dogs is variable, (2) fasted dogs store about 40% of the newly produced bile in the gallbladder and (3) a meal stimulates the release of only between 5 to 65% gallbladder bile. Undoubtedly these physiologic variables in addition to physiological variation in intestinal transit time and concurrent underlying intestinal disease contribute to the dichotomy.

Recently, urinary bile acids have become available as a diagnostic tool. Identifying increased urinary bile acids provides similar information to what is obtained from serum bile acids and neither test appears to be better than the other. The advantage of urinary bile acid measurements would be for the screening of litters of young puppies for suspected inherited vascular anomalies where urine collection is simpler than paired serum samples.

**Coagulation panels**

Major clotting factors are synthesized in the liver (except factor 8) and therefore prolonged clotting time may suggest significant hepatic dysfunction or factor consumption. Because coagulation abilities may not be normal in patients with liver disease, it is advisable to check clotting times prior to performing liver biopsy.

**Ammonia**

High ammonia levels reflects abnormal hepatic portal shunting (acquired or congenital shunts) or significant hepatocellular dysfunction of greater than 70%. The liver detoxifies ammonia that primarily arises from the gastrointestinal tract by conversion to urea. Elevated fasting blood ammonia levels have been shown to be a sensitive (98%) and specific (89%) test for the detection of congenital or acquired portosystemic shunting in dogs. Due to problematic requirements for sample handling and submission, blood ammonia or the ammonia tolerance test is infrequently performed by some clinical practices. However, recent availability of blood ammonia for in-clinic analyzers, has helped make the test more feasible.

**Diagnostic strategies**

In the asymptomatic patient with an increased liver biochemical test(s) the increased value should be confirmed. If no likely explanation for the laboratory abnormalities can be found there are two courses of action that one can take; either begin a diagnostic evaluation of the patient starting with bile acid determinations, or re-evaluate the patient’s liver enzymes at a later date. The diagram below depicts a general algorithm for the work-up of dogs that have abnormal liver enzymes. The identification of abnormal liver enzymes may occur when the sick patient is presented for evaluation or during a routine health screen in the healthy patient. Abnormal liver enzymes in the sick patient could either be the result of primary liver disease/damage or secondary due to a multitude of other non-hepatic disorders. The most common cause of abnormal liver enzymes is in fact, not primary liver disease at all but rather the result of reactive hepatic changes occurring secondary to other non-hepatic causes. Generally, secondary hepatic changes are
Reversible once the primarily disease is treated. Successful resolution of the non-hepatic disease and continued abnormal liver enzymes would be a strong indication for further investigation of the liver for a primary disease process.

**Imaging**

Routine abdominal radiographs are helpful in determining liver size and shape and for detection of other intra-abdominal disorders. Ultrasonography is noninvasive, readily available and is the most informative initial imaging modality for liver disease. Ultrasound can determine parenchymal changes, mass lesions and disorders of the biliary system. Ultrasound however is not accurate in differentiation of the major parenchymal changes.

**Fine needle aspiration** (FNA) for cytological evaluation is safe easily performed using ultrasound direction. One should be cautious in over interpretation of those results however. FNA is best for identification of vacuolar hepatopathies and neoplasia and is poor in detecting inflammatory hepatic changes. In one study we found FNA and cytology to only correlate in about 1/3 of the cases.

**Liver biopsy**

A biopsy is required for a definitive determination of the nature and extent of hepatic damage and to appropriately direct the course of treatment. The method for liver biopsy procurement may be surgery, ultrasound guided needle biopsy or laparoscopy. We believe if a needle biopsy is obtained that at least a 16g biopsy needle or larger be used and multiple liver lobes are biopsied. We generally take 3-4 biopsies with one split for culture and hepatic copper analysis and the remainder placed in formalin for histological evaluation.

**What you might find On a liver biopsy**

When we evaluated 150 consecutive canine liver biopsies we identified the largest category to be secondary reactive hepatopathies (25%) followed then by chronic hepatitis (23%) and then neoplasia and vacuolar hepatopathies making up 69% of the biopsies performed. Smaller categories included vascular anomalies, acute liver damage and other miscellaneous conditions.

**Reactive hepatopathies; A common diagnosis**

The so-called “non-specific reactive hepatopathies” (NSRH) that occur secondary to non-hepatic disease can result in increased serum biochemical hepatic tests and histomorphologic abnormalities. Most of the NSRH cause increases in laboratory tests that evaluate hepatocellular integrity (ALT, AST) and tests of hepatic cholestasis (ALP, GGT). In most cases there are little if any changes in tests that evaluate hepatic function (bilirubin, albumin, glucose, and BUN). Most of the animals with this type of secondary liver disease often retain normal hepatic function (albumin, serum bile acid concentrations), which again supports a concept that there is generally minimal loss of hepatocellular function. NSRH is often characterized by variable amount of hepatocellular degeneration or necrotic changes without evidence of significant chronic progressive inflammation. The reason the liver often undergoes these changes revolves from the fact that the liver is involved in so many metabolic and detoxification functions. Endogenous toxins, anoxia, metabolic changes, nutritional changes and endogenous stress related glucocorticoid release are all examples of conditions responsible for the majority of these changes. Gastrointestinal disease frequently results in secondary hepatic changes uptake of bacteria, toxins or nutrient abnormalities.

Histological findings associated with NSRH changes include descriptors such as vacuolar degeneration, hydropic degeneration, swollen hepatocytes, lipodis, intracellular or intrahepatic cholestasis, mild multifocal hepatitis or periportal hepatitis or variable random hepatic necrosis. These changes are devoid of the typical progressive chronic inflammatory cell infiltrates characteristic of chronic hepatitis. Whenever I observe these changes on histology I always begin a search for an underlying etiology.

A good example that helps explain this concept is inflammatory bowel disease in which it is not unusual to observe mild inflammatory changes around portal triads presumed to be the result of abnormal portal uptake of gastrointestinal “toxins”. Throughout the liver and closely associated with portal areas are Kupffer cells (fixed macrophages) that function to filter the blood of injurious toxins, inflammatory mediators and bacteria. When this macrophage system is abnormally insulted Kupffer cells release their own inflammatory mediators that in turn insult the hepatocytes.

In a review of consecutive liver biopsies at Colorado State University histology grouped as non-specific reactive changes made up the largest category of abnormalities (approximately 25%) In this group we were able to identify an associated disease in many that could explain the likely cause for the hepatic enzyme increases and histological changes observed. Concurrent diseases identified included neoplasia, gastrointestinal, renal, autoimmune, dermatologic, dental, infectious and cardiac disease as a few examples. In some cases an underlying disease is not identified. The ALT values on the average are 1-2 X normal and the ALP values 1-3 X
normal. It is interesting to note that in a series of 32 dogs having reactive hepatopathies, 8/8 cases in which serum bile acids were run, all were within the normal reference range again suggesting hepatic function tends to remain intact.

This category appears to be the most common histological change to occur in dogs and is by far the most common cause of elevated liver enzymes. Based on this fact, dogs presented with elevations in ALT and ALP should always have primary non-hepatic disease ruled out first. These changes are usually very reversible and no specific hepatic therapy is required short of treating the primary disease. The liver changes resolve once the primary etiology is successfully treated. Therapy providing good liver support such as antioxidants may be warranted.

Summary
Abnormal liver enzymes should not be ignored and should be investigated in a systematic manner as previously discussed. Asymptomatic animals with no evidence of significant or treatable disease or in situations where financial constraints limit further work up the patient should be fed a quality maintenance diet for the patient’s stage of life and the possibility of instituting specific liver support therapy should be explored.
Chronic Hepatitis in Dogs: The Latest Updates

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The most important and most common primary liver disease in the dog is chronic hepatitis. Chronic hepatitis is not a single disease but rather the inflammatory changes can be due to many of etiologies. The therapy should be directed first at the cause of the inflammation. In most all cases a liver biopsy is required to confirm the diagnosis before effective therapy can be begun.

Chronic hepatitis is an etiologic diverse and morphologically variable condition associated by mixed inflammatory cell infiltrates. It is characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory infiltrate, regeneration and fibrosis. The proportion and distribution of these components vary widely. Plasma cells, lymphocytes and macrophages predominate with a lesser number of neutrophils. Because we see non-specific mild portal inflammation as a common non-specific reactive change frequently secondary to intra-abdominal disorders like IBD I need the pathologist to tell me the severity of inflammation and chronicity of the disease. The presence of fibrosis in the hepatic biopsy usually denotes to me more serious consequences. As damage progresses cirrhosis can result with diffuse fibrosis, alteration in hepatic lobular architecture with the formation of regenerative nodules and abnormal vascular anastomoses. Cirrhosis, a sequel of some chronic hepatitis cases, is often associated with portal hypertension, ascites and multiple portosystemic collateral veins. Some may show manifestations of liver failure, e.g., hyperbilirubinemia, coagulopathies, edema due to hypalbuminemia, ascites and hepatencephalopathy. This type of chronic inflammation is uncommon in the cat as their inflammatory disease is directed at bile ducts causing cholangitis.

Etiology

The etiology of this chronic inflammatory condition is generally never determined. To date the best-described etiology of chronic hepatitis is the copper associated hepatitis of the Bedlington terrier (see below copper associated hepatitis). This breed and others are thought to have an inherited copper associated chronic hepatitis. Copper accumulates in hepatocyte from abnormal metabolism to a level that then becomes toxic causing hepatocyte death. There are also likely breeds that have difficulty in handling copper if taken in orally in excess amounts.

Infectious chronic hepatitis in man is most often associated with viral etiologies. The search for a viral etiology of hepatitis in the dog however has been unrewarding. The canine adenovirus type 1 given experimentally to partially immune dogs did caused hepatitis and fibrosis. Others identified a suspected acidophil cell hepatitis virus in dogs that were vaccinated with liver homogenates from dogs dying from chronic hepatitis. The vaccinated dogs developed fibrosis and inflammation in their livers. Subsequent further research or publications into viral etiologies are lacking. Chronic hepatitis has also been associated with leptospirosis with the authors describing "atypical leptospures" in a colony of dogs having hepatitis. However we have examined over 50 dogs livers having hepatitis using PCR for Leptospirosis and did not identify a single positive case. Other infectious agents suggested as a possible etiology include Helicobacter sp, Bartonella, and Leishmaniasis.

Chronic liver injury has also been reported in dogs with aflatoxicosis as well as various drug-induced hepatitis. Some dogs treated with anticonvulsant drugs primidone, phenytoin and phenobarbital will develop chronic hepatitis. We have also observed some dogs treated with NSAIDs to also have hepatitis which asks the question of NSAIDs being related to hepatitis. In man alpha-1-antitrypsin (AAT- also referred to as alpha one protease inhibitor) deficiency is known to cause chronic hepatitis and cirrhosis. Investigation by researchers in Sweden using immunostaining for AAT in hepatocytes found some dogs with chronic hepatitis to be positive for AAT in the hepatocytes but the dogs differ from man in that serum AAT remained in the normal range while humans have low concentrations. It is not known if the AAT accumulation is the cause or the result hepatocyte damage. The breed most often associated with AAT accumulation is thought to be the cocker spaniel.

Finally immune associated hepatitis may also occur in the dog. Autoimmune liver disease in humans is an important cause of chronic hepatitis and is associated with diagnostic circulating autoantibodies. It appears that autoantibodies (ANA, antimitochondrial antibodies [AMA], smooth muscle antibodies [SMA], liver membrane autoantibodies [LMA]) are markers of autoimmune hepatitis in humans. A number of studies have been performed in dogs looking for liver associated antibodies and cell-mediated responses to support autoimmune disease as an etiology. Findings so far suggest autoimmune liver disease exists but studies fail to conclusively prove its existence. The pathogenesis proposed is that an insulting agent damages the hepatocytes thus releasing liver antigens that initiate a secondary immune response perpetuating chronic hepatitis. Nonetheless, immune-mediated mechanisms are thought to occur in some cases of chronic hepatitis and this is further supported by the fact that some dogs respond favorably to immunosuppressive therapy.

There are also a number of breeds that have an increased incidence of chronic hepatitis and are thought to be inherited. Some of these breeds have copper associated chronic hepatitis and are discussed below. Other breeds not yet associated with copper include

373
the standard poodle, Cocker spaniel, Springer spaniel and Scottish terrier. The pathogenesis of the hepatitis is yet unknown. Cocker spaniels both English and American tend to be more commonly males and ATT accumulation may play a role in their disease. More recently in Europe English Springer Spaniels have been reported to have a breed associated hepatitis. Standard poodles are more commonly females and tend to have prolonged survival with immunosuppressive therapy. We are currently studying the standard poodle at Colorado State University.

Clinical findings
The incidence of chronic hepatitis makes up approximately one fourth of the cases having liver biopsies at Colorado State University (based on a review of 150 consecutive liver biopsies). Chronic hepatitis is more common in female dogs. The average of presentation ranges from 4 to 10 years. It is interesting to note that in both our series and in studies by others it is uncommon to observe chronic hepatitis/cirrhosis in dogs older than 10 years of age. As a general rule old dogs (> 11 years of age) don’t generally present with chronic hepatitis/cirrhosis or if they do they are at or near end stage disease.

The clinical signs parallel the extent of hepatic damage. Early in the disease there are usually no or minimal clinical signs. Only after the disease progresses do the clinical signs specific for liver disease becomes evident. Frequent early signs are gastrointestinal associated with vomiting, diarrhea and poor appetite or anorexia. Ascites, jaundice and hepatic encephalopathy may then occur as the disease progresses. With development of these late signs the long-term prognosis is generally poor.

The laboratory findings include consistently elevated ALT and ALP. The magnitude of rise need not be marked however. One report found 75% of the cases with abnormal bilirubin elevation (mean elevation of 2.6 mg/dl). Serum proteins are variable. As the lesions become more severe albumin levels decline. Serum bile acids are abnormal in most cases having significant chronic hepatitis and measurement of bile acids appear to be a good screening test for the patient with unexplained elevations in ALT and ALP. In our study all dogs evaluated with chronic hepatitis had abnormal bile acid concentrations. In a second study only 8/26 dogs with chronic hepatitis had normal fasting bile acids. However, postprandial samples were not determined in these cases. Determining postprandial bile acids has been shown to increase the sensitivity of this test.

A presumptive diagnosis is made based on the clinical features and persistent increases of ALP and ALT values. A definitive diagnosis requires a hepatic biopsy showing characteristic morphological patterns. Needle aspirates are not helpful in making the diagnosis of chronic hepatitis because it is important to see the architecture of the liver and location and extent of the inflammation. One must work with the pathologist when making the diagnosis of chronic hepatitis and to be certain that characteristic abnormalities found in chronic hepatitis are present.

Prognosis
There is little information of the prognosis with and without therapy. The prognosis in dogs with advanced chronic hepatitis and cirrhosis is guarded. In a study by Strombeck found mean survivals ranging from 6 to 16 months with therapy. This study also identified that dogs with hypalbuminemia, hypoglycemia and coagulopathies have very guarded prognostic factors and many died within 1 week of diagnosis. A second study of 79 dogs found that dogs with cirrhosis had a survival of less than one month and dogs with chronic hepatitis had a mean survival in the range of about 20 to 30 months. Most of these dogs were not advanced in their disease and had concurrent corticosteroid treatment.

Treatment
I have four general goals in therapy: 1) remove the etiology, 2) provide an adequate diet, 3) give specific therapy and 4) providing general liver support. First step in the therapy for chronic hepatitis and other liver diseases involves removing the primary etiology if it can be identified. Short of treating the primary etiology all other therapies suggested are unproven in the management of liver disease in dogs. Much of the therapy is directed at providing adequate liver support. This often involves the use of multiple therapies.

Diet
Adjusting diet therapy should be considered in all cases however only general guidelines should be given. First, palatability is important to assure adequate energy requirements are met. Next, there is a misconception about diet and liver disease that liver patients should be placed on a protein restricted diet. Protein restriction should only be instituted in the patient that has clinical evidence of protein intolerance (i.e. hepatic encephalopathy). Diets low in copper are recommended for the dogs that have copper associated liver disease based on biopsy. Most formulated “liver diets” have lower copper concentrations and are often supplemented with additional zinc. Homemade diets can also be prepared that do not to contain excess copper. These diets should exclude liver, shellfish, organ meats and cereals that are all high in copper content. Vitamins or mineral supplements should not contain copper or iron.

Antiinflammatory therapy
Decreasing inflammation as a specific therapy for chronic hepatitis in the dog or cholangitis in the cat is unproven although the author’s clinical impression suggests anti-inflammatory therapy is beneficial in some cases. The treatment of chronic hepatitis is quite controversial and there are as yet no good controlled studies in animals to support corticosteroids use in every case. Antiinflammatory
therapy is indicated in suspected immune mediated chronic hepatitis. A suggested dose of 1 to 2 mg/kg/day using prednisolone (prednisone requires hepatic biotransformation) should be instituted. When clinical improvement is suspected or after several weeks the dose is then gradually tapered eventually to a dose of 0.5 mg/kg/day or every other day. The only accurate way to evaluate a response to any therapy is to re-biopsy the patient in 6 months to 1 year because the patient will develop a concurrent steroid hepatoopathy with increased liver enzymes making laboratory determination of any improvement impossible. Alternatively one could stop steroids and recheck enzymes in 1 to 2 months. We have more recently been using cyclosporine in many cases with a good clinical response. Our experience using 5 mg/kg bid or q 24 hrs (without steroids) has been very encouraging in dogs that are thought to have immune mediated chronic hepatitis. The veterinary formulation Atopica™ is a microemulsified preparation with the identical properties to Neoral™ (also sold as modified generic cyclosporine) that ensures more consistent bioavailability. With evidence of clinical response at 5 mg/kg bid I will often decrease to once a day therapy. Using cyclosporine alone one can follow the liver enzymes making the need for a liver biopsy less frequently required.

**Antifibrotic drugs**

Corticosteroids, zinc and penicillamine all have anti-fibrotic effects. Colchicine is a drug that has limited success I chronic hepatitis. Recently it was found that angiotensin II inhibitor Losartan (Zestril™, 0.25-0.5 mg/kg/Day) has effects in reducing or preventing fibrosis in humans by effecting function of stellate (fibrosis producing) cells.

**Choleretic drugs**

Decreasing cholestasis has been shown to be of benefit in humans and animals having cholestatic hepatobiliary disease. As serum bile concentrations increase (these are predominately cytotoxic bile acids) they can cause cell membrane permeability changes and fibrogenesis. Ursodeoxycholic acid (Ursodiol™ -Actigall™, 300 mg caps) is a choleretic agent developed to dissolve gallstones but later found to have positive effects in patients with chronic hepatitis. This drug is a synthetic hydrophilic bile acid that essentially changes the bile acid pool from the more toxic hydrophobic bile acids to less toxic hydrophilic bile acids. Ursodeoxycholic acid has been shown to increase bile acid dependent flow, reduce hepatocellular inflammatory changes, fibrosis and possibly some immunomodulating effects. The hepatoprotective characteristics makes one believe ursodeoxycholic acts as an antioxidant. The dose for ursodeoxycholic acid is 15 mg/kg daily. No toxicity has been observed in dogs and cats at this dose. There has been a concern raised by some that it should not be used if there is any possibility of a bile duct obstruction for fear of biliary rupture. Although with obstruction surgery is indicated ursodeoxycholic acid is not a prokinetic and will not cause a rupture. In fact in experimental bile duct obstructions there was less secondary "toxic" changes in the liver in rats given ursodiol than placebo.

**Antibiotics**

Antibiotics are indicated for primary hepatic infections. There however may be evidence that bacterial colonization may take place in a diseased liver. Kupffer cell dysfunction could be a reason for secondary bacterial infections. It may be prudent for antibiotic therapy or trial for several weeks in patients having significant hepatic disease (i.e. chronic hepatitis). Amoxicillin, cephalosporin, or metronidazole are suggested. Metronidazole may have some immunosuppressive properties as well as antibacterial mechanisms. For liver disease I would use 7.5-10 mg/kg bid a much lower dose used for other bacterial infections because of hepatic metabolism of the drug.

**Antioxidants**

There has been recent interest in the management of certain types of liver disease using antioxidants. Antioxidants in general provide liver support to promote optimal hepatic function. Considerable evidence shows that free radicals are generated in chronic hepatitis and participate in the pathogenesis of oxidative liver injury in dogs and cats.

**Vitamin E** d-alpha tocopherol, functions a major membrane bound intracellular antioxidant, protecting membrane phospholipids from peroxidative damage when free radicals are formed. Vitamin E is shown to protect against the effects of copper, bile acids and other hepatotoxins. In a small study of dogs having chronic hepatitis we found all dogs had evidence of oxidative damage. In a three-month placebo controlled study treating only with vitamin E there was evidence improvement in the oxidant status of the treated dogs however we did not identify changes in clinical, laboratory or histology during this short treatment period. A suggested vitamin E dose is 50 to 400 IU a day. The d-alpha tocopheryl formulation is much more potent than the most common commercial form (dL-alpha tocopheryl). Since bile acids are required for fat-soluble vitamin E absorption and may be reduced in cholestatic liver disease, a water-soluble formulation is suggested. For a water soluble form I use Twin labs Liqui-E. The vitamin E is derived from TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate) and has a rapid absorption. Because of the potential benefits of vitamin E, the lack of side effects and since the drug is inexpensive I place most all my liver patients on E therapy.

**S-Adenosylmethionine (SAMe)** is a naturally occurring molecule found in all living organisms and is involved in a number of metabolic pathways that appear to be beneficial to the liver as well as other tissues. SAMe is involved in three major biochemical pathways. It is involved in cell replication and protein synthesis, has a modulating influence on inflammation and plays a role as a precursor of the antioxidant glutathione in the hepatocyte. Research has demonstrated that the exogenous administration of SAMe to have potential beneficial effects for a number of types of liver damage. In one study giving acetaminophen to cats at a sub-lethal dose we observed protective effects of SAMe when measuring markers of hepatic oxidative damage and RBC fragility. Studies
investigating naturally occurring liver disease in animals are required to determine the benefit of SAMe administration in liver disease. I will routinely prescribe SAMe (Denosyl™) in patients having acute liver toxicity and in many cases having chronic liver disease or other liver disorders. A recommended dose range is 20 mg/kg/day. It should be given on an empty stomach and the tablets not broken. There are numerous commercial sources of SAMe each having variable concentration or purity of the compound. Foil wrapped tablets produced by a company that provides reliable purity and potency is recommended.

Milk thistle has been used for centuries as a natural remedy for diseases of the liver and biliary tract. Silymarin the active extract consists of bioflavonoligans that have been reported to work as antioxidants, scavenging free radicals and inhibiting lipid peroxidation. Several recent human clinical trials have assessed the efficacy of silymarin in the treatment of liver disease. The data is somewhat difficult to interpret because of the limited number of patients, poor study design, variable etiologies, lack of standardization of silymarin preparations with different dosing protocols. There is however compelling evidence to suggest silymarin has a therapeutic effect in acute viral hepatitis, alcoholic liver disease, patients with cirrhosis, and in toxin or drug-induced hepatitis. Unfortunately, the purity of commercial products, and therapeutic dosage is unknown. Clinical trials are limited in small animals and reported success is only anecdotal. Dosage of milk thistle ranges from 50 to 250 mg bid. Milk thistle is reported to have an extremely low toxicity in humans and animals and has been used extensively in clinical patients with little concern for side effects. To date there is only one published clinical study evaluating the efficacy of silymarin in the treatment of liver disease in dogs. In this placebo controlled experimental study dogs were poisoned with the Amanita phalloides mushroom. Researchers showed silymarin to have a significant effect on liver enzymes, the extent of histological liver damage and survival outcome. Based on this canine study and several clinical reports in humans poisoned with Amanita and treated with silymarin having a favorable outcome many physicians in Europe now accept silymarin as part of the standard protocol for mushroom poisoning.

General support therapy
The remainder of the therapy for chronic hepatitis involves treatment of secondary complications. These occur as the disease becomes advanced. Hepatic encephalopathy, GI ulceration and ascites are common clinical occurrences in advanced hepatitis or cirrhosis.
Several hepatobiliary disorders have in the last few years come under increased recognition and interest in dogs. Understanding these specific conditions is essential in the diagnosis and management of canine liver disease.

**Vacuolar hepatopathies**

Hepatic vacuolar change is a common histological diagnosis in dogs but not cats. When we reviewed 150 consecutive liver biopsies performed at Colorado State University approximately 12% of the cases had predominately a vacuolar hepatopathy (VH) as the major histological finding. By definition according to the WSVA Liver Standardization Group VH refers to a reversible parenchymal change that is characterized by swollen hepatocytes with clear cytoplasm due to glycogen without displacement of the nucleus from the center. The distribution and the extent of the lesion can vary being either diffuse, zonal, or involve individual cells. VH is a relatively easy histological diagnosis to make however Periodic acid Schiff (PAS) staining with or without diastase can be used to demonstrate glycogen accumulation. Vacuolated hepatocytes can also result from fat accumulation secondary to abnormal fat metabolism and is referred to as hepatic steatosis or lipodosis. Hepatic steatosis is a distinct histological vacuolar classification associated with abnormal fat metabolism and will not be discussed in this chapter.

VH in dogs is most often associated with hyperadrenocorticism (HAC). The dog is particularly sensitive the effects of glucocorticoids that both induce serum alkaline phosphatase (ALP) steroid isoenzyme activity and causes hepatic glycogen accumulation. (see chapter Evaluation of Elevated Alkaline Phosphatase in Evolve). Congenital glycogen storage disorders, breed specific disorders, hepatic nodular hyperplasia and a variety of stress-associated secondary diseases are conditions that can cause this typical hepatic vacuolar changes. In a large study of 336 histological liver specimens having VH (defined as making up greater than 25% of the hepatocytes) were retrospectively reviewed for an underlying etiology (Hill et al., 2006). The authors report 55% of the cases were associated with either endogenous or exogenous glucocorticoids with the remaining 45% having no known glucocorticoid exposure. Most all of the dogs with no glucocorticoid exposure had other identifiable concurrent illness. Conditions such as renal, immune-mediated, cardiac, hepatic, gastrointestinal disease, or neoplasia accounted for many cases. The author’s hypothesis was that stress-induced hypercortisolism associated with acute or chronic illness likely contributed to the development of the VH. A second in vivo study showed that by experimentally inducing a chronic four to five-fold elevations in plasma cortisol concentrations to simulate a stress-like state in normal dogs inhibited non-hepatic glucose utilization and increased hepatic gluconeogenesis and glycogen formation through enhanced substrate delivery to the liver.

**Idiopathic vacuolar hepatopathy**

There is a subset of dogs having elevations in serum alkaline phosphatase and excessive hepatic glycogen accumulation that do not have evidence of either a stress induced illness, evidence of HAC based on cortisol testing, a history of recent glucocorticoid administration or have a specific hepatic disease. These dogs are referred to as having an idiopathic vacuolar hepatopathy (IVH). They generally have no clinical signs and are usually identified during investigation of unexplained elevations in serum alkaline phosphatase (ALP) found on a routine health screen. Several theories have been put forward as to the cause of IVH. Some believe adrenal progestagens; most likely increases in 17-hydroxyprogesterone and progesterone are responsible as these changes as they are frequently identified to be abnormal when a commercial adrenal steroid panel is performed. However, critical evaluation and validation of the adrenal steroid panel (17-hydroxyprogesterone, progesterone, estradiol, testosterone and androstenedione) is as yet still lacking and a direct association has not be made. Because the VH changes are typical of glucocorticoid excess it is entirely possible that a yet to be identified adrenal steroid could be responsible for the VH. Obviously future research is necessary to delineate this syndrome and the relationship to adrenal steroids.

Scottish terriers are also reported to have a breed-specific syndrome associated with a VH and elevated serum ALP. These affected dogs generally have no clinical signs. The authors found that the elevated ALP was predominately the corticosteroid isofrom and following ACTH stimulation test in conjunction with an adrenal steroid panel found increases in one or more non-cortisol steroid hormones. The authors conclude that affected Scottish terriers have a type of hyperadrenocorticism on the basis of exaggerated adrenal hormone response. We have also observed similar non-cortisol steroid hormone increases in Scottish terriers but also in Scottish terriers without VH or increases in ALP adding more confusion to this syndrome. The reader should refer to Chapter 51, Occult hyperadrenocorticism: Is It Real? for further information concerning adrenal steroids.

Dogs with IVH generally have no clinical signs. They are usually identified serendipitously on a biochemical profile identifying elevations in serum ALP concentrations that subsequently initiates a diagnostic work-up. Most affected dogs are middle-aged or older at the time of diagnosis. There does not appear to be a breed or sex predisposition other than the syndrome described above in the Scottish terrier. A small percent of dogs may have reported polyuria and polydipsia (PU/PD) but the other signs typical of HAC are generally absent. The work up of the asymptomatic dog having an IVH usually begins after the identification of an elevation in serum
ALP. The ALP increases are often 5 to 10 times normal concentrations; the other liver enzymes are usually normal or there are occasional mild elevations in alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT). Marked elevations in liver enzymes other than ALP is not typical of this syndrome and if present other types of liver disease should be investigated. The work-up should first rule out common causes for an elevated ALP such as drug administration (including topical or systemic steroids, phenobarbital, or herbal medications), cholestatic liver disease, or bone disorders. Next adrenal testing (ACTH stimulation or low dose dexamethasone suppression) would be prudent to perform to eliminate possibility of HAC. Determining the percent of ALP steroid isoenzyme is generally not helpful. Dogs with IVH will have predominately a steroid-induced ALP isoenzyme but this is neither specific for HAC or IVH and other non-adrenal illness may also have similar increases in the steroid-induced ALP isoenzyme. Basic tests of liver function tend to be normal however the author has seen a few cases having very mild elevations in serum bile acids. Abdominal ultrasound of the liver is helpful to rule out hepatic nodular hyperplasia, occult hepatic neoplasia or cholestatic disorders that all could be differentials for an elevated ALP. Affected IVH dogs generally have an enlarged uniformly hypechoic liver with rounded borders. Adrenal glands are generally normal. Fine needle aspiration of the liver with cytology supports a diffuse vacuolar change. A PAS stain of the cytology sample can help confirm the presence of hepatic glycogen. A liver biopsy confirms diffuse vacuolar change but is rarely necessary. I generally make the diagnosis of IVH based on the above diagnostic findings and after exclusion of HAC, drugs, hepatic nodular hyperplasia, hepatic neoplasia or cholestatic liver disease.

At this time I believe adrenal sex steroid panel testing for most cases is not necessary for two reasons; first, our inability to adequately interpret the tests results and second, most all IVH dogs are generally asymptomatic and information obtained from the testing offers little important diagnostic or therapeutic information. Several labs offer adrenal hormone analysis and currently the most extensive adrenal steroid hormone profile is offered by the Clinical Endocrinology Laboratory at the University of Tennessee. The protocol for running the test is identical to that for a standard ACTH stimulation test.

Both proteinuria or hypertension are occasionally identified in cases of IVH and the affected dog should be periodically monitored for these complications and if identified, managed appropriately. Dogs with IVH are also thought to have an increased risk for developing biliary mucoceles and there is also some anecdotal evidence to suggest that some Scottish terriers with VH are at an increased risk of development of hepatic neoplasia (hepatocellular adenoma or carcinoma). Consequently it would be prudent to monitor IVH dogs from time with an ultrasound of the liver and biliary system.

The management of IVH is controversial at best and there are no studies critically evaluating therapy for this syndrome. I believe that specific therapy is unnecessary unless complicating factors such as hypertension, proteinuria or significant PU/PD exist. Problem associated with therapy arise from the fact we do not know what the endpoint of therapy should be; is it normalization of adrenal hormones, return of ALP into the normal range or histological resolution of the VH? There are anecdotal reports of dogs with IVH being successfully treated using low doses of mitotane and monitoring clinical parameters and measuring adrenal steroid concentrations including cortisol to assure hypoadrenocorticism does not result. Trilostane often shows a similar clinical response however concentrations of 17-hydroxyprogesterone and progesterone are frequently higher following this therapy. Anecdotal reports of clinical improvement in dogs having IVH using either of these therapies suggesting abnormal adrenal steroid production may be involved in the pathogenesis of this syndrome. However these treatments beg the question if therapy is warranted due to the expense of medication and monitoring and the potential complications associated with the therapy alone. Until more is known about this syndrome this author can’t recommend specific adrenal therapy unless significant clinical findings would warrant a trial therapy.

Alternative therapies suggested include melatonin and flax seed products. Melatonin has been shown to decrease sex hormone concentrations in normal dogs. It is reported to be beneficial in some dogs with alopecia X syndrome, and has also been suggested for IVH. Doses of 3 mg/15 kg q 24h PO has been recommended however here is no published data showing effectiveness for dogs with IVH. Flaxseed hull products with lignans have also been suggested because they compete with estradiol production but again there is no reported evidence of benefit for IVH syndrome.

Liver support therapy using products such as s-adenosylmethionine (SAMe), the milk thistle products, or other antioxidants may have some beneficial effects. One study showed dogs given glucocorticoids and treated with SAMe failed to show a decrease in serum ALP or amount of VH but did have improvement in hepatocyte oxidative status through increased glutathione concentrations. The above products are generally safe for liver support but will unlikely have any effect in the resolution of IVH.

Hepatic nodular hyperplasia
This is a benign process causing an increase in hepatic values and histomorphologic changes that include macroscopic or microscopic hepatic nodules containing vacuolated hepatocytes. Liver function remains unchanged. Grossly, the appearance may be suggestive of chronic hepatitis or neoplasia. The etiology is unknown but appears to be an aging change in dogs; most of those affected are greater than 10 years of age. Laboratory findings include an ALP increase (mean ALP ~ 600 IU/L), but some may have mild increases in ALT and AST concentrations as well. Ultrasound may be normal or may demonstrate larger nodules (many can be only microscopic and not observed on ultrasound). Biopsy confirms the diagnosis, however a wedge section is preferred. A needle aspirate or needle
biopsy may only demonstrate show a vacuolar hepatopathy. There is no specific therapy and it does not progress to a neoplastic process.

**Gallbladder mucocele**

To date greater than 130 cases of gallbladder mucocele have been documented in the literature. A gallbladder mucocele is a condition that is described as an enlarged gallbladder with immobile, stellate or finely striated patterns of mucoid material within the gallbladder lumen detected on ultrasound. The changes described can result in biliary obstruction or gallbladder perforation and peritonitis. Smaller breeds and older dogs are overrepresented. Shetland sheepdogs and Cocker Spaniels are most commonly affected. Most dogs are presented for nonspecific clinical signs such as vomiting, anorexia and lethargy. Abdominal pain, icterus and hyperthermia are common findings on physical examination in advanced cases. Most have serum elevations in bilirubin, ALP, GGT and variable ALT although some dogs are asymptomatic and a mucocele is diagnosed as an incidental finding on abdominal ultrasound. The Shetland sheepdogs tend to have hyperlipidemia and were first thought to have a genetic defect in the ABCB4 hepatobiliary transporter gene involved phosphocholine transport into the bile. That theory is now questioned in a reported second larger study. Risk factors identified in mucocele cases include endocrine disease (hypothyroidism, Cushing’s disease) and idiopathic vacuolar hepatopathy, hyperlipidemia and dogs on high fat diets. Gallbladder mucoceles appear ultrasonographically as an immobile accumulation of anechoic-to-hypoechoic material characterized by the appearance of stellate or finely striated bile patterns (wagon wheel or kiwi fruit appearance). This should be differentiated from biliary sludge (bile sludge can be found in normal animals), by the absence of gravity-dependent bile movement while the mucocele is non-movable. The gallbladder wall thickness and wall appearance are variable and nonspecific. The cystic, hepatic or common bile duct may be normal size or dilated suggesting biliary obstruction. Gallbladder wall discontinuity on ultrasound indicates rupture whereas neither of the bile patterns predicted the likelihood of gallbladder rupture.

Cholecystectomy is the treatment of choice for biliary mucoceles. Following cholecystectomy and recovery of postoperative period the prognosis is excellent especially when the liver enzymes are normal. Mortality rates have been reported to be in the 20% range and some may persist in having liver disease with elevated liver enzymes. There are reports of resolution of some mucoceles using ursodeoxycholic acid (ursodiol) and a low fat diet but this should only be attempted in the healthy patient and with careful monitoring. Ursodeoxycholic acid is thought to up-regulate biliary excretion of phospholipids and increase bile salt dependent flow.

On histopathology the gallbladder demonstrates cystic mucinous hyperplasia. The pathophysiology of this condition is unknown. It is possible biliary stasis and abnormal bile composition or lack of solubility results in gallbladder mucosal irritation and subsequent mucinous hyperplasia. Infection does not appear to be a factor in this condition. A mucocele is reported the most common cause of a gallbladder perforation.

**Portal vein hypoplasia**

Portal vein hypoplasia (PVH), also referred to as microvascular dysplasia (MVD), is a common syndrome in the dog associated with abnormal microscopic hepatic portal circulation. It is thought that PVH is 15 to 30 times more common than a congenital portosystemic shunt (PSS). Hepatic PVH has been suggested as the terminology by the WSAVA Liver Standardization Group that may better reflect the etiology of this condition although MVD is ingrained in the veterinary literature. It is believed that the primary defect in affected dogs is the result of hypoplastic small intrahepatic portal veins. This condition is thought to be a defect in embryologic development of the portal veins. With paucity in size or number of portal veins there is a resultant increased arterial blood flow in attempt to maintain hepatic sinusoidal blood flow. The hepatic arteries become torturous and abundant in the triad. Sinusoidal hypertension occurs under this high pressure system. Lymphatic dilation results and it is thought that this opens up of embryologic sinusoidal vessels to reduce pressure and thus acquired shunts develop to transport some (but not all) of the blood to the central vein thus by-passing the sinusoidal hepatocytes. This results in abnormal hepatic parenchymal perfusion and lack of normal trophic factors bathing the sinusoids causing hepatic atrophy. With portal shunting of blood increased iron uptake also occurs that results in hepatic iron granuloma formation. Ascites or portal hypertension generally do not occur in this condition.

Because similar histologic changes occur in dogs having PVH and PSS (i.e., hepatic hypoperfusion) the diagnosis can be confusing. If an intrahepatic or extrahepatic macroscopic shunt is not observed then PVH becomes the probable diagnosis. Angiography or transcolonic portal scintigraphy fails to demonstrate macroscopic shunting in this condition. Often a needle biopsy is not sufficient to provide enough portal areas to make the diagnosis, and consequently a wedge or laparoscopic biopsy may be necessary. The condition that was first described in Cairn terriers and now is felt to occur in other breeds of dogs. Yorkshire Terriers and Maltese may be over represented. Animals show no outward clinical signs and are usually identified because of elevated liver enzymes (ALT). All patients have abnormal serum bile acid concentrations (usually moderate elevations) but generally they are less than 100 µmole/L. It is reported PVH dogs have normal protein C concentrations while PSS dogs have concentrations less than 70% normal. There is no specific therapy. Some suggest antioxidants (i.e., SAMe, milk thistle etc.). The long-term prognosis is uncertain because of lack of experience with this relative new disease. There may be a small number of dogs developing portal hypertension over time.