Canine inflammatory liver disease – Lecture I

Chronic active hepatitis (CAH) is the descriptive diagnostic terminology for the ongoing inflammatory disease of the liver in dogs. This is thought to result predominantly from a complex immune mediated pathogenesis with concurrent factors relating to the initiation and severity of the disease. A similar/overlapping pathophysiologic process is hypothesized for feline inflammatory liver disease (FILD). Similarly, much of the discussions that follow regarding diagnostic tests, presenting symptoms, treatments, … will be applicable to FILD as well as canine chronic hepatitis. Some of these factors include the sex of the patient, the individual’s genetic haplotype, immunologic responses, and breed related variables such as hepatocellular handling of copper. Other terms used for this disease include chronic hepatitis and immune mediated hepatitis. I personally like the name, chronic immune mediated hepatitis, but I would not say this is a generally accepted term. Another term that may emerge is “canine inflammatory liver disease” (CILD). The differential diagnoses list would include any liver disease that may be chronic in their presentation.

Female dogs are slightly more prone to this condition in some reports. Any dog, mixed or pure bred, can develop CAH. In the mid-Atlantic region, Labrador retrievers are one of our highest frequency breeds at this time. CAH usually develops over months to years, but when an undefined "threshold" is crossed with respect to the degree of loss of normal liver function and/or degree of scar tissue (fibrosis) then clinical signs can appear to have occurred suddenly. The cause of CAH is not often proven. Certain medications, such as phenobarbital, and certain toxins or chemicals may also induce similar histologic disease or accentuate it if already present. These cases are usually thought of as being more drug associated liver disease (DALD) unless the process becomes self perpetuating after withdrawal of the drug. The accumulation of elemental copper in the liver cells has been debated as a cause or effect of liver cell (hepatocytes) death. West Highland White terriers, American Cocker spaniels and Doberman pinschers may have CAH and/or copper associated hepatitis. In reality, any breed may have excessive copper which may not be “breed associated” to our knowledge, yet (e.g., Siberian Husky recently as a clinical case of the author’s). Whatever the initiating factor for an individual case, copper accumulation in the hepatocytes is detrimental and favors increased risk of further liver cell death.

The most common path suspected for the development of CAH in dogs is the result of their own immune system damaging the membranes of liver cells and/or bile duct cells. This loss of self tolerance is not proven in dogs but has strong conceptual support from in vitro and in vivo studies in other species. This immune response is assumed to be heightened/exacerbated by some individual genetic factors, prior or current infections, certain drugs, and occasionally diet or environmental concerns. The triggering link/event is most often not identified. The process is suspected to be related to neoantigen like formations. These develop from molecules derived from bacteria (endogenous flora, pathologic infections), drugs, or other substances that combine with components of cell membrane to form new surface antigens (haptens). More in depth concepts by which the loss of self tolerance occur combines discussions of aberrant toll-like receptor (TLR) function and pattern recognition receptor (PRR) processes. These all participate in the attraction of a lymphoid immune response and cytokine production locally. The death of liver cells attracts inflammation (a
necroinflammatory response) and the effects of chronic inflammation can cause the further death of liver cells in a vicious cycle. A resulting increased rate of hepatocellular apoptosis plays into this pathophysiologic mechanism as large scale hepatocellular necrosis is not as common with CAH. Due to the active vaccination of our pet dog populations, we uncommonly diagnose canine Adenovirus hepatitis (at least in Maryland). But when it occurs and the patient recovers from the acute phase of the disease (acute hepatocellular necrosis), a subsequent chronic hepatopathy can/could develop. Similarly, any toxin that produces a significant degree of hepatocellular necrosis may result in a chronic hepatitis later (e.g., leading to post-necrotic cirrhosis). Leptospirosis may also act in this way and result in an chronic immune mediated hepatitis as well as the more often described chronic interstitial nephritis.

The accumulation of inflammatory cells (usually lymphocytes and plasma cells) in the microscopic areas of biliary and vascular bundles (portal triads) leads to fibrous tissue (scar) deposition. There is often a concurrent loss of hepatocytes and a hepatocellular regenerative response. The presence of fibrosis leads to portal venous hypertension and degrees of cholestasis. The retained bile acids then add to the insult to hepatocellular and canicular cell walls and microsomal functions. Further loss of cell membrane function, poor removal of waste products, and local hypoxia develop. The liver also becomes more prone to secondary (opportunistic) bacterial infections ascending the biliary tract from the duodenum due to the cholestasis. Bile is not normally considered sterile. Acute development of infection can be the reason for a sudden worsening of patient status and the presenting event as seen by the veterinarian and owner. As fibrosis and congestion become more severe, portal hypertension worsens and acquired portal systemic shunts develop.

The result of failure of liver cell function, reduction of hepatocellular mass, and portal systemic shunting of blood can include poor protein metabolism (low BUN, low albumin), low coagulation factor production (risk of bleeding), toxin accumulations, and elevated BUN due to GI bleeding. These events lead to prolonged systemic circulation of waste metabolic products in the blood, mostly from intestinal absorption of various chemicals and toxins. The most recognized are ammonia and LPS like toxins. Symptoms then develop which can include: behavior changes or seizures (hepatic encephalopathy), vomiting, diarrhea, loss of appetite, very prominent malaise or lethargy, and development of blood loss into the gastrointestinal tract via “variceal-like” venous hemorrhage in the stomach and proximal duodenum. This most commonly occurs as an enhanced diapedesis of red cells rather than severe and dramatic esophageal variceal hemorrhages as seen in humans. Ascites develops when an imbalance of the co contributing factors of lower oncotic pressure (as albumin production falls) and increased portal hydrostatic pressure develops.

The common diagnostic tests pursued in patients with symptoms of or suspicion for chronic hepatitis include: serum chemistries profile (notably ALT, ALP, GGT, bilirubin, albumin, & BUN) with electrolytes, CBC with platelet count, urinalysis, serum bile acid panel, abdominal radiography (has not been replaced by ultrasound), full abdominal ultrasound (not just the liver), fine needle aspiration with cytology, hepatic biopsy (an entire discussion unto itself), and coagulation testing. Liver biopsies are obtained in three common ways. The predominant enzyme that marks the active aspect of the disease is the ALT value. This enzyme elevation is often documented as a slow progression over months or years. If the ALT is elevated more than six weeks then I consider it a chronic hepatitis. FNA of the liver is not very helpful usually for cases of CAH. It may add confidence to the clinician that more infiltrative disorders are not present (less likely), e.g., lymphoma, or that a septic suppurative process is present and needs treatment.
Percutaneous liver biopsy is done by the author with a 14 gauge spring loaded True-Cut type biopsy needle. The goal is for multiple portal triad to central vein aspects of lobules to be present when examined with the microscope. Use of an 18 gauge needle is, in this author's opinion, not adequate. The liver should appear as a reasonable sonographic target (normal to large size) and have adequate dimension to allow for the “throw” of the needle's specimen slot. The left lateral lobe is the general target in most situations as it presents itself as a better target and is usually the largest lobe of the canine and feline liver. Ultrasound guidance is highly advised but a “blind” technique has been described. A minimum of three specimens should be obtained, and additional as needed for potential copper quantitative analysis and cultures. Bleeding is the primary risk with this technique, however, biopsy or damage to unintended organs does occur with lack of experience. Samples of diaphragm, myocardium, and stomach have all been reported. This author requires a platelet count, PT, PTT (or an I-Stat ACT) and an oral mucosal bleeding time (OMBT, also called a buccal mucosal bleeding time) test. Some argue that these are not reliable indicators of potential problems with procedure associated hemorrhage. This author feels that the liabilities (“standard of care”) are too high not to do these tests. The OMBT has been the more helpful of the coagulation tests in the author's experiences. No tests will predict a degree of risk for causing bleeding from a hepatic artery. Laparoscopic biopsy is a preferred technique. It is having a bit of a renaissance of interest as equipment costs have declined (new generations of equipment at human medical centers has moved more basic equipment to the veterinary market) and the public (and veterinarians) are interested in “minimally invasive surgery”. This allows for more variation in lobes sampled and for larger pieces of tissue. Visualization of hemorrhage can also occur leading to intervention via the laparoscopic approach or guide a decision regarding “conversion” to full celiotomy. Ascites and known coagulopathy may be reasons to avoid this technique. The investment in equipment, need for familiarity (experience), and amount of staff involvement has led some to use laparoscopy less frequently. It is less invasive in general. It is not less expensive except by choice of the facility. A surgical approach can be via intended full exploratory of the abdomen. It is an option to perform a more minimalistic approach with smaller incision (“key hole” approach). Celiotomy may be more thorough and conservative of time for some experienced surgeons when multiple biopsies are required (e.g., stomach, small intestinal segments, lymph node, pancreas, and liver). There is an element of compromise when more complete examination of the abdomen is not pursued. Ultrasound prior to choice of liver biopsy technique has been very helpful in the past 20 years. The author prefers laparoscopic obtained biopsies for primary diagnosis but the balance of factors leads some clients to prefer percutaneous or surgical approaches.

Treatment and prognosis for CAH are discussed in the third lecture of the author's series, Management of chronic liver disease – Lecture III.

Feline inflammatory liver disease – Lecture II

Feline inflammatory liver disease (FILD) has a variable presentation and histologic appearances than most consider for CAH. There are several forms of this condition that are defined based upon the biopsy description. The pathogenesis of FILD likely shares some related processes with inflammatory bowel disease (IBD), and may coexist with this condition and with pancreatitis (Dave Twedt's “triaditis”). FILD in general can have symptoms of malaise/lethargy, fever, high serum globulins, vomiting, loss of appetite, and diarrhea, weight loss, progressive liver enzyme changes or just losing body condition. This condition is “thought” to have a risk of about 5-10% for transformation to lymphosarcoma but it is unpredictable. The diagnosis is obtained via biopsies of
the liver. Radiographs of chest and abdomen with goal of searching for cancer is usually done first. Abdominal ultrasound is usually used to look at the liver's general structure and appearance. Percutaneous or laparoscopic liver biopsies, or biopsies obtained via abdominal surgery can be done to obtain samples of the liver. The selection is the result of balancing many factors (see prior proceeding’s notes under CAH). Treatment involves use of anti-inflammatory drugs (e.g., prednisone, dexamethasone), immunosuppressive drugs (cyclosporine, chlorambucil), and ursodiol (a bile thinner and mild anti-inflammatory effect). Antibiotics are commonly used/prescribed if secondary bacterial infections occur or are suspected. The prognosis is usually good but variable in its rapidity of response and degree of improvement. Control of the disease is more common than resolution after more than a year of treatment. Reassessments and rebiopsy can be needed if there is poor response, loss of control, or concern that cancer could be present. Ongoing treatment plans are tied to plans for monitoring of response to medications as well as for potential adverse effects of the medications.

FILD pseudonyms have largely been based upon the suspected pathogenesis (e.g., infectious, idiopathic, immunologic) and the histopathologic description (e.g., location of inflammatory cells within the lobular and portal architecture, types of inflammatory cells present, extension through the limiting plate around portal triads, hepatocellular changes, presence and location of fibrosis, biliary epithelial and ductular changes, and vascular changes). The most common names for FILD over the years have included: acute suppurative cholangitis/cholangiohepatitis, long term (chronic) non-suppurative cholangiohepatitis, sclerosing-like cholangitis, lymphocytic cholangitis cholangiohepatitis complex (LCCC), cholangiohepatitis (CH) complex (as acute and chronic forms), progressive lymphocytic-plasmacytic cholangiohepatitis, and lymphocytic portal hepatitis. The current nomenclature for FILD forms are: Acute neutrophilic form (ANF), chronic neutrophilic form (CNF), lymphocytic cholangitis (LC), and portal lymphocytic hepatitis (LPH). A fifth category is feline inflammatory liver disease induced by liver flukes. These definitions are still the subject of ongoing discussions. Confusion/controversy occurs for clinicians and pathologists due to the overlap in histologic descriptions and clinical presentations. It is not clear whether there is a progression of one form to the next or if there are unique pathogenic pathways for each of the forms. There is some thought that in the more chronic forms, the hepatocytes are injured indirectly via the accumulated inflammation. Injury to the liver cells may occur as a result of local cytokines and a toxic microenvironment, direct inflammatory cell injury causing hepatocellular necrosis, with/or induction of hepatocellular apoptosis (a chain of events leading to programmed cell death and drop out of individual hepatocytes).

The development of ANF as a form of cholangiohepatitis has been postulated to start with a systemic bacterial seeding or via ascension of microorganisms via the biliary ductular system and then develop subsequent progressive responses of the immune system that result in inflammation. One hypothesis is that there is a progression from acute neutrophilic form to the chronic neutrophilic form as there is a decreasing presence of neutrophils and increasing numbers of lymphocytic-plasmacytic cells. This then becomes characterized as the lymphocytic form (LC) of FILD. The apparently less pathogenic lymphocytic portal hepatitis (LPH) form would then represent a less pronounced response of the liver to the challenges of living. This is not documented in the literature but is an interesting hypothesis to help explain the difficulty in maintaining complete separation of distinct forms of FILD. The hypothesis is based upon circumstantial evidence used as pieces of a pathogenic puzzle.
The ANF form of FILD was previously called suppurative cholangitis because of the accumulation of neutrophils within the biliary ducts and portal areas. Bacteria have been cultured in some cases and visualized in some. *Escherichia coli*, have been most commonly mentioned but many bacteria have been cultured that generally are similar to those of the gastrointestinal microflora. Younger cats seem more disposed to this form, often in the 1-6 year of age range. It is not uncommon for ANF to present as an acute process with fever, vomiting and/or abdominal pain. Any differential diagnosis that would cause these symptoms would be included in the diagnostic process. The ALT is usually elevated. Bilirubin may not have had time to increase when the cat is presented but generally will go up if not treated. Some cats show an inflammatory left shift and are usually not anemic. Dehydration is variable depending upon how long the pet has been ill, febrile and vomiting. The author feels that many cats are treated for this condition prior to it's being diagnosed or suspected as many feline patients are given a broad spectrum antibiotic fairly quickly in general practice as a pragmatic action. The antibiotics (often Clavamox alone or with a fluroquinolone) are given along with fluid support. Imaging is warranted even if the pet is feeling better in case of structural issues that should be discovered. It is common for cats with this to be tested for pancreatitis simultaneously. Most cats do well and respond in 24-72 hours.

The second form of FILD is chronic neutrophilic form (CNF). This form of the disease involves a possible progression from ANF or uncertain mechanisms. The neutrophil numbers decrease in CNF with an increasing presence of lymphocytes and plasma cells. The combination, to varying levels has led to some of the controversy about past descriptions for these cases (some emphasized the neutrophils, others the lymphoplasmacytic infiltration). When there is a presence of inflammatory cells extending past, or which disrupt, the limiting plate the terminology changes to cholangiohepatitis from cholangitis. The same GI micro flora that can ascend the biliary tree for ANF are thought likely to have participated with the pathogenesis of CNF but it is not proven other than by association. Other bacteria such as helicobacter and bartonella species may be involved based upon research and epidemiology reports as a possible highlight to etiologies. It is thought that an mononuclear immunologic response has been triggered at this point leading to both nonspecific and specific lymphoid cell involvement. Components of bacteria may act as: antigens to the immunologic cells, as haptons that form with host cell membrane components, be related to the haplotypic make up of the individual patient, and reflect a loss of normal pattern recognition response (PRR) to normal GI flora and inappropriate response of toll-like receptor (TLRs) function with apparent loss of self tolerance. These latter two terms are fairly complex concepts. Good discussions on Wikipedia are available for them as representing recent pathophysiologic mechanisms of disease. Newer techniques for detection of bacteria are being used that add some credence to the concept of a bacterial origin for ANF and CNF via fluorescent in-situ hybridization (FISH) technology as well. This technique highlights the presence of bacteria from different targeted species or genera within biopsy tissue. CNF generally occurs in middle age to more mature cats. Diagnostic tests remain similar but there often are more of the liver enzyme changes expected of developing chronic liver disease. Treatment still relies upon use of antibiotics, often for longer periods of time (3 to 12 weeks depending upon clinical impressions of a case), fluids, and supportive care. But as the pet may seem to feel better, the liver enzyme levels often do not return to normal. Biopsy results lead to use of additional medications and supplements. In particular, ursodiol and s-adenosylmethionine (SAMe). Further discussion of treatment for chronic inflammatory liver disease follows in the third lecture/proceedings from the author.

Lymphocytic cholangitis (LC) is the third form of FILD discussed. It involves a marked predominance of lymphocytes. More mature patients are found to have this form of FILD. The cats
frequently seem to just not be feeling well or have symptoms that could overlap inflammatory bowel disease (IBD), chronic active pancreatitis, or the differential diagnoses that would be listed for these types of conditions. Lymphocytic cholangitis (LC) is thought to represent a chronic form of cholangitis that has resolved its suppurative aspects. There is a moderate to severe infiltration of small lymphocytes that are concentrated in portal areas but which may also infiltrate biliary ductules and be found in the hepatic parenchyma. Small areas of lymphoid aggregates can be found. This form may commonly have biliary hyperplasia, distention of bile ductules, and mild degrees of hepatocellular loss, and variable presence of fibrosis. A mixture of other inflammatory cells may be seen in lesser numbers. The treatment will include medications that merge anti-inflammatory and immunosuppressive goals. Prednisolone or other corticosteroids as well as chlorambucil can be used together or separately depending upon the severity of a case. Treatment is often for long periods of time, months to years, in order to maintain reduced liver enzyme values as well as the pet remaining asymptomatic.

The fourth form of FILD is called lymphocytic portal hepatitis (LPH). Again, there may be degrees of overlap in pathologic descriptions with the other forms FILD that require you to provide a good history for your pathologist. Lymphocytes are the predominant cell type and are located within the portal triads. Fibrosis or biliary hyperplasia can be noted. LPH is common in older cats, many of which have no clinical suspicion of FILD until liver enzyme elevations (predominantly ALT) are found on “routine” serum chemistry profiles. It is thought to be slowly progressive and have minimal to modest liver enzymatic changes. It’s etiology is not known but suspected as an extension of immune mediated disease or a result of “non-specific” reactive responses to extra hepatic disease. Some question whether this is a disease or “age related change” as 82% of cats in one study showed some degree of infiltration by small lymphocytes in the portal triads. These cats tend to be diagnosed at greater than 10 years of age and have comparatively good prognoses; often existing with their disease for years. Because it cannot be distinguished from the pre-clinical LC form of FILD, biopsies are still advised. It is likely more pragmatic that many of these cases are treated non-specifically with ursodiol and anti-inflammatory or anti-oxidant nutritional supplements.

Feline liver fluke infections represent the fifth form of FILD. These infections are related to ingestion by the “hunter” cat of small lizards and other reptiles that are the intermediate hosts of the flukes. The most common fluke is Platynosomum concinnum and is found along the coastal regions of Florida, the Bahamas, other Caribbean islands, and Hawaii. Noting the travel history of the patient is important when considering this disease as a differential diagnosis for cats with hepatopathy. The predominant change seen with histopathologic assessment of liver tissue is an eosinophilic response around adult flukes found mostly in intrahepatic bile ducts. However a concurrent suppurative secondary septic inflammation has been noted as the bile ducts are not normally sterile. Presence of operculated eggs of the flukes are often seen in the bile. The eggs are released intermittently with bile so that a single negative fecal sedimentation examination may not suffice for diagnosis. Bile is very viscous with this disease! Ultrasound guided cholecystocentesis is another option for diagnosis and as a means of relieving significant cholestasis if present. However the operator should have familiarity with this technique and its risks. Surgical exploratory surgery with manual milking of the bile through the common bile duct, cholecystoduodenostomy and placement of biliary stents have been described as potentially helpful depending upon the clinical aspects of a specific case. The prognosis is variable based upon the point of clinical diagnosis. Treatment is generally listed as febendazole given at a high daily dose for ten days, then repeated in a few weeks. It is somewhat unique as a preventable FILD via keeping the cat away from ingestion of the intermediate hosts.
Ursodiol is frequently advised as a supportive treatment to assist in reducing the viscosity of the bile and cholestasis.

Management of chronic liver disease – Lecture III

Management of CAH is often complex, involving ongoing monitoring, alterations of treatment plans, and long intense client communications. Clients are often concerned about long term costs of visits, monitoring, medications and the uncertainty of the prognosis. This leads to the thought that referral to a veterinary internist may often being the wisest option when clients intend to aggressively pursue medical efforts for their pet.

The patient status, histopathologic micro description of a liver biopsy, the prognosis, and the selected design of a treatment plan are intricately linked. The treatment plan depends heavily upon pathologist's interpretation of a liver biopsy. This is influenced by the quality of the biopsy specimens, adequateness of history provided, and their interest level for liver disease. The author, as a specialist in internal medicine, feels that most liver biopsies warrant more routine use of special stains (which would make them not quite so special). Masson's trichrome, reticulin, iron and copper stains are helpful. Often, pathologists do not want to do these stains but then change the weighting of their interpretations based upon them. The patient's overall condition, their tolerance for medications (e.g., nausea), and factors affecting hepatic metabolism (e.g., protein levels, coagulation factors, concurrent drugs in use, …) all play additional roles in selection of medications for treatment of chronic liver disease.

We cannot know which patient will or won't respond to treatments. The keys to those cases that do well, in my experience, are the patient's tolerance of numerous oral medications (the pet with the "cast iron stomach"), general tolerance of the administration of the multiple medications by client and patient (compliance), patience of the owners as this is a long term effort, and acceptance of costs of monitoring and adjusting medications. It is best if there is no to minimal fluid (ascites) present as a reflection of the severity of portal venous hypertension (high blood pressure in the portal venous system). Despite efforts a pet may not respond, but since the liver has the potential for regeneration and scar tissue can remodel over time, many dogs do improve. Our efforts will not and do not have to return the normal to "normal"; our goal is to get the liver in good enough condition that symptoms resolve. If one is not tolerated then we either drop it from the regime or we substitute another.

The concept of “polypharmacy” is generally avoided in treatment of many diseases; having the goal to use as few of drugs as possible. However, the management of CAH often utilizes a plan that is directed towards the multiple and different aspects of the suspected/proven pathogenesis of CAH. The factors can influence the therapeutic goals for reduction of inflammation, remodeling of fibrosis, reduction of copper, treatment of microorganisms, and the preservation (cytoprotection) of hepatocytes via use of multiple pharmacologic and nutritional products. The pharmacologic categories or specific drugs that are discussed below are not listed in a particular order. It is important to have the time to implement these many drugs and supplements so that the patient and owner are not overwhelmed. One patient may receive only three drugs in a plan while another patient may need (a relative term) 7 or 8 of them. There can be some “give” on administration by the clients and compliance of the patient regarding missed doses. These drugs take weeks for control of mononuclear inflammation and months to reduce scar tissue (fibrosis) with concurrent hepatocellular regenerative efforts. It is best if they can be introduced two or three per
week until the animal is receiving all that are prescribed. However, some cases have to be approached more aggressively. The results of treatment can include prolonging symptom free life for months or years; or may show little benefit or even hepatotoxicity (e.g., azathioprine, cyclosporine). The treatment does not have to miraculously make the liver normal again. *The treatment plan only needs to improve function or reduce symptoms to a point that restores a quality of life for the pet.* Long term monitoring is a part of treatment and the owner’s patience with the process becomes as important in the treatment plan as any of the medications.

Corticosteroids have been in use for treatment of inflammatory liver disease for many decades. My preferences are for use of prednisone in dogs and prednisolone in cats. However this is not dogmatic. Alternatives that can be tried when there are side effects or inadequate responses are methylprednisolone or dexamethasone with due consideration to their different pharmacokinetics. The benefits of corticosteroid use are the availability, low cost, that it can be anti-inflammatory or immunosuppressive, they can elevate the sense of well being for the patient, and often increases appetite. The downsides to remember are that these are catabolic and have numerous side effects in dogs, less so in cats. Notably in dogs, they can cause glycogen hepatocellular swelling. In particular, there is concern for their use when fibrosis limits the ability for hepatocytes to swell within a pathologic fibrous confine (e.g., nodular hepatopathies, micro or macro nodular cirrhosis). If this situation occurs, and the pet happens to be a very sensitive individual then marked and relatively acute worsening of cholestasis can result. Any dog will have some degree of a dose dependent vacuolar change to hepatocytes with resulting increase of hepatic alkaline phosphatase; but there are also individuals with genotypes that lead to marked increase of glucocorticoid specific alkaline phosphatase. If the latter develops, then it can lead to confusion regarding the presence of rising liver enzyme values in face of treatments and resulting confusion regarding help or harm. Uncommonly, there are dogs that have true drug intolerance or notable increased adverse responses to corticosteroids. These can show outward good health but have massive liver enzyme elevations including ALT and serum bile acids. When there is significant presence of portal venous hypertension, then there is a tendency to increased diapedesis of red blood cells or hemorrhage into the stomach and proximal duodenum. This is the comparative species equivalent, albeit less dramatic, of human esophageal varices. When corticosteroids are used, reduction of the gastric mucous secretion, reduced tensile strength of collagen, and increased microvascular portal congestion, there is an increased risk for upper gastrointestinal bleeding. This then can increase risk for hepatic encephalopathy (HE) and confusion about origin of anemia. How often this plays out clinically is not known (clinical evidence level 4). But anecdotally it does occur. Cats have a good general tolerance for glucocorticoids when compared to dogs or humans. Unmasking of diabetes mellitus (counter-regulatory to insulin) is one of the more common concerns that can add difficulties to management of feline hepatopathies. The use of corticosteroids early in treatments at higher doses can favor patients who are depressed with poor/no appetite. Doses range from anti-inflammatory to immunosuppressive levels and each drug has it’s own pharmacodynamic profile. The long term goal is alternate day administration at the lowest effective dose or withdrawal of the class of drug from the treatment plan when possible. In many canine cases the author does not use corticosteroids, while for most feline cases he does.

Immunosuppressive medications have become a very important component of the armamentarium for treatment of chronic inflammatory liver disorders in dogs and cats. Cyclosporine or azathioprine are used to modulate the immune system in CAH of dogs with an end goal of decreasing inflammation. When considering initiation of treatment with one of these drugs, the author is more comfortable
starting treatment with the brand name products of Atopica™ and Imuran™. When the stakes are high and there could be a question of bioavailability or efficacy, the author wants to know that these are trusted products. There is a generic alternative for the microemulsion formulation of cyclosporine, and a generic for azathioprine. If the pet is doing well after the first couple of months, and a long term treatment plan has evolved for the patient, then the use of generics is inserted. My preference currently for predominantly lymphoplasmacytic hepatopathies is cyclosporine as Atopica™. Azathioprine is less expensive and is a good drug. However there are four drawbacks that we used to deal with but which now lead us more towards cyclosporine.  

First is that some dogs can respond within a couple of weeks to its use. But others who have pharmacogenomic issues (e.g., MDR-1 deficiency) may not respond or have a more delayed response over 4 to 12 weeks. Second is that there is an increased incidence of drug related liver enzyme elevations, including ALT, which can confuse our interpretation of treatment efforts. Third is that azathioprine tends to be more suppressive of bone marrow and harder to balance leukopenia. And fourth is that azathioprine is a potential trigger for drug associated induction of pancreatitis in dogs. Azathioprine use in cats has not been a happy process in the authors' experience with more GI side effects and toxicity issues, notably bone marrow suppression. Monitoring of cyclosporine use for side effects of gingival hyperplasia, hepatotoxicity, bone marrow suppression, and others per the drug insert for Atopica™ but are generally less common in the author's experiences as well as being labeled for use in dogs. If there is concern for response versus dose, it is also possible to check peak and trough levels of cyclosporine in the patient. For immunosuppression in cats, chlorambucil provides an inexpensive and fairly reliable option. Alternatively, cyclosporine can be used. The doses used by the author for these drugs are: azathioprine in dogs 1 mg/kg twice daily for 10 days then 1-2 mg/kg QD and progressing to QOD as possible; cyclosporine in dogs or cats 3-5 mg/kg QD for 10 days, then BID or QOD as needed/adjusted; chlorambucil 0.25 mg/kg Q72 hours (3 days) PO then adjusted to Q48 to Q96 hours per assessments. There are other immunosuppressive drugs that can be used if responses are not adequate but which may require referral. Dogs and cats with significant liver disease may “feel better” if given even small doses of a glucocorticoid medication when immunosuppressive drugs are being used.

D-penicillamine may be used as a copper chelator and anti-inflammatory medication. It is thought to encourage remodeling of fibrosis. It is used predominantly when there is an inflammatory hepatopathy that is related to high copper levels found quantitatively or as consistent with the copper staining and H&E findings. This drug can be quite expensive but is the most common copper chelator used in canine copper hepatopathies. Trientine (2-2-2 tetramine) may be a better copper chelator but is more expensive and potent enough to uncommonly result in copper deficiency. This drug is also expensive. Both are given at 10-15 mg/kg BID. Chelating drugs may have side effects, mainly nausea and vomiting. Some give it twice daily with meals. Other means of reducing copper include blocking of copper intestinal absorption using Zinc (author prefers zinc gluconate). There are a very wide range of doses for this product depending upon the form of zinc administered and clinical experiences. The author “feels” that many doses may be too high and risk zinc toxicity when given for long periods of time. The author give zinc gluconate once daily at 25 mg for dogs < 10 kg and 50 mg for dogs > 10 kg. He has found this to be clinically effective. However, for situations where more aggressive management may be required, doses can be increased (e.g., Bedlington terriers). Serum Zinc level is monitored at 30 days, and then two to three times a year. Copper deficiency is a concern but rarely reported in dogs. This could become more important if copper restricted diet is concurrently being fed. Zinc and copper chelators should not be given at the same time of day (separate by a few hours if possible).
Ursodiol (synthetic bile acid) is a cholorrhetic drug that helps reduce the viscosity of bile, improve the liver cells' tolerance to stress/inflammation, and in various ways reduce inflammation. Ursodiol is commonly used in cats and dogs. The dose is approximately 10 mg/kg (range 5-15 mg/kg depending upon circumstances of each case) per day, sometimes divided. This drug is often used when hepatocellular cytoprotection and/or enhanced bile flow are desired, hence it is commonly included in treatment protocols for chronic inflammatory hepatopathies. It likely does not have significant effects at “dissolving” cholecystoliths as was once believed, however its actions as a cholorrhetic may be helpful in this situation.

Colchicine is given to reduce fibrosis, promote remodeling of existing fibrosis, and inhibit inflammation. These are the goals. There are individual case reports and anecdotal (level 4) clinical evidence for use of this medication when fibrosis is an existing major component of the disease process. This is an inexpensive medication. It is an old drug and still used for people with gout, hence most pharmacies have it in stock. Colchicine does hold risks for side effects involving bone marrow suppression and the GI tract in particular. Exposure to colchicine should be prevented for clients who are pregnant or ill. The author's dose regime is 0.03 mg/kg PO once daily initially. In some cases, with re-assessments and monitoring, I have increased the frequency to BID and in others reduced it to QOD.

Support of hepatocellular metabolism and survival is a goal that we pursue via the use of many nutritional products or supplements (“nutraceuticals”). We do not know how beneficial they are when compared to their cost and added complexity of treatment plans. Antioxidants protect cells from the damaging effects of free radicals, which are molecules that contain an unshared electron. Free radicals damage cells and might contribute to the development of cardiovascular disease and cancer. Unshared electrons are highly energetic and react rapidly with oxygen to form reactive oxygen species (ROS). The body forms ROS endogenously when it converts food to energy, and antioxidants might protect cells from the damaging effects of ROS. The body is also exposed to free radicals from environmental exposures, such as cigarette smoke, air pollution, and ultraviolet radiation from the sun. ROS are part of signaling mechanisms among cells. The author uses these products commonly with the hope that they are reducing the eventual total doses of the more potent medications (e.g., immunosuppressive drugs). There are some human studies having large values for “N” in patients with autoimmune diseases (e.g., rheumatoid arthritis, SLE) that showed statistically relevant reduction in doses of corticosteroids by 10% when vitamin E or omega 3 fatty acids from fish oil were used. Using products with strong reputations for their ingredient analysis and bioavailability is very advised and the author has used products from Nutramax Labs more often for this reason. Trust has to be a major factor in our decision to use nutraceuticals. There are likely many brands for which veterinarians feel confident based upon their experiences as based upon my conversations with veterinarians involved with more alternative modalities of treatment. Nutraceutical products do not replace pharmacologic efforts. There are also a large number of homeopathic and herbal products used for similar goals and with which the author is unfamiliar. Potential drug interactions should be considered when prescribing these products just as with use of any pharmacologic one. What should be kept clear is that these functions have been shown mostly in “deficiency models” and not with pharmacologic levels of supplementation, or in situations of “pre-treatment” prior to exposure to toxic substances or situations.

Vitamin E at 100-400 units per day per patient has been suggested as helpful for support of patients with hepatopathies. Quoted from NIH source: “Naturally occurring vitamin E exists in eight chemical
forms (alpha-, beta-, gamma-, and delta-tocopherol and alpha-, beta-, gamma-, and delta-tocotrienol) that have varying levels of biological activity. Alpha-(or α-) tocopherol is the only form that is recognized to meet human requirements. Serum concentrations of vitamin E (alpha-tocopherol) depend on the liver, which takes up the nutrient after the various forms are absorbed from the small intestine. The liver preferentially resecretes only alpha-tocopherol via the hepatic alpha-tocopherol transfer protein; the liver metabolizes and excretes the other vitamin E forms. As a result, blood and cellular concentrations of other forms of vitamin E are lower than those of alpha-tocopherol and have been the subjects of less research. Vitamin E is a fat-soluble antioxidant that stops the production of reactive oxygen species (free radicals) formed when fat undergoes oxidation. Scientists are investigating whether, by limiting free-radical production and possibly through other mechanisms, vitamin E might help prevent or delay the chronic diseases associated with free radicals.

In addition to its activities as an antioxidant, vitamin E is involved in immune function and, as shown primarily by in vitro studies of cells, cell signaling, regulation of gene expression, and other metabolic processes. Alpha-tocopherol inhibits the activity of protein kinase C, an enzyme involved in cell proliferation and differentiation in smooth muscle cells, platelets, and monocytes. Vitamin-E–replete endothelial cells lining the interior surface of blood vessels are better able to resist blood-cell components adhering to this surface. Vitamin E also increases the expression of two enzymes that suppress arachidonic acid metabolism, thereby increasing the release of prostacyclin from the endothelium, which, in turn, dilates blood vessels and inhibits platelet aggregation.”.

S-adenosylmethionine (SAMe) is commonly used for its many potential benefits. Silybin and sylimarin (from milk thistle) are used to help reduce tendency to fibrosis. There are many in vitro and laboratory in vivo models for use of this nutritional supplement in situations of pre-exposures to hepatotoxins and a few in post-exposure use that support it as a logical product to use in hepatopathies. Some of these studies have been done in cats and dogs lending credence to its use. SAMe is an important hepatic metabolite and glutathione donor that has been well studied in vitro and in vivo. It is used in necroinflammatory, hepatotoxic, and cholestatic liver disorders of dogs and cats. Dose is 20-40 mg/kg daily on fasted stomach using a stabilized product. SAMe given orally as a trusted product is enterically available and imparts biologic effects that might be useful for attenuating systemic or hepatic oxidant challenge to hepatocytes for dogs and cats (Center SA). There are large scale human trials involving alcoholic hepatopathy in humans and SAMe use for hepatocellular cytoprotection.

Cell membrane stabilizers, vitamins, and anti-oxidants can include phosphatidylcholine, vitamin E, vitamin B-complex, cobalamine, thiamine, vitamin K1, superoxide dismutase (Oxstrin™), and omega-3 fatty acid supplements. Special diets that are variably restricted in protein and copper are preferred and may include some of the above supplements. There are too many diets now available, many of high quality but some are difficult to verify their analysis and value, hence it seems logical to prescribe veterinary prescription diets.

Lactulose or similar compounds are given orally, or by enema, to decrease contact time for enteric toxins (laxative effect) and reduce ammonia absorption from the intestines and colon.

Diuretics (e.g., spironolactone, furosemide) help reduce excess intravascular fluid volume and are used judiciously so as to prevent decrease of microvascular perfusion yet encourage loss of ECF volume. Spironolactone is commonly given at 1-2 mg/kg once or twice daily if needed to assist with management of ascites.

The administration of inhibitors of the angiotensin system (e.g. ACE inhibitors, ACE receptor antagonists) may also help reduce ascites production. The most commonly reported and prescribed is enalapril at 0.25-0.50 mg/kg once or twice daily. Due monitoring for adverse effects on renal
perfusion need to be pursued when these drugs are given. The author prefers to use an ACE-I with spironolactone. Rechecks of blood pressure and serum chemistry values at 3-5 days after starting their use is advised.

Use of antacids is also not of proven benefit but is common. Their use is considered more often when vomiting or reflux of gastric acid is presumed to be a negative event for the patient. The author also feels that their use may help reduce risk of concurrent hyperacidity associated gastric and gastroduodenal bleeding. Famotidine is commonly used because it is safe, effective and has minimal affects upon hepatic drug metabolism (which is not the case for ranitidine and cimetidine). Omeprazole is an another option that also has minimal adverse effects. It is controversial whether long term use results in a clinically significant increase of serum gastrin. The author does advise not to suddenly discontinue their use if they have been being given long term. Both are generally administered at 0.5 mg/kg twice daily initially then as needed.

Antibiotics can be used when/if a bacterial infection, primary or secondary, is thought to be involved with pathogenesis of disease or for suspected/proposed production of digestive related neurotoxins of hepatic encephalopathy to reduce gut microflora. Although oral neomycin has been used for decades to reduce GI flora that produce the toxins (e.g., ammonia as one representative compound), it does relatively little to suppress anaerobic bacteria that produce many of these substances. Concurrent use of a fluoroquinolone antibiotic or neomycin with Clavamox™ are common combinations used by the author. Parenteral antibiotic treatments can include clindamycin, metronidazole, ampicillin, meropenem, aminoglycosides when given appropriate thought. The concept of altered gastrointestinal microflora and potential clinical significance are an area of large amounts of research and argument. It is common for numbers of bacteria to return to pre-antibiotic numbers within 10 days of starting their use. This tends to occur whether the antibiotics are discontinued or continued. There certainly can be concerns for upset or displacement of good flora by bad flora (e.g., C. difficile, C. perfringens with enterotoxins, adherent adhesive E.coli, …). These concerns have led to the use of probiotics and prebiotics. There use is often based upon similar proposed goals as for nutraceuticals. Similarly, there are not good clinical trials supporting their use while there is good theory to consider them. If a probiotic is going to be used, it is advised to use one for which there is good rationale.

Vitamin K1 is often given parenteral injection to support production of both pro and anti coagulant proteins by the liver. It is common to give this in situations of decreased hepatic function and/or chronic poor nutritional status where intake may have been decreased.

Fluids – the hydration status of the patient is a primary concern in order to maintain microvascular perfusion in a compromised liver that may also be suffering from accumulation of toxic substances, irritating viscous bile, and hypoxia. To this point, use of parenteral fluids (either IV or SQ based upon patient status) is common for our liver patients until adequate oral intake and homeostasis is present. Use of parenteral nutrition is also often considered. This is pursued more commonly as partial parenteral nutrition (PPN) due to the complexities of dealing with total parenteral nutrition.

Antiemetics are generally used only when needed and with consideration to their potential side effects.
DEFINITION

- A change in the frequency, consistency, and volume of feces for more than 3 weeks or with a pattern of episodic recurrence.
- normal feces is 65-68% water as passed; ingesta in the ileum is near 95% water content
- As little as a 2% increase in fecal water content can result in what we term as diarrhea by appearance.
- Can be either small bowel or large bowel in origin
  a) small bowel diarrhea – often larger volume, normal frequency, more fluid; melena if blood present
  b) large bowel diarrhea – often is more frequent, smaller volume, mucous, bright red blood
  c) mixed/comboination diarrhea – any or all of above descriptive terms

PATHOPHYSIOLOGY

- **Secretory** (often enterotoxin related)
- **Osmotic** (failure to absorb, ingestion of osmotic substances)
- **Motility** (too fast or too slow)
- **Exudative** (high intestinal permeability)
- **Combinations** (is the most common clinical scenario)
- **Obstructive**?

Differential Diagnoses for Chronic Diarrhea

- DAMNIT
- Degenerative
- Dietary
- Anomalous
- Metabolic
- Mechanical (obstructive)
- Maldigestive / Malabsorptive
- Neoplastic
- Immunologic / allergic
- Inflammatory
- Infectious
- parasitic
- fungal
- bacterial
- viral
  - Toxic
  - Traumatic

WHERE TO BEGIN:
- How we are able to investigate chronic diarrhea will always be determined by a balance of factors related to owner perceptions, level of concern, symptoms seen, costs and our clinical judgments.
  - first characterize/describe the diarrhea
  - get a good environmental and medical history – is there likely linkage of chronic diarrhea to other issues/symptoms/signs
    - A medical sign is an objective indication of some medical fact or characteristic that may be detected by a veterinarian during a physical examination of a patient. A symptom is something experienced by the patient and as such is subjective.
  - consider signalment of patient

Hint: “God never said that a patient could only have one disease at a time”. J Hogle at ISU

- obtain/start a data base for chronic diarrhea
  - 1st line: good PE, CBC, FeLV & FIV (reasonably current), serum chemistries with electrolytes, urinalysis, fecal ova and parasites examination; direct fecal smear (“scatology”). “It takes at least two points to graph a line.” MEH
  - 2nd line: abdominal radiographs, possible contrast study, rectal scraping/cytology, Sudan III or IV Staining (direct & indirect), saline wet mount for examination of muscle fibers, xray film digestion test (going old school), TLI, folate, B12; T4 & FT4 if patient is > 7 years of age
  - 3rd line: abdominal sonography, FNAs, titers, PCR testing, fecal sediment examination, fecal cultures, serum fPL, T3 Suppression testing if thyroid status is questioned, FIP serology (if the confusion that might result is outweigh by desire to know the test result)
  - 4th line: PCR diagnostic tests individually or as a panel for chronic diarrhea; transit time studies; MRI / CT
  - 5th line: endoscopic, laparoscopic, or surgical biopsies

Hint: The effectiveness of treatment of chronic diarrhea, even when an etiology is identified, may require months to assess due to villous atrophy, lamina fibrosis, blunted/fused villi, crypt cell population, and GALT considerations

**Drug and toxin related liver disease - IV**
Drug associated liver disease (DALD) is a relatively common diagnosis in veterinary practice. It is a common clinical pathologic reason for discontinuation or alteration of planned use of medications. Veterinarians should be vigilant of the possibility of an adverse drug reaction anytime a drug is prescribed. Do
we know/remember the basic information for the drugs we use every day? Often, a drug has continued to be used while assessing a patient with hepatopathy because it was not questioned. The liver has many functions in the body including recognition and detoxification of foreign substances (xenobiotics) and endogenous wastes, recognition and elimination of toxins, manufacturing of substances, storage of metabolic products, metabolic activations and metabolite eliminations. Drug associated liver disease (DALD) is the result of an adverse effect of a drug or a reactive metabolite of that drug on the liver. Because we are treating ever more complex situations as the level and availability of veterinary medicine evolves, it should be assumed that this would lead to more and more drugs being used in situations where their use, and combinations of use, were not anticipated.

How DALD occurs is similar to same pathophysiologic mechanisms established for many non-pharmaceutical substances that cause hepatotoxicity. These can include drugs, metabolites of drugs, xenobiotics, endogenous toxins or exogenous toxins. The mechanisms are direct or idiosyncratic. Dysfunction of liver metabolism or creation of overt pathology (necrosis) in the liver can occur. If the adverse effect on the liver is considered predictable based upon the dose of a medication as seen across a population of subjects, then it is considered a direct hepatotoxin. Liver damage that appears to be random or unpredicted is the result of an idiosyncratic hepatotoxin. The discovery of an idiosyncratic reaction can take thousands of administrations of the drug before it is seen. This does not help if yours is the case that receives that administration. Logic dictates that there is some overlap with direct and idiosyncratic cases. This develops as large numbers of patients are exposed to a drug as it is released to the market. What was unpreventable may become predictable after 10,000 uses of the drug. Idiosyncratic DILD liver injury remains poorly understood. Affected individuals may have pharmacogenetic underpinnings that require drug exposure in specific settings. One example is the finding of familial lines of herding dogs that are deficient in P-glycoprotein enzymes that limit their metabolism of certain drugs (e.g., ivermectin, azathioprine). At some point after thousands of doses of medication have been used, a relative prevalence is established even for idiosyncratic DALD events despite not understanding its mechanism of development.

The liver is particularly susceptible to hepatotoxins due to portal venous circulation and the unique anatomy and function of the liver. Most drugs are fat soluble. As the liver makes them more hydrophilic as benefits elimination, their chances of causing toxicity may increase. This is also influenced by relatively low oxygen content of portal blood (although it delivers the highest percent of blood flow to the liver). Toxic substances can arrive at the liver via ingestion (portal flow), or parenteral administration (arterial delivery). The acinar zones of the hepatic lobules are not equal. The hepatocytes of each zone have different abilities with different enzyme functions. And oxygen levels decline as blood flows through the sinuoids towards the terminal (central) venule. Metabolic damage can be caused by direct cell death (e.g., hydropic change → interference with cytosolic function → cell membrane leakage → necrosis), induction of cholestasis, disruption of microsomal activity, triggering of immune system activity, and/or production of subsequent inflammation. Injuries can be reversible or non-reversible. But which is which is not known initially. Hepatotoxic effects range from minimal changes in clinical pathologic values with no symptoms up to death of the pet. The next representation of hepatotoxicity as reflected by laboratory and histopathology is a cholestastis. It is more common as an intracellular event with abnormal retention of substrates (e.g., glycogen, bile acids, bilirubin, lipids and other metabolites) or impaired Golgi complex activities at eliminating substances from the hepatocytes to the cannuliculi and sinusoids. If necrosis is the primary event, then ALT seems most elevated. If cholestasis is the more prominent pattern of injury, then ALP, bilirubin and GGT will likely be proportionately higher. Combined patterns of injury can develop in some patients with some drugs. These occurrences may be
related to the offending drug, the degree or pattern of necrosis, repetitive exposures or persistent chronic low level exposures over time. In some situations, there can be development of immune mediated disease directed against biliary epithelium or hepatocytes. Why DALD may develop in one individual over another may be influenced by many things. The drug's class/category and pharmacodynamics may offer some information. A drug with a direct pattern of hepatotoxicity may be detected sooner due to the nature of the hepatocellular injury. The dose regime, sex, species, breed, status of organ systems, concurrent disease and health status, nutrition, age, and concurrent use of other medications also influence severity of DALD.

Sub-clinical DALD events may only be discovered on routine chemistry profiles used for pre-anesthetic or geriatric screening. At the other end of the spectrum, a patient may die within hours or days of developing the problem. Symptoms can include nausea, anorexia, vomiting, jaundice, lethargy, and weakness. Less common symptoms include hepatic encephalopathy, diarrhea, bleeding, increased urination, and other symptoms of liver disease. Jaundice is not a necessary indicator at the time of presentation of an ill patient as icterus may only develop later in the course of disease. Liver enzyme elevations may be mild to severe. Luckily, acute liver failure (ALF) is rare in general veterinary practice. It is more often the case that some of the above symptoms are reported leading to reason for running serum chemistry profile. But delay in diagnosis and continued use of a causative medication may occur if DALD is not on the differential list. The most common values elevated are ALT, ALP, GGTP and bilirubin. Standard tests such as CBC, platelet numbers, full serum chemistry profiles with liver tests and urinalyses should be performed. Hepatic function can be variable at clinical presentation depending upon the severity. Because there can be concern for concurrent use of drugs that require hepatic metabolism for their activation, or which may induce or block enzymatic functions, due consideration has to be given to the drugs selected in treatment or supportive efforts. Coagulation profiles, and prothrombin time in particular, as a reflection of degree of function for the liver (and possible development of disseminated intravascular coagulopathy) is warranted. Use of prothrombin time assay may provide earlier warning of severity of injury. Other lab values used as markers of hepatic function include: albumin, BUN, and rising bilirubin.

A difficult concept is what constitutes “acceptable liver injury”. There are some drugs that are given for which we accept a certain degree of toxicity, e.g., corticosteroids, phenobarbital, azathioprine. In human medicine, DALD is defined by a two fold consistent rise of ALT or conjugated bilirubin; or via a combination of ALP, GGT ALT and bilirubin provided that one is greater than twice an upper normal range. Further, classification of DALD relies upon whether the injury appears to be more hepatocellular (predominant ALT, likely “direct hepatotoxin”) or cholestatic (primarily ALP; likely indirect). Mixed patterns do occur such that the classification of DALD is not perfect. The magnitude of enzyme elevations, even with ALT, are not prognostic of survival. However, high values are clinically more concerning. Survival is not proportionate, in the author’s experience, to the enzyme value. Conceptually, a very high value could be due to the complete lysis/necrosis of a few lobules, with proportionately large release of enzyme, or the same high value could result from widely disseminated injury to many hepatocellular membranes that only leak a little ALT from each cell. This may account for why the degree of elevation is not necessarily prognostic. Ascites is not common at the time of initial presentation unless intrahepatic or portal venous thrombosis has occurred. This and hepatic encephalopathy are, in the author's experiences, negative prognostic signs.

Abdominal radiographs should be taken as this remains the primary method of estimating liver size that is appropriate for a given patient. In acute DALD, the liver may be swollen. While in chronic disease the liver may be atrophied or cirrhotic. Abdominal sonography is now commonly performed to help assess structural changes to the liver. Fine needle aspiration or liver biopsy should only be done if there is a question of
diagnosis or an inconsistent finding found with imaging (e.g., a dog taking an NSAID and phenobarbital that may have developed lymphoma). Prior to invasive testing the patient should be stabilized. Coagulation testing is necessary prior to any invasive tests. The author feels that a buccal (oral) mucosal bleeding time test is more clinically relevant to invasive procedures than PT and PTT. The I-stat activated clotting time, as done in a standardized manner, may also be used to test for severe coagulopathy. The diagnosis of DAL is made using the history, symptoms, and supportive findings in clinical pathology. If a DALD is considered likely then re-exposure should not be tried and notation of the pet's record should be highlighted for the diagnosis/potential. The differential diagnostic list often includes acute leptospirosis, fulminant toxoplasmosis, infectious canine hepatitis, feline infectious peritonitis, per acute RMSF, per acute ehrlichiosis, trauma, septic ascending cholangiohepatitis, Amanita (mushroom) poisoning, aflatoxin ingestion, blue/green algae, DIC, unknown drug ingestion, and acute necrotizing pancreatitis. The process of elimination can lead to a probable diagnosis of DALD.

The degree of treatment intervention required for DALD is case specific. Discontinuation of the drug is the first step and for non alarming situations may be all that is required. For more severe/concerning cases, nursing and supportive care are important. Maintenance of microvascular perfusion in the liver is essential using replacement crystalloid fluids. Assessment of acid base status is part of critical care monitoring but may have pragmatic limitations in obtaining the testing and in medications used to make adjustments. The author commonly uses balanced electrolyte solutions containing 2.5% to 5% dextrose via central access venous catheters. This requires the monitoring blood glucose and electrolyte levels, notably potassium. With low serum albumin, colloid therapy may be warranted (e.g., Hetastarch, frozen plasma). Vitamin K1 is frequently administered subcutaneously 0.5-1.0 mg/kg q12-24h, SQ until coagulation status is clearly established. Nasal oxygen therapy is advised in severe cases, again to assist with likely hypoxia in the edematous, damaged liver. Glutathione is one of the most potent anti-oxidant substances that the liver relies upon in its metabolic detoxification processes. It becomes depleted in many forms of hepatopathy. Administration of glutathione precursors is advised in moderately severe or worse cases. Treatment is with N-acetylcysteine (NAC). The dose is 140mg/kg diluted in equal volume of saline and given by slow IV infusion over several hours. This is followed with 70 mg/kg of NAC diluted in saline, slow IV, q6h for five to eight treatments or until the patient can be given oral medications. This treatment has been helpful for acetaminophen, thiacetarsamide, amanita, suspected acute NSAID related DALD by the author. Other treatments are as described for support of many hepatopathies and as mentioned in the proceedings above (Management of chronic hepatopathies – III).

With treatment, the ALT will often decrease 30-40% in each 24 hour period, but the ALP, and the total bilirubin to a lesser extent, may continue to rise as secondary cholestatic effects become manifest. Consistently rising bilirubin without clinically evident improvement is a poor prognostic indicator in human cases of DALD. It may also be prognostic in veterinary medicine as it can suggest secondary fibrosis resulting from inflammatory events and hence partial or complete extrahepatic biliary obstruction or intracellular cholestasis. For a moderately to severely ill patient, it is not uncommon to be hospitalized for 3 to 10 days. As recovery progresses, it remains important to maintain supportive fluids and medications and to retest chemistries, prothrombin time, urinalyses and blood counts as needed (12-24-48 hours). For several months it is suggested to continue supportive medications (ursodiol, SAMe, milk thistle, vitamin E) and monitoring. At 3 and 6 months the author likes to follow up with paired serum bile acids. These long term concerns in a recovered patient are because of the potential for development of post necrotic cirrhosis. And, in human medicine, some drugs causing DALD (e.g., acetaminophen, dantrolene, isoniazid) have been demonstrated to initiate immune chronic hepatitis and this may be the case in in veterinary medicine as well (?).
<table>
<thead>
<tr>
<th>TABLE 1. <strong>Drug Associated Liver Disease - in Dogs and Cats</strong></th>
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<tbody>
<tr>
<td><strong>Reported Drugs</strong></td>
</tr>
<tr>
<td>acetaminophen</td>
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<tr>
<td>amiodarone</td>
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<tr>
<td>amoxicillin / ampicillin products</td>
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<tr>
<td>azathioprine</td>
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<tr>
<td>azithromycin</td>
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<tr>
<td>CCNU (Lomustine)</td>
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<td>cephalosporins</td>
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<tr>
<td>Cyclosporine</td>
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<td>Diazepam</td>
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<td>diethylstilbesterol</td>
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<tr>
<td>enrofloxacin</td>
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<tr>
<td>Kava Kava</td>
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<tr>
<td>ketoconazole &amp; azole antifungals</td>
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<tr>
<td>glucocorticoids</td>
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<tr>
<td>halothane (particularly repeated exposures)</td>
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<tr>
<td>mebendazole</td>
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<tr>
<td>megesterol acetate</td>
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<tr>
<td>methimazole</td>
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<tr>
<td>NSAIDs - carprofen may have increased awareness</td>
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<tr>
<td>oxibendazole</td>
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<tr>
<td>phenobarbital</td>
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<tr>
<td>phenytoin</td>
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<tr>
<td>Primidone</td>
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<tr>
<td>stanozolol</td>
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<tr>
<td>sulfonamides</td>
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<tr>
<td>tetracycline antibiotics</td>
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<tr>
<td>thiacetarsamide</td>
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<tr>
<td>trimethoprim-sulfa combinations</td>
</tr>
<tr>
<td>ivermectins</td>
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<td>xylitol (an artificial sweetener)</td>
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<thead>
<tr>
<th>TABLE 2. <strong>Anecdotal or Rare Suspected DALD dogs or cats</strong> *</th>
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<tbody>
<tr>
<td>acarbose</td>
</tr>
<tr>
<td>amiodarone</td>
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<tr>
<td>butorphanol</td>
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<tr>
<td>desoxycorticosterone</td>
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<tr>
<td>ethanol</td>
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<tr>
<td>fenbendazole</td>
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<td>isoniazid</td>
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IBD – what do we know? Dr. Hitt's top ten list for 2009 - VI

1) Inflammatory bowel disease (IBD) refers to *idiopathic* inflammation arising from any one or multiple segments of the gastrointestinal tract (pharynx to anus). The main types of IBD described for dogs and cats are lymphocytic-plasmacytic, eosinophilic and granulomatous (dog). Every case can be different.

2) We know more than we did about pathogenesis of IBD.

3) We don’t know all that we want to know, or what all the information means.

4) Canine IBD activity index (CIBDAI) is a useful scoring system for comparison between clinicians and pre and post treatment assessments.

5) Histiocytic ulcerative (PAS positive) colitis of Boxers (predominantly) is associated with (and may be caused by) chronic low level infections with adherent invasive E. coli and is treated long term with fluoroquinolone antibiotics as a primary treatment.

6) Food trials are warranted for first line differentiation of food responsive diarrhea from IBD, including hypoallergenic and fiber enhanced diets; however if a couple of trials do not resolve the problem for the *long term* then seek further! Repeating the same efforts with the same result is not smart.

7) Biopsy results do not correlate with severity of symptoms. Get over it. They are still useful, just not *pathognomic*. IBD is a clinical diagnosis as much as a biopsy defined one. Not all pathologists grade IBD the same, there is inaccuracy at times. Providing multiple representative segmental biopsies (stomach, small intestinal segments) may improve diagnosis as the condition is more or less intense in different segments of the GIT.

8) Treat IBD for a long time. Do not wait for repeated presentations to pursue chronic therapy.

9) Budesonide can provide an alternative corticosteroid treatment for feline and canine IBD, particularly when used for upper GI disease and with other immunosuppressive drugs.

Crohn’s disease and ulcerative colitis are the main forms of IBD in humans and have some similarities to IBD of dogs and cats. These can have a chronic, intermittent or continuous course. IBD is not irritable bowel syndrome (IBS) but both can be present simultaneously. The pathogenesis of IBD in humans has been hypothesized based upon numerous types of research data (comparative, in vitro, in vivo). These are similar to the proposed mechanism of canine CAH and FILD as discussed above. There may be an autoimmune response to a luminal or mucosal antigen; a dysfunctional immune response to a commensal bacterium; an infection with a pathogenic organism that either remains in the tissues resulting in chronic inflammation, or creates ongoing dysregulation of the immune response after resolution of infection (Simpson, K). Breed associations include: Basenjis, Ludenhunds, German shepherd dogs, Shar-peis, Wheaten terriers, Yorkshire terriers and possibly WHWT. There is no consistent age pattern with some authors reporting IBD as a disease of young and others as middle aged to older. The author has diagnosed it as young as 6 months. No sex predilections have been reported. The diagnosis of IBD is made as a chronic condition.
Symptoms have often been present for years when diagnosed. The diagnosis of IBD is suspected when there is a history of recurrent or persistent GI symptoms of vomiting, diarrhea, soft stools, repeated development of intolerances to new foods, weight loss, and low serum proteins. These symptoms may occur individually or a patient may show multiple ones. The diagnosis of IBD involves the ruling out of alternative explanations, e.g., parasites, garbage gut, infections, sudden diet changes, EPI, foreign bodies, presence of cancer, ... . The diagnosis is confirmed with biopsies and clinical assessment. However it is also common from a practical aspect for it to be made as a probable diagnosis via response to medication after eliminating most common differentials. Within a veterinary internal medicine specialty practice, IBD is a common diagnosis. The process of assessment involves use of CBC, serum chemistries, urinalysis, fecal parasite checks, direct saline fecal smears, abdominal radiographs, abdominal sonography, and many specialized tests (e.g., pancreatic lipase, TLI, folate, B12, ...). Less commonly employed due to false positive and false negative results are fecal cultures. There is a growing use of PCR technology to look for evidence of less common or more difficult to diagnose infectious diseases.

One factor less explored at this time in dogs but thought significant based upon breed susceptibilities includes genetic and haplotype predisposition (the genotype). Immunohistochemical studies of canine IBD have demonstrated an increase in the T cell population of the lamina propria, including CD3+ cells and CD4+ cells, macrophages, neutrophils, and IgA plasmacytes. Up-regulation of type II MHCs have been seen as well with enterocytes. Enterocytes are capable of behaving as antigen-presenting cells, and interleukins (e.g., IL-12, IL-7 and IL-15) stimulate the cells of the gut associated lymphoid tissues (GALT). Many of the immunologic features of canine IBD can be explained as an indirect consequence of mucosal T cell activation. Different patterns of interleukin production could lead to shifts in the balance of immune cell numbers seen (e.g., lymphocytes, plasma cells, eosinophils) such that food responsive, food allergic, and idiopathic IBD may share similar/overlapping mechanisms. However, research has shown that not all information regarding cytokines and species is transferable to dogs and cats. It is also seen that (with a degree of confusion) resolution of symptoms following treatment does not always alter the original abnormal histopathologic findings. Factors in the pathogenesis of IBD can include inappropriate programing of PRRs (pathogen pattern recognition receptors) and toll like receptors (TLRs). PRRs are proteins expressed by cells of the innate immune system. These allow the innate immune cells to identify pathogen-associated molecular patterns which are associated with microbial pathogens or expression with cellular stress. They signal for response to the so-called “super antigens” such as LPS. Toll-like receptors (TLRs) are a class of proteins that also play a role in the signaling within the immune system. They are cell membrane receptors that recognize structurally conserved molecules derived from microbes. Once these microbes have breached physical barriers such as the skin or intestinal tract mucosa, they are recognized by TLRs which activates immune cell responses. The TLRs are not supposed to respond to non-pathogens existing as normal GI microflora. TLRs are thought to become “tolerant” of normal gut flora in the neonatal stage of the animals exposure to normal flora. But if there has been a breakdown in the recognition patterns, they could signal for response to innate microflora or combination antigens (haptens) that have formed. Subsequent damage results from the elaboration of cytokines, release of proteolytic and lysosomal enzymes, complement activation secondary to immune complex deposition, and the generation of oxygen free radicals. Delayed gastric emptying and intestinal motility can also develop with chronic inflammatory disease of the gut. Hence, diarrhea developing from IBD may be result of malabsorptive, secretory, exudative, motility issues, and likely combinations of these dysfunctions depending upon the individual patient, the pet's past environmental exposures/infections, and its genotype. The differentiation between inflammatory bowel disease (IBD) and food responsive diarrhea (FRD) is difficult and argued. In some locales, a majority of suspected cases are “resolved” with diet change. While in other areas, treatment is
found to require use of anti-inflammatory or immunosuppressive medications. In one research study, there were some differences between dogs thought to have food responsive diarrhea and IBD regarding their cytologic populations. However, the overall mRNA levels (associated with cellular transcription) related to the relevant cytokine increases found have not shown clear differences between FRD and IBD that would allow clear separation of their pathophysiology.

An interesting twist in support of the above hypothesis for IBD comes from information recently reported by Dr. Kenny Simpson, et al, at Cornell University. Histiocytic ulcerative colitis of boxers is not idiopathic. The presence of adherent and invasive *E. coli* as detected by culture and FISH technology are thought potentially to play a significant role in the pathogenesis of the disease. Treatment with enrofloxacin (5-10 mg/kg ONCE per day for 16 weeks) leads to a long term treatment success for most cases (85% ish). *Similar to the above proposed mechanisms for development of IBD, the histiocytic colitis of Boxers may entail an exuberant immune response to intestinal microflora in genetically susceptible individuals.*

A report from Dr. Simpson, in JSAP in 2004, included interesting information regarding IBD of dogs as scavenged from the literature and then compared to their own cases. The goal was to shed some light on the complexity and numerous findings associated with IBD. Of reported dogs, up to 12.5 per cent were thrombocytopenic but not clinically affected. Thrombocytosis was present in five dogs (7 per cent), this may be a response to chronic inflammatory stimulation to the bone marrow with reduced half life of platelets and hence increased compensatory production. It was not clinically significant in dogs nor related to severity of disease. **Hypoalbuninemia** was strongly associated with a poorer outcomes (P=0.0007). The pathophysiology of this may involve anorexia, malabsorption due to villus atrophy and reduced surface area, fibrosis, hemorrhage or exudation of protein into the gastrointestinal tract, and increased intestinal permeability. Hypoalbuninemia was not correlated to severity of histologic scoring with many being mild to moderate. In the report, there was no association between the sites and type of IBD versus the severity of disease and outcome. Eosinophilic IBD did not have a worse outcome when critically examined. The remission rate reported was a dismal 26 percent but this was based upon a strict criteria for no symptoms over six months.

The canine inflammatory bowel disease activity index (CIBDAI) was developed by Jergens, 2002, and uses six different clinical findings: attitude/activity, appetite, vomiting, stool consistency, stool frequency, and weight loss. Another scoring system proposed includes hypoalbuninemia. In a study using CIBDAI as an index, the serum concentrations of CRP were significantly (P < .02) increased in dogs with CIBDAI scores > or = 5 (mild disease activity or greater) compared to controls. Among IBD dogs, the CIBDAI showed good correlation (r = 0.82, P < .0001) to both histology and HAP scores, but CRP also was a strong co-correlate of disease activity. The IBD dogs showed significantly (P < .0001) decreased (improved) CIBDAI and CRP values after medical therapy compared to pretreatment values. Dr. Jergens concluded that the CIBDAI was a reliable measure of inflammatory activity in canine IBD and that CRP was suitable for laboratory evaluation of the effect of therapy in these patients. However, there is no consensus that measurement of CRP is at a point of being clinically relevant.

Recently, the World Small Animal Veterinary Association (WSAVA) gastrointestinal standardization group has tried to be an arbiter for defining a histopathologic standard for inflammatory bowel disease (IBD). This group involves both pathologists and internists, largely from Europe and the US. This standard uses histologic criteria of the type of inflammatory infiltrate (neutrophilic, eosinophilic, lymphocytic, plasmacytic, granulomatous), associated mucosal pathology (villus atrophy, fusion, crypt collapse), distribution of the lesion (focal or generalized, superficial or deep), severity (mild, moderate, severe), mucosal thickness (mild,
moderate, severe), and topography (gastric fundus, gastric antrum, duodenum, jejunum, ileum, cecum, ascending colon, descending colon). Despite these efforts, a degree of subjectivity remains. In recent years, publications by Willard have also added interest, yet confusion, because of finding evidence of this subjectivity. When the same histopath slides from cases of IBD were blindly circulated between five different pathologists at multiple academic locations, the results for diagnosis of IBD varied from minimal disease to lymphoma with poor correlation between pathologists for each sample.

In summary, there is evidence supporting a link between clinical findings, immunohistochemical and histopathologic lesions in dogs with IBD. There is some evidence that dogs with moderate to severe IBD (and accompanied by elevated CRP levels) are more likely to have significant histologic lesions than those dogs having only mild clinical signs. Cats have shown a clearer relationship of IBD with the morphologic changes (e.g., epithelial alterations, villus fusion, atrophy), symptoms and up-regulated expression of pro-inflammatory cytokines (Janeczko et al. 2008).

Described treatments of canine IBD are mostly empirical and are numerous. Treatments for canine and feline IBD have been generally extrapolated from human medicine. The efficacy of various treatments for IBD are debated. Often the reporting of combinations of medications across various anatomic locations of disease, species, breeds, and diets lends confusion to making any assumptions from anecdotal reports or groups created by combining uncontrolled cases. Some drugs may be better for induction of control, others for maintenance. Some patients may benefit from diets and probiotics while others do not. Because of the memory involved with the gut associated lymphoid tissues (GALT), cure is a term not used, and the need for treatments is often measured in years. Owner-evaluated quality of life after treatments was significantly associated with outcome at a high value (p=0.006). The owners’ perceptions as a monitoring tool for response to treatment was supported. The outcomes of treatment may be complete improvement of symptoms, partial response, intermittent recurrence, or no response. Each client and patient situation will dictate what degree of control is adequate and considered as “success”. Without treatment, it is the author's belief that IBD is often progressive and that a line may be crossed where morphologic change to the intestinal lining cannot be completely restored even with control of inflammation (e.g., fibrosis, villous atrophy, villi fusion).

Dietary treatments for IBD focus on novel content (for the individual), hypoallergenic diets and enrichment of fiber. An elimination diet without other treatment would be ideal. But the nature of referral specialty practice makes this unlikely as our cases are rarely nouveau and elimination diets are very difficult in practice as the patient may not want to eat what is offered and many owners are not compliant with true dietary restriction. Food allergy is less common than “food intolerance” or food responsive diarrhea. One specific situation for use of a restricted diet is presence of gluten enteropathy (Celiac like disease). Gluten enteropathies are not common. Irish setters have been most reported but the condition is not likely restricted to them. If there is a history of repeated GI problems that have been treated by the introduction of new diets over a period of years, then IBD should be considered as a primary differential. The intention is to alter or reduce the antigenic load to the gut where primary or acquired intolerances (versus true food allergies) may then worsen or perpetuate clinical signs. Diets are fed exclusively for a minimum of 3-4 weeks although in many cases some degree of initial response is seen within 10 days if it is FRD. A new food component may be introduced subsequently at 7-10 day intervals. The goal is a nutritionally balanced diet. Animals are said to be food responsive if symptoms significantly improve while only on dietary therapy and this response is maintained. The author does not count success as needing a new diet every six months, then every four months, then every three months, .... The next option is to feed novel protein and carbohydrate diets or hydrolyzed diets with the same
basic goals. These have helped as well with true food allergic patients as a true elimination diet may be avoided.

Fiber supplementation is often more beneficial for the treatment of chronic diarrhea where inflammation is not present (e.g., FRD). Increased fiber in the diet may slow the gastric emptying to help with dampening the nutrient absorption curve and allowing greater contact time for enzymes. Some fiber supplements also act as prebiotics (FOS). Fiber helps with colon segmental contractions and fluid absorption in the large intestine. If a diet enriched with soluble fiber is not helpful, then a trial of insoluble fiber may be beneficial, e.g., if I/D doesn't help then try W/D.

Cobalamin (Vitamin B12) has been proposed as a treatment for dogs and cats with chronic enteropathies and in unusual cases of true deficiency. This is reported more often in cats. The author believes that cobalamin may transiently help some cases of chronic enteropathies involving the ileum but that most cases are not truly deficient and the observed benefits diminish with time if no other treatments are begun. How much of this may be a placebo effect is also not known. Exocrine pancreatic insufficiency has also been associated with low levels of serum cobalamin, especially in cats. If low serum levels are found, then a good response to treatment may not be seen until treatment is given. A common dose recommended is cyanocobalamin 250ug/cat and 250-1500ug/dog given SQ once weekly for 4 weeks, then given every 2-4 weeks as needed by monitoring of serum levels.

When given the opportunity, the author likes to include a diet enriched with omega-3 fatty acids as a supplement from deep marine fish oils. As with hepatic therapy, the goal is a reduction in dependence upon more potent medications.

If prebiotics or probiotics are utilized, then selection of veterinary products that are designed with attention to species variations of the GI microflora as well as demonstration that the products contain what they say they do is needed. Use of these products concurrently with oral antibiotics has some intrinsic conflict that has not been acknowledged by many prescribing their use. In some clinical studies from laboratory animals, normal intestinal flora re-establishes itself within 10 days of use, and continued use, of many common antibiotics. Similar restoration of the normal flora is seen in most studies with ongoing use of probiotics. In the end, small intestinal bacterial overgrowth (SIBO) is hard to prove and has not been demonstrated to be a routine part of most cases of IBD. Does it exist, yes. German shepherds may be more prone to the condition, but it is an area of ongoing discussion. Is SIBO a common component of chronic enteropathies? In the author's assessment, not likely. More research is needed to understand the potential and proposed benefits to altering or “improving” upon the natural intestinal flora of dogs and cats. If serum folate levels are elevated significantly, then use of an antimicrobial is appropriate by today's clinical standards. However, there are enough anecdotal (experiences or single case reports) cases that seem to show better clinical response than was previously seen that would add credence to their use.

Use of glutamine (an amino acid), as a nutritional effort to support enterocytes, has been discussed. But proof of efficacy in clinical settings is lacking. The goal, as demonstrated in “glutamine deficient/deprived” lab mice and rat models, is to improve function, maturation, and regeneration of enterocytes.

Use of metronidazole and tylosin has been pursued for long periods of time in dogs and cats with IBD, more commonly in those cases with large bowel symptoms. The antimicrobial activity is likely not as important as their proposed immunomodulatory functions. Effects on cytokine production have been shown in vitro for these and other antibiotics. Metronidazole is often used long term at a dose of 5-10 mg/kg once or twice daily.
Tylosin is usually prescribed at 20 mg/kg given two to three times a day. Relapse of symptoms upon withdrawal of their use is a reason to continue/restart them. If one has not been successful, then the other might. So it is common that one or both have been used in many/most chronic cases.

The mainstay of IBD treatment protocols is immunosuppressive therapy. As with treatment of CAH and FILD, glucocorticoids and more potent immunosuppressive drugs are used when clinical situation warrants it. Use of these drugs without biopsies has to be a distinct clinical decision. The interpretation of biopsies for the diagnosis of IBD is complicated enough without having these medications in use. If biopsies have not been obtained, yet are desired after starting these drugs, then a washout period is advised to reduce confusion in histopath interpretation. But if one considers the literature, the histologic findings before and after treatment with prednisone have been similar within individual patients. The readers are directed to the information on immunosuppressive medications provided in the previous proceedings: Management of chronic liver disease.

A newer drug being used is budesonide. This is a glucocorticoid. It is about 5-15 times more potent than prednisone at the GI mucosal cell receptor level. But because it undergoes near 99% first pass metabolism in the liver via portal circulation, the systemic side effects are much less. Any side effect seen with other glucocorticoids can be seen with budesonide. They just tend to be less severe and not as multiple. There is demonstrable pituitary-adrenal axis suppression demonstrated in dogs. There is no standard dose accepted yet. A general treatment dose has been 2-3 mg/m2 given orally. The pharmacy available form is as an enteric coated product, Enterocort™ that dissolves more in the distal ileum and colon via bacterial modulated pH. Hence most of the drug activity occurs within the terminal ileum and colon for this human trade name preparation. In veterinary medicine, budesonide is more commonly prescribed as a compounded product that hence has its main activity in the stomach and upper small intestine as it is no longer in its proprietary protected formulation. If IBD is thought to be primarily present in the stomach or upper small intestine then budesonide is a reasonable alternative to other more systemically active glucocorticoids. When prescribed there is the presumption that either severity of disease, prior experience of systemic side effects from common glucocorticoids, or presence of other diseases/disorders (e.g., hepatopathies, diabetes, renal disease) warrant its use. Long term remission of marked IBD usually relies on concurrent use of one of the other immunosuppressive drugs in concert with budesonide. The author commonly uses it with cyclosporine or azathioprine in dogs and with chlorambucil in cats. The author feels that budesonide has been a helpful new alternative treatment for IBD but that the potential for overuse is present. It has been very helpful in a few of the author’s cases of canine eosinophilic gastroenteritis when used with cyclosporine as well as in some cats with diabetes mellitus.