THE CLINICAL APPROACH TO ABNORMAL LIVER ENZYMES

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A common clinical situation is finding abnormal liver enzymes on a biochemical profile. In some cases, abnormal liver enzymes are first identified in the clinically normal patient on a routine health screen or as a pre-anesthetic screen prior to an elective surgery. Frequent abnormal liver enzymes are identified in sick patients as part of a complete diagnostic work-up. Some of those sick patients may have primary liver disease but most usually have some other primary disorder with a so-called secondary “reactive” liver changes. The clinician is often left with questions on how to approach these case two case scenarios in a logical and reasonable manner for both the patient and client. In the following pages I describe how to interpret abnormal liver tests and how I clinically approach those cases.

The identification of abnormal liver enzymes (ALT, AST, ALP, GGT) usually indicates liver damage but rarely provides a diagnosis or etiology. Abnormal liver enzymes are common and in a study of 1,022 blood samples taken from both healthy and sick dogs and cats in one diagnostic laboratory found 39% had ALP increases and 17% had ALT increases. The identification of liver biochemical abnormalities in conjunction with the clinical findings suggest certain diagnostic possibilities and will indicate further steps into the investigation of possible liver disease.

Liver biochemical enzymes can be insensitive or nonspecific for primary liver disease and in addition some of the enzymes can have isoenzymes from other tissue not associated with the liver. An understanding of the liver biochemical tests is essential when evaluating the patient in question. Liver biochemical test abnormalities are categorized into groups that reflect 1) hepatocellular injury, 2) cholestasis or 3) tests of impaired metabolic function or synthetic capacity.

Tests of Hepatocellular Injury

Increases in either alanine aminotransferase (ALT) or aspartate aminotransferase activity (AST) indicate hepatocellular membrane damage and leakage of the enzymes. Canine and feline hepatocyte cytoplasm is rich in ALT and contains lesser amounts of AST. Altered permeability of the hepatocellular membrane caused by injury or a metabolic disturbance results in a release of this soluble enzyme. This could be due to death of the hepatocyte or from hepatocyte degeneration where the membrane becomes permeable. Conceptually ALT and AST should be thought of as hepatocellular “leakage” enzymes. Subsequent to an acute, diffuse injury, the magnitude of increase crudely reflects the number of affected hepatocytes. It is however neither specific for the cause of liver disease or predictive of the outcome. The plasma half-life of ALT and AST is about 2.5 days in dogs, however ALT concentrations may take days to weeks to decrease following an acute insult. This persistent increase following acute damage may reflect continued injury or possibly elevations associated with hepatocyte regeneration. Persistent increases of ALT over weeks are very characteristic of chronic hepatitis in the dog. I believe ALT increases should be investigated when they are greater than twice normal or persistently abnormal over weeks to months. There is a small amount of ALT found in muscle but for significant serum ALT increases to occur there must be extensive muscle damage.

A variety of tissues, notably skeletal muscle and liver, contain high aspartate aminotransferase activity (AST). Hepatic AST is located predominately in hepatocyte mitochondria (80%) but also soluble in the cytoplasm. Marked increases in hepatic AST concentrations generally indicate more severe or deeper hepatic damage that is associated with hepatic mitochondrial AST release. Skeletal muscle inflammation invariably causes a serum AST increase that exceeds the serum ALT activity and can be further defined as muscle origin by the measurement of the serum creatine kinase activity (CK), a specific muscle enzyme. Clinical experience in veterinary medicine indicates that there is value in the interpretation of the serum activities of ALT and AST for liver disease. The half-life for AST is 0.5 days. Following an acute injury resulting in a moderate to marked increase in the serum ALT and AST concentrations, the serum AST will return to normal more rapidly (hours to days) than the serum ALT (days) due to their difference in plasma half-life and cellular location. By determining these values every few days following an acute insult, a sequential “biochemical picture” indicative of resolution or persistent pathology is obtained. AST elevations are more sensitive but less specific for liver disease than ALT.

In cats both ALT and AST tend to be less indicative of primary hepatic disease as most feline liver diseases are cholestatic in nature. No published values exist for ALT half-life but it is presumed that ALT is much shorter (around 6 hours) and AST half-life is 77 minutes in the cat. The short half-lives may explain the variability of ALT and AST values in liver disease of cats and if marked elevations are found tend to reflect a relative acute ongoing episode.

Tests of Cholestasis

By definition cholestasis refers to the decreased flow of bile. Alterations in bile flow can occur within the hepatocyte and bile canaliculi or within the small or large bile ducts. Cholestatic syndromes are grouped as hepatic cholestasis and extrahepatic cholestasis. Alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) show minimal activity in normal hepatic tissue but can become increased in the serum subsequent to increased enzyme production stimulated by either impaired bile flow or drug-induction. These enzymes have a membrane bound location at the canalicular surface; ALP associated more with the canalicular membrane and GGT associated more...
with epithelial cells comprising the bile ductular system. With cholestasis, surface tension in the canaliculi and bile ductules increases and these surface enzymes are then up-regulated into production.

Alkaline phosphatase is also present in a number of tissues but the only two that are diagnostically important are the bone and liver. The plasma half-life for hepatic ALP in the dog is 66 hours in contrast to 6 hours for the cat and the magnitude of enzyme increase (presumably a reflection of the synthetic capacity) is greater for the dog than the cat. Bone source arises from osteoblastic activity and is elevated in young growing dogs before their epiphysial plates close or in some bone osteoblastic activity (bone tumors) or lytic lesions. In the adult without bone disease, an increased serum ALP activity is usually of hepatobiliary origin. A study identified some dogs with osteogenic bone tumors to have increased ALP concentrations tended to indicate a poorer prognosis probably from diffuse bone metastasis. Minor bone source of ALP could result from osteomyelitis and secondary renal hyperparathyroidism.

An increase in the serum ALP and GGT activity can be induced by glucocorticoids (endogenous, topical or systemic), anticonvulsant medications and possibly other drugs or herbs. There is remarkable individual variation in the magnitude of these increases and there is no concomitant hyperbilirubinemia. A moderate to marked increase in serum ALP activity without concurrent hyperbilirubinemia is most compatible with drug-induction and warrants a review of the patient’s history (topical or systemic glucocorticoids) or evaluation of adrenal function. The increased ALP has long been attributed to a glucocorticoid-stimulated production (hepatic gene induction) of a novel ALP isoenzyme in the dog and can be distinguished from the cholestasis-induced hepatic ALP isoenzyme by several procedures. It was initially thought that the glucocorticoid-associated isoenzyme could be used as a marker of exogenously administered corticosteroids or increased production of endogenous glucocorticoids. Unfortunately, the glucocorticoid-associated isoenzyme is also associated with hepatobiliary disease as well and differentiation steroid from liver ALP is rarely helpful.

Cats are unique compared to dogs in that ALP is not induced by glucocorticoids, has a shorter half-life and is presumed cats have lower hepatic ALP concentrations. Consequently, ALP dose not rise to the magnitude of ALP in dogs having a similar disease condition.

Hepatic GGT is located predominately on the canalicular membrane and bile ducts. Chronic elevations in GGT tend to reflect hepatobiliary tract disease. In dogs GGT has a lower sensitivity (50%) but higher specificity (87%) for hepatobiliary disease than total ALP. If an elevated ALP with a concurrent increase in serum GGT, specificity for liver disease increases to 94%. The most marked elevations in GGT result from diseases of the biliary epithelium such as bile duct obstruction, cholangiohepatitis, cholecystitis and glucocorticoid administration in the dog. Bone does not contain GGT and the administration of anticonvulsant medications to dogs does not cause an increase in the serum GGT activity. Colostrum and milk have high GGT activity and nursing animals have increased serum GGT activity shortly after nursing; a simple test to determine if the pup received colostrum.

Tests Involving Liver Function

The evaluation of liver function depends on tests that reflect the synthetic or excretory capacity of the liver. Synthetic failure is generally observed when 60-70% of the liver loses function because of the great hepatic reserve capacity. There is however no specific liver function test that reflects the over all functional status of the liver. On a routine biochemical profile it is important to note the liver function tests including bilirubin, albumin, glucose, BUN, and cholesterol. Bilirubin is the most sensitive and specific function test of hepatobiliary tract disease once hemolytic disease has been ruled out. Bilirubin is affected by hepatocellular metabolism (uptake, protein binding, conjugation and excretion) and due to alteration in biliary excretion. It is also known that metabolic conditions such as endotoxins, inflammatory cytokins, fatty acids, protein deficiency can interfere with bilirubin metabolism without structural damage to the hepatocyte or bile ducts. It appears that cats tend to have increases in bilirubin concentrations quite easily and sometimes not associated with primary liver disease. In an ACVIM Forum Abstract (Bradley A. 2010) we reported on 180 cats with bilirubin concentrations above the normal reference range and found approximately half the cats did not have primary hepatobiliary tract disease at all but rather “other” non-hepatic disorders having a mean bilirubin concentration of 1.2 mg/dl.

Albumin is exclusively made in the liver and if not lost from the body (GI or renal), sequestered or diluted, a low concentration would suggest significant hepatic dysfunction. It may take greater than 60% hepatic dysfunction for albumin concentrations to decline. Be aware however albumin is a negative acute phase reactive protein so inflammatory conditions could lower albumin concentrations due to transient reduced production.

Hypoglycemia occurs when 75% or greater liver mass is lost. Cholesterol is quite variable and is often low in dogs having portal-systemic shunts (PSS) and is elevated in cholestatic or obstructive liver disease. The BUN may be low in dogs having a PSS or chronic liver disease from the failure to convert ammonia to BUN. Major clotting factors (except factor 8) and fibrinogen are made in the liver therefore prolonged clotting time suggests significant hepatic dysfunction or factor consumption. Low fibrinogen concentrations with liver disease also suggests reduced hepatic consumption.

Blood ammonia or the ammonia tolerance test is infrequently performed and tends to reflect abnormal hepatic portal shunting (acquired or congenital shunts) or to detect significant hepatocellular dysfunction (likely greater than 70% hepatic dysfunction). The liver detoxifies ammonia, primarily arising from the gastrointestinal tract converting
ammonia to urea. Elevated fasting blood ammonia levels (>46 µmol/L) have been shown to be a sensitive (98%) and specific (89%) test for the detection of congenital or acquired portosystemic shunting in dogs. Because of the complexities in collection and performing the test it is not routinely used in clinical situations. Dry chemistry tests for blood ammonia provide variable results.

**Bile Acids**

Serum bile acids are thought to be the most sensitive function test that is readily available for use in small animals. Bile acids are synthesized from cholesterol in the liver and then conjugated and excreted into the bile. Bile acids are transported to the gallbladder and following a meal CCK is released causing gallbladder contraction excreting bile acids into the intestine where they emulsify fat for absorption. In the distal small intestine bile acids are actively resorbed and return to the liver where they are efficiently extracted by the hepatocytes, excreted and then re-circulated back into the bile. Only a small fraction of the total bile acid pool ever escapes into the systemic circulation. Thus the enterohepatic circulation of bile acids occurs with an approximate 95-98% efficiency.

The fasting total serum bile acid concentration (FSBA) is a reflection of the efficiency and integrity of the enterohepatic circulation. Pathology of the hepatobiliary system or the portal circulation results in an increased FSBA prior to the development of a clinical sign requiring its usefulness in the icteric patient. An increase is not specific for a particular type of pathologic process but is associated with a variety of hepatic insults or abnormalities of the portal circulation. I personally use bile acids to screen patients with abnormal liver enzymes to determine if there could be loss of hepatic function adding further support for investigation of the case. I also use bile acids to screen for animals having FSB or portal vein hypoplasia (PVH, also called microvascular dysplasia)

The current suggestion for the determination of the bile acids is to differentiate between congenital portal vascular anomalies and liver insufficiency prior to the development of jaundice. The determination of total bile acids can contribute to the decision to obtain histological support for the diagnosis of this last group of hepatic diseases. When the fasting value is greater than 25 µmol/L for the dog there is a high probability that the histology findings will define a lesion. When the total fasted bile acid concentration is normal or in the “gray zone” the FSBA should be followed by a 2-hour postprandial serum total bile acid (PPSBA) looking for an increase greater than 25 µmol/L. The diagnostic value of determining PPSBA concentration is increased sensitivity for the detection of hepatic disease and congenital portal vascular anomalies. In dogs the specificity of fasting and postprandial bile acids for hepatobiliary disease is 95% and 100% when cutoff values greater then 15 µmol/L and 25 µmol/L are used, respectively. When using these guidelines it is prudent to recognize that a small number of healthy dogs have been reported with PPSBA values above 25 µmol/L and these may actually reflect dogs having PVH.

Occasionally the FSBA value is greater than the PPSBA value. The reason for this non sequitur is unclear but probably multifactorial. It has been shown that (1) the peak PPSBA concentration for individual dogs is variable, (2) fasted dogs store about 40% of the newly produced bile in the gallbladder and (3) a meal stimulates the release of only between 5 to 65% gallbladder bile. Undoubtedly these physiologic variables in addition to physiological variation in intestinal transit time and concurrent underlying intestinal disease contribute to the dichotomy.

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

In summary, there are a variety of markers with variable sensitivity and specificity that reflect hepatic tissue and portal vasculature pathophysiology. I support the conclusion of another study that found that the optimal test combination is the serum ALT activity and bile acid concentrations. This pairing provided the best sensitivity and specificity for primary liver disease in dogs. Clinical experience indicates that elevated serum AST concentration along with an elevated ALT helps to support a diagnosis of hepatocellular disease and that the PPSBA concentration enhances the evaluation of hepatic function with chronic hepatitis being a likely possibility.

**Abnormal Liver Enzyme Workup Algorithm**

I use a general algorithm for the work-up of dogs having abnormal liver enzymes (ALT, AST, ALP and or GGT). (Refer to Abnormal Liver Enzyme Workup Algorithm figure) The identification of abnormal liver enzymes occurs either when the sick patient is presented for evaluation or abnormal enzymes identified during a routine health screen in the healthy patient. Abnormal liver enzymes in the sick patient could either be the result of primary liver disease or secondary to a multitude of other non-hepatic disorders. The most common cause of abnormal liver enzymes is in fact not primary liver disease at all but rather the result of reactive hepatic changes occurring secondary to other non-hepatic diseases. The asymptomatic patient with an increased liver biochemical test should have the value confirmed at least once to exclude a spurious result from laboratory error and to avoid unnecessary and costly additional testing. A careful history is first essential to exclude drug associated enzyme elevations. That history should also include all non-traditional therapies such as herbs or neutraceuticals that could potentially cause a drug-induced hepatopathy. Next the signalment of the patient may also provide an insight to the possible etiology. Old dogs tend to get more diseases than the young patient. For example, old dogs frequently have benign hepatic nodular hyperplasia, endocrine disease, many types of neoplasia or systemic disease. On the other hand the most common primary hepatic disease in dogs is chronic hepatitis (CH). Chronic hepatitis is observed in younger to middle aged
dogs and certain breeds are predisposed to developing chronic hepatitis. Dogs with early CH are asymptomatic and only have abnormal liver enzymes. As CH progress to advanced then clinical signs occur.

A careful physical examination may also provide clues to the diagnosis. Examples of non-hepatic conditions would include intra-abdominal disorders (IBD, pancreatitis, nutritional abnormalities), cardiovascular disease or metabolic derangements (hypothyroidism, Cushing’s disease) as just a few examples. Generally these secondary hepatic changes are reversible once the primarily disease is treated. Successful resolution of the non-hepatic disease and continued abnormal liver enzymes would be a strong indication for further investigation of the liver.

If there is no evidence of a primary non-hepatic disease or a drug history then the liver should be investigated. Evaluation of the liver might include liver function tests (bile acids, clotting times, ammonia concentrations) and imaging studies ultimately resulting in liver biopsy of some of those cases. Generally the next liver evaluation involves imaging using radiographs or preferably liver ultrasound. During ultrasound I routinely perform fine needle aspiration of the liver and cytology. It is however important to note that hepatic cytology does not always correlate with histopathology interpretation. In most instances imaging and biochemical testing and liver cytology cannot replace a liver biopsy. A liver biopsy is required for a definitive determination of the nature and extent of hepatic damage and to appropriately direct the course of treatment. The method for liver biopsy procurement may be surgery, laparoscopy, or needle biopsy. Each has certain advantages and disadvantages and the decision of which procedure to use should be made in light of all the other diagnostic information, always considering what is in the best interest of the patient and the client.

Identification of the asymptomatic patient having increased liver enzymes becomes more problematic. As stated above the history and physical examination should be comprehensive looking for clues of occult disease. If there is no drug history or clues to other systemic disease I personally believe it is rational to simply re-evaluate the patient in approximately 6 to 8 weeks. If at that time the liver enzymes are still abnormal and unexplained I would further investigate the patient. I will perform serum bile acids and if they are also abnormal and I know it is not due to a PSS then it tells me there is altered liver function and prompt hepatic evaluation is indicated. As a general rule, persistent elevated unexplained liver enzymes over approximately 6 to 8 weeks and or in conjunction with elevations in serum bile acids is an indication to recommend further evaluation of the liver. In most cases delaying the work-up by approximately 6 to 8 weeks in an asymptomatic patient likely does not result in significant progressive hepatic deterioration. During the waiting period symptomatic therapy may be rational to provide. During the waiting period one
may consider trial therapy using antibiotics on the chance of a bacterial cholangitis, chronic leptospirosis or other infectious cause. One might also consider providing non-specific liver support therapy. Liver support therapy generally involves antioxidants such as S-adenosylmethionine (SAMe), milk thistle (silibin) or other therapy.

REFERENCES

Abnormal liver enzymes are a common encounter in the dog and can be due to a number of etiologies. The following discussion includes some common conditions. Another common histological diagnosis is chronic hepatitis but this will be discussed elsewhere as there are important implications of specific diagnostic testing, therapy, and prognosis.

** Reactive Hepatopathies**

These occur secondary to non-hepatic disease with increased serum biochemical hepatic tests (ALT, AST, GGT, ALP) and histomorphologic abnormalities. In most cases there are little if any changes in tests that evaluate hepatic function (bilirubin, albumin, glucose, BUN and bile acids). Histological findings associated with secondary reactive changes include descriptors such as vacuolar degeneration, hydropic degeneration, swollen hepatocytes, lipidosis, intracellular or intrahepatic cholestasis, mild multifocal hepatitis and periportal or variable hepatic necrosis. These changes are devoid of the typical progressive chronic inflammatory cell infiltrates characteristic of chronic hepatitis. The reason the liver often undergoes these changes revolves from the fact that the liver is involved in many metabolic and detoxification functions. Endogenous toxins, anoxia, metabolic changes, nutritional changes and endogenous stress related glucocorticoid release are examples of conditions responsible for the majority of these changes. Even non-specific mild liver changes routinely also occur following general anesthesia. In a review of liver biopsies at Colorado State University reactive hepatopathies made up the largest category of abnormalities (approximately 25%).

Mild portal hepatitis is a common histology thought to be secondary to uptake of enteric bacteria, toxins, irritating food substances or inflammatory cytokines. Mild ALT and ALP increases can occur. I always look for underlying GI disease and anecdotally have had some resolve feeding a hypoallergenic diet (such as hydrolyzed proteins), enteric antibiotic therapy or ursodiol. Although chronic in nature I avoid putting patients on immunosuppressive therapy. Often the disease does not progress.

** Abnormal ALP in the Asymptomatic Dog**

A very common and often frustrating clinical problem encountered by many veterinarians is the identification of elevations in only the serum ALP in dogs completely asymptomatic. In these cases, a number of clinical conditions could be responsible. **(Refer to Abnormal ALP Workup Algorithm figure)** One must keep in mind the three major isoenzymes of ALP are bone, liver, steroid or drug induction. Bone source is relative easily eliminated if the patient is not a young dog with open growth plates that returns to normal when the dog matures. Siberian Husky puppies are reported to have a benign familial hyperalkalinphospahtasemia from bone origin. Osteoblastic bone tumors can also be associated with elevations in bone source ALP. Most all dogs with bone tumors present with clinical signs relative to the tumor. Osteogenic sarcomas having concurrent ALP increases generally have a very guarded prognosis.

A drug history is important including administration of herbal medications, phenobarbital or glucocorticoids causing steroid ALP induction. It is important to remember that topical steroids (otic, ophthalmic and cutaneous) will also cause ALP elevations. Although hyperadrenocorticism (HAC) can cause marked increases in ALP (and sometimes mild ALT increases), dogs generally have clinical signs referable to Cushing’s disease. Dogs with HAC and without systemic signs would be quite uncommon. Specific testing with an ACTH stimulation test, dexamethasone suppression test and/or urine cortisol to creatinine ratio usually will rule out HAC as the cause of ALP elevations.

At this point in the work up the next diagnostic test I perform is an abdominal ultrasound carefully examining the liver and biliary system. The main differentials for asymptomatic ALP increases include gallbladder mucocele, hepatic nodular hyperplasia, hepatic neoplasia or an idiopathic vacuolar hepatopathy. Gallbladder mucoceles have a characteristic ultrasound appearance and early mucocele formation could cause cholestasis without clinical signs. Other cholestatic conditions such as cholecystitis, cholangitis or cholelithiasis are also possible etiologies.
Vacuolar Hepatopathy

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

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

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

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

Most affected dogs are middle-aged or older at the time of diagnosis. There does not appear to be a breed or sex predisposition other than the syndrome described above in the Scottish terrier. A small percent of dogs may have reported polyuria and polydipsia (PU/PD) but the other signs typical of HAC are generally absent. The work up of the asymptomatic dog having an IVH usually begins after the identification of an elevation in serum ALP. The ALP increases are often 5 to 10 times normal concentrations; the other liver enzymes are usually normal or there are occasional mild elevations in alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT). Marked elevations in liver enzymes other than ALP is not typical of this syndrome and if present other types of liver disease should be investigated. The work-up should first rule out common causes for an elevated ALP such as drug administration (including topical or systemic steroids, phenobarbital, or herbal medications), cholestatic liver disease, or bone disorders. Next adrenal testing (ACTH stimulation or low dose dexamethasone suppression) would be prudent to perform to eliminate possibility of HAC. Determining the percent of ALP steroid isoenzyme is generally not helpful. Dogs with IVH will have predominately a steroid-induced ALP isoenzyme but this is neither specific for HAC or IVH and other non-adrenal illness may also have similar increases in the steroid-induced ALP isoenzyme. Basic tests of liver function tend to be normal however the author has seen a few cases having very mild elevations in serum bile acids. Abdominal ultrasound of the liver is helpful to rule out hepatic nodular hyperplasia, occult hepatic neoplasia or cholestatic disorders that all could be differentials for an elevated ALP. Affected IVH dogs generally have an enlarged uniformly hyperechoic liver with rounded borders. Adrenal glands are generally normal. Fine needle aspiration of the liver with cytology supports a diffuse vacuolar change. A PAS stain of the cytology sample can help confirm the presence of hepatic glycogen. A liver biopsy confirms diffuse vacuolar change but is rarely necessary. I generally make the diagnosis of IVH based on the above diagnostic findings and after exclusion of HAC, drugs, hepatic nodular hyperplasia, hepatic neoplasia or cholestatic liver disease.

At this time I believe adrenal sex steroid panel testing for most cases is not necessary for two reasons; first, our inability to adequately interpret the tests results and second, most all IVH dogs are generally asymptomatic and information obtained from the testing offers little important diagnostic or therapeutic information. Several labs offer adrenal hormone analysis and currently the most extensive adrenal steroid hormone profile is offered by the Clinical Endocrinology Laboratory at the University of
Tennessee. The protocol for running the test is identical to that for a standard ACTH stimulation test. Both proteinuria or hypertension are occasionally identified in cases of IVH and the affected dogs should be periodically monitored for these complications and if identified, managed appropriately. Dogs with IVH are also thought to have an increased risk for developing biliary mucocoeles and there is also some anecdotal evidence to suggest that some Scottish terriers with VH are at an increased risk of development of hepatic neoplasia (hepatocellular adenoma or carcinoma). Consequently it would be prudent to monitor IVH dogs from time with an ultrasound of the liver and biliary system.

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

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

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

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

Hepatic Neoplasia
In the dog liver tumors can be either metastatic or primary. Metastatic tumors are more common and would include the carcinomas and sarcomas. Hepatocellular adenoma is common in dogs and generally restricted to a single liver lobe. Previous terminology calls these tumors as hepatomas human terminology that is incorrect. These tumors are very slow growing and often are found as an incidental finding on ultrasound as a work up for abnormal liver enzymes. There is no spread to this tumor. Often we will just watch them using ultrasound every several months and if they grow in size rapidly then surgery can be suggested. If they become large they may not lend to resection or may become necrotic and rupture causing abdominal bleeding. Hepatocellular carcinomas are malignant neoplasms that can be either solitary (more slowly growing) or diffuse having a poor prognosis. Sometimes telling the
difference from adenoma and carcinoma is difficult FNA or a biopsy sample. It has also been reported that large liver masses may be associated with hypoglycemia due to production of an insulin like factor. The more diffuse cholangiocellular and hepatic carcinomas have poorer prognosis and do not respond well to chemotherapy.

**Selected References**

Chronic hepatitis is an etiologic diverse and morphologically variable condition associated by mixed inflammatory cell infiltrates. It is characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory infiltrates, regeneration and fibrosis. The proportion and distribution of these components vary widely. Plasma cells, lymphocytes and macrophages predominate with a lesser number of neutrophils. Because we see mild portal inflammation as a common non-specific reactive change it is important that pathologist conveys that there is moderate to severe inflammation and necrosis and that the disease is chronic. The presence of fibrosis in the hepatic biopsy usually denotes to me more serious consequences. As damage progresses cirrhosis results with diffuse fibrosis, alteration in hepatic lobular architecture with the formation of regenerative nodules and abnormal vascular anastomoses. Cirrhosis is often associated with portal hypertension, ascites and multiple portosystemic collateral shunts. Some may show manifestations of liver failure, e.g., hyperbilirubinemia, coagulopathies, edema due to hypoalbuminemia, ascites and hepatic encephalopathy.

Etiology. The etiology of chronic hepatitis is often never determined. A known etiology of chronic hepatitis in the Bedlington terrier is the result of metabolic defect in copper metabolism and subsequent hepatic copper accumulation (refer to copper associated liver disease). Copper associated chronic hepatitis has also been documented in many breeds and the precise mechanism of copper accumulation in non-Bedlington terrier is poorly understood. But regardless of the etiology, as copper accumulates in hepatocyte it becomes toxic to hepatocytes and causes hepatitis.

Infectious chronic hepatitis in man is most often associated with viral etiologies. The search for a direct link to a viral etiology and hepatitis in the dog however has yet been unrewarding. Infectious canine hepatitis virus has caused chronic hepatitis in experimental cases. Chronic hepatitis has also been associated with leptospirosis with authors describing "atypical leptospires" in a colony of dogs having a reactive type of hepatitis. Other infectious agents suggested by others as a possible etiology include Helicobacter sp, Bartonella, Leishmaniasis and others.

Chronic liver injury has also been reported in dogs with aflatoxicosis as well as various drug-induced hepatitis. Some dogs treated with anticonvulsant drug phenobarbital will develop chronic hepatitis. We have also observed some dogs being treated with NSAIDs to also have hepatitis that brings the questions of a link between NSAIDs and hepatitis. NSAIDs have been associated with acute hepatic necrosis. In man alpha-1-antitrypsin (AAT- also referred to as alpha one protease inhibitor) deficiency is known to cause chronic hepatitis and cirrhosis. Investigation by researchers in Sweden using immunostaining for AAT in hepatocytes found some dogs with chronic hepatitis to be positive for ATT in the hepatocytes but the dogs differ from man in that serum AAT remained in the normal range while humans have low concentrations. It is not known if the AAT accumulation is the cause or the result hepatocyte damage.

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

**Clinical Findings.** The incidence of chronic hepatitis makes up approximately one fourth of the cases having liver biopsies at Colorado State University (based on a review of 150 consecutive liver biopsies). Chronic hepatitis is more common in female dogs. The average of presentation ranges from 4 to 10 years (mean age 7.5 years). It is interesting to note that in both our series and in studies by others it is uncommon to observe chronic hepatitis/cirrhosis in dogs under 2 years of age and in older dogs >11 years of age. In general old dogs (> 11 years of age) don’t present with chronic hepatitis/cirrhosis or if they do they are at or near end stage disease. The clinical signs parallel the extent of hepatic damage. Early in the disease there are usually no or minimal clinical signs. Only after the disease progresses do the clinical signs specific for liver disease becomes evident. Frequent early signs are gastrointestinal associated with vomiting, diarrhea and poor appetite or anorexia. Ascites, jaundice and hepatic encephalopathy may then occur as the disease progresses. With development of these late signs the long-term prognosis is generally poor.

The laboratory findings include consistently elevated ALT and ALP. The magnitude of rise need not be marked however. One report found 75% of the cases with abnormal bilirubin elevation (mean elevation of 2.6 mg/dl [44.5µmole/L]). Serum proteins are variable. As the lesions become more severe albumin levels decline. Serum bile acids are abnormal in most cases having significant chronic hepatitis and measurement of bile acids appear to be a good screening test for the patient with unexplained elevations in ALT and ALP. In our study, all dogs evaluated with chronic hepatitis had abnormal bile acid concentrations. In a second study, only 8/26 dogs with chronic hepatitis had normal fasting bile acids. However, postprandial samples were not determined in these cases. Determining postprandial bile acids has been shown to increase the sensitivity of this test.

A presumptive diagnosis is made based on the clinical features and persistent increases in ALT values. A definitive diagnosis requires a hepatic biopsy showing characteristic morphological patterns. Needle aspirates are not helpful in making the diagnosis of chronic hepatitis because it is important to see the architecture of the liver and location and extent of the inflammation. In human pathology, at least 5 portal triads are required to make an accurate diagnosis. One must work with the pathologist when making the diagnosis of chronic hepatitis and to be certain that characteristic abnormalities found in chronic hepatitis are present.

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

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

**Diet.** Adjusting diet therapy should be considered and formulated for the individual case. However, a few general guidelines should be kept in mind. First, palatability is important to assure adequate energy requirements are met. Next, there is a misconception about protein and liver disease as many believe all patients should be placed on a protein-restricted diet. Protein restriction should
only be instituted in the patient that has clinical evidence of protein intolerance (i.e. hepatic encephalopathy). The goal of dietary therapy is to adjust the quantities and types of nutrients to provide nutrient requirements but to avoid the production of excess nitrogen by-products associated with liver disease. As a general recommendation the dietary protein should represent 17 to 22% of digestible Kcal. High carbohydrate and moderate fat content is important to supply caloric needs. Mineral supplementation containing high concentrations of both copper and iron should be avoided. Diets low in copper are recommended for the dogs that have copper associated liver disease based on liver biopsy. Most formulated “liver diets” have lower copper concentrations and are recommended. Homemade diets can also be prepared so that they do not to contain excess copper.

**Antiinflammatory Therapy.** Decreasing inflammation with anti-inflammatory therapy is indicated for chronic hepatitis in the dog. The treatment of chronic hepatitis however is controversial and there are as yet no good controlled studies in dogs that support corticosteroids or immunosuppressive drugs. Antiinflammatory therapy is indicated in suspected immune mediated chronic hepatitis in humans and likely indicated in immune mediated hepatitis in dogs.

A study by Strombeck found some dogs with chronic hepatitis had a prolonged survival when treated with corticosteroids when compared to dogs not given corticosteroids. This retrospective study is flawed because of the wide diversity of different breeds and multiple other concurrent therapies used. But none-the-less, it appears that corticosteroids offer benefit with prolonged survival in at least some cases (around 25% in Strombeck study). A suggested initial dose of 1 to 2 mg/kg/day of prednisolone is given. When clinical improvement is evident or after several weeks of therapy the dose is then gradually tapered eventually to a dose of 0.5 mg/kg/day or given every other day. The only accurate way to evaluate a response to corticosteroid therapy is to re-biopsy the patient after approximately 6 months to 1 year of therapy. During therapy it is impossible to interpret liver enzymes or predict improvement because the patient has a concurrent steroid hepatopathy. Short of biopsy one could also stop corticosteroids and then after a period of approximately 1 to 2 months determine if there is improvement in liver enzymes. This time period is required to remove the steroid effects causing elevations in liver enzymes and the steroid hepatopathy.

Because of the side effects of corticosteroids and the failure to successfully monitor liver enzymes while receiving steroid therapy other immune suppressive therapy may be a more rational approach. Azathioprine is an effective immunosuppressant drug that has shown to increase survival in man when treated for chronic hepatitis in conjunction with corticosteroids. This therapy may also be beneficial in dogs (don’t use in cats) by increasing the immunosuppressive response and enabling a reduction of both steroid dose and their side effects. A dose of 2.2 mg/kg/day is the suggested starting dose and after several weeks given every two days. The level of glucocorticoids can frequently be reduced when using azathioprine. It is important to note that azathioprine has occasionally been associated with a drug induced hepatic necrosis or acute pancreatitis and although relative inexpensive I personally tend not to use this drug.

We have more recently been using cyclosporine in most chronic hepatitis cases with a very good clinical response. Our experience using initially 5 mg/kg bid (without steroids) has been very encouraging in dogs that are thought to have immune mediated chronic hepatitis. The veterinary formulation Atopica™ is a microemulsified preparation with the identical properties to the human product Neoral™ and is also sold as modified generic cyclosporine that ensures more consistent bioavailability and better than the other human product Sandimmune™ (also available as non-modified generic cyclosporine). I only measure blood level at the trough (right before the next pill) if I feel the patient is not responding adequately to the therapy to assure adequate dosing is present. The ideal range of blood levels are within 400-600 ng/ml. Some dogs will develop gingival hyperplasia at the higher concentrations of cyclosporine. Reducing cyclosporine dose and treating with azithromycin (10 mg/kg/day for 4-6 weeks) will often decrease the gingival hyperplasia. Vomiting is a common side effect and giving the drug with a small amount of food or giving the capsules frozen help with the vomiting. With evidence of clinical response at 5
mg/kg bid (normalization of ALT) I will often decrease to once a day or even every other day therapy. The advantage of using cyclosporine alone is one can follow the liver enzymes making the need for a liver biopsy less frequently required. Other immunosuppressive drugs such as mycophenolate or leflunomide have also been used but I have less experience with these drugs and hepatitis.

**Antifibrotic Drugs.** The best way to prevent fibrosis is to stop the inflammation. Corticosteroids, zinc and penicillamine all have anti-fibrotic effects. Colchicine is a drug that has been used in treating persons with chronic hepatitis and other types of liver fibrosis. This drug interferes with the deposition of hepatic collagen and stimulates collagenase activity to breakdown deposited fibrous tissue in the liver. It also is shown to have anti-inflammatory properties. However there is still the lack of convincing data in humans and dogs with liver disease that colchicine is beneficial. A critical appraisal of colchicine in human liver disease having chronic hepatitis now questions its effectiveness and failed to show benefit in a placebo controlled meta analysis of over 1000 patients. There are only 3 case reports of colchicine in dogs with all having questionable results. Recently it was found that angiotensin II receptor blockers (ARB) such as losartan (0.25-0.5 mg/kg/day) or telmisartan have effects in reducing or preventing fibrosis in humans by inhibiting hepatic stellate (fibrosis producing) cells. We have used ARBs in dogs having a primary fibrotic component of their liver disease but no controlled studies are available to determine effectiveness. I personally do not use colchicine in my hepatitis cases.

**Choleretic Drugs.** Decreasing cholestasis has been shown to be of benefit in humans and animals having choledystatic hepatobiliary disease. As serum bile acid concentrations increase (these are predominately cytotoxic bile acids) they can cause cell membrane permeability changes and fibrogenesis. Ursodeoxycholic acid (ursodiol) is a choleretic agent developed to dissolve gallstones but later found to have positive effects in patients with chronic hepatitis. This drug is a synthetic hydrophilic bile acid that essentially changes the bile acid pool from the more toxic hydrophobic bile acids to less toxic hydrophylic bile acids. Ursodeoxycholic acid has been shown to increase bile acid dependent flow, reduce hepatocellular inflammatory changes, fibrosis and possibly some immunomodulating effects. The hepatoprotective characteristics of ursodeoxycholic are that of a super antioxidant. The dose for ursodeoxycholic acid is 10-15 mg/kg daily. No toxicity has been observed in dogs and cats at this dose. There has been a concern raised by some that it should not be used if there is any possibility of a bile duct obstruction for fear of biliary rupture. Ursodeoxycholic acid is not a prokinetic and will not cause a gallbladder rupture.

**Antibiotics.** Antibiotics are indicated for primary hepatic infections. However, secondary bacterial colonization may also take place in a diseased liver due to Kupffer cell dysfunction. Kupffer cells function as the primary filter of portal blood entering the liver. It is known that portal blood is not sterile and with hepatic disease and poor Kupffer function bacteria may enter the liver. It may be prudent for antibiotic therapy trial for several weeks in patients having significant hepatic disease (i.e. chronic hepatitis). Amoxicillin, cephalosporin, or metronidazole is suggested. If metronidazole is prescribed we suggest 7.5-10 mg/kg bid which is a much lower dose used for other bacterial infections because of hepatic metabolism of the drug. Because leptospirosis has been associated with chronic hepatitis amoxicillin may be a logical empirical antibiotic choice if an occult leptospirosis hepatitis is present.

**Antioxidants.** There has been recent interest in the management of certain types of liver disease using various antioxidants as liver support. Antioxidants in general may help promote optimal hepatic function. Considerable evidence shows that free radicals are generated in chronic hepatitis and participate in the pathogenesis of oxidative liver injury in dogs and cats. Normally there is an extensive system of cytosolic and membrane bound enzymatic and non-enzymatic antioxidants which function to prevent oxidative damage by “scavenging” or “quenching” free radicals that are formed. It is reported that close to half the dogs and cats with liver disease have reduced glutathione concentrations in the blood and liver supporting that oxidative damage is present.
**Vitamin E**, d-alpha tocopherol, functions as major membrane bound intracellular antioxidant, protecting membrane phospholipids from peroxidative damage when free radicals are formed. Vitamin E is shown to protect against the effects of copper, bile acids and other hepatotoxins. A suggested vitamin E dose is 10 IU/kg/day up to a maximum or 400 IU. At this dose vitamin E is very safe. I generally prescribe a water-soluble d-alpha tocopherol (natural vitamin E) as it has better bioavailability.

**S-Adenosylmethionine (SAMe)** is a naturally occurring molecule found in all living organisms and is involved in a number of metabolic pathways that appear to be beneficial to the liver as well as other tissues. SAMe is involved in three major biochemical pathways. It is involved in cell replication and protein synthesis, has a modulating influence on inflammation and plays a role as a precursor of the antioxidant glutathione in the hepatocyte. Studies show with therapy glutathione concentrations increase in the liver.

**Milk thistle** has been used for centuries as a natural remedy for diseases of the liver and biliary tract. Silymarin the active extract consists of bioflavonolignans that have been reported to work as antioxidants, scavenging free radicals and inhibiting lipid peroxidation. Several recent human clinical trials have assessed the efficacy of silymarin in the treatment of liver disease. The data is somewhat difficult to interpret because of the limited number of patients, poor study design, variable etiologies, lack of standardization of silymarin preparations with different dosing protocols. There is however compelling evidence to suggest silymarin has a therapeutic effect in acute viral hepatitis, alcoholic liver disease, patients with cirrhosis, and in toxin or drug-induced hepatitis. Unfortunately, the purity of commercial products, and therapeutic dosage is unknown. Milk thistle is reported to have an extremely low toxicity in humans and animals and has been used extensively in clinical patients with little concern for side effects. Silibin appears to be a principle active isomer of the silymarin extract. Bioavailability is increased by complexing with phosphatidylcholine. Denamarin™ (Nutramax Laboratories) is available containing SAMe and silybin and is a compound the author has done research on.

**General Support Therapy.** The remainder of the therapy for chronic hepatitis involves treatment of secondary complications. These occur as the disease becomes advanced. Hepatic encephalopathy, GI ulceration and ascites are common clinical occurrences in advanced hepatitis or cirrhosis.

**Selected References.**

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

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

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

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

If the liver biopsy of a dog with hepatitis and significant abnormal hepatic copper accumulation, a low copper diet and copper chelation should be started. I believe hepatic copper levels of greater than 1000 µcg/g dry weight (dw) liver (normal <400 µg/g dw) requires therapy to reduce copper concentrations. I tend to be less aggressive with chelation if the biopsy shows primary cholestasis with impression the copper is secondary to cholestasis. Chelator treatment using penicillamine is the primary therapy for copper associated liver disease. Penicillamine binds with copper and then promotes copper removal through the kidneys. Penicillamine is the most frequent copper chelator recommended for use in dogs. The human product is very expensive and I use compounded penicillamine or DePen from pharmacies out of Canada. The dose is 10-15 mg/kg bid given on an empty stomach. Side effects include anorexia and vomiting but can be managed by starting at a lower dose and then increasing the dose over time or by giving it with a small amount of food or using maropitant as needed. Penicillamine therapy takes months to cause a substantial reduction in hepatic copper concentrations. The length of chelation therapy is variable but based on past experience some general recommendations can be made. Ideally repeat liver biopsies should be obtained to determine success of the chelation and to direct duration of therapy. The following is only a general recommendations. Bedlington terriers and Dalmatians will likely require lifetime Cu chelation therapy to achieve normal Cu concentrations. Other breeds including the Doberman and Labrador usually only require short-term therapy. I believe chelation therapy should be instituted in dogs when hepatic Cu concentrations approach or greater than 1000 µg/g dry weight liver. In one 4-month study giving penicillamine to 5
Doberman pinschers with sub-clinical hepatitis and abnormal hepatic Cu concentrations (mean concentration of 1036 µg/g dry weight liver) had a significant decrease in mean hepatic Cu concentration by 407 µg/g dry weight with a significant improvement in liver pathology. In another larger placebo controlled study of forty affected Labrador retrievers with Cu associated hepatitis treated for 3 months with either penicillamine or placebo resulted in a mean reduction of 863 µg/g dry weight copper in the treated group (mean pretreatment Cu concentration was 1511 µg/g) while the placebo treated group had no significant change in Cu concentrations. Chelation for 4 to 6 months may be adequate to decopper the liver of other breeds such as the Labrador retriever and Doberman pincher but the length of therapy can only be determined following a repeat biopsy and Cu quantitation. The table above shows my rough guidelines on duration of chelation therapy. Following clinical improvement either intermittent chelation therapy, oral zinc therapy and or low copper diets are required to prevent further intestinal absorption of Cu. Ideally the patient should be re-biopsied after 4-6 months of treatment. Often that is not possible to rebiopsy and so below are rough guidelines on chelation therapy I use. I also monitor serum ALT concentrations and when levels return to normal would be a time I would discontinue penicillamine therapy but continue low copper diets. Ideally repeat liver biopsies with copper quantitation is the gold standard to direct therapy. I supplement antioxidants such as vitamin E (10 IU/kg/day) and or other liver support therapy.

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

Gallbladder Mucocele. To date greater than 130 cases of gallbladder mucocele have been recently documented in the literature. 15-20 years ago a mucocele was a very rare pathological finding. A gallbladder mucocele is a condition that is described as an enlarged gallbladder with immobile stellate or finely striated patterns of mucoid material within the gallbladder lumen detected with ultrasound. The changes described can result in biliary obstruction or gallbladder perforation and peritonitis. Smaller breeds and older dogs are overrepresented. Shetland sheepdogs and Cocker Spaniels are most commonly affected. Most dogs are presented for nonspecific clinical signs such as vomiting, anorexia and lethargy. Abdominal pain, icterus and hyperthermia are common findings on physical examination in advanced cases. Most have serum elevations in bilirubin, ALP, GGT and variable ALT although some dogs are asymptomatic and a mucocele is diagnosed as an incidental finding on abdominal ultrasound. The Shetland sheepdogs tend to have hyperlipidemia and were first thought to have a genetic defect in the ABCB1 hepatobiliary transporter gene involved phosphocholine transport into the bile. That theory is now questioned in a reported second larger study. Risk factors identified in mucocele cases include endocrine disease (hypothyroidism, Cushing’s disease) and idiopathic vacuolar hepatopathy, hyperlipidemia and dogs on high fat diets. Researchers have also reported abnormal gallbladder mucous production and another studied reported abnormal bile acid composition. It is possible that abnormal bile composition causes gallbladder irritation leading to cystic mucinous hyperplasia and subsequent mucocele formation.

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

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

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

Because similar histological changes occur in dogs having PVH and PSS (i.e., hepatic hypoperfusion) the diagnosis can be confusing. If an intrahepatic or extrahepatic macroscopic shunt is not observed then PVH becomes the probable diagnosis. Angiography or transcolonic portal scintigraphy fails to demonstrate macroscopic shunting in this condition. Often a needle biopsy is not sufficient to provide enough portal areas to make the diagnosis, and consequently a wedge or laparoscopic biopsy may be necessary. The lesion may be patchy or involving different liver lobes so multiple biopsies should be taken from different lobes.

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

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

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

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

Selected References.

Liver disease is common in the cat and the finding of icterus is a frequently a clinical clue that the cat has primary liver disease. The types of liver disease as well as differences in laboratory tests for the cat are very different from disorders observed in the dog. This is due in part to specific anatomical and metabolic differences of the cat. The following includes an overview of these differences with updates of newer information on feline hepatic disease and their therapy.

**Laboratory Testing.** A sick cat may become icteric (jaundice) without having primary liver disease. This is because of the complexities of bilirubin metabolism combined with cat’s weak ability to conjugate compounds. Normal hepatic bilirubin metabolism must go through several steps in the hepatocyte before excretion into the bile. This metabolism can be affected by inflammatory cytokines or endotoxins and from nutritional alterations due to mobilization of free fatty acids delivered to the liver or from protein deficiencies resulting from catabolic conditions. Cats also have inherent low concentrations of glucuronyl transferase, an enzyme required to convert bilirubin to water-soluble form prior to hepatic excretion. It is this complex pathway that can result in icterus without evidence of significant structural liver disease. We recently reviewed 180 cats having elevated bilirubin concentrations and cases were grouped them into those clinically icteric (bilirubin > 3.0 mg/dl, 51 µmol/L) or those with biochemical icterus (having only icteric serum with bilirubin ranging from 0.5 to 2.9 mg/dl). Clinically icteric cats (bilirubin > 3.0 mg/dl) likely have primary hepatobiliary disease when hemolytic disease is ruled out. Cats having biochemical icterus (bilirubin < 3.0 mg/dl) do not always have primary hepatobiliary disease and many have other non-hepatic disorders with the liver being secondarily affected with what is often referred to as a secondary reactive hepatopathy. For example, it is not unusual to find elevations in bilirubin concentrations in cats with inflammatory disease such as pyothorax, abscesses or tissue necrosis. We also found the higher the bilirubin the poorer the survival rate. Those having only mild increases in bilirubin tended to have a better prognosis however the prognosis was influenced by the underlying primary liver disease.

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

The ALT and AST are quite variable and reflect hepatocellular leakage from either degeneration or necrosis. These liver enzymes are less predictive of primary inflammatory liver disease than ALP and GGT (tests that reflect cholestasis). No published values exist for ALT half-life but it is presumed that ALT is much shorter (around 6 hours) than that of dogs (2.5 days). AST half-life is 77 minutes in the cat. The short half-lives may explain the variability of ALT and AST values in liver disease of cats and if marked elevations are found tend to reflect a relative acute episode. Increases in ALT alone without other enzyme elevations is often observed in cats having secondary liver involvement from some other primary non-hepatic condition for example hyperthyroidism.

**Types of Liver Disease.** The incidence of liver disease in the cat is unknown but considered to be common. In an unpublished review of 175 consecutive liver biopsies performed on cats at Colorado State University several large categories were observed. Making up 87% of the liver biopsies were 4 groups: Lipidosis (26%, both idiopathic and secondary), Cholangitis (25%), Neoplasia (20%) and Secondary Reactive Hepatopathies (16%). Hepatic cysts and hepatic cyst adenomas both now thought to be ductal plate anomalies are occasional findings in some cats and rarely cause problems. Lipidosis and cholangitis were the most common conditions and will be discussed below. Reactive hepatopathies refer to changes in the liver that occur secondary to a primary non-hepatic disorder such as inflammatory bowel disease, hyperthyroidism and cardiac disease as a few examples. Usually there is also a degree of secondary lipidosis associated with reactive hepatopathies. Hepatic neoplasia was also common. Cats are different than dogs in the fact that benign tumors are more common than malignant hepatic neoplasia. Bile duct carcinoma the most common malignant neoplasia when hematopoietic tumors (ie, lymphoma) are excluded from the hepatic neoplasia group.

**Hepatic Lipidosis.** Lipidosis is common in the cat but relative uncommon in the dog. Hepatic lipidosis can occur as either a primary idiopathic syndrome or secondary to a number of other primary disease conditions. Lipid accumulation in the liver is simply the result of nutritional, metabolic or toxic insults to the hepatocyte and the degree of lipid accumulation can be quite variable but the process is reversible. For example, a common secondary disease associated with significant hepatic triglyceride accumulation is diabetes mellitus. Hepatic lipid accumulation can also result secondary to a number of other disease syndromes associated with anorexia and weight loss such as pancreatitis, inflammatory bowel disease or other major organ dysfunction. These secondary conditions generally have less severe lipidosis than the clinical syndrome associated with idiopathic hepatic lipidosis in which there is no identifiable etiologic factor. Essentially any conditions leading to anorexia can also cascade into secondary hepatic lipidosis. I believe anorexic cats develop hepatic lipidosis very easily. Interestingly in recent years we have seen fewer cases of the idiopathic form of hepatic lipidosis, perhaps since veterinarians are more comfortable in handling these cases.

The etiology of idiopathic hepatic lipidosis is unknown and several theories have been put forward without substantial evidence. One proposal is that there is a defect in hepatic lipid mobilization and decreased ability for hepatic fat oxidation, decreased synthesis of apoproteins and decreased lipoprotein removal from the liver. In the idiopathic form affected cats generally are older and obese and usually have undergone a stressful episode in the recent history followed then by a period of complete anorexia with a
dramatic aversion to food. There is rapid weight loss (up to 40-60% body weight over 1-2 weeks), depression and icterus. The weight loss involves muscle mass loss while abdominal and inguinal fat stores often being spared. The diagnosis of idiopathic hepatic lipidosis is supported by the clinical history and laboratory findings. Icterus and marked elevations in ALP are consistent findings. ALT levels are variable and GGT concentrations are normal or only moderately increased. Icterus with a very high ALP and normal GGT should be a clue to likely idiopathic lipidosis when appropriate clinical features are present. Hypercholesterolemia, hyperammoniemia and abnormal bile acid levels are characteristic. About 1/3 of the cats have a nonregenerative anemia, hypokalemia and clotting abnormalities and about 1/2 the cats demonstrate poikilocytes in the RBC's. Finding severe hypokalemia, anemia or other concurrent disease (i.e., pancreatitis) with lipidosis has a poor survival rate. A definitive diagnosis requires a liver biopsy or presumptive diagnosis supported by a fine needle aspirate of the liver with cytological evidence of many vacuolated hepatocytes.

The therapy for idiopathic hepatic lipidosis requires aggressive management. I believe up to an 85% or higher survival rate should be expected. Initial therapy requires fluid and electrolyte replacement. Adequate nutrition next becomes the most important part of the therapy for hepatic lipidosis. Placement of a 20 French red rubber esophageal feeding tube is necessary for nutritional support. The nutritional recommendations for idiopathic hepatic lipidosis are completely empirical and poorly documented. Recovery formulations providing adequate calories and protein are used. I calculate the caloric needs for the cat’s ideal weight and then divide the feedings into 4 to 6 daily feedings. However, feeding too much too soon may result in vomiting and could precipitate a refeeding syndrome. Consequently I begin by providing 25% of the patients’ caloric needs the first day and then gradually increase the amount over several days to get to the calculated needs. There is also no good data on the benefit of various dietary supplements. Suggestions include arginine, carnitine, B vitamins, SAMe, other antioxidants and appetite stimulants. Some cats may have cobalamin deficiency (vitamin B₁₂) and if so should be supplemented. The prognosis is good with aggressive nutritional therapy and most cats recover if the lipidosis is not secondary to serious other primary disease. Vomiting can be controlled with maropitant (0.5 mg/kg/day) and mirtazapine (1.5 mg/kg q 48h) as an appetite stimulant that also has antiemetic effects.

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

**Neutrophilic Cholangitis.** This classification has previously been referred to as suppurative or exudative cholangitis/cholangiohepatitis and is the most common type of biliary tract disease observed in cats in North America. Neutrophilic cholangitis is thought to be the result of biliary tract infection from bacterial translocation from the gastrointestinal tract. In the acute neutrophilic form (ANF), the lesions are exclusively neutrophilic or suppurrative but over time it is thought that some cases may progress to a chronic neutrophilic form (CNF) (nonsuppurative) with a mixed inflammatory pattern containing variable numbers of neutrophils, lymphocytes and plasma cells.
In the ANF coliforms (predominately E. coli and enterococcus) are frequently cultured from the liver or bile. Inflammation can also extend into the hepatic parenchyma causing a cholangiohepatitis. Cats with this syndrome can be of any age and present with a more acute illness usually a week or less in duration. They may have evidence of a fever, anorexia, vomiting or lethargy. A leukocytosis may be identified on the CBC. The ALT/AST and ALP/GGT are usually increased but quite variable and cats are frequently icteric. Ultrasound should be performed to rule out pancreatitis, biliary obstruction or other intra-abdominal disorders. In some cases we will perform an ultrasound-guided cholecystocentesis for cytology and culture. It is generally considered to be a safe procedure and may provide important diagnostic information. A liver biopsy is required for histology and will confirm the diagnosis. The liver biopsy should always also be cultured because of the relationship of bacteria and cholangitis. If obstruction is identified surgery becomes indicated to decompress and flush the biliary system. However, I always try to avoid surgical diversion surgery of the biliary system unless it becomes the last resort and temporary stent placement should be considered. In some cases a cholecystectomy may be required with severe gallbladder involvement. Concurrent pancreatitis may be diagnosed with an elevated feline PLI and pancreatic ultrasound changes. Inflammatory bowel disease (IBD) is diagnosed by presence of GI signs, intestinal ultrasound changes and or an intestinal biopsy showing chronic inflammation.

Therapy first includes fluid and electrolyte replacement if needed. Antibiotics are also a critical part of the therapy in ANF. Culture and sensitivity of the liver or bile will drive antibiotic selection. Without a positive culture I would consider the likelihood of E. coli or other enteric aerobe (i.e., enterococcus or other gram negative enteric). Ampicillin, ampicillin-clavulanic acid, cephalosporins and fluoroquinolones have been suggested as likely effective antibiotics. Ampicillin or ampicillin-clavulanic acid is often my choice because of the likelihood of E. coli and the fact that both antibiotics are concentrated in the bile. Some authors recommend ticarcillin and a fluoroquinolone combination. It is recommended that affected cats be treated for at least 1-2 month or even longer with antibiotics as a short duration of therapy may result in reoccurrence of clinical signs. Ursodeoxycholic acid (Ursodiol 10-15 mg/kg/day) is also recommended if bile duct obstruction is not evident. Abdominal discomfort and vomiting may be associated with hepatobiliary pain and buprenorphine should be administered. Most cats if treated with appropriate antibiotics respond but may require long term therapy.

The CNF (neutrophilic, mixed or lymphocytic-plasmacytic also referred as nonsuppurative) cholangitis may be the result of progression of the acute neutrophilic cholangitis. In the chronic stage the liver lesions are associated with the presence of a mixed inflammatory infiltrates in the portal areas consisting of neutrophils, lymphocytes and plasma cells. Possibly fibrosis, ductular proliferation or extension of inflammation into the hepatic parenchyma can occur as well. Generally, both clinically and laboratory wise these cases can’t be differentiated from the ANF. Histology, cultures help differentiate these cases. Ultrasound examination is quite variable and in fact some have normal ultrasonographic findings but thickened gallbladder, dilated ducts and pancreatic changes are the most common abnormalities observed.

In a recent study using FISH analysis we identified the presence of bacteria in 2/3 of the cases having the CNF. The most common bacteria identified was E. coli followed by enterococcus. Historically the CNF was treated with corticosteroid therapy but in light of our findings we recommend if cultures are negative that antibiotic therapy be instituted prior to corticosteroid therapy. Remainder of the management is similar to the acute form.
It has been argued that many cases do not improve until corticosteroids or other immunosuppressive therapies are given (see below Lymphocytic Cholangitis). Steroid improvement may be due to the fact many cats also have concurrent inflammatory bowel disease and/or chronic pancreatitis. One study found 83% of affected cats had inflammatory bowel disease (IBD) and 50% had concurrent chronic pancreatitis. The association of the three together has been referred to as “feline triaditis syndrome”. IBD is generally treated with corticosteroids and diet and clinical improvement may actually be due to the IBD therapy.

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

The syndrome is usually chronic progressing over months to years and complete recovery is uncommon. The clinical features are often similar to the neutrophilic form but advanced disease can result in ascites, jaundice, and hypergammaglobulinemia (in almost all cases). In advanced cases, ultrasonographic examination may demonstrate dramatic changes intra and extra-hepatic bile ducts with marked segmental dilations and areas of stenosis that may lead the operator to believe there is an obstruction. Ascites and hepatic encephalopathy occur late in the disease as a result of acquired portal hypertension and hepatic dysfunction.

The treatment for the chronic lymphocytic cholangitis involves using anti-inflammatory (prednisolone) and/or immunosuppressive therapy (I frequently use chlorambucil in severe cases) in addition to supportive therapy as described with neutrophilic cholangitis. Ursodeoxycholic acid has been shown to have a positive treatment effect in humans having chronic primary biliary cirrhosis having a very similar histologic pattern to these chronic cases and may be a helpful adjunct therapy if obstruction is not present. However one study reports prednisolone had better results than ursodiol.

Feline Triaditis Syndrome. The term “triaditis” is used to describe concurrent inflammation of the pancreas, liver and small intestines and is based on histological conformation. However, the specific conditions that constitute the diagnosis of triaditis include any inflammatory process within these organs but is most often is associated with a combination of pancreatitis, cholangitis and inflammatory bowel disease (IBD). Triaditis has been reported in 50-56% of cats diagnosed with pancreatitis and 32-50% of those with cholangitis or inflammatory liver disease. Cats tend to present with anorexia and vomiting and generally triaditis cats have more severe IBD. It tends to occur in older cats (>8 yrs.).

Although there appears to be a direct association between the three organ involvement, the etiology and pathophysiology of this syndrome is yet unknown. Likely causes of
inflammation include bacterial infection, immune mediated or idiopathic mechanisms. When all three organs (liver, pancreas and intestine) become inflamed it becomes triaditis. Because the etiology of this syndrome is unknown it is difficult to know how to best treat it. Since it is likely several etiologies are responsible and the specific therapies are also variable and will differ from case to case.

**Bacterial Theory.** One theory for triaditis is that both acute and chronic pancreatitis could be the result of an extension of ductular inflammation from the biliary system. This is because the common bile duct and pancreatic duct both merge into a common channel before entering into the intestine. It is possible bile and enteric bacteria from the common channel enter both the pancreatic duct and common bile duct and are responsible for both inflammatory liver and pancreatic changes. With the theory of ascending bacteria from the intestine bacteria may be responsible for both cholangitis and pancreatitis. It is known that cats also have on the order of 100 times higher concentrations of bacteria in the proximal duodenum than do dogs or humans (dogs 10^3 cfu/g vs cats 10^5 to 10^8 cfu/g). High enteric bacterial concentrations coupled with inflammatory changes in the intestine would be a likely source of bacterial seeding either via the common channel or through intestinal translocation with hematogenous seeding. In either case IBD would likely potentiate bacterial movement.

FISH analysis (fluorescence in situ hybridization [FISH] using a 16S rDNA probe that recognizes a specific class of enteric bacteria) is a non-culture method staining technique for bacteria. In a published study we found through FISH analysis that enteric bacteria was present in liver tissues of 69% of the cats having a chronic or acute inflammatory liver disease. The most common bacteria identified in the livers with cholangitis are *E. coli* and *Enterococcus*. In yet another, but yet unpublished study, we used FISH to examine the pancreas of cats with either acute or chronic pancreatitis and found a relatively high frequency of bacteria in that organ (35% or 11/31 cases). Infection was most prevalent in cats with moderate to severe acute or chronic pancreatitis. The localization and type of intra-pancreatic bacteria suggests translocation of enteric bacteria. The most common organisms identified were *E. coli*, *Streptococcus* spp and *Enterococcus* spp. Further, an experimental pancreatitis study in cats clearly demonstrated that *E. coli* translocated from the intestines into experimentally induced acutely inflamed pancreas as well as into the liver and gallbladder supporting the intestinal translocation theory. These findings have substantial implications for the diagnosis and management of cats with pancreatitis.

**Immune-mediated Theory.** Cats having chronic lymphocytic pancreatitis or lymphocytic cholangitis invasive bacteria are less commonly visualized. With the combination of lymphocytic (chronic) pancreatitis, lymphocytic or mixed lymphocytic and neutrophilic cholangitis and lymphocytic plasmacytic enteritis may all be a consequence of an immune-mediated process rather than active bacterial infection. In people and experimental animals autoimmune pancreatitis and cholangitis are recognized as extra-intestinal complications of IBD, with immune attack frequently directed against bile and pancreatic ducts. Immune mediated damage may either be a consequence of immune responses against bacteria (that may or may not have established an active infection) that cross-react with host tissues with resultant innocent by-stander immune responses in the intestines, liver and pancreas, or immune attack directed against host antigens unmasked by tissue damage. In further support for an immune etiology are human studies demonstrating that a variety of autoantigens have been implicated again suggesting that immune responses to translocated bacteria, perhaps facilitated by a leaky gut, and may promote an immune inflammation in a susceptible individuals. We also know feline IBD when not dietary or
antibiotic responsive often improves with immunosuppressive therapy supporting again a possible the immune theory. At this point there are no reliable clinical tests to detect an immune response.

The definitive diagnosis of triaditis involves histopathology from each organ. It is important whenever doing an exploratory surgery for a biopsy of intestine, pancreas or liver that all three organs should be carefully inspected and biopsied even if they appear normal because triaditis is so common. Evidence of liver disease is based on identification of elevations in liver enzymes and or total bilirubin. Liver ultrasound findings in cats are quite variable and many affected livers can appear normal. Abnormal ultrasound changes in cholangitis include prominent portal areas, duct distention and thickened gallbladder wall. In some cases bile duct obstruction can occur from duct inflammation, cholelithiasis or thick bile sludge. Surgical flushing or even temporary stent placement may be required in these cases. I will also always culture the liver biopsy and bile that has been obtained from a gallbladder aspirate. A presumptive diagnosis of pancreatitis includes an elevated serum pancreatic lipase immunoreactivity test (fPLI) and abdominal ultrasound showing abnormal pancreatic changes. In one study the fPLI sensitivity is reported to be 67% and the specificity of the fPLI to be 91%. Ultrasound will detect anywhere from 35 to 67% of cats with pancreatitis. Pancreatic biopsies are safe and easy to perform either at surgery or via laparoscopy. I also now culture most of my pancreatic biopsies as well. Intestinal disease is often diagnosed based on signs of GI disease (vomiting or diarrhea) and ultrasound changes in the bowel with mucosal thickening or loss of layering. Some cats may also have decreased folate of cobalamin (B12) serum concentrations with triaditis. Intestinal biopsies confirm inflammatory intestinal disease and are obtained via endoscopy or surgery. It is ideal to biopsy each segment of the small intestine because the IBD can be regional. Further, the most common area for GI T-cell lymphoma is the ileum that must be reached endoscopically via colonoscopy.

Since the etiology of feline triaditis is unknown it is almost impossible to make absolute treatment recommendations. The first step in the therapy should be directed to the organ that is thought to be primarily responsible for the clinical signs. Because we believe that both bacterial and immune-mediated theories are possible one should use all the clinical information available to help direct the course of therapy.

**Inflammatory Bowel Disease (IBD).** The etiology of IBD is unknown. Possibly dietary constituents, bacterial causes or an abnormal immune response are all thought to be likely etiologies. Lymphocytic plasmacytic enteritis frequently responds to dietary modification with an antigen restricted (novel protein) or a hydrolyzed diet. Refractory patients typically escalate to diet plus antimicrobial therapy using enteric antibiotics such as tylosin (15 mg/kg bid), metronidazole (7-10 mg/kg bid) or amoxicillin. If the patient fails to respond to more conservative therapy then I will then institute anti-inflammatory therapy using prednisolone (1-2 mg/kg q 24h with gradual dose reduction based on response). Often B12 supplementation is required (250 µg SQ weekly). Concurrent low-grade small T-cell intestinal lymphoma can respond well to therapy with chlorambucil (2 mg PO given 3 times a week), prednisolone and supplementation of B12.

**Pancreatitis.** Acute pancreatitis is less common than chronic pancreatitis but acute can often progress to chronic pancreatitis or even exocrine pancreatic insufficiency. Acute (suppurative) pancreatitis carries a particularly poor prognosis. Complicating factors that can modify the situation are bacterial translocation and biliary obstruction. Fluid therapy, analgesics, antiemetics and assisted alimentation are the basis of therapy. Antimicrobial
therapy is warranted in moderate to severe cases and is supported by the finding of positive FISH staining in over 1/3 of the cases investigated. E. coli, Streptococcus spp and Enterococcus spp are the most common organisms identified. Amoxicillin-clavulanic acid, cephalosporins, fluoroquinolones or metronidazole are reasonable considerations. In cats with suspected disease exploratory laparotomy with biopsy of the pancreas, liver and intestine with appropriate cultures of pancreas and liver is frequently required to optimize therapy. Persistent biliary obstruction from pancreatitis is another indication for surgery and may be amenable to stenting or cholecystojejunostomy. It should be noted that corticosteroids are not typically employed in the treatment of feline acute pancreatitis.

**Chronic pancreatitis** is more common than acute pancreatitis in the cat. Lymphocytic or lymphocytic plasmacytic pancreatitis with fibrosis is the characteristic finding. In some cases the pancreatic damage can be so severe resulting in exocrine pancreatic insufficiency requiring pancreatic enzyme supplementation. Bacteria can also be a component of chronic pancreatitis so I generally begin with antibiotic (same listed above) and antioxidant therapy (i.e. SAMe, milk thistle, vitamin E). If there is a failure to respond to antibiotics or with evidence of IBD and or lymphocytic cholangitis then corticosteroid therapy would be indicated. Many cats will also require vitamin B₁₂ supplementation.

**Cholangitis.** The management of cholangitis is based in part on culture results and histopathology. The acute neutrophilic (suppurative) cholangitis or chronic neutrophilic (lymphocytic plasmacytic neutrophilic) cholangitis are often associated with bacteria. The specific antibiotic therapy to use is best determined based on culture and sensitivity of the liver biopsy or bile aspirate. Short of a positive culture antibiotic therapy should be directed at enteric coliforms as suggested in the pancreatitis section. Other adjunct therapy may include ursodiol (ursodeoxycholic acid 10-15 mg/kg q 24h or divided bid), SAMe, milk thistle products or other antioxidants. The acute form usually responds quickly while the chronic form is less predictable. Generally a 4-week course of antibiotic therapy is indicated. If the patient fails to improve after several weeks of antibiotics I will begin prednisolone therapy. The lymphocytic cholangitis is thought to be likely immune mediated and rarely has a bacterial component. But because pancreatitis is common with cholangitis and bacteria could play a role in both I will usually also institute a course of antibiotic therapy. Cats having lymphocytic cholangitis will however generally require prednisolone therapy and sometimes even immunosuppressive therapy such as chlorambucil or others. A recent study found ursodiol was inferior to steroids based on follow up biopsies after a course of therapy. I use ursodiol as an additional adjunct therapy in these cases. General supportive therapy, antioxidants and vitamin B₁₂ are generally used in these cases.

**Selected References.**

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LATEST UPDATE ON ACUTE PANCREATITIS IN THE DOG

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

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

Clinical Conditions

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

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

Diagnosis

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

Amylase and lipase have been used for years to diagnose pancreatitis in the dog but unfortunately they are not consistently reliable. The specificity of amylase and lipase is approximately 50%. Factors such as azotemia increases serum amylase and lipase due to decreased renal removal and dexamethasone will increase serum lipase levels. More recently cPLI or Spec cPL was found to be more diagnostic. In a prospective study of cases with clinical evidence of pancreatitis found the test had a 93% sensitivity and a 78% specificity using the IDEXX cutoff value of <200 µg/L as normal. The conclusion was if the Spec cPL was < 200 µg/L (normal) that it was likely that the patient did not have pancreatitis. If the value was above the normal reference range pancreatitis should be included in the differential diagnosis and other tests are required to support the diagnosis.
Traditional lipase is measured using a catalytic assay. More recently newer lipase assays including a DGGR lipase and a Fuji dry chemistry assay appear to have better correlation with PLI activity. Antech now offers a Precision Pancreatic Specific Lipase (Precision PSL) on their profiles. Further studies are required to support these initial observations.

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

**Treatment**

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

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

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

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

**Antiemetics** usually are given routinely if the patient has nausea and vomiting to help prevent fluid loss and make the patient more comfortable and possibly enhance return to early nutrition. The ideal antiemetic for pancreatitis should work both centrally and peripherally. Metoclopramide is suggested by some for their antiemetic effects and to improve gastrointestinal tone (0.2–0.4 mg/kg four times daily (QID) PO or SC, or 0.01–0.02 mg/kg/hr CRI). Metoclopramide, a dopamine antagonist, has poor prokinetic effects and is limited as an
acute management of cases. Studies show that perfusion of the pancreas with free radical scavengers
oxidative damage is thought to be the result of cellular membrane death antioxidants may be of benefit in the
significant cholestasis.

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

Other therapy should be considered only after careful evaluation of the individual case. Because oxidative damage is thought to be the result of cellular membrane death antioxidants may be of benefit in the acute management of cases. Studies show that perfusion of the pancreas with free radical scavengers ameliorates the severity of pancreatitis in experimental canine models. Vitamin E is a potent membrane antioxidant and S-adenosyl L-methionine (SAMe) replaces glutathione stores that may have some benefit in pancreatitis. We now believe that severe vomiting and/or pain associated with eating would be the only reasons to fast patients. If the patient is not expected to be eating on its own within 3 days nutritional support is indicated. Nutrition not only improves patient survival but improved gut integrity. Parenterl nutrition is expensive and fraught with complications. It appears that enteral feeding does not significantly increase pancreatic secretions and actually improves gut integrity, with clinical improvement in the patients being fed. Free choice feeding or tube feeding (nasoesophageal, esophageal, gastrostomy or jejunostomy tube feeding) should be considered in moderate to severe cases. Some prefer low fat liquid nutrition that requires use of human products (Vivonex TEN™ (powder) 3% fat 1 Kcal/ml). Others feed CliniCare™ Canine/Feline Liquid Diet (45% fat, Abbott Animal Health) through a small-diameter feeding tube. During recovery I generally feed a low-fat diet given in small frequent meals.

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

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

Nutritional supplementation in severe pancreatitis cases very important. Enteral nutrition is favored
over parenteral nutrition. Pancreatic rest in the form of fasting has been the traditional recommendation for any
patient with pancreatitis by giving nothing per os (NPO) for several days. The belief is that feeding results in the
release of pancreatic secretory stimuli that will stimulate pancreatic secretions and exacerbate the pancreatitis.
Studies have now shown, however, that adequate nutrition improves survival in experimental and human
pancreatitis pancreatitis. We now believe that severe vomiting and/or pain associated with eating would be the
only reasons to fast patients. If the patient is not expected to be eating on its own within 3 days nutritional support
is indicated. Nutrition not only improves patient survival but improved gut integrity. Parenteral nutrition is
expensive and fraught with complications. It appears that enteral feeding does not significantly increase
pancreatic secretions and actually improves gut integrity, with clinical improvement in the patients being fed. Free
choice feeding or tube feeding (nasoesophageal, esophageal, gastrostomy or jejunostomy tube feeding) should
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products (Vivonex TEN™ (powder) 3% fat 1 Kcal/ml). Others feed CliniCare™ Canine/Feline Liquid Diet (45%
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Surgery for pancreatitis is controversial and indications would include septic peritonitis, to lavage the
abdomen, treatment of pancreatic abscesses, feeding tube placement, or possibly for treatment of a biliary
obstruction. Surgery for pancreatitis or obstructive biliary tract disease generally has a guarded prognosis.
However we have a small series of cases that underwent laparoscopic exploration, lavage and jejunostomy tube
placement that did well. Most obstructive biliary complications will resolve as the pancreatic inflammation
obstructing the common bile duct resolves. In some cases we will place a temporary biliary stent if there is
significant cholestasis.

Anticholinergic agents are contraindicated because of profound effects on decreasing GI motility and little if any
effects in decreasing pancreatic secretion. The serotonin antagonists such as ondansetron is a broad spectrum
antiemetic but may have some effects in decreasing GI motility as well. My antiemetic of choice is maropitant
(Cerenia, 1 mg/kg every 24 hours given SC or IV slowly or 2 mg/kg every 24 hours given PO). It is a broad-
spectrum antiemetic that works both centrally and peripherally. Recent evidence by us has shown that maropitant
also blocks visceral pain – at least in a visceral pain model given at the dose 1 mg/kg. There is also evidence that
maropitant also helps with nausea as well although this is a subjective concept. Maropitant is a neurokinin-1
antagonist that blocks receptors found in the emetic center, CRTZ, and in peripheral afferent nerves. At higher
doses it is effective blocking vestibular input from motion sickness.

Other therapy should be considered only after careful evaluation of the individual case. Because oxidative damage is thought to be the result of cellular membrane death antioxidants may be of benefit in the acute management of cases. Studies show that perfusion of the pancreas with free radical scavengers ameliorates the severity of pancreatitis in experimental canine models. Vitamin E is a potent membrane antioxidant and S-adenosyl L-methionine (SAMe) replaces glutathione stores that may have some benefit in pancreatitis. Pancreatic enzyme supplementation has been reported to decrease the pain that accompanies chronic pancreatitis in humans by the feedback inhibition by endogenous pancreatic enzyme secretion. It is not
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corticosteroids are indicated or beneficial for acute pancreatitis. Hypertriglyceridemia is common in the
Schnauzer and contributes to secondary pancreatitis. Triglycerides >500 mg/dl present after a 12- to 18-hour
fasted sample should be treated first with a low fat diet (RC Low Fat or Hills I/D Low fat). If they persist omega-3
dose (70–100 mg/kg body weight) should be added and increased as needed up to the National Research
Council safe upper limit (200 mg/kg body weight). Lastly I would consider gemfibrozil (dogs, 7.5 mg/kg body
weight PO q12h; cats, 10 mg/kg body weight PO q12h). Gemfibrozil does have side effects and should only be
considered only when diet cannot maintain serum triglyceride <500 mg/dL.

Antibiotics should be considered for prophylactic therapy in the severe case or whenever there is
evidence of sepsis or pancreatic infection. Infectious etiology of pancreatitis is rare in dogs but an experimental
pancreatitis study in dogs suggests antibiotic therapy improves survival. Broad-spectrum antibiotics effective
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Selected References


DRUGS COMMONLY USED IN PANCREATITIS THERAPY

<table>
<thead>
<tr>
<th>Action</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic</td>
<td>Fentanyl</td>
<td>2-10 µg/kg/h</td>
<td>IV</td>
<td>CRI</td>
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<td>Analgesic</td>
<td>Morphine</td>
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<td>IV, IM</td>
<td>Prn</td>
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<tr>
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<td>Butorphanol</td>
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<td>SQ</td>
<td>q6h</td>
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<tr>
<td>Analgesic</td>
<td>Hydromorphone</td>
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<td>IV, IM, SQ</td>
<td>q6-8h</td>
</tr>
<tr>
<td>Analgesic</td>
<td>Methadone</td>
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<td>IV, IM, SQ</td>
<td>q6-8h</td>
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<tr>
<td>Analgesic</td>
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<td>CRI</td>
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<tr>
<td>Analgesic</td>
<td>Lidocaine*</td>
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<td>CRI</td>
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<td>Chlorpromazine</td>
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<tr>
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<td>IV</td>
<td>CRI q24h</td>
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<tr>
<td>Antiemetic</td>
<td>Ondansetron</td>
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<td>IV</td>
<td>q8-12h</td>
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<td>Antiemetic</td>
<td>Maropitant</td>
<td>1 mg/kg</td>
<td>SQ, IV</td>
<td>q24h</td>
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