Approach to Elevated Liver Enzymes: A Review of Common Cases

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Liver Enzyme Activity – A Review

Enzyme	Source	Half life	Notes
ALP	Cholestatic	Dog: 70 hrs Cat: 6 hrs	Steroid isomer of ALP is elevated secondary to glucocorticoids and hyperadrenocorticism, but also secondary to other disease therefore is non-specific. Cats have lower levels of ALP than dogs.
GGT	Cholestatic	Dog: 72 hrs Cat: ?	Dogs: lower sensitivity but higher specificity for hepatobiliary disease than total ALP. Cats: higher sensitivity but lower specificity for hepatobiliary disease than total ALP.
AST	Hepatocellular	Dog: 12-22 hrs Cat: 77 min	Less specific than ALT (also found in muscle). Some studies found AST more reliable hepatic injury marker than ALT in cats.
ALT	Hepatocellular	Dog: 2.5 days Cat: 3.5-6 hrs?	Some reports of muscle necrosis in dogs show elevation in ALT independent of liver injury.

Tests of Liver Function

Liver Synthetic Markers

Synthetic markers of liver function present on most biochemical profiles include bilirubin, albumin, glucose, cholesterol, and urea. These parameters are not overly sensitive or specific, but are widely available and can help provide supportive evidence for hepatic dysfunction. Bilirubin is the most sensitive of these parameters for hepatobiliary dysfunction. Impairment of hepatic bilirubin uptake, conjugation, or excretion can lead to hyperbilirubinemia. Post-hepatic disease (e.g., biliary duct obstruction) can also elevate bilirubin concentration.

Loss of other synthetic liver markers occurs when >70-75% liver function is impaired. Hypoglycaemia, hypoalbuminemia, and low urea can be observed; cholesterol changes are variable as this parameter can be decreased when liver synthesis is impaired but cholesterol can be elevated secondary to cholestasis.

Bile acid measurement
Bile acids are the major component of bile and are synthesized by the liver from cholesterol. Food stimulates gall bladder contraction and release of bile acids into circulation. Impaired hepatic function decreases post-prandial bile acid clearance. Measurement of pre- and 2-hour postprandial bile acids are used to assess hepatic function. Elevated bile acids occur from portovascular abnormalities, hepatic insufficiency, and cholestasis. One study reported that pre-prandial bile acid elevations >20 umol/L or post-prandial elevations >25 umol/L have a specificity of 100% for detecting hepatobiliary disease. However, other conditions can cause mild elevations in bile acid levels. These include extrahepatic biliary duct obstruction (e.g., pancreatitis), altered gastrointestinal motility, and glucocorticoid therapy. Elevations caused by these non-hepatic causes are generally mild.

Ammonia Level
Hyperammonemia can occur secondary to portal vascular abnormalities or significant hepatic dysfunction (estimated >70% loss). Because ammonia is not stable in plasma, in-house analysis is necessary and therefore the test is not widely available.

Common Conditions Causing Liver Enzyme Abnormalities in Dogs

Liver enzyme abnormalities are common features of bloodwork performed in ill patients, and can also be present in some apparently healthy patients. Liver enzyme abnormalities could reflect primary liver disease, while many patients with these changes have reactive changes secondary to non-hepatobiliary conditions.

Liver enzyme abnormalities can be classified as predominantly cholestatic, predominantly hepatocellular, or a mixed pattern. Conditions causing primarily hepatocellular patterns often have a lesser degree of cholestasis present, and similarly diseases causing primarily cholestatic patterns will have a small degree of hepatocellular damage. Evaluating the type of pattern can give ideas about differential diagnoses. The following patterns reflect common conditions in dogs:

Predominantly cholestatic patterns	**Predominantly hepatocellular patterns**	**Mixed enzyme patterns**
• Vacuolar hepatopathy • Benign Nodular Hepatopathy • Gall bladder mucocoele	• Acute hepatitis • Chronic hepatitis (+/- copper hepatopathy) • Portal vein hypoplasia	• Reactive hepatopathy • Hepatobiliary neoplasia

Vacuolar Hepatopathy

Vacuolar hepatopathy is a reversible change due to hepatocyte swelling often with accumulation of glycogen, lipid, and/or other substances in the hepatocytes. Vacuolar hepatopathy occurs secondary to other conditions, such as hyperadrenocorticism, diabetes mellitus, glucocorticoid or other medication administration, hypercortisolemia from other illness, breed-related conditions (e.g. Scottish Terriers), and idiopathic.

Dogs with idiopathic vacuolar hepatopathy are asymptomatic, and elevated ALP is the primary abnormality detected when bloodwork is performed for routine health screening. Significant elevations of other liver enzymes are typically not found, and if present warrant investigation for other hepatobiliary disease. Some dogs with vacuolar hepatopathy will have proteinuria and/or hypertension. These changes could be linked to the cause of vacuolar hepatopathy (e.g., hyperadrenocorticism), or independent changes in truly idiopathic cases. Specific treatment and management of proteinuria and/or hypertension (e.g., treatment with ACE inhibitor therapy, periodic monitoring) might be indicated.

Specific treatment of idiopathic vacuolar hepatopathy is likely not necessary. Role of antioxidants in this condition is not known and is not likely to resolve the condition, and animals usually remain asymptomatic. Vacuolar hepatopathy secondary to underlying illness usually resolves when that illness is treated. Prognosis for idiopathic vacuolar hepatopathy is good, provided concurrent illness is not detected.

Benign Nodular Hepatopathy

The specific cause of benign nodular hyperplasia is not known, but appears to be an age-related change as the condition is typically found in older (>10 year) dogs. The primary laboratory abnormality is an elevation in ALP, +/- mild ALT elevation. Liver functional parameters remain normal. Ultrasound often shows large hepatic nodules, but can be normal. Specific therapy is not indicated.

Gall Bladder Mucocoele

Bile is important in digestion of food, and is released upon gall bladder contraction into the duodenum via the common bile duct. Diseases impairing the release of bile cause cholestasis. Common causes of biliary obstruction in dogs include gall bladder mucocoele, pancreatitis, and cholecystitis.

Gall bladder mucocoele (GBM) is characterized by the presence of mucoid material within the gall bladder, and is becoming a very common cause of gall bladder disease in the dog. Predisposing factors include endocrinopathies (hyperadrenocorticism, hypothyroidism), hyperlipidemia disorders, disorders leading to biliary stasis, and exogenous steroid administration. Mucocoeles are diagnosed at higher frequency in some breeds including the Shetland sheepdog, Miniature Schnauzer, and Cocker Spaniel. Average age at diagnosis is 10 years, but great variability in age can be observed.

Clinical signs of GBM are variable depending on stage of disease. Due to the insidious onset of the condition, GBM can be an incidental finding in some dogs. Other dogs will present with signs of an acute abdomen and non-specific signs of vomiting, lethargy, and anorexia. Icterus is noted in approximately 40% of patients.

Bloodwork most commonly reveals elevation in ALP, as well as frequent elevation in GGT, ALT, and bilirubin. Extent of changes can vary depending on stage of the condition. Cholesterol elevations are common with biliary obstruction. The complete blood count can show neutrophilic leukocytosis, and this is most frequent in dogs presenting with acute clinical signs. Ultrasound reveals a variable appearance of hyperechoic gall bladder contents, often immobile and in a stellate pattern. The gall bladder wall may be normal to thickened. Severity of disease is difficult to ascertain based on gall bladder appearance. Biliary distension can be observed in cases of marked obstruction. Abdominal free fluid and/or hyperechoic abdominal fat can suggest rupture of the GBM.

Treatment for dogs with acute clinical signs centres on surgical removal of the gall bladder. Post-operative therapy with life-long ursodiol +/- antioxidant therapy is recommended following cholecystectomy.

In less severe cases, medical management can be attempted. Medical resolution of GBM can be achieved in some cases where the underlying cause is addressed (e.g., endocrinopathy), in addition to therapy with choleretics (ursodiol), low fat diet, and in some cases antimicrobial therapy. Frequent monitoring of these patients is recommended to determine progression or resolution of the GBM, and treatment is expected for at least several months. Success rates for medical management are reportedly low.

Chronic Hepatitis

Chronic hepatopathies are common conditions in dogs, and will be discussed elsewhere in the proceedings. Dogs with chronic hepatopathy typically have predominantly hepatocellular liver enzyme elevations.

Acute Hepatitis

Acute hepatitis is less common than chronic hepatitis in dogs, and can arise from multiple factors including infectious (viral, bacterial), toxin/drugs, and copper accumulation secondary to chronic hepatitis.

Dogs with acute hepatitis often present with clinical signs of systemic illness including anorexia, vomiting, diarrhea, dehydration, depression, and icterus. Depending on extent of disease, physical examination can reveal icterus, abnormal abdominal palpation (hepatomegaly, abdominal pain), signs of coagulopathy, and in severe cases signs of shock.

The most prominent feature of labwork is usually marked elevation of hepatocellular enzymes. Elevation in bilirubin and markers of cholestasis are

common findings. Depending on extent of disease, markers of synthetic liver function could be decreased. Imaging findings are non-specific and could include hepatomegaly on radiographs or ultrasound. Patients with acute hepatitis are usually not good candidates for general anaesthesia; therefore histopathology is typically not used in the diagnostic approach.

Treatment is focused on supportive care as well as specific therapy for likely causes. Therapy often includes anti-oxidants, choleretics, and antimicrobial therapy in addition to fluid therapy and other support. Dogs with hepatitis can be at risk of gastric ulceration therefore antacid therapy can be warranted. Dogs recovering from the acute phase have a good prognosis; some will have persistent chronic liver disease.

Portal Vein Hypoplasia

The WSAVA Liver Histopathology standardisation group has proposed the term "portal vein hypoplasia" (PVH) as a more accurate term than microvascular dysplasia. However, work is ongoing to further characterize microscopic vascular changes in the liver, and their relationship to ductal plate abnormalities. Portal vein hypoplasia is a congenital microscopic malformation of hepatic vasculature. Hypoplasia of the portal veins results in vascular abnormalities that cause decreased hepatic parenchyma perfusion and subsequent hepatic atrophy. Histological changes are very similar to portosystemic shunts and the two conditions can coexist in the same patient. Portal vein hypoplasia and is thought to be much more common in dogs than portosystemic shunts.

Dogs with PVH are usually young at the time of diagnosis, and the condition is most commonly observed in small breed dogs. Dogs with PVH are often asymptomatic, and the condition is often noted due to mild ALT elevations +/- other liver enzyme values on routine bloodwork. Synthetic liver parameters are normal. Pre- and post-prandial bile acid elevations are commonly identified in these patients, but magnitude of elevation is usually less than that observed with PSS dogs (i.e., post-prandial bile acid level generally <100 umol/L; anecdotally average post-prandial levels ~30 to 40 umol/L). In contrast to some PSS dogs, PVH dogs have normal protein C. The role of antioxidant therapy in these dogs is not known. Low protein diets are not necessary. Long-term prognosis is not known, but anecdotally dogs with this condition have minimal progression in their liver enzyme elevation and remain asymptomatic long-term without therapy.

There is a more severe form of PVH that is associated with portal hypertension and ascites. This variant is likely due to a ductal plate malformation and is characterized by fibrosis around the portal tracts. Portal hypertension, ascites, and multiple acquired shunts can be observed in this condition. Dogs are usually young at diagnosis. Bloodwork reveals variable elevations in liver enzyme activity, as well as indications of liver dysfunction in many cases (e.g., hypoalbuminemia, elevated bile acids). Ultrasound often reveals small liver and possibly multiple acquired shunts in some cases. Dogs with this condition have a poor prognosis. Supportive therapy

with antifibrotics and therapy for hepatic encephalopathy can provide some improvement.

Reactive Hepatopathy
Reactive hepatopathy is a common cause of liver enzyme elevation, and can be caused by various inflammatory conditions. Mild to moderate elevations in hepatocellular and cholestatic enzyme activity are observed in reactive hepatopathies. Markers of hepatic function are usually normal. Conditions commonly linked to reactive hepatitis include gastrointestinal inflammation (e.g., acute gastroenteritis, inflammatory bowel disease), pancreatitis, and infections. Reactive hepatopathy changes are typically reversible once the inciting cause is treated. Specific therapy is not usually indicated.

Hepatic Neoplasia
Liver enzyme elevation is frequently found in patients with hepatic neoplasia. Metastatic lesions are more common than primary hepatobiliary tumours. Neoplasia of the spleen, gastrointestinal tract, and pancreas can easily metastasize to the liver. Primary tumours can be classified as massive, nodular, or diffuse. Common primary hepatobiliary neoplasia includes hepatocellular carcinoma or adenoma, biliary adenoma or adenocarcinoma, sarcomas (e.g., hemangiosarcoma), and neuroendocrine disorders. Lymphoma as part of a multicentric process can affect the liver, and primary hepatic lymphoma can also occur.

Hepatobiliary neoplasia can cause non-specific changes to the CBC and biochemical profile. Liver enzyme elevations are frequently observed. One study reported than primary hepatic neoplasia caused higher elevations in ALP and ALT than metastatic lesions, while elevated bilirubin was more common in metastatic lesions versus primary tumours. Hepatocellular carcinoma and other neoplasia can cause hypoglycaemia as a paraneoplastic effect, and this appears rare. Surgery is recommended for solitary primary hepatobiliary tumours, and prognosis after surgery can be favourable depending on tumour type.

Common Conditions Causing Liver Enzyme Abnormalities in Cats

Liver abnormalities can be common findings in cats, and causes are very different from those that occur in dogs. Additionally, interpretation of biochemical abnormalities in cats can be unique to this species.

Liver enzymes have much shorter half-lives in cats versus dogs, making elevations variable and in some cases of primary liver disease enzyme levels are normal. Cats have approximately 1/3 the amount of ALP compared to dogs, making GGT more sensitive for cholestasis in this species (although ALP usually exceeds GGT in cases of hepatic lipidosis). Cats lack a corticosteroid-induced isoenzyme of ALP. The low concentrations of glucuronyl transferase in this species predispose cats to elevated bilirubin and icterus even without substantial hepatic disease.

Some of the conditions discussed above can occur in cats as well. Reactive hepatopathies arise from non-hepatic disease, and a degree of hepatic lipidosis could be a sequela of the primary disease. Similar to dogs, metastatic lesions are more common than primary hepatobiliary neoplasia in the cat. Aside from lymphoma, biliary tumours are the most common types of primary hepatobiliary neoplasia in cats. Benign hepatobiliary tumours are more common than malignant in the cat.

Neutrophilic Cholangitis

The most common inflammatory liver diseases in cats are neutrophilic or lymphocytic hepatitis. Cholangitis secondary to liver flukes can also cause inflammatory hepatitis in cats. Cats of any age and breed can be affected by any of these conditions.

Neutrophilic cholangitis of cats is most commonly an acute condition, thought to be caused by bacterial infection translocating from the gastrointestinal tract. *E. coli* or *Enterococcus spp* are often cultured in this condition. Inflammation from cholangitis can become more generalized into the hepatic parenchyma, causing cholangiohepatitis. Concurrent disease (pancreatitis, inflammatory bowel disease) is common.

Clinical signs of neutrophilic cholangitis are non-specific and include anorexia, vomiting, diarrhea, weight loss, and/or lethargy. Physical examination findings often include icterus, dehydration, ptylism, abdominal pain, and pyrexia. Signs of hepatic encephalopathy might be present. Clinicopathological abnormalities include elevated white cell count (predominantly neutrophilic), and variably increased ALT, AST, ALP, and GGT. Bilirubin is frequently elevated. Prolongation of coagulation times (prothrombin time, partial thromboplastin time, and/or activated clotting time) can be observed. Abdominal radiographs can reveal mild hepatomegaly. Ultrasound is non-specific, and can show enlarged hyperechoic liver, distended biliary tracts, hyperechoic gall bladder contents, and thickened gall bladder wall. Ultrasonographic appearance overlaps with lymphocytic cholangitis. Concurrent pancreatitis could be observed on laboratory tests or ultrasound. Bile cytology and culture, and liver biopsy are required for definitive diagnosis. Treatment includes supportive care.

Specific therapy involves antibiotics. While culture & sensitivity is ideal to guide choice of antimicrobial, this is not often performed and instead empirical therapy targets the most likely bacterial agents (gram negative/enteric). Ampicillin, amoxicillin, and amoxicillin-clavulanic acid can be good empirical choices. Fluoroquinolones can be used, but with caution in cats due to rare but possible retinal detachment reported with enrofloxacin. Ursodeoxycholic acid (ursodiol) can be helpful due to its anti-inflammatory and choleretic properties, anti-oxidant therapy can also be helpful. Treatment for 1-2 months is recommended. Supportive care includes IV fluid therapy, analgesia, vitamin K1 (if coagulopathic), anti-nausea treatment, and nutritional support. Neutrophilic cholangitis can progress to a

chronic form, with mixed inflammation in the liver. Prognosis is generally good with treatment of acute cases; more chronic cases could be a sequela of untreated or incompletely treated acute cases.

Lymphocytic Cholangitis

Lymphocytic cholangitis is most typically a chronic, insidious condition. The inciting cause is unknown, but could be secondary to an immune mediated or other inflammatory process. Due to the chronic nature of this condition, waxing and waning clinical signs can be observed. Patient history can include weight loss, polyphagia, vomiting, anorexia, lethargy, and polyuria/polydipsia. Physical examination can reveal low body condition, icterus, and hepatomegaly. In progressive cases, ascites can be observed.

Unlike neutrophilic cholangitis, CBC findings in cats with lymphocytic cholangitis are usually normal. Variable increases in liver enzyme activity are observed, and liver enzyme elevations are usually of lesser magnitude than in neutrophilic cholangitis. Marked hyperglobulinemia can be observed. Cytological analysis of ascites fluid reveals lymphocytic to mixed inflammation with a high protein count. Ultrasound typically reveals biliary tract dilation. Characteristic histological signs include lymphocytic infiltration of the liver, mostly concentrated around the portal regions. Over time, liver parenchyma can undergo marked distortion.

Treatment for lymphocytic cholangitis involves supportive care plus anti-inflammatory and/or immunosuppressive therapy. Common therapeutic agents include prednisolone (initially immunosuppressive dose that is slowly tapered to lowest effective dose) and ursodiol. Further study is needed to determine the optimal treatment regimen, but previous studies indicate that survival times are similar when 1 or 2 mg/kg/day prednisolone is used, and also that cats receiving prednisolone had better outcomes than cats treated only with ursodiol. Chlorambucil may be added in severe cases. Complete resolution of the disease is often not achieved and most cats will require long-term or life-long therapy.

Hepatic Lipidosis

Hepatic lipidosis will not be covered extensively in this section, but laboratory abnormalities of this condition will be discussed.

Hepatic lipidosis can exist concurrently with cholangitis as discussed above, or secondary to other disorders. The most prominent laboratory abnormalities are marked elevations in ALP and bilirubin. While GGT is more sensitive for cholestasis secondary in cats, hepatic lipidosis causes a different liver enzyme pattern. The magnitude of ALP elevation in cats with hepatic lipidosis typically exceeds that of GGT. ALT elevations are variable in this condition. Cats often have clinical signs of icterus and hepatic encephalopathy. If an ammonia level can be measured, it is often high. Coagulopathy is common. Other laboratory findings can be reflective of a primary, underlying disorder.