Liver Enzymes and Liver Function Testing

CHAPTER 1

Nick Bexfield

Department of Veterinary Medicine, The Queen's Veterinary School Hospital, University of Cambridge, Cambridge, United Kingdom

KEY POINTS

- Liver enzymes are sensitive indicators of hepatic insult but lack specificity for liver function.
- Reduced albumin, urea, cholesterol, glucose, or elevated bilirubin can indicate impaired hepatic function in advanced disease. Although bilirubin can be elevated for pre- or post-hepatic causes.
- Total serum bile acids are the most reliable routine marker for detecting hepatic dysfunction although they are not interpretable in patients with hyperbilirubinemia due to hepatic or post-hepatic cholestasis.

LIVER ENZYMES

INTRODUCTION

Liver enzymes are typically categorized based on their origin and function into hepatocellular (or leakage) enzymes and biliary (or inducible) enzymes. This classification helps guide the interpretation of laboratory findings in veterinary patients. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are key markers of hepatocellular injury, while alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) are markers of biliary tract disease or enzyme induction. Understanding the origin, behavior, and species-specific differences in these enzymes is essential for accurate clinical interpretation.

HEPATOCELLULAR ENZYMES: ALT AND AST

ALT is a cytosolic enzyme predominantly found in hepatocytes. When hepatocyte membrane integrity is compromised, as seen with inflammation or necrosis, ALT is released into the bloodstream. It is considered a sensitive and relatively liver-specific enzyme in both dogs and cats. While ALT is also present in skeletal muscle and kidney tissue, elevations due to these sources are usually minor unless there is significant muscle damage. The half-life of ALT in dogs varies in the literature but ranges from 6 hours to 2.5 days. In cats, the half-life is much shorter, which means that even mild ALT elevations are more clinically significant in this species (Stockham and Scott 2020).

ALT elevations can occur rapidly, within 24–48 hours, following hepatic injury, with peak values around day five. These elevations may be dramatic, sometimes exceeding 10 times the reference range. In cases of acute injury, a decline in ALT by 50% every 2–3 days is generally considered a positive prognostic sign. Chronic liver diseases, such as canine chronic hepatitis, are often present with persistent ALT elevations. Importantly, ALT can also rise in response to cholestasis or hepatotoxic drugs like corticosteroids and phenobarbital, though the pattern and degree of increase vary. Interpretation of ALT must be contextual and include assessment of other diagnostic findings, patient history, and breed-specific considerations.

Disorders of the Liver, Exocrine Pancreas, and Gastrointestinal Tract in Dogs and Cats, First Edition. Edited by Harry Cridge et al. Published 2026 by John Wiley & Sons, Inc. Companion Website: www.wiley.com/go/cridge/disorders

AST is another marker of hepatocellular damage. Like ALT, it is found in hepatocytes, but also in skeletal and cardiac muscle. Approximately 30% of AST in the liver is located in mitochondria, making it a marker of more severe injury when elevated. The half-life of AST is shorter than ALT, about 4–20 hours in dogs and approximately 1 hour in cats. In liver disease, AST usually increases in parallel with ALT but normalizes more quickly due to its shorter half-life. Persistent AST elevation may suggest ongoing hepatocellular necrosis and may carry a poorer prognosis (Center 2007). As AST is present in muscle tissue, it should be interpreted alongside creatine kinase (CK) to differentiate between hepatic and muscular sources, especially if ALT is not elevated.

CHOLESTATIC OR INDUCIBLE ENZYMES: ALP AND GGT

ALP is a membrane-bound enzyme found in liver, bone, kidney, and intestinal tissues. It has higher sensitivity but poorer specificity for hepatobiliary disease in dogs. In contrast, ALP has lower sensitivity but higher specificity for hepatic disease in cats. This reflects differences in ALP isoenzyme production and clearance between species. Dogs express several isoenzymes including liver ALP (L-ALP), bone ALP (B-ALP), and glucocorticoid-induced ALP (G-ALP), while cats mainly produce L-ALP and B-ALP. The lack of G-ALP in cats contributes to their more specific ALP responses in liver disease, particularly hepatic lipidosis.

ALP elevations in dogs can result from cholestasis, induction of synthesis by drugs or endogenous corticosteroids, bone growth in young animals, or bone lesions such as osteosarcoma. In cats, ALP has a much shorter half-life, around six hours, meaning that elevations tend to be modest but often more clinically meaningful. In dogs, values may rise four to five times the reference range with relatively benign causes, while cats with liver disease may only show two- to threefold increases.

ALP activity increases in dogs with cholestasis and corticosteroid exposure. While corticosteroids are known to induce ALP synthesis via glucocorticoid-responsive elements, the role of bile acids in transcriptional induction remains unproven in dogs, and increases may instead reflect cholangiocellular membrane injury or altered enzyme clearance. Corticosteroid induction occurs within 24–48 hours and may persist for weeks after exposure ends. This can obscure interpretation, particularly in dogs receiving chronic medications or topical corticosteroids. G-ALP increases are not specific to corticosteroid use; they also occur in diabetes mellitus, liver disease, and chronic illnesses. Thus, isoenzyme analysis has limited utility in clinical practice.

Persistent ALP elevation is generally more concerning than a single abnormal result. A study involving 270 dogs with confirmed liver disease found that the highest ALP increases occurred with cholestasis (median tenfold), followed by steroid hepatopathy, chronic hepatitis, and hepatic necrosis (Center et al. 2012). ALP levels did not reliably correlate with disease severity or prognosis. Other conditions that may increase ALP include endocrine disorders such as hyperadrenocorticism, chronic drug administration (e.g. corticosteroids), and some extrahepatic diseases such as pancreatitis.

GGT, another membrane-bound enzyme, originates primarily from biliary epithelial cells. Like ALP, its serum levels increase with cholestasis and enzyme induction. GGT is more liver-specific than ALP, as it lacks bone isoforms. Although it may also be induced by corticosteroids, GGT is less responsive to phenobarbital. GGT and ALP often rise in parallel and comparing both enzymes can help clarify the nature of liver injury, particularly in dogs where multiple isoenzymes may be present. GGT is also helpful in distinguishing hepatic from bone causes of ALP elevation.

CONCLUSION AND CLINICAL RELEVANCE

In summary, liver enzymes are valuable tools in detecting liver injuries but have limitations in specificity and prognostic value. ALT and AST provide information about hepatocellular integrity, while ALP and GGT reflect cholestasis, bile duct epithelial injury, or enzyme induction. Interpretation must always be integrated with the patient's clinical picture, history, and results from other diagnostic modalities. Serial monitoring enhances clinical insight, as patterns over time can help differentiate transient insults from chronic liver disease. Ultimately, careful interpretation of enzyme data contributes significantly to diagnosing and managing liver disorders in both dogs and cats.

LIVER FUNCTION TESTING

INTRODUCTION

Assessing liver function involves evaluating parameters that reflect the liver's synthetic and excretory capacity. Due to its significant functional reserve, signs of hepatic impairment often do not become apparent until around 75% of liver mass is lost. In acute hepatocyte loss, functional deficits can occur more rapidly, whereas chronic diseases may allow time for compensation by remaining hepatocytes.

Several liver function tests are commonly included in standard biochemical profiles, such as albumin, blood urea nitrogen (BUN), cholesterol, and glucose, but these are not particularly sensitive or specific. More useful tests include total serum bile acids (TSBAs), plasma ammonia, bilirubin, and coagulation proteins. These can often help to differentiate primary hepatic disease from secondary or reactive hepatopathies. However, in cats, reduced liver function is not always observed even with primary liver disease. While portal and bridging fibrosis are commonly seen in conditions such as lymphocytic and chronic cholangitis, progression to cirrhosis and hepatic failure appears to be relatively uncommon in this species.

ALBUMIN

Albumin is synthesized solely by the liver, and serum levels are regulated by the balance between production and degradation. Hypoalbuminemia may suggest reduced hepatic function or liver hypoperfusion, but is not liver-specific, as it may also result from protein-losing nephropathy, enteropathy, or inflammation.

Due to albumin's relatively long half-life (8–10 days in dogs and cats) and the liver's synthetic reserve, hypoalbuminemia generally indicates chronic, advanced liver disease. An exception is acute hepatic inflammation, where albumin may fall due to a negative acute-phase response, though this tends to be mild. Serum protein electrophoresis can help differentiate hypoalbuminemia due to liver dysfunction from that related to inflammation. Studies have shown that low albumin levels combined with low acute-phase protein concentrations suggest a poor prognosis in liver failure, whereas low albumin with normal or elevated acute-phase proteins suggests a better outlook (Gagne et al. 1999).

BLOOD UREA NITROGEN

The liver converts ammonia to urea, which is then excreted by the kidneys. Reduced liver function may lead to decreased BUN, but this is only seen in advanced disease and is not specific, as many nonhepatic conditions can also lower BUN. Therefore, it is a poor standalone marker for liver function.

CHOLESTEROL

The liver plays a central role in lipid metabolism, including the synthesis and breakdown of cholesterol. While advanced liver disease can cause hypocholesterolemia, this finding is inconsistent and nonspecific as it can also occur with systemic diseases such as protein-losing enteropathy, sepsis, or endocrine disorders. Hence, changes in cholesterol concentration should be interpreted alongside other markers.

GLUCOSE

The liver contributes to glucose homeostasis through gluconeogenesis, glycogen storage, glycogenolysis, and insulin degradation. Hypoglycemia can occur with severe hepatic dysfunction due to reduced glucose production and impaired insulin clearance. When present, it is more often associated with acute hepatic injury (AHI) or fulminant liver failure. However, it remains uncommon in dogs and is rarely seen in cats, even in advanced liver disease, due to the liver's substantial compensatory capacity.

TOTAL SERUM BILE ACIDS

TSBAs are among the most sensitive markers of hepatic function. Bile acids are synthesized from cholesterol in the liver, conjugated, and stored in the gallbladder. After a meal, cholecystokinin stimulates bile release into the intestine, where bile acids aid fat digestion and are then reabsorbed in the ileum and returned to the liver through enterohepatic circulation, which is over 95% efficient.

In liver dysfunction, portosystemic shunting, or cholestasis, this circulation is disrupted, causing elevated TSBAs. A paired test, with measurements taken after a 12-hour fast and 2 hours post-meal, provides greater sensitivity. In normal animals, postprandial values may be three to four times higher than fasting values. Elevated fasting or postprandial TSBAs indicate impaired bile acid clearance, but elevations in jaundiced animals reflect cholestasis rather than functional loss and thus add little diagnostic value in that context.

Cutoff values for diagnosis vary. In dogs, fasting values over 15 μmol/L and postprandial levels over 25 μmol/L are highly specific for hepatobiliary disease (Pena-Ramos et al. 2021). In cats, similar cutoffs show specificities of 96 and 100%, respectively. Sensitivity ranges from 54 to 74%, though values up to 100% have been reported in cirrhotic dogs (Johnson et al. 1995).

Clinicians should remember that secondary hepatopathies, including extrahepatic causes of cholestasis such as pancreatitis or bile duct obstruction, and gastrointestinal conditions like small intestinal bacterial overgrowth (SIBO), may also affect bile acid metabolism. In SIBO, bacterial deconjugation can increase levels of unconjugated bile acids in the intestine, although whether this leads to a quantifiable increase in TSBA concentrations in dogs or cats has not been clearly established (Simpson 2004). Levels above 50 μmol/L are more suggestive of primary hepatic disease and may warrant further investigation such as liver biopsy. However, overlap exists, and significantly elevated TSBAs can occasionally occur in secondary disease (Pena-Ramos et al. 2021).

Test interpretation can be affected by several factors. There is no standardized test meal, and variables such as gallbladder contraction timing, gastric emptying, and intestinal motility can influence results. Occasionally, fasting values may exceed postprandial values, possibly due to spontaneous gallbladder contraction. In these cases, the higher of the two values should be used. Lipemia and hemolysis may also falsely elevate results.

AMMONIA

Ammonia is produced in the gastrointestinal tract from protein metabolism and enters the portal circulation. A healthy liver extracts nearly all of it and converts it to urea. In liver dysfunction or portosystemic shunting, this process is impaired, resulting in hyperammonemia.

Because of the liver's reserve capacity, fasting ammonia levels are relatively insensitive indicators of liver failure (Center 2007). Ammonia tolerance testing was once used to improve diagnostic sensitivity, but oral or rectal administration of ammonium salts can trigger hepatic encephalopathy and is now discouraged.

Sample handling is critical. Ammonia samples must be collected in heparinized tubes on ice, centrifuged quickly, and plasma separated and analyzed within 30 minutes. Hemolysis, delays, or poor handling can cause spurious results. While conventional lab testing is cumbersome, newer point-of-care analyzers have improved the feasibility and accuracy of in-clinic testing.

TOTAL SERUM BILIRUBIN

Bilirubin is produced during red blood cell breakdown and circulates bound to albumin. In the liver, it is conjugated and excreted into bile. Hyperbilirubinemia can arise from hemolysis, hepatocellular dysfunction, or biliary obstruction.

In liver disease, hyperbilirubinemia reflects impaired uptake, conjugation, or excretion, referred to as intrahepatic cholestasis. However, significant liver dysfunction must be present for bilirubin to rise, making it an insensitive marker of early disease. Measuring conjugated versus unconjugated bilirubin is not generally clinically helpful in dogs or cats, although a predominance of unconjugated bilirubin may be seen in cases of sepsis (Odunayo et al. 2010).

COAGULATION PROTEINS

The liver synthesizes most coagulation factors and also contributes to vitamin K metabolism. Reduced hepatic function may alter coagulation parameters, though these changes are neither sensitive nor specific. Changes may include prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT), and reduced levels of fibrinogen, protein C, or vitamin K-dependent proteins.

CONCLUSIONS AND CLINICAL RELEVANCE

While routine biochemical tests offer some insight into liver function, they lack sensitivity and specificity. More informative functional assessments include TSBAs and, to a lesser extent, ammonia, bilirubin, and coagulation parameters. TSBAs remain the most practical and reliable functional test for both dogs and cats, provided that sample handling and interpretation consider physiological and pathological variables.

REFERENCES

Center, S.A. (2007). Interpretation of liver enzymes. *Veterinary Clinics of North America: Small Animal Practice* 37 (2): 297–333. https://doi.org/10.1016/j.cvsm.2006.09.006.

Center, S.A., Warner, K.L., Corbin, J.E. et al. (2012). Evaluation of 270 dogs with clinical hepatobiliary disease: retrospective study from 1983 to 1998. *Journal of Veterinary Internal Medicine* 26 (4): 844–854. https://doi.org/10.1111/j.1939-1676.2012.00944.x.

Gagne, J.M., Weiss, D.J., Armstrong, P.J. et al. (1999). Acute phase protein concentration and hepatic function in dogs with chronic hepatitis. *Journal of Veterinary Internal Medicine* 13 (6): 606–609. https://doi.org/10.1111/j.1939-1676.1999.tb01482.

Johnson, S.E., Center, S.A., McDonough, S.P. et al. (1995). Resting and postprandial serum bile acid concentrations in dogs with liver disease. *Journal of the American Veterinary Medical Association* 207 (4): 456–460.

Odunayo, A., Tobias, K.M., and Sharp, C.R. (2010). Hyperbilirubinemia in critically ill dogs: prevalence, causes and diagnostic approach. *Journal of Veterinary Emergency and Critical Care* 20 (6): 576–585. https://doi.org/10.1111/j.1476-4431.2010.00596.

Pena-Ramos, J., Barker, L., Saiz, R. et al. (2021). Resting and postprandial serum bile acid concentrations in dogs with liver disease. *Journal of Veterinary Internal Medicine* 35 (3): 1333–1341. https://doi.org/10.1111/jvim.16134.

Simpson, K.W. (2004). Bacterial flora of the gastrointestinal tract. *The Veterinary Clinics of North America. Small Animal Practice* 34 (2): 341–355. https://doi.org/10.1016/j.cvsm.2003.10.003.

Stockham, S.L. and Scott, M.A. (2020). *Fundamentals of Veterinary Clinical Pathology*, 3e. Ames, IA: Wiley-Blackwell.

Webster, C.R.L., Center, S.A., Cullen, J.M. et al. (2019). ACVIM consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. *Journal of Veterinary Internal Medicine* 33 (4): 1173–1200. https://doi.org/10.1111/jvim.15475.