

Liver Enzyme Elevations in Dogs: Physiology and Pathophysiology*

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At a Glance

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Abstract: Increased liver enzyme activities are sensitive indicators of primary hepatic disease, but they are also associated with extrahepatic diseases. The patient's signalment, clinical status, and pattern of liver enzyme activity can help in interpreting findings. The three basic liver enzyme patterns are (1) cholestatic, (2) hepatocellular leakage, and (3) mixed. Predominant increases in the activities of the cholestatic or inducible enzymes, alkaline phosphatase and γ -glutamyl transpeptidase, occur with endocrine disorders, cholestasis, neoplasia, benign nodular hepatic hyperplasia, and administration of certain drugs and occur idiopathically in certain breeds. Predominant increases in the activities of the hepatocellular leakage enzymes, alanine aminotransferase and aspartate aminotransferase, occur with circulatory disturbances, hepatotoxicities, infectious diseases, hepatitis, and neoplasia. A mixed pattern of increased liver enzyme activities may occur with hepatotoxicity or concurrent cholestasis and hepatocellular injury or necrosis.

Primary liver disease is often diagnosed after hepatic damage is irreversible. Biochemical screening during routine wellness visits facilitates detection of hepatopathies in asymptomatic patients, when medical intervention is more likely to be successful.

Increased liver enzyme activities are common in dogs. Serum biochemistry testing conducted on 1022 samples from dogs showed that 39.1% and 17.4% had increased alkaline phosphatase (ALP) and alanine aminotransferase (ALT) activities, respectively.¹ Although liver enzyme activity increases are highly sensitive biomarkers of hepatobiliary disorders, interpretation of these increases is complicated by the fact that breed variations and extrahepatic diseases often cause similar laboratory findings. Discerning which abnormal findings warrant further investigation can be challenging.

This article reviews the physiology of

the inducible liver enzymes, ALP and γ -glutamyl transpeptidase (GGT), and the hepatocellular leakage enzymes, ALT and aspartate aminotransferase (AST). Breed-specific abnormalities and underlying etiologies associated with cholestatic, hepatocellular leakage, and mixed patterns of injury are presented.

Inducible Liver Enzymes

The activities of ALP and GGT, the inducible or cholestatic liver enzymes, increase with a variety of conditions (BOX 1). Both enzymes are found along the canalicular membrane of hepatocytes; their expression is increased with intrahepatic or extrahepatic cholestasis. Inducible ALP isoenzymes are found in intestine, kidney, liver, and bone tissue.² Measured ALP activity in serum or plasma generally comprises liver (L-ALP), bone (B-ALP), and corticosteroid (C-ALP) isoenzymes.³ In healthy dogs, L-ALP accounts for the

*A companion article, "Liver Enzyme Elevations in Dogs: Diagnostic Approach," begins on page 416.

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largest fraction of measured ALP activity. B-ALP activity is highest in growing animals and animals with osteolytic disorders. Little or no C-ALP activity is found in normal dogs. Because corticosteroids may increase the activity of multiple ALP isoenzymes,^{3,4} determination of the predominant isoenzyme increase rarely aids in identification of the underlying pathophysiologic disorder. There are no commercially available tests for the differentiation of ALP isoenzymes.²

GGT is a membrane-bound protein found lining biliary surfaces and within periportal hepatocytes. Although high concentrations are present in the kidney and pancreas, circulating GGT activity principally originates from liver tissue. GGT has a lower sensitivity but higher specificity than ALP for primary hepatobiliary disease⁵ and is exquisitely sensitive to cholestasis. The specificity of concurrent increased activities of ALP and GGT for hepatobiliary disease is >90%, versus 51% for increased ALP activity alone and approximately 80% for GGT alone.⁶

Increased cholestatic enzyme activity is associated with a number of breeds. Marked increases in ALP activity may occur with benign familial hyperphosphatasemia, described in Siberian huskies and Scottish terriers.^{7,8} Scottish terriers may have ALP activity that is five times higher than that in other breeds; ALP activity increases with age in this breed, independent of ALP-inducing disease.⁹ Other breed associations with increased ALP activity may reflect underlying disease. Moderate to severe hypertriglyceridemia in miniature schnauzers has been associated with moderate increases in ALP and mild increases in ALT activity.¹⁰ It is unknown whether these increases correlate with underlying primary diseases such as biliary mucoceles or secondary processes such as vacuolar hepatopathy. Activity increases greater than two times the reference interval in miniature schnauzers warrant further investigation.¹⁰ Shetland sheepdogs may have increased concentrations of triglycerides and cholesterol and increased cholestatic liver enzyme activities due to clinically silent gallbladder disorders.¹¹

Cholestatic enzyme activity may be increased by numerous extrahepatic conditions. Increased activities of ALP and GGT secondary to hepatic lipid or glycogen accumulation have been

BOX 1

Conditions/Factors Associated With Enzyme Activity Increases in Cholestatic Patterns

Breed

- ▶ Scottish terrier
- ▶ Miniature schnauzer
- ▶ Siberian husky

Drug administration

- ▶ Corticosteroids
- ▶ Phenobarbital

Endocrine disorders

- ▶ Diabetes mellitus
- ▶ Hyperadrenocorticism
- ▶ Hypothyroidism

Neoplastic enzyme induction

- ▶ Osteosarcoma
- ▶ Mammary carcinoma
- ▶ Lymphoma
- ▶ Biliary or hepatocellular carcinoma

Intrahepatic cholestasis

- ▶ Portosystemic vascular anomalies, microvascular dysplasia
- ▶ Vacuolar hepatopathy^a
- ▶ Nodular hepatic hyperplasia
- ▶ Neoplasia
- ▶ Sepsis

Extrahepatic cholestasis

- ▶ Gallbladder disease or neoplasia
- ▶ Pancreatitis
- ▶ Inflammatory bowel disease
- ▶ High intestinal obstruction

^aSepesy L, Center SA, Randolph JF, et al. Vacuolar hepatopathy in dogs: 336 cases (1993-2005). *JAVMA* 2006;229:246-252.

reported with hyperadrenocorticism, diabetes mellitus, and hypothyroidism.^{12,13} Increased concentrations of progesterone and 17-hydroxyprogesterone may cause similar enzyme changes.¹³ ALP and GGT activities increase with altered bile flow secondary to pancreatitis, inflammatory bowel disease, cholangitis, cholecystitis, and biliary obstruction. Sepsis can cause cholestasis through multifactorial mechanisms, including altered hepatocyte function.¹⁴ Benign nodular hepatic hyperplasia may stimulate inducible enzyme activity increases. Canine hepatocellular carcinoma cells have been demonstrated

QuickNotes

An increase in the activities of ALP and GGT in tandem has greater specificity but lower sensitivity for primary hepatobiliary disease than an increase in either enzyme activity alone.

BOX 2

Conditions Associated With Enzyme Activity Increases in Hepatocellular Injury or Necrosis Patterns

Infection

- ▶ Canine adenovirus 1
- ▶ *Leptospira* spp,^a ascending or hematogenous bacterial infection
- ▶ *Leishmania*,^b *Toxoplasma*, *Neospora*, *Hepatozoon* spp
- ▶ *Histoplasma capsulatum*
- ▶ *Dirofilaria immitis*

Cardiovascular disturbance

- ▶ Congestive heart failure
- ▶ Anemia
- ▶ Shock

Neoplasia

- ▶ Primary (hepatocellular or biliary carcinoma)
- ▶ Metastatic

Hepatobiliary disease

- ▶ Hepatotoxicity
- ▶ Chronic hepatitis
- ▶ Inborn errors of metabolism (copper storage disorders)
- ▶ Amyloidosis
- ▶ Portosystemic vascular anomalies, microvascular dysplasia
- ▶ Reactive hepatopathy^c
- ▶ Liver lobe torsion
- ▶ Hepatic abscess

^aAdamus C, Buggin-Daubie M, Izembart A, et al. Chronic hepatitis associated with leptospiral infection in vaccinated beagles. *J Comp Pathol* 1997;117:311-328.

^bRallis T, Day MJ, Saridomichelakis MN, et al. Chronic hepatitis associated with canine leishmaniosis (*Leishmania infantum*): a clinicopathological study of 26 cases. *J Comp Pathol* 2005;132:145-152.

^cBrellou GD, Kelinschmidt S, Meneses F, et al. Eosinophilic granulomatous gastroenterocolitis and hepatitis in a 1-year-old male Siberian husky. *Vet Pathol* 2006;43:1022-1025.

to express a unique thermostable isoenzyme of ALP, resulting in increased serum ALP activity.¹⁵ **Pancreatic neoplasia** may also induce ALP and GGT expression. Persistently increased ALP activity is a negative prognostic indicator for dogs with osteosarcoma¹⁶ and is common in dogs with mammary carcinoma¹⁷ and lymphosarcoma.

Exogenous substances may also induce cholestatic enzyme increases. **Glucocorticoid** administration in dogs causes moderate to marked increases in serum GGT and ALP activities and mild increases in ALT and AST activities.³ **Phenobarbital** can increase ALP activity without causing liver injury.¹⁸ Infrequently, phenobarbital causes idiosyncratic hepatotoxicity with attendant clinical signs.¹⁸

Hepatocellular Leakage Enzymes

ALT and AST are hepatocellular leakage enzymes. Found primarily in the **cytosol** of hepatocytes, ALT is released into circulation after hepatocellular membrane disruption. **The magnitude of ALT activity increase approximates the degree of hepatocyte damage.** Because the liver has a remarkable regenerative capacity, the degree of ALT increase should not be used as a prognostic indicator. In dogs, **ALT generally has a circulating half-life of 2 to 3 days.**⁵ Decreases in serum ALT activity of 50% every 2 to 3 days suggest that hepatocyte damage is resolving.⁵ **Normalization of ALT activity with the concurrent appearance of biomarkers for hepatobiliary dysfunction, such as hypoalbuminemia, hypoglycemia, or hypocholesterolemia, suggests loss of functional hepatic parenchyma.**

AST is found in the **cytosol** and **mitochondria** of hepatocytes and myocytes. Given the presence of AST in **myocytes**, increased AST activity is less specific for hepatic damage than ALT. **When increased AST activity is secondary to hepatic damage, it generally increases proportionally to ALT activity.** If AST activity is increased disproportionately, especially when creatine kinase (CK) activity is increased, primary muscle damage should be suspected. **Because increased AST activity is more sensitive than ALT activity for some types of liver damage, hepatocellular membrane disruption should be considered when AST activity is increased and CK and ALT activities are within their reference intervals.**⁵

A variety of extrahepatic and hepatic disorders can cause increased hepatocellular leakage enzyme activity (**BOX 2**). Because the portal circulation provides at least half of the hepatic blood flow, the liver is particularly vulnerable to vascular compromise.¹⁹ Anemia, congestive heart failure, and shock can moderately increase ALT and AST activities. Mild

QuickNotes

Although ALT activity increases proportionally to hepatocyte damage, a single measurement of severely increased ALT activity should not be used for prognosis because of the regenerative capacity of the liver.

BOX 3

Hepatotoxins Reported in Veterinary and Human Medicine**Dose-dependent**

- ▶ **Herbal supplements:** Chaparral leaf^a, germander^a, jin bu huan^a, kava^b, pennyroyal oil^c
- ▶ **Drugs:** Acetaminophen^b, amiodarone^b, lomustine (CCNU)^d, stanozolol^b
- ▶ **Environmental:** Aflatoxins^e, *Amanita* mushrooms^c, bacterial lipopolysaccharides^f, blue-green algae^c, carbon tetrachloride^c, cycad (sago) palm^c, heavy metals^c, phosphorus^g
- ▶ **Other:** Xylitol^h

Idiosyncratic

Drugs: Azathioprineⁱ, chloramphenicol^j, clindamycin^b, clopidogrel^b, cyclosporine^k, fluconazole^a, fluoroquinolones^l, glucocorticoids^m, griseofulvin^c, halothaneⁿ, ketoconazole^a, mirtazapine^b, mitotane^o, nitrofurantoin^a, NSAIDs^a, phenobarbital^p, potentiated sulfonamides^q, synthetic penicillins^a, tetracyclines^q

^aPratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med* 2000;342:1266-1271.

^bNavarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med* 2006;354:731-739.

^cCooper JC, Webster CRL. Acute liver failure. *Compend Contin Educ Pract Vet* 2006;28:498-514.

^dKristal O, Rassnick KM, Gliatto JM. Hepatotoxicity associated with CCNU (lomustine) chemotherapy in dogs. *J Vet Intern Med* 2004;18:75-80.

^eDereszynski DM, Center SA, Randolph JF, et al. Clinical and clinicopathological features of dogs that consumed foodborne hepatotoxic aflatoxins: 72 cases (2005-2006). *JAVMA* 2008;6(9):1329-1337.

^fBarton CC, Barton EX, Ganey PE, et al. Bacterial lipopolysaccharide enhances aflatoxin B1 hepatotoxicity in rats by a mechanism that depends on tumor necrosis factor α . *Hepatology* 2001;33(1):66-73.

^gZimmerman HJ. *Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver*. Philadelphia: Lippincott, Williams and Wilkins;1999: 229.

^hDunayer EK, Gwaltney-Brant SM. Acute hepatic failure and coagulopathy associated with xylitol ingestion in eight dogs. *JAVMA* 2006;229(7):1113-1117.

ⁱFavrot C, Reichmuth TO. Treatment of canine atopic

dermatitis with azathioprine: a pilot study. *Vet Rec* 2007;160:520-521.

^jDoshi B, Sarkar S. Topical administration of chloramphenicol can induce acute hepatitis. *Br Med J* 2009;338:b1699.

^kWhiting PH, Thomson AW, Simpson JG. Cyclosporine: toxicity, metabolism, and drug interactions—implications from animal studies. *Transplant Proc* 1985;17(4):134-144.

^lRegmi NL, Abd El-Aty AM, Kuroha M. Inhibitory effect of several fluoroquinolones on hepatic microsomal cytochrome P-450 1A activities in dogs. *J Vet Pharmacol Ther* 2005;28:553-557.

^mMarinó M, Morabito E, Brunetto MR, et al. Acute and severe liver damage associated with intravenous glucocorticoid pulse therapy in patients with Graves' ophthalmopathy. *Thyroid* 2004;14:403-406.

ⁿTopal A, Gul N, Ilcol Y. Hepatic effects of halothane, isoflurane or sevoflurane anaesthesia in dogs. *J Vet Med A* 2003;50:530-533.

^oWebb CB, Twedt DC. Acute hepatopathy associated with mitotane administration in a dog. *JAAHA* 2006;42:298-301.

^pGaskill CL, Hoffmann WE, Cribb AE. Serum alkaline phosphatase isoenzyme profiles in phenobarbital-treated epileptic dogs. *Vet Clin Pathol* 2004;33:215-222.

^qThiim M, Friedman LS. Hepatotoxicity of antibiotics and antifungals. *Clin Liver Dis* 2003;7(2):381-399.

to moderate increases may occur with strenuous exercise and should resolve consistent with their half-lives after exertion is discontinued. Hepatotoxicity and hepatitis result in hepatocellular membrane disruption. Underlying etiologies for hepatitis include infectious agents, inborn errors of metabolism, immune-mediated inflammation, and reactive hepatopathies. Copper-associated hepatopathy occurs as an autosomal recessive disorder in Bedlington terriers and has been described in West Highland white terriers, Skye terriers, dalmatians, Doberman pinschers, and Labrador retrievers.^{20,21} Heritability of copper-associated hepatopathy has recently been demonstrated for Labrador

retrievers,²² which also have an increased prevalence of idiopathic chronic hepatitis.²³ Rarely, liver lobe torsion has been described in large-breed dogs presenting with nonspecific clinical signs (vomiting, anorexia, lethargy) and increased hepatocellular leakage enzyme activities.²⁴ Hepatic abscesses and primary or metastatic neoplasia are also associated with increased hepatocellular leakage enzyme activities.

Mixed Liver Enzyme Patterns

A mixed pattern of increased cholestatic and hepatocellular leakage enzyme activities suggests concurrent disorders, hepatocellular inflammation and necrosis with secondary cholestasis, or drug

induction resulting in concomitant mild cholestatic and hepatocellular leakage enzyme activity increases.

Serial monitoring may aid in identification of the primary pattern, and a comprehensive diagnostic workup is often warranted. Portosystemic vascular anomalies and microvascular dysplasia may cause hepatocellular, cholestatic, or mixed patterns of injury.²⁵

Hepatotoxins (**BOX 3**) can cause hepatocellular, cholestatic, or mixed patterns of injury. Because nutrients, bacteria, drugs, and other xenobiotic agents are delivered hematogenously from the gastrointestinal tract to the liver, the liver is at higher risk than other organs for toxic insult.¹⁹ A drug may cause dose-dependent (predictable), idiosyncratic (unpredictable), or both types of toxicity. Dogs with low glutathione transferase activity or decreased inherent protective mechanisms may be predisposed to liver injury.²⁶

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Conclusion

Given their high sensitivity and limited specificity for hepatic disease, liver enzyme activity increases may be difficult to interpret. The patient's signalment, clinical status, and pattern of liver enzyme activity increase may aid practitioners in ranking diagnostic differentials. Predominant increases in ALP and GGT activities characterize a cholestatic liver enzyme pattern. Causes include breed-specific abnormalities, endocrine disorders, hepatic and posthepatic cholestasis, neoplasia, benign nodular hepatic hyperplasia, and induction by drugs. A hepatocellular leakage pattern is characterized by increases in ALT and AST activities. Etiologies include circulatory disturbances, hepatotoxins, hepatic infection and inflammation, and primary hepatic neoplasia. Mixed patterns occur with hepatotoxicity, progressive hepatic disease, and concurrent disorders. **C**

QuickNotes

A mixed liver enzyme pattern can be caused by simultaneous hepatocellular injury and cholestasis and often warrants a comprehensive diagnostic workup.

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- 1. Which breed has been documented to have increased ALP activity independent of underlying disease?**
 - a. Scottish terrier
 - b. miniature schnauzer
 - c. Siberian husky
 - d. Shetland sheepdog
- 2. ALP isoenzymes are not found in the**
 - a. intestines.
 - b. kidneys.
 - c. bones.
 - d. lungs.
- 3. GGT has _____ sensitivity and _____ specificity than ALP for hepatobiliary disease.**
 - a. higher; higher
 - b. lower; lower
 - c. higher; lower
 - d. lower; higher
- 4. Which endocrine disorder has not been associated with increased cholestatic enzyme activities?**
 - a. diabetes mellitus
 - b. hypothyroidism
 - c. hyperadrenocorticism
 - d. hypoadrenocorticism
- 5. Which type of neoplasia has not been associated with ALP induction?**
 - a. mammary carcinoma
 - b. insulinoma
 - c. osteosarcoma
 - d. lymphosarcoma
- 6. Increase in the activity of _____ best approximates the degree of hepatocyte damage.**
 - a. ALP
 - b. ALT
 - c. AST
 - d. GGT
- 7. CK activity needs to be considered when interpreting the activities of which enzymes?**
 - a. ALP and ALT
 - b. ALT and AST
 - c. AST and GGT
 - d. GGT and ALP
- 8. Which statement is correct with regard to AST?**
 - a. It is more specific for liver damage than ALT.
 - b. It is released from osteocytes and hepatocytes.
 - c. Increases in activity occur secondary to membrane disruption.
 - d. Its production in myocytes is induced.
- 9. Copper-associated hepatopathy has a proven heritable basis in which breed?**
 - a. dalmatian
 - b. Labrador retriever
 - c. Scottish terrier
 - d. West Highland white terrier
- 10. _____ does not result in a mixed liver enzyme pattern.**
 - a. The presence of concurrent cholestatic and hepatocellular disorders
 - b. Hepatocellular damage with secondary cholestasis
 - c. Drug induction leading to cholestasis with secondary hepatocyte damage
 - d. Osteolytic disease and paraneoplastic expression of ALP by hepatocellular carcinoma cells