Approach to Elevated Liver Enzymes

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Common Small Animal Diagnoses—Section 6 Elevated Liver Enzymes

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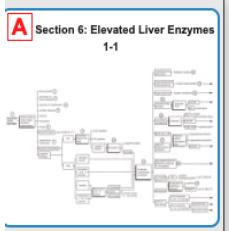

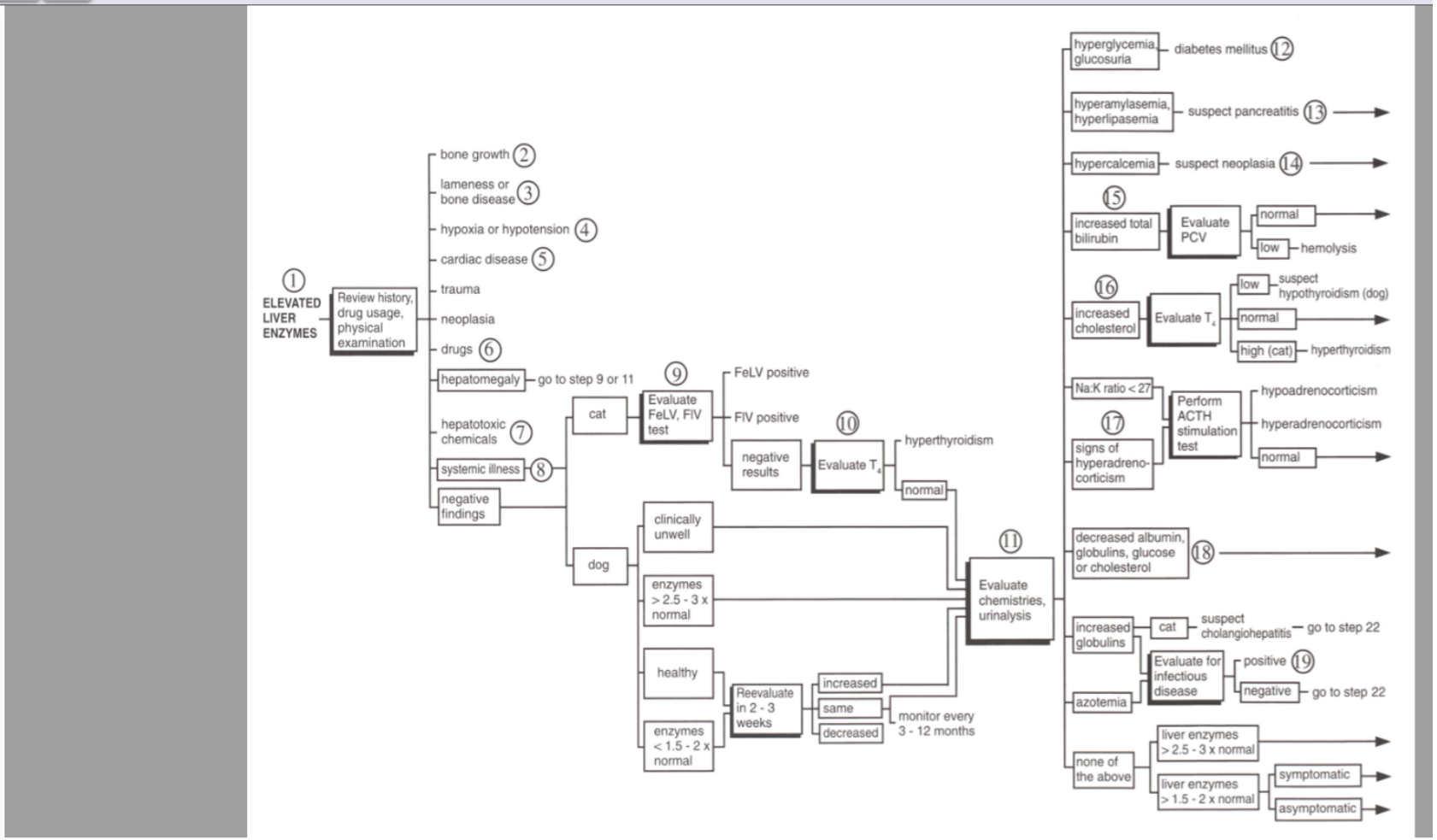

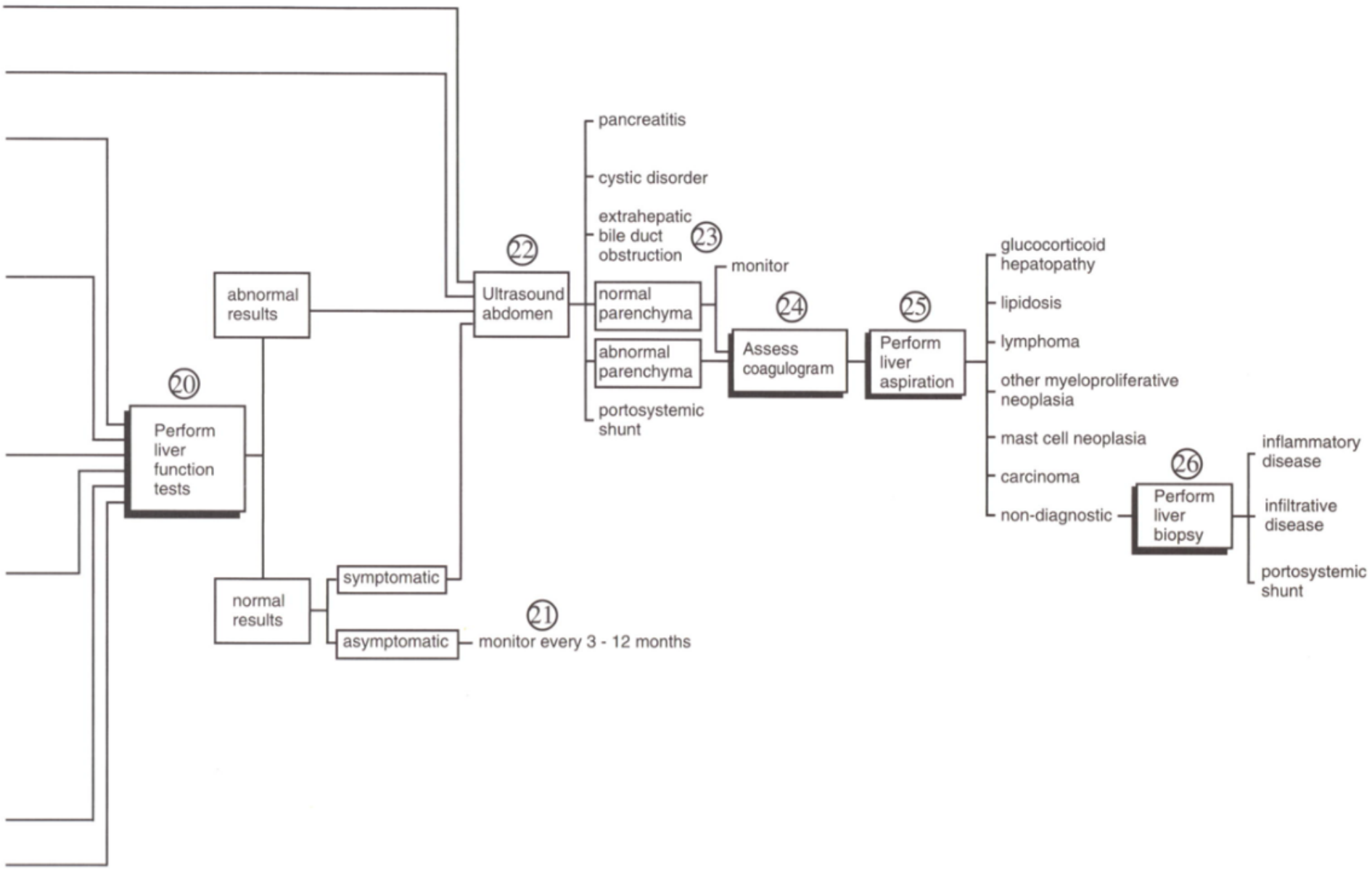
20
Perform liver function tests
abnormal results
normal results
22
Ultrasound abdomen
symptomatic
asymptomatic
21
monitor every 3 - 12 months
pancreatitis
cystic disorder
extrahepatic bile duct obstruction
23
normal parenchyma
abnormal parenchyma
portosystemic shunt
monitor
24
Assess coagulogram
25
Perform liver aspiration
glucocorticoid hepatopathy
lipidosis
lymphoma
other myeloproliferative neoplasia
mast cell neoplasia
carcinoma
non-diagnostic
26
Perform liver biopsy
inflammatory disease
infiltrative disease
portosystemic shunt

Increased liver enzyme activity is seen commonly but is not necessarily associated with clinically significant liver disease. Nor does it provide information on the liver's functional capabilities. In some cases (e.g., portosystemic shunt or cirrhosis), severe liver dysfunction can exist in the presence of normal or only mildly elevated enzyme concentrations. Nonetheless, liver enzyme elevations are associated with many liver, endocrine, and infectious disorders. There are numerous hepatic enzymes, but ALT and ALP are the most useful for evaluating hepatobiliary disease in dogs and cats. Increased ALT is generally associated with hepatocellular damage or regeneration, while increased ALP is associated with cholestasis, steroid use, bone growth or disease, and the use of many drugs. The half-life of ALP is short in cats, and the total liver content is 50% less than that in dogs. There is no corticosteroid-induced isoenzyme of ALP in cats. For these reasons, any ALP elevation in a cat should be considered significant and investigated. Clinically, the largest increases in ALP in cats are seen with intra- or extrahepatic cholestasis especially associated with hepatic lipidosis, cholangiohepatitis, or common bile duct obstruction.

2.

Young growing dogs up to 7 months of age often have slightly increased serum concentrations of ALP because of osteoclast activity.

3.

Bone lysis, with osteomyelitis or osteosarcoma, can cause a two- to fivefold increase in ALP. However the half-life of the bone-origin isoenzyme is short.

4.

Hypoxia or hypotension often results in increased ALT and occasionally mild increases in ALP. Conditions associated with hypoxia include congestive heart failure; acute severe blood loss; status epilepticus; septic shock; circulatory shock; and hypoadrenocorticism.

5.

Passive congestion of the liver from right heart failure can cause mild increases in ALP and ALT.

6.

Many drugs can cause an elevation in ALP, ALT, or both. Glucocorticoids induce production of a unique liver isoenzyme of ALP in dogs. Elevations can persist long after discontinuation of the glucocorticoid. Glucocorticoids also can induce hepatic production of ALT and produce pathological changes (steroid hepatopathy) that cause hepatocellular leakage of ALT. Anticonvulsants, notably phenobarbital, primidone, phenytoin, and carbamazepine, often cause increases in ALP and ALT. In cats, diazepam can induce hepatic necrosis and elevations of ALT and ALP. Other drugs that can elevate liver enzymes consistently include griseofulvin, phenylbutazone, thiacetarsamide, ketoconazole, mebendazole, and oxibendazole.

7.

Hepatotoxins include aflatoxins, carbon tetrachloride, arsenic, chlordane, chlorinated hydrocarbons, mercury mushrooms, tetrachloroethane, and many others.

8.

Common infectious diseases that localize in the liver or infect the liver as part of a more systemic process include infectious canine hepatitis, canine herpes virus, FIP, histoplasmosis, toxoplasmosis, leptospirosis, and *Bacillus piliformis*.

9.

Evaluating a cat's FeLV/FIV status is prudent since these viruses can affect the liver or influence how far the client is willing to pursue the problem of elevated liver enzymes.

10.

The most common laboratory abnormalities in cats with hyperthyroidism are increased serum concentrations of ALT and sometimes ALP. Azotemia, hyperglycemia, hyperphosphatemia, and hyperbilirubinemia are seen at times. Any cat over 8 years of age with increased ALT and ALP should be evaluated for hyperthyroidism, although the mean age for the disease is approximately 13 years. The reason for hepatic degeneration and necrosis is unknown, but concurrent hepatic dysfunction is rare.

11.

If elevated liver enzymes are found in a clinically ill dog or if the enzymes are more than 2.5 times normal in a healthy dog, evaluate a full serum chemistry profile and urinalysis. If the dog is healthy and enzymes are less than 1.5-2 times normal, then reevaluation in 2-3 weeks is in order. If the enzymes remain the same, either monitor them every 3-12 months as long as he dog is healthy or pursue further evaluation via a serum chemistry profile.

12.

Diabetes mellitus is associated with increased ALT in dogs and cats and increased ALP in dogs. Increased ALP is less common in diabetic cats.

13.

Pancreatitis causes increases in ALT and ALP by hepatic ischemia, exposure of the liver to toxic and inflammatory portal venous drainage of the inflamed pancreas, or posthepatic obstruction of the common bile duct. The entire abdomen should be imaged.

14.

Hypercalcemia in conjunction with increased ALT and/ or ALP should raise the suspicion of neoplasia, particularly lymphoma.

15.

Hyperbilirubinemia in the face of normal RBC counts signifies inadequate up take or conjugation of bilirubin (hepatocellular disease), inadequate excretion of bilirubin (biliary disease), or both. Neither the ratio of conjugated (direct) or unconjugated (indirect) bilirubin nor the measurement of urobilinogen has proved useful in differentiating intra- and extrahepatic causes of hyperbilirubinemia.

16.

Increased cholesterol is associated with increased hepatic synthesis and/or decreased biliary excretion of cholesterol.

17.

In the dog, both hypo- and hyperadrenocorticism can cause elevation of liver enzymes.

18.

Hypoalbuminemia associated with liver disease suggests chronic, marked liver dysfunction. Inhibition of albumin release due to hyperammonemia and dilution in ascitic fluid can lower the serum concentration of albumin further. Hypoglycemia can result from diffusely impaired glycogen storage, gluconeogenesis, and insulin degradation or, rarely, as a paraneoplastic hepatic disorder. Low BUN occurs with liver failure, hepatic masses, or portosystemic shunting. Liver function testing should be pursued if any of these abnormalities are found.

19.

Immunoglobulins are not synthesized in the liver but can increase in chronic inflammatory diseases. Hypergammaglobinemia is found in about one-half of cats with cholangiohepatitis.

20.

Liver function tests include measurement of serum bile acids (SBA) pre- and postprandial or fasting/ postchallenge plasma ammonia concentrations. In the general practice setting, the SBA concentration is a practical and generally sensitive indicator of hepatocellular, biliary and portal circulatory function. To evaluate SBA, fast the patient for 12 hours and take a serum sample (preprandial) for measurement of bile acid concentrations. Feed the patient to stimulate bile flow and gallbladder contraction and take another sample (postprandial) 2 hours after feeding. Evaluation of fasting pre- and postprandial SBA is particularly important in identifying abnormal hepatic blood flow. Bile acids do not always identify severe hepatic dysfunction, however. Fasting plasma ammonia concentration also is a fairly sensitive test of hepatic and portal circulatory function. However, false-positive results occur if stringent handling requirements are not followed. Plasma ammonia measurement is best reserved for rapid assessment of the critical patient with encephalopathic signs of unknown origin. Administration of oral or rectal ammonium chloride (the ammonia challenge test) also can assess liver function. However, this test should be performed with caution because of the risk of causing encephalopathy in seriously affected patients.

21.

If liver function test results do not indicate liver dysfunction and the patient is asymptomatic, then monitoring for the development of clinical signs is a reasonable approach. Liver enzymes should be evaluated periodically to determine if they are decreasing or increasing. If enzymes increase over time, then progress to step 22.

22.

Ultrasonography of the liver (as opposed to plain film radiography) provides more information about liver structure. Abnormalities commonly identified ultrasonographically include diffuse or focal parenchymal disease, changes in hepatic size and margination, cystic lesions, vascular disorders, distention or abnormal contents of the gallbladder, biliary obstruction or inflammation, perihepatic disease, masses, and abdominal effusion. Normal ultrasound examination results do not exclude hepatobiliary disease. Although in some instances a strong correlation can be made between changes in echogenicity and histological findings (notably hepatocellular carcinoma in the dog and hepatic lipidosis in the cat), a definitive diagnosis cannot be made by ultrasonography alone. The main uses of ultrasonography are to assist with biopsy planning, to identify surgically correctable vascular anomalies, and to differentiate intra and extrahepatic causes of cholestasis.

23.

The ability of ultrasonography to diagnose extrahepatic bile duct obstruction is hampered slightly by gallbladder distention and bile sludging that often is found in anorectic patients. Additionally, persistent dilation of bile ducts can be observed after resolution of chronic obstruction, especially in cats.

24.

If the liver parenchyma appears abnormal, then liver aspiration for cytological examination is recommended. Because the liver produces many clotting factors, a coagulogram may be needed prior to aspiration.

25.

Ultrasound-guided liver aspiration has the advantage of being a relatively noninvasive procedure and increases the probability of sampling discrete lesions, avoiding inadvertent puncture of major biliary or vascular structures, and obtaining representative specimens in diffuse hepatobiliary disease. While cytological findings of inflammation, cholestasis, necrosis, or hepatocyte hyperplasia or degeneration do not constitute a diagnosis, such findings can provide objective evidence of liver disease. The value of fine-needle aspiration cytology is that occasionally a definitive diagnosis of neoplasia (especially round cell tumors or carcinomas) or infection can be established. Because of the possibility of tumor seeding into the abdominal cavity or along the needle tracks, aspiration of a solitary hepatic mass is not advocated if surgical excision is planned.

26.

If liver aspiration cytology does not yield a reasonable explanation for the increase in liver enzymes, then liver biopsy can be performed in patients whose clinical signs warrant further investigation. Indications for liver biopsy include persistently elevated liver enzymes, abnormal hepatic function, or ultrasonographically identified hepatic changes. Common methods of liver biopsy include needle biopsy (blind or ultrasonographically guided percutaneous, keyhole, laparoscopic) and surgical biopsy (requires exploratory surgery). In general, needle biopsies are useful for primary and diffuse parenchymal diseases. Anesthesia is often required even for percutaneous biopsies in small animals. Complications of needle biopsy include bleeding and bile peritonitis. Contraindications to needle biopsy include microhepatica, severe and uncorrectable coagulation abnormalities, large-volume ascites (which interferes with hemostasis and makes the liver lobes excessively mobile within the fluid), hepatic cysts or abscesses, vascular tumors, or a lesion adjacent to the major bile ducts. A surgical biopsy is warranted in such cases. Other indications for an exploratory procedure include a single resectable hepatic mass, mechanical extrahepatic bile

duct obstruction, presumptive congenital vascular anomaly, septic cholangiohepatitis, and diagnostic failure of previous needle biopsy. Laparotomy offers advantages over percutaneous biopsy techniques, including the ability to evaluate the entire abdomen, prevent and control hemorrhage, collect bile for culture, perform manometry and portovenography, and correction of certain conditions (e.g., tumor excision or congenital portosystemic shunt ligation). However, many animals with chronic, severe hepatic dysfunction are in a relatively precarious state of compensation that could be overwhelmed by surgery.

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