Bile Acids in Companion Animals

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Bile acids are used to screen patients with abnormal liver enzymes to look for loss of liver function and patients suspected to have portosystemic shunt (PSS).

Total serum bile acids (BA) are thought to be the most sensitive liver function test that is readily available for use in small animals. Bile acids are used to screen patients with abnormal liver enzymes to determine if there could be loss of hepatobiliary function and for patients suspected to have portosystemic shunt (PSS), either congenital or acquired.[1] Bile acids are synthesized from cholesterol within the hepatocyte, conjugated to either taurine or glycine and secreted into the bile canaliculi. Bile acids then flow into the gallbladder and, following a meal, cholecystokinin (CCK) is released, causing gallbladder contraction emptying bile acids into the intestine where they aid in the emulsification and digestion of fats. In the ileum, BA are actively resorbed and returned to the liver through the portal circulation. As BA flow through the small sinusoids of the liver, they are taken up by the hepatocytes and then re-secreted back into the bile. Only a small fraction of the total BA pool ever escapes into the systemic circulation. Thus, the enterohepatic circulation of BA occurs with an approximate 95%-98% efficiency.[2] There are a variety of hepatobiliary insults or disruptions of the portal systemic circulation that may increase BA concentrations.

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BA testing should be used for patients having unexplained elevations in liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] and/or gamma-glutamyl transferase [or transpeptidase; GGT]) or unexplained tests on the biochemical profile that are altered by abnormal hepatic function (albumin, glucose, BUN, or cholesterol). Abnormal liver enzymes and abnormal BA concentrations help identify occult liver disease, indicating the need for further diagnostic investigation. [Refer to Figure 1.] In one study, abnormal BA concentrations were detected in more than 90% of patients with morphological or a clinical liver disease diagnosis.[3] Non-hepatic conditions that may result in abnormal liver enzymes usually do not result in significant hepatobiliary dysfunction causing abnormal BA concentrations.[4] Occasionally, BA concentrations may have mild elevations resulting from extrahepatic causes, such as steroid hepatopathies, lipidosis, or secondary reactive hepatopathies.[3]

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Bile acids testing is also used to screen for PSS, either congenital or acquired, or when clinical signs are suggestive of hepatic encephalopathy. Bile acids testing may also be helpful in monitoring recovery of congenital PSS surgery or from therapy for hepatobiliary disease. Successful complete ligation of PSS in affected dogs often will have mild elevations in BA concentrations postoperatively that are usually not clinically significant.[5]

Standard BA testing involves collection of both a pre- and post-prandial blood sample. Performing pre- and post-prandial sample testing increases the sensitivity and specificity of the test.[6] The pre-prandial sample is collected after a 12-hour fast. Normal fasting serum bile acid concentration (FSBA) reflects an efficient and intact enterohepatic circulation. Pathology of the hepatobiliary system or the portal circulation results in an increased FSBA prior to the development of hyperbilirubinemia, negating its usefulness in the icteric patient. A FSBA 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. Normal fasting or random BA concentrations do not rule out hepatobiliary dysfunction or portosystemic shunting. This scenario requires a post-prandial sample testing to assure diagnostic accuracy. However, finding a significantly abnormal, fasted or random sample precludes the need for post-prandial sample collection.

The post-prandial sample should be collected two hours following a meal.[6] For post-prandial sample collection, feeding a small meal of canned food immediately after the pre-prandial sample collection is recommended. Lipemia will falsely increase BA concentration, so feeding a large fatty meal should be avoided.[7] The presence of fat in the meal causes the release of CCK, resulting in gallbladder contraction sending much higher BA concentrations into the enterohepatic circulation than in the fasted state. The diagnostic value of determining post-prandial BA concentration is increased sensitivity for the detection of hepatic disease and congenital, portal vascular anomalies. The post-prandial BA concentrations may identify alterations in portal vascular integrity or hepatic function that may not occur in the fasted state, with fewer BA entering the enterohepatic circulation. Collecting only a single fasted or random BA sample is not recommended, as it may not identify a disruption in the enterohepatic circulation.[7] Cholecystectomy also precludes determining a post-prandial BA concentration as BA concentrations vary through the day.[8] Patients having hepatic or post-hepatic hyperbilirubinemia invariably will also have abnormal BA concentrations because of the similar excretion paths, which negates the usefulness of performing BA testing in cases with hyperbilirubinemia.

Increased serum BA concentrations in dogs and cats have a high diagnostic sensitivity for hepatobiliary dysfunction.

In patients unequivocally having primary liver disease, determining BA concentrations offers no additional useful information as to the type of lesion, severity, reversibility, or prognosis.[9] Determining urinary bile acid concentrations has a similar performance as measuring serum BA concentrations, but is less commonly performed because testing is not offered by many diagnostic laboratories.[10]

Normal pre- and post-prandial BA concentrations should be less than 20 µmol/L in dogs and less than 15 µmol/L in cats.[3] In the author's experience, a grey zone range of 20-30 µmol/L in dogs and 15-30 µmol/L in cats (based on multiple reference laboratory intervals) can occur in normal animals, but may also suggest hepatobiliary disease.[6] On the VETSCAN® VS2 analyzer, reference intervals and estimated grey zones are listed in Table 1.[11]

Table 1.
VETSCAN® VS2 Reference Ranges*

Bile Acids (µmol/L)	Canine	Feline
Pre-prandial	1-4	1-3
Post-prandial	2-15	7-9
Grey Zone	15-25	10-25

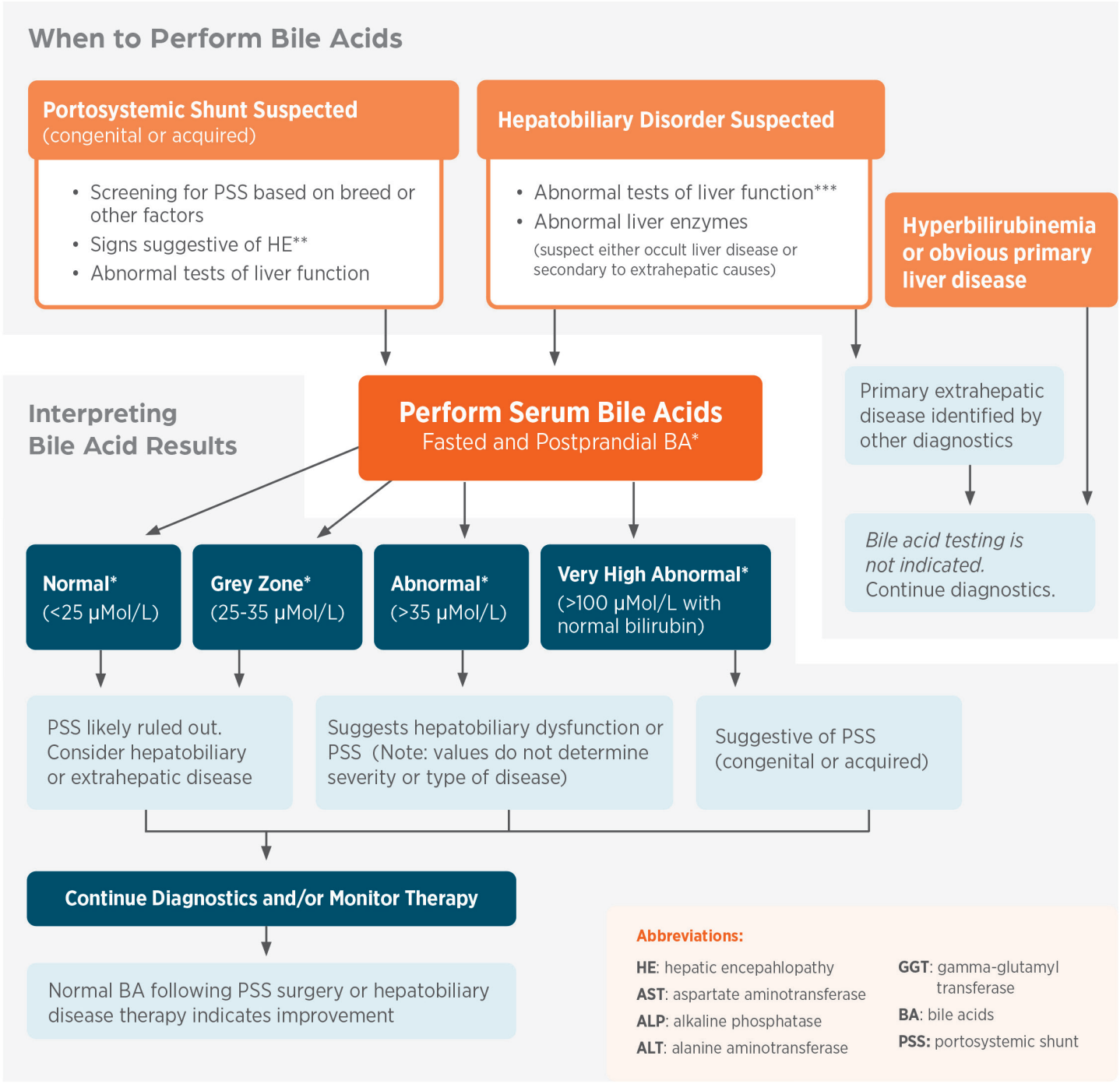
*Reference intervals for canine and feline appear as 0-25 µmol/L on VETSCAN VS2 results, regardless of sample timing. Above reference intervals are published in VETSCAN VS2 Reference Ranges.[11]

The specificity for pre- and post-prandial BA for hepatobiliary disease in dogs is reported 95% and 100% using a cutoff value of >15 µmol/L and >25 µmol/L, respectively. Using similar cutoff values in cats, the specificity is 96% and 100%, respectively.[12] When the fasting value is greater than the cutoff value for the dog, there is a high probability that the histology will define an hepatic lesion.[13] The sensitivity of BA identifying dogs with primary hepatobiliary disease ranges from 54% to 74% and is not high enough to recommend the routine use of BA measurement as a screening test for hepatobiliary disease.[12] Dogs with early liver disease may have normal BA concentrations. In congenital PSS cases in dogs and cats using a BA upper limit of 20 µmol/L, the sensitivity and specificity of BA was 93% and 67% in dogs and 100% and 71% in cats, respectively.[13] Two identified exceptions are congenital portosystemic vascular anomalies in dogs and cats and cirrhosis in dogs, for which the sensitivity of post-prandial BAs at the above cutoff value was 100%.[12] In the author's experience, patients with BA concentrations >100 µmol/L with normal serum bilirubin are likely to have either a congenital or acquired PSS. [Note: reference intervals stated in this paragraph are generalizations from multiple sources and chemistry analyzers. It is always best practice to refer to the manufacturer-specific reference intervals and cutoff values when making clinical decisions.]

Occasionally, the fasting serum BA value is greater than the total post-prandial BA value.[12] Higher fasting than post-prandial values may result from spurious gallbladder contraction. Lower post-prandial BA may occur from: hypomotility of gallbladder, stomach, or intestine; an inadequate test meal (low fat content); or severe ileal disease that decreases BA resorption. The long-term administration of ursodeoxycholic acid may also slightly increase BA concentrations, but values generally remain in the normal reference intervals.[14] [Note: Ursodeoxycholic acid (or ursodiol) is a secondary bile acid used in extra label fashion to treat various cholestatic diseases in small animals.]

In summary, increased serum BA concentrations in dogs and cats have a high diagnostic sensitivity for hepatobiliary dysfunction. Several different primary and secondary liver diseases can cause the dysfunction, such as decreased portal blood flow, decreased functional hepatic mass, diffuse hepatocellular disease, and hepatic or post-hepatic cholestasis. Measuring serum BA is helpful in screening and monitoring patients with PSS and in patients with unexplained elevations in liver enzymes and/or unexpected changes to liver products on a routine chemistry panel that may lead to suspicion of liver dysfunction.

Figure 1. Utilizing and Interpreting Bile Acids in Dogs and Cats



* Reference ranges vary by analyzer and those stated in this algorithm pertain to the VETSCAN VS2 canine cut-off and adjusted per author. Please refer to the manufacturer's guidance or reference laboratory for guidance on interpretation.
** HE signs may include: cognitive and/or behavior changes, ataxia, blindness, seizures.
*** Abnormal tests of liver function include: unexplained low glucose, low albumin, low BUN, and/or low cholesterol.

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