Elevated liver enzymes in cats – Case discussions and review of liver function and physiology

Assessment of the liver

Developing a standard approach to assessing blood tests related to the liver is key.

1. Liver enzymology (leakage enzymes, induced enzymes)
2. Bilirubin
3. Indirect liver function tests (glucose, urea, albumin, cholesterol, PT/PTT)
   - Decreases in glucose, urea/BUN, albumin, and/or cholesterol support hepatic insufficiency (especially when multiple effected); abnormal clotting times also expected given lack of production of clotting factors from failing liver
4. Direct liver function tests (ammonia, bile acids)

Functional liver microanatomy and physiology

Understanding of enzymology, sources of bilirubin, and functional tests is maximized when one is able to keep in mind liver anatomy, microanatomy, and physiology.

The classic hepatic lobule is hexagonal where the aptly-named central vein is at the center of the lobule, and portal areas are at the periphery, including a branch of the portal vein, a branch of the hepatic artery, a bile duct, and a lymphatic vessel.

Zones of hepatocytes are relative to where the blood comes in (portal area) and exits (central vein):
- **Periportal hepatocytes** - Near the portal area and receive nutrients, oxygenated blood, and, potentially, toxins first
- **Mid-zonal hepatocytes** - Midway down the sinusoids; some toxins target these cells preferentially
- **Centrilobular hepatocytes** - Located in the center, near the central vein and receive blood last (so sensitive to decreased blood flow and/or hypoxemia)

<table>
<thead>
<tr>
<th>Blood flow</th>
<th>The portal vein carries blood from the abdomen/GI tract to the liver. A branch enters at the portal region, mixes with oxygenated blood from a branch of the hepatic artery, &amp; provides blood to hepatocytes via the sinusoids, &amp; then drains via the central vein.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile flow</td>
<td>Bile flow is in the opposite direction of blood flow, toward the portal area. Bile ducts originate as bile canaliculi, which are invaginations of the cell membrane. The wall of the canaliculus is the cell membrane of adjacent hepatocytes. Material (e.g. bile acids, bilirubin, other waste products) excreted by the hepatocyte enters into the bile canaliculus as bile &amp; flows toward to portal area, coalescing to become bile ductules, then bile ducts, then the major bile duct, eventually entering into the common bile duct. The bile ducts are a low pressure system, i.e. easily collapsed; this is relevant when discussing hepatic swelling, portal fibrosis, &amp; portal infiltrates (i.e. neoplasia, inflammation) causing cholestasis.</td>
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<tr>
<td>Lymphatic flow</td>
<td>Lymph flow is also opposite to blood flow, going towards the portal area. It originates in the space of Disse around sinusoids.</td>
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<tr>
<td>Sinusoids</td>
<td>Sinusoids are lined by a discontinuous, fenestrated endothelium; these openings allow for direct communication between fluid in sinusoids and spaces of Disse, i.e. uptake of nutrients and waste products from sinusoids (fed by the portal blood flow) and release from hepatocytes into sinusoids of various products (e.g. glucose, urea). Proteins can also be released into sinusoidal circulation (&amp; general circulation) or via space of Disse into lymphatics (liver lymph has higher protein).</td>
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Follow along and review liver microanatomy – we will fill in the paths of blood and bile as well as review the various areas, discussing how liver and non-liver disease are related to microanatomy.
Assessment of the liver - Enzymology

Where do serum enzymes originate? There are numerous sources that can enter into blood:

Limitations of enzymes

- Increases may be due to diseases of the liver AND/OR when the liver is secondarily affected (e.g. anemia, GI disease, pancreatic disease, shock, cardiac failure).
- The magnitude of liver enzyme elevated may not correlate with prognosis.
- Liver enzyme increases do not provide any information on hepatic function.
- Additionally, end-stage chronic liver failure may lack liver enzyme increases as there are insufficient functional hepatocyte numbers to actually produce enzymes.

Leakage enzymes

These enzymes are present free within the cell cytoplasm/cytosol.

The numbers of cells injured + the severity of the injury results in a greater amount of enzyme leaked into the serum. Leakage enzymes increase due to cell injury and/or cell death. Because the enzyme is free within the cell cytosol, increases in these enzymes are fast, i.e. hours.

<table>
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<th>Enzyme</th>
<th>Tissue specificity</th>
<th>Interpretation</th>
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</table>
| ALT    | Liver specific – Dogs, cats | Increases (dogs, cats) due to: hepatocyte injury or death  
               - Magnitude of increase parallels severity of injury or cell death  
               - Lack of increase due to: chronic liver failure (hepatocytes cannot make enzymes) |
| AST    | Liver, muscle, RBCs – All species | Increases (all species) due to: hepatocyte or muscle injury or death  
               Dogs + cats:  
               ↑AST + ↑ALT = Liver &/or muscle, check CK + relative increases  
               ↑AST + normal ALT = muscle  
               ↑AST + normal CK = Liver (ALT should be increased)  
               RBC lysis (in vitro > in vivo) can also increase AST |
**Induced enzymes**

These enzymes are membrane bound within the cell. A small amount is normally released during cell function and turnover.

With cell ‘stress,’ more enzyme is produced (i.e. induced) so that greater amounts of the enzyme are released. Induced enzymes increase due to cell stress & greater production of the enzyme.

Induction enzyme increases are usually slower to manifest as it is a result of increasing production. With massive cell death, there can be an increase, however, in induced enzymes as the cell membrane integrity is compromised allowing for release.

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<td>ALP</td>
<td>Liver, bone, corticosteroids, mammary</td>
<td>ALP has several isoenzymes (different forms) that increase due to different reasons. There are species &amp; tissue differences. ALP on a chemistry panel includes all ALP forms.</td>
</tr>
<tr>
<td>ALP-L</td>
<td>Liver – all</td>
<td>Increases (all species) due to: <strong>cholestasis</strong> &amp;/or <strong>biliary hyperplasia</strong>  Cholestasis* can be intra- or post-hepatic. Differentiating cholestasis from biliary hyperplasia** is not possible via blood work.</td>
</tr>
<tr>
<td>ALP-B</td>
<td>Bone - all</td>
<td>Increases (all species) due to: <strong>increased osteoblastic activity</strong> (bone growth/production)  Examples: bone growth young animals, osteosarcoma, fracture repair</td>
</tr>
<tr>
<td>ALP-CS</td>
<td>Corticosteroid isoenzyme – dog</td>
<td>Increases (dogs only) due to: liver production of ALP-CS from <strong>endogenous or exogenous</strong> corticosteroids</td>
</tr>
<tr>
<td>GGT</td>
<td>Hepatocytes, biliary, mammary, renal tubular cells</td>
<td>Increases (all species) due to: <strong>cholestasis</strong> &amp;/or <strong>biliary hyperplasia</strong>  Cholestasis *can be intra- or post-hepatic. Differentiating cholestasis from biliary hyperplasia is not possible via blood work. Increases with colostrum ingestion in some neonates. GGT levels (in urine only) can increase with renal tubular injury.</td>
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</tbody>
</table>
**Bilirubin metabolism and hyperbilirubinemia**

**Hemolysis (Pre-hepatic)**

+/- hepatic if there is end-organ damage from anemia and/or thromboembolic disease

Support for diagnosis:
- Regenerative anemia
- RBC changes supporting hemolysis (e.g. oxidative injury, hemic parasites, IMHA, RBC shearing)
- Unconjugated > conjugated bilirubin?? Depends on duration of hemolysis (so not a great measure)

**Obstructive cholestasis**

Decreased excretion of conjugated bilirubin
- Hepatic
  - Obstructed bile canaliculi or bile ductules or bile ducts
  - Causes: hepatocyte swelling (lipidosis), infiltration of hepatic parenchyma and/or portal areas with neoplasia (e.g. lymphoma), infection + inflammatory leukocytes, fibrosis around portal areas, migrating parasites, stones
- Post-hepatic
  - Pancreatitis, gall bladder inflammation/infection/stone, pancreatic, bile duct, intestinal neoplasia causing an obstruction

Support for diagnosis:
- Concurrent increases in GGT, ALP
- With pancreatitis – inflammatory leukocyte, hypocalcemia, dehydration, abnormal PLI
- May need AUS for differentiation of hepatic vs. post-hepatic

**Functional cholestasis**

Impaired excretion of Bc from hepatocytes into bile canaliculi due to infection; mediated by TNF alpha + others

Support for diagnosis:
- Inflammatory leukogram
- Expect normal ALP, GGT

**Hepatic failure**

Hyperbilirubinemia may not be present. If it is, it is likely multifactorial and dependent on cause of hepatic failure, e.g. some cause cholestasis. Other mechanisms: Decreased uptake & conjugation of Bu; Decreased excretion of Bc.

Support for diagnosis:
- Abnormal indirect function tests: Decreased glucose, urea, albumin, cholesterol; prolonged PT & PTT
- Abnormal direct function tests: Hyperammonemia, Elevated bile acids (BAs can also increase from cholestasis)

**Tests of liver function:**

**Indirect liver function tests**
- Decreases in products made by the liver support decreased hepatic function: hypoglycemia, low BUN, hypoalbuminemia, hypcholesterolemia (not all are always present); Prolonged PT/PTT

**Direct liver function tests**
- Increased ammonia (hyperammonemia) due to decreased urea $\rightarrow$ conversion from insufficient numbers of functional hepatocytes
- Elevated bile acids due to decreased clearance from circulation, decreased conjugation, +/- portal hypertension
There are numerous reasons liver enzymes can be elevated in cats or why hepatic function is compromised. Below is a list of common and less common causes of liver disease, which may cause injury and/or cholestasis and/or failure, depending on the cause, severity, and duration of disease.

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular (V)</td>
<td>Malformations, severe anemia or hypovolemia (resulting in centrilobular necrosis), right heart failure/insufficiency</td>
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<tr>
<td>Infectious (I)</td>
<td>Leptospirosis, bacterial (from biliary tree, intestine vs. systemic), fungal (Histoplasmosis, Coccidiomycosis), protozoal (Toxoplasmosis), parasitic (flukes) viral (FIP, severe virulent Calicivirus)</td>
</tr>
<tr>
<td>Inflammatory (non-infectious or infectious)</td>
<td>Cholangitis/cholangiohepatitis, pancreatitis, lymphocytic portal hepatitis, intestinal inflammation/triaditis</td>
</tr>
<tr>
<td>Neoplasia (N)</td>
<td>Lymphoma, hepatocellular carcinoma, biliary carcinoma, mast cell tumor, metastatic disease, nodular hyperplasia (dogs)</td>
</tr>
<tr>
<td>Drugs (D)</td>
<td>Oral diazepam (cats), acetaminophen, NSAIDs, phenobarbital, others</td>
</tr>
<tr>
<td>Iatrogenic (I)</td>
<td>Drugs, surgery</td>
</tr>
<tr>
<td>Congenital/Inherited (C)</td>
<td>Storage (lysosomal, etc) diseases, PSS (dogs&gt;cats), Polycystic diseases, Amyloidosis (Siamese cats), PPDH</td>
</tr>
<tr>
<td>Autoimmune (A)</td>
<td>Certain types of cholangitis, cholangiohepatitis</td>
</tr>
<tr>
<td>Trauma (T)</td>
<td>HBC, Attack by another animal, etc</td>
</tr>
<tr>
<td>Endocrine/Metabolic (E)</td>
<td>Hepatic lipidosis, diabetes mellitus, hyperthyroidism</td>
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