Elevated Liver Enzymes: Now What? 
A Diagnostic Approach to Hepatopathies

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Providing the best quality care and service for the patient, the client, and the referring veterinarian.
Liver Enzymes

- **Alanine Aminotransferase (ALT):**
  - Hepatocellular leakage enzyme
  - Cellular injury and necrosis
  - Relatively liver-specific
Liver Enzymes

- Aspartate Aminotransferase (AST):
  - Not liver specific
  - Muscle, RBCs
    - Check CPK, as well
Liver Enzymes

● Alkaline Phosphatase (ALP):
  – Multiple isoenzymes: hepatic, bone, intestine, steroid (dog)
  – Liver isoenzyme: cholestasis
    ● Dogs > Cats
Liver Enzymes

- Gamma Glutamyl Transpeptidase (GGT):
  - Cholestasis
  - More specific than ALP, but not 100% liver specific
Liver Production Parameters

- Albumin
- BUN
- Glucose
- Cholesterol
- +/- Bilirubin
Next Step Testing

- Liver Function Testing:
  - Bile Acids
    - Fasting and 2hr post-prandial
    - Unnecessary with elevated Bili
      - Impaired enterohepatic circulation
  - Ammonia
    - Handling crucial
    - Fasting sample
Imaging

- Abdominal radiographs:
  - Hepatomegaly
  - Microhepatica
  - Potential Hepatic Masses
  - Effusion/Poor serosal detail
Hepatic Cytology

- Can be diagnostic in a non-invasive way
  - Infiltrative processes, masses
  - Relatively inexpensive

- Can be misleading
  - May not be representative
  - Can cause hemorrhage
    - PT/PTT
Bile

- Cholecystocentesis
  - Cytology
  - Culture and Sensitivity
    - More sensitive than liver
  - Complications
    - Bile peritonitis
    - Hemorrhage
Still no answers…?

- BIOPSY!
Indications for biopsy

- Elevated liver enzymes (ALT, AST, +/- ALP, GGT, Bili)
  - Progressive in nature
  - Non-responsive to therapy
  - Patient becoming clinical for hepatopathy

- To definitively define a congenital abnormality
  - Portal Vein Hypoplasia
Why not just treat empirically?

- How do you know what you’re treating?
- Basing therapy on:
  - Aspirates?
    - May or not be representative of the true etiology
  - Bloodwork abnormalities?
    - Not specific – can give you a hint, but not a diagnosis
  - “Shotgun” therapy?
    - What are we missing by doing this?
    - Disservice to our patients and clients
    - Should only be used as a last resort ($)
How to biopsy the liver….

- Percutaneous tru-cut?
  - Ultrasound-guided
- Laparoscopy?
- Full Laparotomy?
Advantages of percutaneous (Tru-cut) biopsies

- Minimally invasive
- Does not always require general anesthesia
- Rapid recovery/healing time
- Relatively inexpensive
Disadvantages of percutaneous (Tru-cut) biopsies

- Relatively small sample size – 14g Tru-cut biopsy needle
- Inability to control bleeding/hemorrhage
- Can be contraindicated with coagulopathies or massive ascites
- Can be difficult to locate and biopsy focal lesions
Disadvantages of percutaneous (Tru-cut) biopsies

- Not as efficacious in providing a definitive diagnosis as one might think.
  - 2002 JAVMA study by Cole et al. showed that Tru-cut biopsies coincided with the definitive diagnosis in 40% of animals with liver disease and in 48% of all animals sampled (both diseased and normal liver).
  - 1985 Vet Rad study by Hager, Nyland, and Fisher showed that 60/63 liver biopsy samples or 90.5% were adequate to obtain a definitive diagnosis.
  - 1999 Vet Rad and Ultrasound study by de Rycke et al. showed that of 30 biopsy attempts, only 77% contained liver tissue while others contained nothing, skeletal muscle, blood, or small intestine.
Advantages of surgical (laparotomy) biopsies

- Large sample size/diagnostic in vast majority of cases
- Ability to sample various lobes of the liver
- Ability to visualize other abdominal organs and biopsy if indicated
- Ability to biopsy specific lesions if the liver is not diffusely affected
- Ability to visualize and control any hemorrhage that occurs
Disadvantages of surgical (laparotomy) biopsies

- Exploratory laparotomy is invasive
- Relatively long recovery/healing time
- Most expensive of the three options
- Possible post-operative complications
  - Post-operative bleeding
  - Wound dehiscence
Advantages of laparoscopic biopsies

- Large sample size/diagnostic in vast majority of cases
- Ability to sample various lobes of the liver
- Ability to visualize other abdominal organs and biopsy if indicated
- Ability to biopsy specific lesions if the liver is not diffusely affected
- Ability to visualize and control any hemorrhage that occurs
  - Not quite to the extent as with laparotomy
Plus….

- Less invasive than full laparotomy
- Faster recovery time
  - Can be done on an outpatient basis
Disadvantages of laparoscopic biopsies

- More invasive than percutaneous
- More expensive, as well
- May need to convert to laparotomy if excessive bleeding
“Quagmeyer” Neumann

- 9yo MC Yellow Lab
- Presented for evaluation of persistently elevated ALT, **no clinical signs**
- ALT from 360-542 over a 4 mo span
- AUS: mildly coarse echotexture to the liver
- No response to Denamarin and Royal Canin Hepatic LS
Chronic active hepatitis: idiopathic inflammatory condition, possibly associated with immune-mediated attack of liver leakage enzymes after hepatocellular damage.

Copper-associated hepatopathy: copper storage accumulation in hepatocyte lysosomes. Can be primary hereditary disorder or secondary to underlying liver pathology.
Neoplasia:
Bacterial hepatitis:
Toxins:
- Amanita mushroom:
  - drugs (phenobarb, TMS, methimazole)
Infectious canine hepatitis (CAV-1)
Quagmeyer's Plan

- Laparoscopic Biopsy
  - Adv: large biopsies, minimally invasive, short anesthesia time, less expensive than ex lap
  - Dis: unable to access texture through touch, may be difficult to obtain bile sample for culture to rule out bacterial hepatitis.
  - Submit biopsies for histopathology, heavy metal analysis and tissue culture.

BMBT
  - Rule out coagulopathy before surgery
    - result WNL (2 minutes)
    - PT/aPTT also WNL
Quick note about Coags

- Unpublished study out of CSU (Twedt)
- No correlation between coags (PT/aPTT/BMBT) and bleeding in laparoscopic liver biopsies
- Still done in every patient
Quaggie’s Laparoscopy
Quaggie’s laparoscopy
Quaggie’s laparoscopy
Results:

1. Anaerobic and aerobic tissue culture: negative for growth

2. Histopathology: LIVER: SEVERE BRIDGING CHRONIC LYMPHOPLASMAMCYTIC AND NEUTROPHILIC HEPATITIS WITH SEVERE FIBROSIS, MILD BILE DUCT HYPERPLASIA, AND KUPFFER CELL HEMOSIDEROSIS

3. Heavy metal analysis: 3100 ppm dry weight. Once heptic copper concentrations exceed 2000ppm dry weight, severe liver lesions are usually observed.
Treatment of Copper-associated hepatopathy

1. Chelate Copper:
   a. In liver:
      D-Penicillamine (10-15 mg/kg BID): Induces hepatic metallothionine which binds copper in a non-toxic form and promotes its excretion in the urine. Also may inhibit collagen deposition and has immunomodulatory and immunosuppressive effects (help prevent progression to cirrhosis).
   b. In gut to prevent further absorption of copper
      Zinc Gluconate (10 mg/kg SID): induces metallothionine within enterocytes. Copper from the gut is then bound to metallothionine and is lost in the stool with normal epithelial sloughing and turn over.
Treatment of Copper-associated hepatopathy

2. Diet
   a. Hepatic diet (Royal Canin Hepatic LS, Hill’s L/D):
      Low in copper (ideally <0.5 ppm Cu), higher in zinc, avoids liver/organ meat and lamb (all high in Cu)
Treatment of Copper-associated hepatopathy

3. Protect liver from further damage:
   a. Anti-inflammatory:
      
      **Ursodeoxycholic Acid (Actigall)** (15 mg/kg SID): Synthetic hydrophobic bile acid that displaces hepatotoxic bile acids.

      - Used in Quaggie for its stabilization of hepatocyte membranes, cytoprotective and immunomodulatory effects

      **Prednisolone** (0.5 mg/kg SID): Anti-inflammatory dose to help modulate development of fibrosis.
Treatment of Copper-associated hepatopathy

b. Anti-oxidants

**Sam-E**: Glutathione precursor. Helps liver produce adequate amounts of glutathione to protect against oxidative damage.

**Milk thistle (silymarin)**: Nutraceutical with hepatoprotective effects (free radical scavenger)
Treatment of Copper-associated hepatopathy

c. Antibiotics:

Clavamox (15 mg/kg BID): Unable to culture bile and neutrophilic component to histopathology result.
“Lucy” Callahan

- 9 yo FS Terrier X
- Vague clinical signs of decreased appetite and lethargy
- Chem: ALT 642, AST 312, ALP 476, GGT 15, Bili 1.4
- Non-responsive clinically and biochemically to clavamox and sam-E
Further diagnostics

- Abdominal ultrasound: Mildly hyperechoic hepatic parenchyma with mildly irregular borders to the liver
- PT/aPTT: WNL
- BMBT: Normal
Lucy’s laparoscopy
Lucy’s results

- **Histopath:** SEVERE CHRONIC ACTIVE PERIPORTAL TO RANDOM LYMPHOCYTIC, NEUTROPHILIC AND EOSINOPHILIC HEPATITIS WITH PIECEMEAL NECROSIS, DISSECTING FIBROSION, NODULAR REGENERATION, AND KUPFFER CELL HYPERPLASIA (CHRONIC ACTIVE HEPATITIS WITH CIRRHOSIS)

- **Bile culture:** E. coli sp.

- **Copper quant:** WNL (1200 ppm)
Lucy’s therapy

- Antibiotics for the bacterial cholecystitis and for the neutrophilic component to the hepatitis
  - Baytril and Clavamox
- Anti-oxidants:
  - Denamarin
- Anti-inflammatory:
  - Prednisolone to help with inflammation and to help prevent further fibrosis/cirrhosis
Lucy

- Lucy did very well for about 9 months prior to clinically deteriorating.

- Prescription diet was not used in her case, but would not have been a wrong decision.
"Meeshka" White

- 14yo MC DSH
- 2-3 week history of lethargy and poor appetite
- Elevated ALT, AST, ALP on bloodwork
- Non-responsive to Clavamox and Denosyl
Meeshka

- Abdominal ultrasound: Enlarged, slightly hyperechoic liver

- FNAs: Lymphocytic inflammation with moderate vacuolar change (could not rule out lymphoma)
Meeshka’s laparoscopy
Meeshka’s laparoscopy
Meeshka’s results

- Small cell lymphoma; moderate hepatic lipidosis
- Diagnosis obtained, when an aspirate didn’t suffice
- E-tube placed while under anesthesia, as well
Meeshka’s treatments

- Prednisolone, Chlorambucil
- Tube feedings
- Lots of diligent work on behalf of the owner and rDVM
- Meeshka is doing well at home
The future of liver biopsies?

Percutaneous transjugular approach
Questions?

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