VET 433B Liver Lectures

Liver I: Overview

Key points to assess when evaluating a chemistry panel

- Signalment
  - Young vs old
  - Cat vs dog
  - Breed predispositions
- Clinical signs
- Hepatocellular (ALT, AST) or cholestatic (ALP, GGT) or mixed hepatopathy
- Severity of liver enzyme elevations
  - Mild 1-2x
  - Moderate >2-5x
  - Severe >5x
- Chronicity of elevations
- Liver function parameters
  - Albumin
  - BUN
  - Bilirubin
  - Cholesterol
  - Glucose

Clinical signs of liver disease (can often be subclinical)

Non-specific	Specific
Anorexia	PU/PD
Weight loss	Seizures
Vomiting	Fever
Weakness	Ascites
Lethargy	Obtundation
	Melena
	Icterus
	Pigmentation
	Grey Feces

Classifying Hepatopathies

Hepatocellular	Cholestatic
ALT	ALP
AST	GGT

ALT: cytosolic (liver specific) *never ignore an elevated ALT

AST: cytosolic but also in the mitochondria and skeletal muscle (AST, CK), can be increased by ex vivo hemolysis

ALP: Bound to hepatocyte and bile canaliculi membrane, three isoforms: liver, bone (osteoblastic, and corticosteroid (dogs only)

GGT: Produced by bile duct epithelium

Difference in liver enzymes between dogs and cats

- The half-life of liver enzymes is much shorter in cats
    - ALT and ALP: 2.5 days in dogs vs 6 hours in cats
    - AST: 12 hours in dogs vs 1 hr in cats
- ALP is more specific for liver in cats
    - They do not have the corticosteroid isoform
- Bilirubinuria is always abnormal in a cat
    - 9x renal threshold for bilirubin vs dogs
    - Cats can't conjugate bilirubin in the renal tubules

What are the liver function parameters?

- Albumin
- BUN
- Cholesterol
- Glucose
- Bilirubin

*Elevated liver enzymes are not a marker of liver dysfunction!

Additional Tests of Liver Function

Bile Acid Testing	Can be elevated with shunting, liver dysfunction, or cholestasis Can assess pre and post shunt correction (post-prandial BA <30 umol/L better sensitivity than pre-prandial BA If the post-prandial is lower than the pre-prandial it may be due to a lack of GB contraction or decreased intestinal absorption of BA Normal bile acids do not rule out liver disease
Ammonia	Used to evaluate for a shunt or liver dysfunction 12 hour fasting ammonia > 59 umol/L

	(similar to slightly lower sensitivity, better specificity than BA for shunt) Needs to be processed quickly after collection 6h postprandial ammonia can improve the sensitivity
Coagulation Panel (including Fibrinogen)	
Protein C	

What are some conditions that may cause secondary hepatopathies?

- GI disease (inflammatory enteropathy)
    - The liver receives portal blood with exposure to cytokines and endotoxin from the GIT
- Dental disease
- Hypoxemia
- Hypo/hyperthyroidism
- Pancreatitis
    - Can cause extrahepatic biliary duct obstruction
- Heart failure, hepatic congestion

In dogs with a hepatocellular hepatopathy what are some of your ddx?

- Hepatic
    - Chronic hepatitis
        - Immune-mediated
        - Copper-associated
    - Vascular anomaly
    - Neoplasia
    - Toxic
- Reactive hepatopathy
    - GI disease *most common
    - Dental disease
    - Hypoxemia
    - Endocrine disease

In dogs with a cholestatic hepatopathy what are some of your ddx?

- Hepatic
    - Benign nodular hyperplasia
    - Vacuolar hepatopathy
        - Idiopathic (Scottish Terrier)

        - Hepatocutansous syndrome
    - Endocrine/Metabolic disease
        - Hypothyroidism (mild mixed)
        - Hypercortisolism (cholestasis)
        - Diabetes Mellitus (mixed but predominantly cholestatic)
        - Hyperlipidemia
    - Hepatocellular carcinoma/adenoma
    - Leptospirosis (liver and renal injury)
- Biliary
    - Bacterial cholangitis / cholangiohepatitis
    - Gall bladder mucocele
    - Cholelithiasis
    - Pancreatitis
    - Biliary/pancreatic neoplasia
    - Stricture
    - Ductal plate malformation

Differentials for Hepatopathy – Cat

- Hepatic
    - Endocrine/metabolic disease
        - Hyperthyroidism (mild to moderate mixed, often hepatocellular)
        - Diabetes mellitus (could have a mild hepatopathy)
        - Hyperlipidemia
    - Hepatic lipidosis
    - Biliary cystadenoma or neoplasia
    - FIP
    - Toxoplasmosis
    - Less commonly
        - Vascular
        - Toxic
- Biliary
    - Non-suppurative cholangitis/cholangiohepatitis syndrome
    - Suppurative cholangitis/cholangiohepatitis syndrome
    - Liver flukes
    - Pancreatitis, triaditis (Liver, Pancreas, Intestines)
    - Biliary/pancreatic neoplasia
    - Cholelithiasis
    - Stricture
    - Ductal plate malformation

Diagnostic Evaluation of Liver Disease

- Imaging
    - Abdominal Ultrasound
    - CT scan
    - Technetium Scan
- Sampling the liver
    - Evaluate coagulation before sampling!!
    - Liver FNA
    - Liver biopsy

Abdominal Ultrasound findings associated with Liver Disease

- Marked dilation of extrahepatic and intrahepatic bile ducts
- Hyperechoic biliary material/debris
- Cholecystic debris, thickened GB wall
- Normal pancreas

Liver II: Hepatic Disease in Cats

Hepatic lipidosis

- Primary
    - Decreased food intake or availability
    - Secondary (50-95% of cases)
        - Underlying disease
- Pathophysiology
    - Anorexia or negative energy balance leading to lipidosis and free fatty acid influx into the liver
    - Obesity or stress leading to insulin resistance and increased free fatty acids
    - Causes intrahepatic cholestasis
- Diagnosis
    - Signalment and history
    - PE: Icterus, possibly obtunded
    - ALP>GGT, hyperbilirubinemia
        - +/- hepatocellular enzymopathy
        - +/- other abnormal liver function parameters
    - Hyperechoic, enlarged liver on AUS
    - Liver FNA – vacuolar hepatopathy
- Treatment

- Nutrition!
  - Feeding tube preferred
  - Start with ¼ RER split over 4 feedings, increase daily until RER is met
  - Diet: Recovery or GI diet
- Treat underlying condition
- Unknown efficacy of supplements
  - SAMe, Ursodiol, Vitamin B12, Taurine, Arginine, L-carnitine, Omega 3's
- Vitamin K if coagulopathy: 0.5 to 1.15mg/kg SQ q12 for 3-4 doses
- Lactulose if hepatic encephalopathy
- Prognosis: better if primary

Feline (Biliary)

- Cholangitis / Cholangiohepatitis
  - Neutrophilic/suppurative
  - Lymphocytic/non-suppurative
  - Fluke-associated
  - Destructive cholangitis

Clinical signs

- Hyporexia to anorexia, GI signs
- Fever
  - More likely with neutrophilic
- Abdominal pain
- Icterus
- CBC
  - Possibly a neutropenia and left shift with NC
- Chemistry
  - Hepatopathy (mixed, GGT typically increased) hyperbilirubinemia
  - Possible hyperglobulinemia
- AUS
  - GB and or biliary wall thickening, debris, duct dilation, hyperechoic normal size or enlarged liver
    - Ascites can occur with lymphocytic cholangitis

Neutrophilic (suppurative) Cholangitis/Cholangiohepatitis

- Bacterial etiology
  - E. coli, enterococcus, clostridium
  - Ascending

    - Translocation from GI
- AUS to evaluate GB, biliary tract
    - Underlying obstruction
    - Concurrent enteropathy, pancreatitis, or triaditis
- Diagnosis
    - Cholecystocentesis (US guided or intra-operative) for bile cytology and culture
    - +/- liver biopsy to demonstrate neutrophilic inflammation
- Treatment
    - Antimicrobials for 4-6 weeks
    - Treat underlying obstruction or enteropathy

Lymphocytic/Non-suppurative Cholangitis/Cholangiohepatitis

- Suspect immune-mediated cause
- AUS
- Diagnosis
    - Liver biopsy: Lymphocytic inflammation +/- fibrosis/cirrhosis, ductopenia
    - Cholecystocentesis (U/S guided or intra-operative)
- Treatment
    - Prednisolone (1-2mg/kg/day) or chlorambucil (2mg ever 48hrs)
    - Ursodeoxycholic acid for bile flow
- Prognosis
    - Variable, worse compared to neutrophilic cholangitis

Triaditis

- Cats with cholangitis can commonly have concurrent enteritis, pancreatitis, or both
- Hypothesis
    - Enteropathy leads to dysbiosis and GI translocation or extension of inflammation
- Need to consider concurrent disorders when formulating a treatment plan

Cholelithiasis

- Bilirubin
    - Secondary to infection (likely E. coli)
- Calcium carbonate

Hepatic / Biliary Neoplasia

- Lymphoma
- Bile duct adenoma/cystadenomas
    - Well circumscribed, often cystic
    - No clinical signs unless large and compressive
- Bile duct adenocarcinoma/cholangiocarcinoma
    - Highly malignant
- Mast cell neoplasia
- Solitary hepatic tumors are uncommon
    - Adenoma
    - Carcinoma
    - Neuroendocrine tumors
    - Hemangiosarcoma

Canine Hepatic Disorders

Common Hepatic Disorders in Dogs

- Chronic hepatitis
    - Immune-mediated chronic hepatitis
    - Copper-associated chronic hepatitis
- Portosystemic shunts
    - Portal venous hypoplasia
- Hepatic neoplasia
    - Lymphoma
    - Hepatocellular carcinoma
    - Histiocytic Sarcoma
    - Hemangiosarcoma

Etiologies of Chronic Hepatitis

- Immune-mediated (~66%)
- Copper-associated (~ 33%)
- Infectious
    - Leptospirosis
    - Leishmania
    - Mycobacteria
    - Histoplasma
    - Protozoa (Neospora, Toxoplasma)

- Drugs/Toxins
    - Doxycycline
    - Phenobarbital
    - Carprofen

Immune-mediate and Copper-associated Chronic Hepatitis

- Immune-mediated: Presumed autoimmune disorder
- Copper-associated chronic hepatitis: excessive copper accumulation in the liver
    - Genetics
        - Bedlington terrier: COMMD1 gene
        - Labrador retriever: ATP7B mutation
    - Diet
        - Increase copper content and bioavailability linked to an increase prevalence
        - Copper concentration in dog foods often exceeds AAFCO minimum by 2-4x!

Clinical Features of Chronic Hepatitis

- Signalment
    - Age can vary, middle age to older is more common
- Breeds
    - Immune: Labrador retriever, Doberman, Standard Poodle
    - Copper: Labrador, Doberman, WHWT, Dalmatian, Bedlington terrier
- 25% are subclinical, signs develop later
- PE: Icterus, Ascites
- CBC: +/- anemia, +/- thrombocytopenia
- Chemistry
    - Hepatocellular hepatopathy to mixed
    - Hyperbilirubinemia (50%), hypoalbuminemia or other abnormal liver function parameters

Work-up to Diagnose Chronic Hepatitis

- Abdominal Ultrasound
- +/- Liver FNA
- Liver Biopsy
    - Laparoscopy or laparotomy
    - Evaluate risk of bleeding prior to this! (Run a coagulation panel)
- Obtain > 5 liver biopsies from > 2 liver lobes!

- Histopathology (3 biopsies)
- Aerobic and anerobic culture (1 lobe)
- Copper quantification (1-2 lobes): need 10mg of liver dry weight

Histology

Overview

- Portal infiltration of mononuclear cells to mixed inflammation
- Hepatocyte cell death (apoptosis or necrosis)
- +/- Fibrosis
- +/- Nodular regeneration

Immune-Mediated Chronic Hepatitis

- Features of chronic hepatitis (above)
- Interface hepatitis
  - Portal inflammation extending past the limiting plate into the hepatic parenchyma
  - +/- hepatocyte cell death at the limiting plate

Copper-Associated Chronic Hepatitis

- Features of chronic hepatitis (above)
- Histochemical staining of copper (rhodanine stain)
  - Copper granulomas
  - Centrilobular accumulation (panlobular)
- Quantification of hepatic copper
  - Digital image analysis of rhodamine stained sections

Treatment

Immune-Mediated Chronic Hepatitis

- Immunosuppression
  - Cyclosporine: 5mg/kg BID (freeze to reduce GI effects, monitor for gingival hyperplasia)
  - Prednisone: Attempt to taper or avoid due to the adverse effects
  - Mycophenolate
- GI protectants

    - Omeprazole only if GI hemorrhage is observed
- Copper-restricted diet if hepatic copper is elevated
- Antioxidants (Denamarin Advanced)
- Ursodeoxycholic acid
- Treat hepatic encephalopathy and ascites if present

Copper-Associated Chronic Hepatitis

- Dietary copper restriction if Cu is >600 ppm
- Copper chelation (guideline says to do this when Cu is > 1000 ppm)
    - D-penicillamine: Giving with food decreased the absorption but improves GI signs
        - 10 mg/kg BID or lower
    - Trientine (Syprine)
- Zinc
    - Zn gluconate on an empty stomach
    - Mechanism: outcompetes Cu, induces metallothionein
    - Maintenance tx do not give with a chelator
- Hepatoprotectants
    - Anti-oxidants (Denamarin Advanced)
    - Vitamin E

Portosystemic Shunts

- Portal blood bypassing the liver
- Congenital: Single connections between portal and caudal vena cava/azygous
    - Small breeds: Extrahepatic
    - Large breeds: Intrahepatic
- Acquired: Multiple, secondary to portal hypertension

Clinical Features

- Signalment
- Signs: lethargic, poor growth, HE, GI signs, Urinary signs (cystoliths)
- CBC: Monocytosis
- Chemistry Panel
    - Mild to moderate hepatocellular to mixed hepatopathy
    - Hypoalbuminemia
    - Low BUN

    - Hypocholesterolemia
    - Hypoglycemia
    - Uncommon to have hyperbilirubinemia
- Urinalysis
    - Decreased USG
    - Ammonium biurate crystalluria

Diagnosis

- Bile acids > 30 umol/L
- Ammonia > 59 umol/L
- Protein C < 70%
- Abdominal Ultrasound
    - Locate shunt vessel
    - Microhepatica, renomegaly, cystolithiasis
- CT scan
- Hepatic scintigraphy
    - Transplenic > per-rectal
- Exploratory laparotomy

Treatment

- Surgical correction
    - Ameroid constrictor or cellophane band
    - Risk: portal hypertension or post-attenuation neurologic signs
- Medical management
    - Protein restricted diet
    - Lactulose (0.25mL/kg PO q8-12h)
    - +/- Antimicrobials (amoxicillin)

Portal Vein Hypoplasia

- Most are subclinical
- Mild to moderate hepatopathy, elevated serum bile acids
- No abnormalities in liver function
- Diagnosis
    - No macroscopic vascular shunt
    - Histology: small to absent portal veins, atrophy of hepatocytes, possibly plump arterioles
- Treatment: none, +/- Denamarin?
- Long term prognosis is good for most