

Liver Failure

References:

DeNovo RC, Chapter 5, "Diseases of the Stomach," in Todd R Tams *Small Animal Gastroenterology, 2nd Edition*.

Richter KP, Chapter 9, "Diseases of the Liver and Hepatobiliary System," in Todd R Tams *Small Animal Gastroenterology, 2nd Edition*.

I. Etiopathogenesis:

A. Etiology:

1. DDx hepatic icterus in dogs and cats.
 - a. Metabolic. (reactive hepatopathy)
 - 1) Portal inflammation/toxicity.
 - i. Inflammatory bowel disease.
 - ii. Bacterial enteritis.
 - iii. Viral enteritis.
 - iv. Pancreatitis.
 - v. Splenitis.
 - 2) Systemic inflammation/toxicity
 - i. Sepsis.
 - ii. Pancreatitis.
 - iii. Systemic hypoxia.
 - iv. Anemia.
 - v. Ischemic injury.
 - vi. Caval syndrome.
 - 3) hepatic lipidoses – causes:
 - i. Prolonged overeating.
 - ii. Starvation.
 - iii. Obesity.
 - iv. Protein deficiency (particularly carnitine).
 - v. Diabetes mellitus.
 - vi. Bacterial endotoxins.
 - vii. Hypoxic injury.
 - viii. Often concurrent:
 - i. Pancreatitis.
 - ii. IBD.
 - iii. Cholangiohepatitis.
 - b. Infectious.
 - 1) Infectious Canine Hepatitis - acute or chronic.
 - 2) Leptospirosis – acute or chronic
 - 3) Fungal.
 - i. Histoplasmosis.
 - ii. Blastomycosis.
 - iii. Coccidiomycosis.
 - 4) Parasites.
 - i. *Platynosomum*.
 - ii. *Heterobilharzia*.

- iii. *Cyrtosporidium*.
- iv. *Opisthorchis*.
- v. *Amphimerus*.
- vi. *Metorchis*.
- vii. *Clonorchis*.

c. Inflammatory.

- 1) One of the most common forms of liver disease.
- 2) Divided into:
 - i. Primary hepatic inflammation.
 - ii. Hepatopathy secondary to systemic inflammatory disease or “leaky gut.”
- 3) Chronic active hepatitis of dogs.
 - i. Copper storage disease.
 - ii. Breed related immune mediated disease (Doberman, West Highland White).
 - iii. Previous infection with Infectious Canine Hepatitis.
 - iv. Auto-immune response to damaged hepatocytes.
- 4) Feline cholangitis/cholangiohepatitis complex.
- 5) Acute hepatic necrosis.
 - i. Hepatotoxins (see below).
 - ii. Septicemia.
 - iii. Pancreatitis.
 - iv. IBD.
 - v. Infectious Canine Hepatitis.
 - vi. Hypoxia.
 - vii. Ischemia.
 - viii. SIRS.

d. Toxic hepatopathy.

- 1) Drugs.
 - i. Acetaminophen.
 - ii. Anabolic steroids.
 - iii. Anticonvulsants.
 - iv. Antineoplastics (CCNU, methotrexate, L-asparaginase)
 - v. Arsenicals.
 - vi. Carprofen.
 - vii. Diazepam.
 - viii. Diethylcarbamazine.
 - ix. Griseofulvin.
 - x. Itraconazole.
 - xi. Ketoconazole.
 - xii. Oxabendazole.
 - xiii. Mebendazole.
 - xiv. Mitotane.
 - xv. Sulfonamides.
 - xvi. Thiabendazole.
 - xvii. Trimethoprim-Sulfa.
- 2) Aflatoxins.
- 3) Copper storage disease.
- 4) Saw palmetto.
- 5) Mushrooms.

a. Portosystemic shunt.

- 1) Congenital
- 2) Acquired – chronic portal hypertension.

2. DDx post-hepatic icterus in dogs and cats (in order of frequency):
 - a. Pancreatitis.
 - b. Pancreatic neoplasia.
 - c. Other neoplasm putting pressure on the common bile duct (lymphoma, intestinal neoplasia, etc.).
 - d. Bile duct carcinoma.
 - e. Inspissated bile plugs.
 - f. Cyst, abscess or granuloma putting pressure on the common bile duct.
 - g. Cholelithiasis.
 - h. Choledocholithiasis.
 - i. Cholecystitis.
 - j. Duodenal foreign body.
 - k. Parasite migration.

B. Pathogenesis:

1. Bilirubin Metabolism:
 - a. Kupffer cells (macrophages) in the liver phagocytize senescent RBCs, and release free hemoglobin into circulation.
 - b. Protein bound hemoglobin is again phagocytized by Kupffer cells.
 - c. Enzyme heme oxygenase in liver cells converts hemoglobin to biliverdin.
 - d. Biliverdin reductase converts biliverdin to lipid soluble free bilirubin, which is released into circulation.
 - e. Lipid soluble free bilirubin is bound to albumin to form unconjugated or indirect bilirubin.
 - 1) unconjugated bilirubin is usually not found in the urine, unless there is significant glomerular disease
 - f. Indirect bilirubin is taken up again by hepatocytes, where it is conjugated (mainly by glucuronide) to direct bilirubin.
 - 1) Conjugated bilirubin is freely filtered into urine.
 - 2) The dog has a low threshold for conjugated bilirubin excretion, so that bilirubinuria increases before plasma bilirubin increases.
 - 3) The cat has a higher renal threshold for bilirubin excretion.
 - g. Direct bilirubin is secreted into bile, stored in the gall bladder, and expressed into the gut.
 - h. Delta bilirubin is albumin-bound conjugated bilirubin.
 - 1) It can become elevated with cholestatic disease.
 - 2) It does not appear in the urine
 - 3) It does not have significant hepatic uptake.
 - 4) Its half life is that of albumin – about 14 days.
 - 5) Delta bilirubin is the reason that liver failure patients often remain for days to a week after they seemed to have recovered from liver failure and/or biliary obstruction.
2. Bile Acid Metabolism:
 - a. Bile contains:
 - 1) Bile acids (bile salts) – enterophepatic circulation.
 - i. These are most abundant (75% of solids).
 - ii. They are a product of cholesterol metabolism.
 - iii. Secreted into the bile canaliculi by hepatocytes.
 - iv. Feeding stimulates bile acid secretion into the intestines, which in turn stimulates release of pancreatic enzymes.
 - v. Small intestinal bacteria deconjugate and dehydroxylate bile acids.

- vi. Unaltered and metabolized bile acids are passively and actively absorbed from the ileum into portal circulation.
 - vii. Bile acids are removed by hepatocytes from circulation, reconstituted if necessary, and resecreted in bile.
 - hepatocytes have a large excess capacity for this
 - during a typical meal, the entire bile acid pool is recirculated 2-3x by enterohepatic circulation.
 - viii. Very small amounts of bile acids are lost in the feces.
 - ix. Enterohepatic circulation is so efficient that only minimal hepatocellular production of bile acids is required.
- 2) Bile pigments (primarily bilirubin).
 - 3) Cholesterol.
 - 4) Phospholipids.
 - 5) Hepatic enzymes (such as GGT and SAP).
3. Albumin metabolism:
 - a. Albumin makes up 25% of the protein produced by the liver.
 - b. Other proteins usually decrease before albumin production is decreased.
 4. Carbohydrate metabolism.
 - a. Stores glucose in the liver for future use as glycogen.
 - b. Releases glucose into the bloodstream as needed by glycogenolysis and gluconeogenesis (the latter from proteins and amino acids).
 - c. Gluconeogenesis result in muscle wasting and increase ammonia levels.
 5. Drug and hormone metabolism.
 - a. Hepatic microsomal enzymes metabolize many drugs and hormones.
 - b. Liver failure can result in delayed clearance of drugs and hormones.
 - c. Drugs that are highly protein bound can have potentiated biologic effects due to low albumin and other protein levels.
 - d. Hormones cleared by the liver:
 - 1) Cortisol.
 - 2) Estrogens.
 - 3) Androgens.
 - 4) Progesterones.
 - 5) Insulin.
 - 6) Glucagon.
 - 7) Thyroxine.
 - 8) Pituitary hormones.
 - 9) Gastrin.
 - 10) Aldosterone.
 - e. Drugs cleared by the liver are probably too numerous to list here.
 6. The liver and coagulation.
 - a. The liver makes coagulation factors
 - 1) I
 - 2) II
 - 3) V
 - 4) VII
 - 5) IX
 - 6) X
 - b. The liver synthesizes, catabolizes and clears other components of the coagulation system.

- 1) AT3 – made by the liver
 - 2) FDPs – cleared by the liver; FDPs are not only products of excessive fibrinolysis caused by liver failure, but are also anticoagulant per se, potentially worsening coagulopathy due to liver disease.
 - 3) Plasminogen activators – cleared by the liver
 - c. The liver also makes activators and inhibitors of fibrinolysis.
 - 1) Antiplasmins
 - d. Bile acids are necessary for vitamin K absorption.
 - 1) Chronic biliary obstruction can impair vitamin K absorption.
 - 2) Vitamin K is necessary for production of factors 2, 7, 9 and 10.
 - 3) Long term antibiotic therapy is common with liver disease, and can impair bacterial vitamin K synthesis.
 - e. Fulminant hepatic necrosis can release tissue thromboplastin.
 - f. Liver failure can alter platelet function.
7. Hepatic Reticuloendothelial System (RES).
- a. RES removes from blood:
 - 1) Toxins.
 - 2) Foreign substances.
 - 3) Cellular debris.
 - 4) Microbes.
 - 5) Drugs.
 - 6) Endotoxins.
 - 7) Antigens.
 - b. Liver is one of the most important RES organs, as it has sole responsibility for detoxifying the blood from the gut and other organs in portal circulation, before blood moves on to systemic circulation.
 - c. Liver failure or shunting can result in failure of RES.
 - d. Failure of hepatic RES can result in:
 - 1) Sepsis.
 - 2) Endotoxemia.
 - 3) Chronic bacterial hepatitis.
8. Hepatic icterus:
- a. Abnormal hepatic uptake of unconjugated bilirubin
 - b. Abnormal bilirubin conjugation
 - c. Abnormal secretion of conjugated bilirubin into bile
 - d. Impairment of bile flow through bile canaliculi due to hepatocellular swelling, inflammation or fibrosis.
 - e. Lysosomal enzymes released from damaged hepatocytes can deconjugate bilirubin.
 - f. Inflammatory cells invading the liver can deconjugate bilirubin.
 - g. Since any or all of the above can occur simultaneously with hepatocellular disease, ratios of direct to indirect bilirubin are seldom clinically significant.
9. Post-hepatic icterus – conjugated bilirubin is regurgitated into circulation from the biliary tract.
- a. Intrahepatic biliary obstruction
 - b. Extrahepatic biliary obstruction
 - c. Unconjugated bilirubin is usually also elevated with post-hepatic icterus because:
 - 1) Post-hepatic icterus is usually accompanied by secondary hepatic disease due to cholestasis.
 - 2) Inflammatory cells in the liver can deconjugate bilirubin.

- 3) Conjugated bilirubin competes with unconjugated in circulation for hepatic reuptake
2. GI hemorrhage.
 - a. Decreased hepatic clearance of gastrin.
 - b. Increased bile acids stimulate increased gastric acid production.
 - c. DIC can decrease the ability of the GI tract to withstand injury.
 - d. Treatment with prednisone can exacerbate GI ulceration.
 - e. GI hemorrhage can exacerbate hepatic encephalopathy (HE), because blood is a substrate for ammonia production in the colon.
 - f. A large GI bleed can deplete platelets and factors, and cause further bleeding elsewhere.
 3. DIC
 - a. Liver failure causes decreased antipiasmin and AT3 synthesis .
 - b. Liver failure causes decreased clearance of activated clotting factors and plasminogen activator.
 - c. Severe disease can induce SIRS.
 - d. More common with acute liver failure than chronic liver failure.
 4. Hepatic Encephalopathy (HE): abnormal mental status in patients with severe hepatic insufficiency.
 - a. Can be cause by liver insufficiency per se, or shunting (congenital or acquired) of portal blood around the liver.
 - b. Encephalopathic toxins (synergistic):
 - 1) Ammonia.
 - a) Colonic bacteria (gram negatives and to a lesser degree anaerobes) convert proteins and other nitrogenous products to ammonia.
 - b) Ammonia is absorbed into portal circulation.
 - c) The liver normally detoxifies ammonia by forming urea.
 - d) Can be exacerbated by GI hemorrhage, as blood is a substrate for ammonia production in the colon.
 - 2) Benzodiazepine-like substances
 - 3) Amino acids.
 - 4) Mercaptans.
 - 5) Fatty acids.
 - c. Other factors that contribute to HE:
 - 1) Changes in blood-brain barrier due to SIRS.
 - 2) Abnormal neurotransmitter balance.
 - 3) Abnormal cerebral metabolism.
 - 4) Metabolic abnormalities.
 - a) Azotemia (uremic encephalopathy).
 - b) Hypoxia (due to anemia).
 - c) Electrolyte imbalances (due to anorexia, vomiting, diarrhea).
 - d) Hypoglycemia due to liver failure.
 - e) Tranquilization due to antiseizure medications.
 - f) Alkalosis due to liver failure.
 - g) Hypovolemia due to adipsia.
 - d. Severity of HE does not always seem to correlate with apparent severity of liver pathology.
 - e. Factors that can precipitate HE.
 - 1) Increased protein intake.
 - 2) GI hemorrhage.
 - 3) Diuretics.

- 4) Barbiturates or other sedatives.
- 5) Uremia.
- 6) Infection or Endotoxemia.
- 7) Constipation.
- 8) GI bacterial overgrowth.
- 9) Methionine.

5. Ascites

a. Caused by:

- 1) First - -increased renal salt and water retention caused by chronic liver disease.
 - a) Increased sensitivity to aldosterone.
 - b) Failure to release or respond to natriuretic hormone, in response to expanded plasma volume.
 - c) Normal negative feedback for the renin-angiotensin-aldosterone system is not effective, because high aldosterone levels do not return effective plasma volume to normal in the presence of ascites, despite sodium retention.
- 2) Chronic portal hypertension.
 - a) Fibrosis (cirrhosis) causes increased resistance in hepatic sinusoids.
 - b) Hepatocellular swelling can also cause similar increased resistance in the sinusoids.
 - c) Increased hepatic blood flow during acute hepatitis can also contribute.
 - d) Acquired PSS can occur in response to chronic portal hypertension.
- 3) Hypoalbuminemia.
 - a) Ascites increases volume of distribution for albumin, thus further decreasing albumin.
 - b) This lowers plasma oncotic pressure, further contributing to ascites.
 - c) When hypoalbuminemia is a sole cause of ascites, albumin must be lower than 1.5 g/dl, and is usually accompanied by peripheral edema.

6. Chronic Active Hepatitis.

- a. Inflammation starts at the portal triads.
- b. Then extends into the hepatic lobule.
- c. Eventually results in necrosis and bridging fibrosis between adjacent portal areas.
- d. Predominantly mononuclear inflammation.
- e. Bile duct hyperplasia and cholestasis.
- f. Nodular hyperplasia occurs.
- g. Secondary copper accumulation can occur due to cholestasis, and can accelerate further disease.

7. Feline Cholangitis/Cholangiohepatitis Complex.

a. Forms:

- 1) Lymphocytic-plasmacytic.
- 2) Suppurative chronic bacterial etiology is suspected.
- 3) Lymphocytic.
- 4) Biliary cirrhosis (end stage).
- 5) Eosinophilic – immune mediated or parasitic.

- b. Concurrent diseases:
 - 1) Pancreatitis.
 - 2) IBD.
 - 3) Bile duct obstruction.
 - 4) Systemic infection.
 - 5) Cholelithiasis.
 - c. Portal triad fibrosis.
 - d. Bile duct proliferation.
 - e. Cholestasis.
 - f. Nodular regeneration.
8. Copper storage disease.
- a. Copper accumulation in the liver is toxic to hepatocytes.
 - b. Copper is eliminated in the bile, so can accumulate in any animal with cholestatic disease.
 - c. Massive release of copper from damaged hepatocytes which have accumulated it in the lysosomes can result in a hemolytic crisis.
 - d. Dobermans with chronic active hepatitis often have high liver copper, but not usually Westies.
 - e. Three types in Bedlingtons:
 - 1) Severe disease in young dogs – dismal prognosis.
 - 2) Middle aged with insidious onset to end stage liver.
 - 3) Asymptomatic.
9. Portosystemic shunt.
- a. Other names:
 - 1) Portal vascular anomalies.
 - 2) Portacaval shunts.
 - 3) Portosystemic vascular anastomoses.
 - b. Two types of pathogenesis .
 - 1) Congenital.
 - i. Patent ductus venosus.
 - With hypoplastic portal system.
 - Without hypoplastic portal system.
 - ii. Single porto-caval vessel.
 - iii. Portal vein atresia, with secondary multiple shunts.
 - iv. Single porto-azygous shunt.
 - v. Porto-azygous shunt with discontinuation of pre-renal caudal vena cava/
 - vi. Left gastric vein to caudal vena cava.
 - vii. Intrahepatic arterovenous (AV) fistula
 - viii. HMD – hepatic microvascular dysplasia.
 - ix. Portal veins are hypoplastic.
 - x. All of the portal venules are dilated, and do some shunting.
 - xi. Also called macroscopic shunt NEW NAME.
 - 3) Acquired
 - i. Due to chronic portal hypertension.
 - ii. Elevated portal pressures lead to opening of the fetal veins that bypassed the liver
 - iii. Multiple extrahepatic shunts
 - iv. Tortuous.
 - v. Variable in location
 - vi. Causes of portal hypertension
 - i. Cirrhosis
 - ii. Fibrosis

- d. As the shunting is established, further liver atrophy occurs due to lack of hepatotrophic factors from the gut, spleen and pancreas.
 - 1) Glucagon.
 - 2) Insulin.
- e. Histopath of PSS:
 - 1) Hepatic atrophy – close proximity of portal triads, compressed hepatic cords, inconspicuous portal veins.
 - 2) Lobular collapse.
 - 3) Proliferation of small hepatic arterioles “reduplication.”
- f. Histopath of HMD:
 - 1) Small Intrahepatic portal vessels.
 - 2) Portal endothelial hyperplasia.
 - 3) Portal vein dilation.
 - 4) Random juvenile intralobular vessels.
 - 5) Central venous mural hypertrophy and fibrosis.

II. Epidemiology/Signalment

A. Breed.

1. Bedlington terrier (copper storage disease and associated chronic active hepatitis) – autosomal recessive.
2. West Highland white terrier (chronic active hepatitis).
3. Doberman pinscher (chronic active hepatitis).
4. Skye terrier (chronic active hepatitis).
5. Scottish terriers – high liver enzymes with seemingly no liver pathology.
6. Yearly bloodwork even in young dogs is very important in these breeds (catching chronic active hepatitis early is key to being able to treat it).
7. Congenital Intrahepatic shunts – large breed dogs.
 - a. Doberman.
 - b. Golden retriever.
 - c. Labrador retriever.
 - d. Irish setter Samoyed.
 - e. Irish Wolfhound,
8. Congenital extrahepatic shunts – small breed dogs.
 - a. Miniature schnauzer.
 - b. Yorkshire terrier.
 - c. Miniature Poodle.
 - d. Dachshund.
9. Only 2% of PSS in small animals occur in cats.
10. HMD.
 - a. Yorkshire terrier.
 - b. Cairn terrier.

B. Sex.

1. Female – chronic active hepatitis.
2. Male – feline suppurative cholangiohepatitis.

C. Age.

1. Intrahepatic PSS in large breed dogs show signs younger than:
2. Extrahepatic PSS in small breed dogs.
3. PSS usually diagnosed prior to 1-2 years of age, but mild cases can be founding advanced age.

III. History – often vague and non-specific.

- A. Hematemesis, melena, hematochezia, ecchymoses, petechiae.
- B. Pale (acholic) feces.
- C. Jaundice or dark (orange, red, brown) urine.
 - 1. Rare with PSS.
- D. Signs of hepatic encephalopathy – especially 1-3 hours after a meal.
 - 1. Anorexia and lethargy in its mildest form.
 - 2. May progress to weight loss.
 - 3. Ataxia.
 - 4. Confusion, stupor, decreased responsiveness, loss of training – most common sign of HE).
 - 5. Pacing and wandering.
 - 6. Twitching to seizures.
 - 7. Vomiting, diarrhea.
 - 8. PU-PD.
 - 9. Temporary blindness.
 - 10. Severe dementia, seizures and coma in its most severe form.
 - 11. Neurological signs can often not be localized by neurologic exam.
- E. Enlarging abdomen (may be interpreted by owner as weight gain).
- F. PU-PD.
- G. Weight loss, anorexia.
- H. History of known exposure to hepatotoxins:
 - 1. Corticosteroids.
 - 2. Anticonvulsants.
 - 3. Mebendazole, oxbendazole.
 - 4. Acetaminophen.
 - 5. Mushrooms.
 - 6. Sago palm (especially the seeds).
- I. It is not uncommon for pets with very severe liver disease to have an apparently acute presentation.
- J. Abdominal pain if bacterial hepatitis.
- K. Signs of PSS in young dogs:
 - 1. Chronic lethargy.
 - 2. Retarded growth.
 - 3. Weight loss.
 - 4. “Didn’t do well” for days to weeks after being spayed or neutered.
 - 5. Poor doer.
 - 6. Signs of liver failure.
 - 7. Hepatic encephalopathy.
- L. Cats with PSS
 - 1. Salivation.
 - 2. Hepatic encephalopathy.
 - 3. GI signs.

IV. Physical Exam

A. Icterus

- 1. Total bilirubin above 0.6-0.8 mg/dl can result in bilirubinuria.
- 2. Total bilirubin usually has to be above 1.0 mg/dl to cause icterus of serum.
- 3. Total bilirubin usually must be above 2-3 mg/dl in order to see icterus on exam.
- 4. Icterus can appear at lower bilirubin if most of the bilirubin is conjugated due to cholestasis.

5. Can see icterus best at:
 - a. sclerae.
 - b. Penile mucosa.
 - c. Soft palate.
 - d. Under the tongue.
6. Common with chronic active hepatitis and feline cholangiohepatitis.

B. Bleeding.

1. Spontaneous bleeding of liver failure patients is unusual, with the exception of GI hemorrhage.
2. Excessive bleeding following surgical procedures, or even liver aspiration or venipuncture does happen with some regularity.
3. Petechiae, bruising, or bleeding into cavities may indicate severe disease.

C. **Neurologic abnormalities** (see History for HE above) – due to HE or hypoglycemia.

D. **Ascites** – fluid wave balloted in abdomen.

E. **Enlarged liver** on abdominal palpation if acute liver failure.

F. **Pale (acholic) feces.**

G. **Fever** – common with feline cholangiohepatitis.

V. Diagnosis

A. CBC

1. Schistocytosis if DIC.
2. Thrombocytopenia
 - a. Patients with hepatic failure are prone to DIC.
 - b. Consumption can occur due to coagulopathy and bleeding.

B. Serology:

1. Increased liver enzymes – indicate breach of integrity of hepatocytes and/or the biliary tract, rather than indicating hepatic dysfunction.
 - a. Hepatocellular enzymes – ALT (formerly SGPT) and ADT (formerly SGOT)
 - 1) ALT found only in the cytoplasm of the hepatocyte.
 - 2) AST is not as specific for liver – also contained in RBC and muscle. When AST is significantly higher than ALT, hemolysis and muscle disease should be considered.
 - 3) ALT is highest with:
 - i. Chronic active hepatitis.
 - ii. Primary hepatic neoplasia.
 - iii. Hepatic necrosis.
 - 4) Can be normal with chronic disease (lack of active hepatocellular injury) and/or severe reduction of hepatic mass.
 - i. Steroid hepatopathy
 - ii. Metastatic neoplasia.
 - iii. PSS.
 - iv. Cirrhosis.
 - v. Pancreatitis in cats.

- vi. Hepatic lymphosarcoma in casts.
 - vii. FIP.
- 5) Extrahepatic causes of hepatocellular damage (reactive hepatopathy) and increased ALT.
- i. Severe muscle disease.
 - ii. Hypoxia (heart failure, respiratory disease, severe anemia, etc).
 - iii. Cholestatic disease.
 - iv. Inflammatory disease in organs drained by portal circulation (gut, pancreas, spleen, etc).
- b. Bile epithelium enzymes - SAP/ALP and GGT.
- 1) More sensitive indicator of cholestasis than bilirubin.
 - 2) Periportal pathology is more likely to increase SAP and GGT than centrilobular.
 - 3) SAP isoenzymes is found in:
 - i. Bile epithelium– half life is 3 days in the dog.
 - ii. drug-induced isoenzyme.
 - i. Does not necessarily indicate hepatic damage – this isoenzyme is induced by corticosteroids.
 - ii. Stays high for weeks to months after drug administration.
 - iii. There are assays that distinguish between bile and drug-induced isoenzymes, but their results do not reliably distinguish hepatic significant disease from corticosteroid induction.
 - iv. Drugs that can induce SAP:
 - corticosteroids.
 - barbiturates (can also cause hepatotoxicity).
 - iii. Bone – increases with osteoblastic activity.
 - growing animals.
 - bone neoplasia.
 - osteomalacia.
 - hyperparathyroidism.
 - iv. Gut.
 - v. Placenta.
 - vi. Kidney.
 - 4) Bile and bone are most clinically significant, because half life of SAP from other organs is only minutes.
 - 5) Half life of Biliary SAP is 3 days in dogs and 6 hours in cats.
 - 6) Can be normal in:
 - i. Feline cholangiohepatitis.
 - ii. Metastatic neoplasia.
 - iii. PSS.
 - iv. Cirrhosis.
 - 7) Most common causes of SAP elevation in cats:
 - i. LSA.
 - ii. Cholangiohepatitis.
 - iii. Biliary obstruction (including pancreatitis).
 - iv. Hyperthyroidism.
 - 8) SAP elevation is usually more likely to be clinically significant in cats when compared to dogs.
 - i. SAP half life is much shorter in the cat (6 hours as opposed to 3 days).
 - ii. Less feline SAP is produced secondary to biliary obstruction as compared to the dog, because the feline

liver contains 1/3 the SAP per gram when compared to the canine liver.

- 9) GGT isoenzymes are in:
 - i. Liver – the only one with half life long enough to be clinically significant.
 - ii. Kidney.
 - iii. Pancreas,
 - iv. Intestine.
 - 10) GGT may increase earlier than SAP in cholestatic disease.
 - 11) Marked GGT increase with corticosteroid enzyme induction.
 - 12) GGT in cats has higher sensitivity but lower specificity for biliary disease.
 - 13) GGT in dogs is less sensitive but more specific than SAP for biliary disease.
 - 14) Only in hepatic lipidosis does SAP elevation significantly exceed GGT elevation.
2. High or low glucose.
 - a. Fasting hypoglycemia.
 - 1) Loss of 70% of hepatic mass results in inadequate glycogen storage and gluconeogenesis.
 - 2) Congenital hepatic glycogen storage disease can accompany PSS, and is present in some toy breeds.
 - b. Post-prandial hyperglycemia.
 - 1) Deficiency of hepatic enzymes necessary to metabolize carbohydrates from a meal (inadequate glycogenesis).
 - 2) Decreased hepatic clearance of glucocorticoids.
 3. Low albumin.
 - a. Due to decreased hepatocellular synthesis
 - b. Because ammonia inhibits release of albumin from hepatocytes.
 - c. Because abnormal insulin and glucagon levels caused by hepatic disease, in turn inhibit release of albumin from the hepatocytes.
 - d. When ascites is present, there is increased volume of distribution of albumin.
 - e. Albumin most likely to be low with:
 - 1) Chronic active hepatitis.
 - 2) PSS.
 - 3) Cirrhosis.
 4. High globulins.
 - a. Due to RES failure and exposure of the rest of the body to increased antigen load and/or infectious organisms.
 - b. Release of antigens from injured hepatocytes can also contribute, and can in turn stimulate further hepatocyte damage by autoimmune response.
 - c. High globulins can worsen hypoalbuminemia.
 5. Low BUN
 - a. Liver fails to convert ammonia to BUN in the urea cycle.
 - b. Most likely to be decreased with:
 - 1) Chronic active hepatitis.
 - 2) PSS.
 - 3) Cirrhosis.
 6. Increased bilirubin.
 - a. Significant icterus without anemia rules out pre-hepatic icterus.

- b. Considerable hepatocyte dysfunction must occur in order for hepatic icterus to occur, because the normal liver can process up to 30x the normal bilirubin load.
- c. Increased bilirubin is an insensitive indicator of hepatocellular dysfunction.
- d. For this reason, even slight elevations of serum bilirubin are often clinically significant.
- e. Bilirubinemia without bilirubinuria suggests delta bilirubin, which in turn suggests cholestatic disease.
- f. Bilirubin is almost never elevated with steroid hepatopathy or PSS.

C. Hepatic function tests.

1. Bile acids.

- a. Protocol:
 - 1) First take a 12-hour fasting sample.
 - 2) Feed the dog or cat a small (1 Tbsp.) high protein, high fat meal.
 - 3) Take a 2-hour post-prandial sample.
 - 4) A small amount of high protein food usually will not induce HE.
- b. Increased bile acids Can be caused by:
 - 1) Post-hepatic icterus. – bile acids leak into circulation.
 - 2) Abnormal portal circulation (PSS bypasses the liver).
 - 3) Poor hepatic reuptake, conjugation and resecretion.
- c. Cause direct toxicity when high.
 - 1) Hepatotoxicity.
 - 2) Gastric hyperacidity.
 - 3) Diarrhea.
- d. Do not run on lipemic samples
 - 1) Will falsely elevate bile acids with enzymatic method.
 - 2) Will falsely lower bile acids with RIA method.
- e. Steroid hepatopathy causes mild if any increase in fasting bile acids.
- f. Specificity of bile acids in cats is virtually 100%.
- g. Sensitivity of bile acids in cats is the highest for any test, but is only 60-70%.
- h. Running bile acids in icteric patients is probably moot – you already know they are very, very high.
- i. Bile acids above 30-40 umol/L in the dog and above 20-30 umol/L in the cat warrant further investigation of liver disease.
- j. SNAP test for bile acids is only a screening test – it tells you whether bile acids are greater than 10 umol/L.
 - 1) Negative SNAP test means the pet likely has no clinically significant liver insufficiency.
 - 2) Positive SNAP test warrants sending bile acids to an outside lab to see if they are truly abnormal.

2. Blood ammonia.

- a. Portal blood ammonia is usually around 350 ug/dl in the dog and 700 ug/dl in the cat.
- b. Venous blood ammonia is normally 20-80 ug/dl in the dog and 20-120 ug/dl in the cat.
- c. The normal liver has a large capacity for ammonia removal, and considerable liver disease must be present for venous ammonia levels to increase.
- d. Ammonia tolerance test can reveal liver disease when resting ammonia levels are normal.
 - 1) 12 hour fasting baseline ammonia.
 - 2) Feed or give ammonium chloride.

- i. Capsules orally at 45 mg/lb (maximum dose 3 g). Max out at a t 67 lbs body weight.
 - ii. Can also dilute in water and give by orogastric tube.
 - iii. Can also give 1 ml/lb of 5% solution per rectum after cleansing enema.
- 3) 30 minutes post-ammonia sample.
- 4) Normal dogs should have less than 32% increase in ammonia.
- 5) Sample handling is critical.
 - i. Venipuncture must be rapid and clean.
 - ii. Sample must be immediately placed in an ammonia-free heparinized tube and placed in an ice bath.
 - iii. Centrifuged and decanted within 30 minutes.
 - iv. Sample must be assayed within 2 hours.
 - i. Value can increase with time due to deamination of proteins, breakdown of ADP, or hydrolysis of other ammoniagenic compounds.
 - ii. Value can decrease with time due to vaporous loss.
 - v. RBCs elaborate ammonia and will false increase blood ammonia if sample is not handled properly.
 - vi. Hemolysis will falsely increase blood ammonia.
- 6) Ammonia tolerance test is nearly 100% sensitive for PSS.
- 7) In rare cases, ammonia tolerance test could induce or worsen HE.
- 8) Ammonia should probably not be administered to patients who have significantly elevated resting ammonia.

D. Urinalysis

- 1. Color – dark yellow, orange, red, brown.
- 2. Bilirubinuria
 - a. A small amount of bilirubin can be normal in dogs, because:
 - 1) Renal threshold for conjugated bilirubin is low in the dog.
 - 2) Canine kidneys conjugate a small amount of indirect bilirubin, releasing it into the urine.
 - b. Any bilirubinuria is usually clinically significant in cats because:
 - 1) Renal threshold for conjugated bilirubin is high in cats.
 - 2) Feline kidneys do not conjugate indirect bilirubin.
 - c. Bilirubinuria is a more sensitive test for hepatocellular dysfunction than bilirubinemia in both dogs and cats.
 - d. Resolution of bilirubinuria is also a sensitive indicator of resolution of cholestatic disease.
- 3. Ammonium biurate crystals.
 - a. Think PSS.
 - b. 1/3 to 1/2 of dogs with PSS have these crystals.

E. Fecal sedimentation – fluke eggs (especially in cats).

F. Coagulation Tests.

- 1. Increased PT, PTT, ACT.
 - a. Decreased production of coagulation factors (must be 30% of normal for PT and PTT to be elevated).
 - b. Liver failure patients are also prone to DIC
- 2. Decreased AT3.
 - a. Decreased production.
 - b. Increased consumption if DIC.
- 3. Increased FDPs.
 - a. FDPs normally cleared by the liver.

- b. Decreased antiplasmin production increases fibrinolysis.
 - c. Decreased clearance of plasminogen activators increased fibrinolysis.
 - d. DIC increases FDPs.
4. Low fibrinogen
 - a. If DIC.
 - b. Decreased hepatic synthesis late in severe liver failure.
 - c. Increased fibrinolysis due to liver failure (see pathogenesis section I.B.5. above) and/or SIRS.
 - d. Surgery can contribute to fibrinogen depletion.
 5. Increased BMBT.
 - a. Factor deficiency.
 - b. Decreased vitamin K availability.
 - c. Platelet dysfunction (can cause bleeding even if other coags are normal).
 - d. Thrombocytopenia and factor consumption if DIC.
 6. Thrombocytopenia if DIC.
 7. PIVKA is more sensitive for coagulopathy due to liver disease than PT and PTT, which are in turn more sensitive than ACT.
 - a. PIVKA is twice as sensitive in dogs.
 - b. And three times as sensitive in cats.

G. Fluid analysis or ascitic fluid.

1. Often a pure transudate (see appendix 7).
2. Can also be a modified transudate (see appendix 7).

H. Imaging is the best way to tell if you've got hepatic icterus, post-hepatic icterus, or both.

1. Abdominal radiographs
 - a. Loss of abdominal detail if ascites is present.
 - b. Small liver size.
 - 1) Radiographic signs of small liver.
 - i. Decreased distance between the diaphragm and the liver.
 - ii. Gastric axis shift – pylorus is ventral or cranioventral to the fundus rather than caudoventral.
 - iii. Cranial displacement of cranial duodenal flexure, right kidney, or transverse colon.
 - iv. Especially noteworthy in a puppy, who should have a larger liver than an adult.
 - 2) Liver may be small due to:
 - i. Congenital PSS due to lack of portal trophic factors to the liver.
 - ii. Fibrosis of chronic liver disease.
 - iii. Hepatic atrophy.
 - iv. Hepatic necrosis.
 - v. Microhepatia.
 - vi. Pseudomicrohepatia – diaphragmatic hernia.
 - vii. May appear smaller in deep chested breeds, due to relative increase in depth of costal arch.
 - c. Hepatomegaly.
 - 1) Radiographic signs of large liver.
 - i. Extension of the liver margin caudal to the costal arch.
 - ii. Rounding of the caudal margins of the liver on lateral view.
 - iii. Displacement of the stomach caudally and to the left.

- iv. Caudal displacement of cranial duodenal flexure, right kidney, or transverse colon.
 - 2) Liver may be large due to:
 - i. Acute hepatitis.
 - ii. Hepatic neoplasia.
 - iii. Corticosteroid toxicity (exogenous or hyperadrenocorticism).
 - iv. Hepatic lipidosis.
 - Diabetes mellitus.
 - Feline hepatic lipidosis
 - Glycogen storage disease.
 - v. Hepatic or biliary cyst or abscess.
 - vi. Liver lobe torsion.
 - vii. Puppies and kittens usually have a relatively larger liver than adults.
 - viii. Passive congestion.
 - ix. Glycogen storage disease.
 - x. Liver can be displaced caudally by a deep inspiration.
 - d. Urinary calculi – ammonium biurate or urate, especially with PSS.
 - e. Choleliths – indicate biliary disease.
 - f. Emphysematous cholecystitis – gas in the gall bladder.
2. Abdominal ultrasound.
- a. Ascites may be present (hypoechoic or anechoic fluid).
 - b. The best non-invasive method to determine whether you have hepatic icterus, post-hepatic icterus or both.
 - c. Hyperechoic liver (relative to fat)
 - 1) Can be caused by:
 - i. Hepatic lipidosis.
 - ii. Steroid hepatopathy.
 - iii. Fibrosis/cirrhosis.
 - 2) Sonographic signs - whiter than fat
 - d. Hypoechoic liver.
 - 1) Can be caused by:
 - i. Passive congestion (very large hepatic and splenic veins).
 - ii. Lymphoma.
 - iii. Acute hepatitis.
 - 2) Sonographic signs.
 - i. Blacker than the kidney.
 - ii. Prominent portal veins.
 - e. Hepatic masses:
 - 1) Neoplasia (primary or metastatic).
 - 2) Extramedullary hematopoiesis.
 - 3) Nodular hyperplasia .
 - 4) Cysts.
 - 5) Abscesses.
 - 6) Granulomas.
 - f. Urinary calculi – ammonium biurate or urate, especially with PSS.
 - g. PSS – finding the shunt on US can be difficult.
3. Thoracic radiographs.
- a. For hepatomegaly or masses seen on ultrasound, to rule out metastatic disease.
 - b. May see military pattern if histoplasmosis.

- c. Pulmonary edema if dangerously low albumin (<1.5 g/dl), especially if concurrent heart disease.

I. Nuclear scintigraphy.

1. Well tolerated and rarely requires sedation.
2. Procedure:
 - a. Technetium placed into the rectum, and is absorbed into the portal system.
 - b. Normally, the liver lights up first.
 - c. In a dog with shunting, the heart will light up first.
3. What a rectal portogram can tell us:
 - a. Whether there is Portosystemic shunting.
 - b. Sometimes whether it is Intrahepatic or extrahepatic.
 - c. Sometimes can distinguish between single and multiple extrahepatic shunts.
 - d. The fraction of (severity) of shunting.
 - e. Can give some information about whether the patient is a good surgical candidate.
 - f. HMD looks normal on scintigraphy.

J. Liver aspiration cytology.

1. Can confirm:
 - a. Inflammation (include CBC results with the cytology submission)
 - b. Hepatic lipidosis.
 - c. Some neoplasias.
 - d. Sometimes cholestasis.
 - e. Fungal hepatitis.
2. Of little use for PSS.
3. Are prone to sampling error.
4. Does not characterize type and location of inflammation well.
5. Can not assess fibrosis.
6. Culture in feline cholangiohepatitis can be helpful.

K. Bile Culture (and sensitivity)

1. Can be very helpful in treating chronic bacterial cholangiohepatitis.
2. Easily performed with ultrasound guidance if gall bladder is enlarged.
3. Highly recommend deep sedation or short general anesthesia.
4. Often positive with feline cholangiohepatitis – don't know if primary or secondary.

L. Surgery – liver biopsy.

1. Gross appearance of the liver can be normal with severe disease.
2. Patient preparation.
 - a. PSS should be ruled out prior to liver biopsy, especially in young dogs.
 - b. Non hepatic causes of liver enzyme elevation should be ruled out first.
 - 1) Hyperadrenocorticism.
 - 2) Diabetes mellitus.
 - 3) Congestive heart failure.
 - 4) Feline hyperthyroidism.
 - c. Coagulation status should be evaluated.
 - 1) Coag profile abnormalities are not very accurate predictors of which patients are most likely to bleed after liver biopsy.

- 2) Patients whose factor levels are low but above 30% (normal PT, PT and ACT) can be depleted by demands of surgery, and bleed (PT and PTT would likely be elevated after surgery).
 - 3) BMBT seems to be more indicative of likelihood to bleed (anecdotal personal experience).
 - 4) Patients with DIC are of course most likely to bleed.
 - 5) Risk of bleeding after surgery might be increased after depletion of platelets and factors by a large GI bleed.
3. Intraoperative support.
 - a. Administer vitamin K 5 mg/kg 1-2 hrs prior to surgery.
 - b. Blood pressure monitoring is essential – vasoaction in hepatic failure patients is abnormal.
 - c. Some recommend dripping heparinized plasma or fresh whole blood during liver biopsy of any patient with significant hepatic disease.
 - d. I wouldn't recommend doing surgery on a liver failure patient without hetastarch on hand.
 - e. Make sure the patients oncotic pressure is restored prior to surgery. IV fluids plus low albumin = pulmonary edema.
 - f. Monitoring venous or arterial blood gases is helpful.
 - g. Have fresh whole blood on hand. Stored blood cells should be avoided, due to high ammonia levels.
 4. Hepatic biopsy is the only way to definitely diagnose liver failure, if it is possible to do so.
 - a. Biopsy of a severely fibrotic or cirrhotic liver is rarely helpful, and is done at great risk to the patient.
 - b. Reasons to do liver biopsy.
 - 1) Significantly elevated bile acids.
 - 2) Liver of abnormal size.
 - 3) Live abnormalities on ultrasound.
 - c. Liver biopsy can help characterize liver disease, to guide therapy and give information about prognosis.
 - d. Liver tissue can be sent for copper analysis.
 - 1) Normal <400 ug/g.
 - 2) Formalin fixed tissue is fine.
 - 3) Most affected dogs have 5-50x normal.
 5. Liver biopsy methods:
 - a. Blind percutaneous - I don't recommend this, due to risk of puncturing the portal vessels or gall bladder.
 - b. Ultrasound guided percutaneous.
 - 1) Very difficult when the liver is small.
 - 2) Diffuse lesions:
 - i. Enter just caudal and to the left of the xyphoid.
 - ii. Angle 45 degrees cranial and ventral.
 - iii. Can also go transthoracic, but not prior to endoscopy or laparoscopy, where there will be insufflation of the abdomen with air.
 - 3) Recovery is usually very quick.
 - 4) Lower risk of dehiscence due to hypoalbuminemia.
 - 5) Get correct diagnosis only 50-60% of the time.
 - 6) Not usually possible to diagnose HMD.
 - c. Laparoscopy guided biopsy
 - 1) Can get larger and more diagnostic biopsies than US guided.
 - 2) Can do an exploratory laparoscopy.

- 3) Shorter surgery time than laparotomy.
 - 4) Faster recovery time and less likely to dehiscence than laparotomy.
 - 5) Air embolism is extremely rare but possible.
- d. Laparotomy.
- 1) Allows more complete visualization of the abdomen.
 - 2) Allows biopsies of more organs than with laparoscopy.
 - 3) Can treat disease if it is surgically correctible.
 - 4) Recovery is longer, and likelihood of dehiscence in a hypoalbuminemic patient is greater.
 - 5) Much riskier for patients with confirmed coagulopathy.
 - 6) Can catheterize the gall bladder through the duodenum and even leave a stent if bile sludging.

VI. Treatment

****REMEMBER: DRUGS AND HORMONES THAT ARE METABOLIZED BY THE LIVER AND/OR HIGHLY PROTEIN BOUND WILL HAVE AN ENHANCED EFFECT IN THE LIVER FAILURE PATIENT****

C. Nutrition.

1. protein and amino acids
 - a. Protein restriction if bile acids are significantly elevated (clinically significant hepatic insufficiency), or if there is hepatic encephalopathy.
 - b. Some recommend less than 20% protein for dogs and less than 35% protein for cats if protein is to be restricted.
 - c. Protein restriction too early in disease (especially in cats), can lead to accelerated protein catabolism and impaired protein synthesis.
 - d. Highly digestible, (high quality or bioavailability) proteins will minimize deamination that might contribute to hepatic encephalopathy.
 - e. Taurine for cats when cholestasis is present. Taurine is produced in the liver, and is used exclusively to conjugate bile salts. Taurine deficiency is not common in dogs with liver disease, but it can help with cholestasis in cases of cholestasis.
 - f. Carnitine for cats with hepatic lipidosis, and dogs with high triglycerides or fat deposition in the liver (carnitine transports long chain fatty acids into the mitochondria for beta-oxidation).
 - g. Increased arginine. Cats with liver disease can develop hepatic encephalopathy if arginine deficient. Arginine can not be synthesized from other amino acids adequately in dogs and cats (especially in cats), and is required to convert ammonia into urea.
 - h. Minimize aromatic amino acids which are normally metabolized by the liver (tyrosine, phenylalanine, tryptophan) and may contribute to hepatic encephalopathy.
 - i. Increased branched chain amino acids which are metabolized by peripheral tissues.
2. carbohydrates
 - a. Increased fermentable fiber for portosystemic shunts, cirrhosis, and chronic hepatitis. Fermentable fibers increase microbial nitrogen fixation, reduce ammonia production, and promote colonic evacuation.
 - b. Increased digestible grains (30-50%) can minimize hepatic encephalopathy in dogs with shunts.
 - c. Increased bulk fiber if hepatic encephalopathy (decreases intestinal transit time and moves anaerobes out more quickly, so they don't have a much time to produce ammonia which can contribute to hepatic encephalopathy). Fiber also binds noxious bile acids and endotoxins and can help maintain euglycemia in dogs.

- d. Minimize simple sugars if hyperglycemic.
- 3. fats
 - a. Sufficient caloric density (4.4 kcal/g) to prevent catabolism of amino acids for energy, to inhibit peripheral lipolysis and to avoid hepatic lipid accumulation.
- 4. minerals
 - a. To minimize adverse effects of poorly regulated renin-angiotensin-aldosterone system.
 - b. Avoid excess sodium if ascites, portal hypertension or significant hypoalbuminemia.
 - c. Potassium supplementation if hypokalemia, which can exacerbate hepatic encephalopathy.
 - d. Avoid excess copper in Bedlington Terriers with Copper Storage Disease.
 - e. Zinc for Copper Storage Disease. (see below)
- 5. vitamins
 - a. Vitamin K if prolonged or severe cholestasis or prolonged clotting times.
 - b. B vitamins if diuretic therapy for ascites or significant PU-PD.

D. Treat fluid and electrolyte imbalances.

- 1. rehydration
- 2. Hypokalemia is common, and can worsen lethargy and anorexia. If prolonged or severe, can cause nephropathy and generalized muscle weakness (see appendices 3 and 4).
- 3. Spironolactone might be indicated for ascites.

E. Treat coagulopathy.

- 1. Vitamin K (5 mg/kg SQ the first day, then 2.4 mg/kg SQ or PO SID thereafter).
- 2. If clotting times are prolonged cue to vitamin K deficiency, administration of vitamin K should bring them back to normal within 24 hours.
- 3. Heparinized plasma and/or fresh whole blood.
- 4. Treat GI ulceration with Carafate or barium and H2 blockers.

F. Treat hypoglycemia.

G. Treat HE.

- 1. Consider ammonia trapping when significantly low albumin, even if no HE, because ammonia prevent release of albumin from the hepatocytes.
- 2. Avoid drugs that exacerbate HE:
 - a. Benzodiazepines for seizure activity, as they can worsen HE.
 - b. CNS depressants.
 - c. Drugs metabolized by the liver.
- 3. Cleansing enemas to decrease bacterial numbers.
 - a. 25 ml/lb body weight).
 - b. Warm soapy water.
 - c. Can add low dose of gentocin to kill urease-producing bacteria (0.45 mg/lb).
 - d. Every 2 hours.
- 4. Oral antibiotics.
 - a. Anaerobes and gram negatives produce ammonia.
 - b. Aminoglycosides or quinolones for negatives.
 - c. Beta lactams for anaerobes.
 - d. Neomycin 9 mg/lb PO TID.
 - e. Metronidazole 3-5 mg/lb BID-TID (low dose).
- 5. Lactulose
 - a. Metabolized by colonic bacteria to lower the pH in the colon.

- b. Traps ammonia there as ammonium
 - c. Also an osmotic cathartic.
 - d. 0.5 ml/lb PO TID (up to every 2-4 hours in emergency)
 - e. If stuporous, give by enema.
 - f. Titrate dose to slightly loose stools.
6. Withhold food until HE crisis stabilizes, and then feed very low protein food.

H. Control GI hemorrhage – see section on Vomiting.

I. Treat sepsis if present – see section on Pancreatitis.

J. Manage ascites.

- 1. Abdominocentesis as needed.
- 2. Salt restricted diet to minimize sodium retention of already activated rennin-aldosterone-angiotensin system (RAAS).
- 3. Diuretics.
 - a. Spironolactone may be preferred as it interrupts the RAAS more effectively than furosemide.

K. Treat specific hepatopathy:

- 1. Chronic active hepatitis – early detection is essential.
 - a. Immunosuppression – studies show mixed results; much anecdotal support for success.
 - 1) Prednisolone rather than prednisone.
 - i. Liver has to convert.
 - ii. Theoretical benefit.
 - iii. Studies show no difference in blood levels in people with liver failure.
 - iv. No studies in dogs.
 - v. Start at 0.5-1 mg/lb/day for 3-4 weeks.
 - vi. Wean down to 0.2 mg/lb/day.
 - 2) Azathioprine (Imuran).
 - i. 50 mg/m² SID for 2-3 weeks, then QOD.
 - ii. Can taper further after pred dose is low.
 - b. Ursodiol (Actigall or Urso) for cholestasis.
 - 1) Ursodeoxycholic acid is a naturally occurring bile acid which has anti-inflammatory properties.
 - 2) Can help dissolve gall stones (1mm per month, works best on stones smaller than 20 mm).
 - 3) Powerful cholagogue, for bile sludging.
 - 4) Can bring about a dramatic positive response.
 - 5) Dose – 6-7 mg/lb/day PO SID or divided BID.
 - 6) Should be given with food.
 - c. Antioxidants.
 - 1) Very important part of therapy, as free radical positive feedback is a problem with this disease.
 - 2) Vitamin E 7 U/lb PO BID.
 - 3) Milk thistle.
 - i. Dried herb: 15-20mg/lb SID
 - ii. Concentrated extract: 2-5 mg/lb BID-TID
 - iii. Alcohol extract: 2-5 mg/lb BID-TID (cats HATE this form)

- 4) SAME.
 - i. Also raises glutathione levels.
 - ii. Glutathione depletion is associated with about 50% of canine hepatopathies.
 - iii. 9 mg/lb PO divided BID.
 - iv. Absorption is best given on an empty stomach.
 - v. Should not be used if there is hepatic encephalopathy, because it contains methionine which precipitates hepatic encephalopathy in animals with very severe liver disease.
 - 5) Cell Advance form VetriScience.
- d. Copper chelators if copper levels high – see copper storage disease below.
 - e. Colchicine if fibrosis is severe.
 - 1) 0.014 mg/lb PO SID.
 - 2) If GI side effects, reduce by 25%.
2. Feline Cholangitis/Cholangiohepatitis Complex.
 - a. Surgical correction of bile duct obstruction may be necessary.
 - b. Glucocorticoids if lymphocytic plasmacytic inflammation.
 - c. Immunosuppression.
 - 1) Prednisolone.
 - i. Improved bioavailability over prednisone in cats.
 - ii. 1-2 mg/lb PO BID x 4 weeks.
 - iii. Tapered over 2-3 months to 0.7 mg/lb/day.
 - 2) Methotrexate 0.13 mg PO BID for three doses; do this every 7-10 days.
 - d. Antibiotics according to bile/liver culture, or empirically if suppurative inflammation.
 - 1) Amoxicillin/ampicillin 10 mg/lb PO BID.
 - 2) I don't usually use Clavamox if vomiting.
 - 3) Baytril 5 mg/kg/day PO.
 - 4) Continue for 2-6 months.
 - e. Metronidazole 3.5 mg/lb BID – immunomodulatory effects.
 - f. Antioxidants (see CAH above).
 - g. Actigall (see CAH above).
 - h. Consider feeding tube if not eating, to prevent hepatic lipidosis.
 3. Copper storage disease – early detection is essential.
 - a. D-penicillamine (Cuprimine)
 - 1) 4.5-7 mg/lb PO BID.
 - 2) Will remove 1000 ug/g/year.
 - 3) GI side effects – divide QID to help alleviate.
 - b. Trientine (Syprine).
 - 1) Drug of choice.
 - 2) 7-14 mg/lb PO BID.
 - 3) Side effects minimal.
 - 4) If having trouble getting it, your pharmacist can order it directly from Merck.
 - c. Zinc
 - 1) Prevents intestinal absorption of copper.
 - 2) Increases intestinal copper chelators (metallothionein).
 - 3) Zinc deficiency is well documented in people with liver disease, but has not been evaluated in dogs and cats with liver disease.
 - 4) Zinc is required to maintain the urea cycle, and some supplement animals with liver disease with zinc.

- 5) Zinc gluconate PO 0.7-1.15 mg/lb TID
 - 6) Zinc sulfate 0.3 mg/lb PO TID.
 - 7) Zinc acetate 100 mg PO BID.
 - d. Vitamin C –decreases copper absorption, and increases urinary copper excretion. 12 mg/lb/day PO with a meal.
 - e. Low copper diet.
 - 1) Hills L/D.
 - 2) Purina HiPro.
 - 3) Purina Fit & Trim.
 - 4) Pedigree.
 - 5) Nutro Natural Choice.
 - 6) Natural Choice.
 - 7) Precise.
 - f. Avoid high copper diets and foods.
 - 1) Eukanuba.
 - 2) Science Diet.
 - 3) Blue Seal Natural.
 - 4) Eggs.
 - 5) Liver.
 - 6) Shellfish.
 - 7) Organ meats.
 - 8) Beans/legumes.
 - 9) Mushrooms.
 - 10) Chocolate.
 - 11) Nuts.
 - 12) Cereals.
4. Bacterial hepatitis
- a. Antibiotics – gram negatives and anaerobes.
 - 1) IV for a few days, until improving.
 - 2) Beta lactam and quinolone – see pancreatitis.
 - 3) Clindamycin and quinolone.
 - 4) Metronidazole and quinolone.
 - b. Surgery may be needed for hepatic abscesses, or necrotic gall bladder disease.
5. Liver flukes – praziquantel 2.3 mg/lb PO BID x 3 days.
6. Fungal hepatitis.
- a. Itraconazole 5-10 mg/kg PO divided BID.
 - b. Fluconazole 5-10 mg/kg PO divided BID.
 - c. Avoid generic itraconazole bulk powder – its bioavailability is just about zero.
7. Portosystemic shunts – surgery.
- a. Get HE under control prior to surgery.
 - b. Not effective if PSS is acquired and secondary to chronic portal hypertension.
 - 1) Ligating the above PSS will cause gut necrosis due to severe portal hypertension.
 - 2) Signs:
 - i. Abdominal pain.
 - ii. Bloody diarrhea.
 - iii. Endotoxic shock.
 - iv. Usually leads to Death.

- c. Can be very effective for single congenital PSS, if secondary liver fibrosis does not preclude ligation.
- d. Extrahepatic shunts (small dogs) are usually easier to find than Intrahepatic shunts (large dogs).
- e. Always perform liver biopsies.
- f. Ameroid constrictors are now being used for gradual ligation.
- g. Urinary calculi and other additional procedures are usually done under separate anesthesia.
- h. Post-op complications.
 - 1) Portal hypertension and gut necrosis (rare with ameroid constrictor).
 - 2) Hypoglycemia.
 - 3) HE – poor prognosis if status epilepticus.

VII. Monitoring

A. Progression of improvement:

1. AST will improve first (shortest half life).
2. Then ALT close behind.
3. Then SAP (half life 3 days in dogs and 6 hours in cats) and GGT.
4. Then bilirubinuria.
5. Then bilirubinemia (delta bilirubin due to cholestasis can take longer).
6. Then jaundice will resolve (this can take days after serum bilirubin has returned to normal).
7. Persistently elevated bile acids indicate persistent liver disease that needs ongoing treatment and monitoring.

B. If on Imuran

1. CBC 3-4 weeks after starting therapy.
2. Then every 2 months.
3. difficult to monitor for liver disease if it already exists.
4. If liver enzymes increase consider Imuran therapy as well as worsened disease as possible causes.

C. Serial biopsies are the best way to monitor non-infectious inflammatory hepatopathy.

D. Post-op PSS ligation.

1. Liver tests at 1, 3 and 6 months.
2. Persistent abnormalities suggests:
 1. Incomplete shunt ligation.
 2. Portal vein hypoplasia.
 3. Portal hypertension and multiple extrahepatic shunts.
 4. Scintigraphy is indicated.

VIII. Sequella/Prognosis

A. Sequellae of Liver Failure:

1. DIC – virtually impossible to distinguish this from coagulopathy due to liver disease without histopath (DIC shows widespread microthrombosis)
 - a. Can lead to bleeding.
 - b. Or thrombosis.
2. SIRS (see appendix 9).
3. Overwhelming infection or toxicity due to failure of RES.
4. Uncontrollable bleeding.

5. Pulmonary edema due to low plasma oncotic pressure.
- B. Prognosis.**
1. **PSS.**
 - a. Without correction – depends on shunting fraction.
 1. If high shunting fraction, progressive hepatic atrophy leads to cirrhosis.
 - b. With total successful ligation – excellent.

IX. Public Health Significance

A. Leptospirosis.

2. Potentially fatal to people.
3. Can be contracted by exposure to urine of infected dogs.
4. Any owner of a pet who may have Leptospirosis should be warned of this.
5. Hospitalized “Lepto suspects” should be handled according to a special protocol.
 - a. Gloves and mask if any staff member comes in contact with:
 1. The cage or anything in it.
 2. The animal.
 3. Anything the animal has touched.
 - b. Wash hands after removing gloves.