Symptoms of Liver Disease

- **Diarrhea**
  - Cholestasis: decreased BA secretion → decreased fat digestion/absorption → increased portal hypertension
  - Portal hypertension: decreased water absorption from GI
- **Vomiting**
  - Shunting: increased toxins activate CRTZ and affect GI lining
  - Hepatomegaly or biliary obstruction: increased vagal tone
  - Icterus: decreased clearance of bilirubin
  - Hepatic encephalopathy
    - 2nd to congenital or acquired PSVA
    - Cats: HE 2nd to HL w/out shunting (lack of AA due to liver dz/malnutrition)
- **PU/PD**
  - Caused by HE: abnormal neuroT → stimulate ACTH/prod → increased cortisol → decreased response to ADH → PU → PD to correct dehydration
  - Other theories:
    - Decreased urea prod → medullary washout
    - Increased GFR (cause?)
    - Vomiting and diarrhea

- **Dysuria**
  - From urolithiasis (ammonium biurate)
- **Anesthesia intolerance:**
  - Decreased hepatic metabolism
- **Acholic feces:**
  - Arsenic/GABA-ergic drugs (ie. benzodiazepines)
  - Decreased hepatic metabolism
- **Hypoglycemia**
  - Young animals: no glycogen stores
  - PSS animals
  - Older animals:
    - Synthesis hepatic failure
  - Hepatic neoplasia (insulin-like growth factor)
- **GI bleeding**
  - Portal hypertension
  - Coagulopathies, DIC
Important History Info

- Appetite
- Stool consistency and color
- Urination: dysuria? polyuria?
- Vaccines
- Diet (raw food?)
- Toxin/drug exposure?
  - TMS, NSAIDs, anticonvulsants, methimazole, doxycycline/tetracycline, acetaminophen, plants
- Travel?
  - Parasites (liver flukes), protozoal, fungal disease
- Organisms
  - Lepto, HW (caval syndrome), Tularemia (rabbits)

Breeds

- Bedlington terrier: Cu
- Skye terrier: Cu
- Doberman: chronic hepatitis, Cu
- Labradors: chronic hepatitis, Cu
- Dalmation: Cu
- Standard Poodle: chronic hepatitis
- English Springer Spaniel: chronic hepatitis
- Cocker spaniel: chronic hepatitis, fibrosis, Cu
- Westie: Cu, PSS
- Yorkie: WVD, PSS
- Maltese: WVD, zone 3 (centrilobular) inflammatory hepatopathy
- Scottish Terrier: degenerative vacuolar hepatopathy
- SharPei and Abyssinian: amyloidosis

CBC

- Microcytosis in PSS (impaired iron transport)
- Target cells
  - Sign of altered cell membranes (altered lipoprotein or cholesterol synthesis and transport)
  - Not specific of any disease process
- Heinz bodies
  - Common in cats w/ HL
  - GSH (glutathione) deficiency
Chemistry Profile
- Markers of hepatic damage: ALT, AST
- Markers of cholestasis: ALP, GGT
  - Cats w/ HL: incr ALP w/ normal GGT (pathognomonic)
- Markers of hepatic function
  - Albumin
  - Cholesterol
  - Glucose
  - BUN
  - Bilirubin

Urinalysis
- Iso or hyposthenuria
- Bilirubinuria: always abnormal in cats
- Sediment
  - Ammonium biurates
  - Bilirubin crystals
  - Lipid droplets in cats w/ HL

Laboratory
- Ammonia:
  - PRO: Great test (sensitive/specific)
  - CON: labile, spin on ice (not as practical)
- Bile acids:
  - Very stable (avoid hemolysis and lipemia)
  - Increased if altered enterohepatic circulation
  - Decreased if ileal disease (ie. IBD or GI lymphoma)
  - Higher pre than post possible in 20% of cases due to random contraction of the gall bladder
Coagulation

- Need to specify which tests are requested
  - Clotting times: PT, aPTT
  - Antithrombin
  - Fibrinogen
  - FDPs or D-dimer
  - Protein C
- PT, aPTT most important
- Subclinical coagulopathies common
- Caution with cholestatic liver disease!

Imaging

- Abdominal radiographs
  - Best to assess liver size or look for choleliths
- Abdominal ultrasound
  - Best for everything else!
- Nuclear scintigraphy
  - Gold standard to diagnose PSS

Cytology vs Biopsy?

- DON’T rush to do FNA during U/S!
- FNA better for lipidosis, vacuolar change, exfoliative neoplasia
  - FNA not always innocuous
  - Bleeding from coagulopathies...most risky if severe cholestasis (ie. lipidosis)
  - You CAN NOT definitively diagnose hepatitis or fibrosis with FNA
- Overall poor correlation between FNA cytology and biopsy
  - Wank, KY, et al. JAVMA 2004: 97 cases: 30% correlation for dogs, 51% correlation for cats
- FNA cytology more sensitive for vacuolar hepatopathy than inflammation or neoplasia BUT vacuolar hepatopathy also most common misdiagnosis
The Liver Biopsy...

- Ultrasound guided Tru-Cut
  - 50% discordance compared to other techniques
  - May not give large enough sample
  - Can’t get enough tissue for copper measurement

- Laparotomy
  - Better if you need to assess other organs, anticipate need for surgical intervention, contraindications for laparoscopy
  - More healing time

- Laparoscopy
  - Less invasive, less healing time

Laparoscopic Liver Biopsy

- Great, non-invasive way to obtain biopsy
- Can assess other organs as well
- Get (gently) pancreatic biopsy if necessary
- Can aspirate GB, assess portal pressure
- Can get full-thickness intestinal biopsy!
- Quick recovery, go home next morning
- Get big pieces of tissue
- Contraindications
  - Abdominal adhesions
  - Other reasons to need surgical exploratory

What to do with the liver biopsy?

- Histopathology
- Culture
  - Aerobic
  - Anaerobic
- Quantitative metal analysis
  - Copper!
- +/- special stains, cultures, molecular testing!
Treatment

- IV fluids
  - Monitor hydration status and BP closely
  - Avoid lactated products (need hepatic metabolism)
  - Careful if ascites: avoid excessive Na load
    - 200 mL of 0.45% NaCl = 2.5% dextrose
  - Monitor electrolytes closely (K+)
  - Avoid alkalosis in HE
  - Add B vitamins to IV fluids: 1-2 mL/L
    - Hydrosoluble vitamins are lost w/ diuresis + decreased intake if sick
  - Glucose supplementation
    - If BG < 60 mg/dl, give IV bolus (0.5 mL/kg of 50% dextrose, 1:1 in saline)
    - If BG < 80 mg/dl, start 2.5% dextrose in fluids
    - No more than 5% dextrose through peripheral IV catheter

- Anti-emetics
  - Metoclopramide
    - Caution: toxicity looks like HE!
  - Cerenia, Ondansetron

- Appetite stimulant
  - Mirtazapine

- Gastroprotectants
  - Decrease GI bleeding (bleed worsens HE)
  - Famotidine (no effect on P450 enzymes)
  - Sucralfate (not if constipated)

- Management of ascites/3rd spacing
  - Avoid Na overload (fluid, diet)
  - Furosemide 1-2 mg/kg q 12 hrs
  - Spironolactone 1-4 mg/kg q 12 hrs
  - Monitor BW and girth to titrate drugs
  - Increase colloid oncotic pressure (serum albumin < 1.5 g/dl or COP < 15 mmHg)
    - Mannitol increases COP more, but can lead to thrombocytopenia and bleeding
    - Plasma is preferred for severe liver patients

- Hepatic encephalopathy
  - Enemas (warm water; lactulose retention enemas)
  - Antibiotics
    - Neomycin (10-20 mg/kg PO or rectally q 12 hrs): watch nephrotox/ototox if GI bleeding
    - Metronidazole (1.5 mg/kg PO q 12 hrs)
    - Ampicillin (10-15 mg/kg PO q 12 hrs)
    - Lactulose (0.25-0.5 mL/kg PO q 8-12 hrs)

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Treatment

Coagulopathies

- Vitamin K 0.5-1 mg/kg q 12 hrs SQ
- Use small needle (bleeding at injection site)
- Repeat 3 times (more if needed)
- Monitor PT
- Most important with cholestatic liver disease (decreased enterohepatic circulation → decreased absorption of Vit K)
- Fresh frozen plasma (FFP)
  - Gives clotting factors, albumin, AT, PC, globulins
  - 10-20 ml/kg per DAY
- Packed RBCs
  - If bleeding & anemic (meeting transfusion trigger criteria)
  - Use freshest products available (ammonia exacerbates HE)

Antibiotics

- If acute hepatitis: ampicillin for Lepto 1st
- Risk of bacterial translocation from gut
- Need broad-spectrum coverage
  - Gram positive, gram negative, anaerobic
  - Ampicillin +/- Baytril +/- Metronidazole
- Ultimate choice depends on patient status
- Caution when selecting a dose (adjust for liver disease)

Nutrition

- NG tubes can be placed fairly early on, but not necessarily on the 1st night (need to evaluate patient more thoroughly 1st)
- Other feeding tubes (ET, PEG)
- Parenteral nutrition may be considered after initial stabilization (few days)
Amanda Leigh

- 5 yr old, FS, English Cocker Spaniel
- Presented for continued evaluation of chronic, waxing/waning, anorexia, lethargy, PU/PD, weight loss and behavioral changes
- Signs first noted 4 months ago after boarding
- Signs seem to wax and wane with no apparent pattern
- Behavior changes → aggressiveness and territoriality
- DVM labs: ALT 462 U/L (10-100); AST 238 U/L (0-50)
- Treated with Ciprofloxacin, Amoxicillin and Zentonil
- Initial non-sustained improvement in signs
- Repeat chemistry profile → no improvement in liver values
- No past pertinent medical/travel history

Physical Examination

- T: 103.2     P: 108 bpm         R: 36 bpm
- Weight: 10.9 kg        BCS 2.5/5
- QARH
- Severe gingivitis and tartar
- H/L: WNL
- ABD: soft, non-painful, NSF
- PLN: WNL
- M/S: WNL

Minimum Data Base

- CBC:
  - Microcytosis
  - Mild non-regenerative anemia
- Chemistry profile:
  - Elevated ALT/AST (450/200)
  - Elevated ALP (386)
  - Mild hypocholesterolemia (86)
  - Albumin, glucose, BUN = low normal
  - Hyperbilirubinemia (0.6)
- Urinalysis (cystocentesis)
  - SG 1.028, pH 8.0, trace protein, 2+ bilirubin
Abdominal Ultrasound

Subjective microhepatica

Additional testing

- Pre and post prandial bile acids
  - Pre: 288 umol/L
  - Post: 483 umol/L
- Urine culture
  - Negative for bacterial growth
- Hemostasis screen
  - PT: 8.55 sec (6-7.5; control sample 7.35)
  - APTT: 22.5 sec (9.21; control sample 16.3)
Plan

- Empiric hepatic encephalopathy treatment
  - Lactulose
  - Amoxicillin
  - Dietary modification (Hills L/D)
- Non-specific liver supportive treatment
  - Denosyl (S-adenosyl-l-methionine)
  - Elevolored ALT
- Vitamin K1
- Prolonged coagulation times
- Recheck in 4 weeks
- Surgery?

Recheck Visit

- Amanda’s attitude, behavior and appetite improved with treatment
- Plan made for exploratory laparotomy
- Pre-surgical diagnostic testing:
  - Progressive hyperbilirubinemia (1.5)
  - Prolonged coagulation times
    - PT 12.1 sec (6-7.5, control 7.13)
    - APTT 20.2 sec (9-21, control 14.9)
- Presurgical fresh frozen plasma transfusion

Exploratory Laparotomy

Firm, mottled, nodular, small liver
Multiple extrahepatic portocaval shunting vessels
Normal Liver

Amanda's Liver

Severe acute & chronic neutrophilic, lymphocytic & histiocytic periportal bridging & lobular hepatitis

Atrophy of the hepatic cords
Dilation and congestion of the sinusoids
Rare foci of single cell hepatocyte necrosis
Bile duct hyperplasia

Changes consistent with infection, copper excess or idiopathic drug reaction

Bacterial cultures negative

Hepatocellular vacuolar degeneration consistent with lipidosis

Quantitative copper analysis:
2020 ppm

Plan

- Continue medical management for HE
  - Hills L/D diet, Lactulose, Amoxicillin
  - Denosyl (SAM-e)
    - Hepatic anti-oxidant support
  - Prilosec
    - Reduce GI acidity and stimulate appetite
  - Sucralfate
    - Presumptive GI ulceration 2o to portal hypertension
  - Cupramine (D-penicillamine)
    - Hepatic copper chelation therapy
  - Prednisone
    - Anti-inflammatory dose for ongoing hepatitis
  - Staple removal in 2 weeks; recheck in 4 weeks
After 5 months of therapy

- Chemistry profile
  - ALT 212 U/L, AST 172 U/L, albumin 2.7 g/dl, globulin 2.1 g/dl
  - Normal bilirubin
- Hemostasis screen: Mildly prolonged APTT (plasma)
- Dental cleaning/extractions & laparoscopic liver biopsy

No ascites seen!

Mottled, nodular liver

Multiple acquired shunting vessels

Laparoscopy

Diffusely, moderately fibrotic portal areas with bile duct proliferation
Mild periportal lymphocytic and plasma cell infiltrate

Multifocal nodular regeneration
Resolved necrosis and inflammation
Mature periportal and bridging fibrosis

Copper laden hepatocytes are multifocally and randomly distributed with some predilection for fibrotic foci probably reflecting previous inflammatory foci.

Quantitative copper analysis: 192 ppm

Plan
- Continue:
  - L/D diet or homemade reduced protein diet
  - Prilosec
  - Denosan (SAM-e)
  - Ursodiol (Actigall)
  - Prednisone
  - Furosemide
  - Spironolactone
  - Lactulose PRN for signs of HE
  - Clindamycin
- For dental disease
- Discontinue:
  - Cupramine (D-penicillamine)
- Add:
  - Zinc
  - To limit intestinal copper absorption
Canine Chronic Hepatitis

- Heterogenous group of diseases
- Chronic inflammation
- Necrosis
- Progresses to cirrhosis
- Cause usually unknown
  - Leptospirosis, CAV-1
  - Copper
  - Drugs, toxins
  - Autoimmune
  - Idiopathic

Copper Hepatitis

- Genetic defect
  - Primary copper retention
  - Central lobular distribution
- Secondary accumulation
  - Chronic hepatitis → cholestasis → decreased copper excretion → copper accumulation in periportal regions
- Diagnosis
  - Quantitative copper level → BK!
  - Biliary copper measurement in future??
Copper Hepatitis

- Penicillamine (Cupramine)
  - Serious complication in 10-20% treated humans
  - Fever, arthralgia, rash, lymphadenopathy, immune-mediated disease
  - B6 (pyridoxine) depletion with chronic use

- Trientine
  - Less side effects
  - Ammonium tetrathiomolybdate
  - Complexes with copper in food and blood

- Zinc
  - Induces intestinal metallothionein → binds copper in duodenal enterocytes
  - Copper lost when enterocyte is shed during normal cell turnover
  - Also induces hepatic metallothionein → reduces damaging (free) copper
  - Side effects common
    - Anorexia, bloating, vomiting, diarrhea, pancreatitis
    - Try lower dose, splitting dose, giving with food

- Copper Hepatitis
  - Bedlington terrier
    - Autosomal recessive
    - Very high copper levels; Tx aggressively
  - West highland white terrier
    - Thornburg et al. The relationship between hepatic copper content and morphologic changes in the liver of West Highland White Terriers. Vet Path 1996;33:6
    - Variable amount and distribution of copper
    - Not always progressive or needing treatment
  - Skye terrier
    - McGrotty et al. Diagnosis and management of hepatic copper accumulation in a Skye terrier. J Sm Anim Pract 2003;44
  - Dalmatian
    - Centrilobular distribution and high copper concentrations suggests primary metabolic defect
  - Labrador
    - Hoffmann G et al. Copper-associated chronic hepatitis in Labrador Retrievers. JVIM 2006;20
    - Centrilobular distribution and moderate copper concentrations suggestive of primary pathology in some; others appear to have non-copper chronic hepatitis

- Copper Hepatitis
Chronic Hepatitis

- Doberman
  - Often subclinical: Incidentally discovered ALT elevation
  - Variable copper level → role of copper unclear
  - Mandigers PJJ et al. Association between liver copper concentration and subclinical hepatitis in Doberman Pinschers. JVIM 2004;18
  - Mandigers PJJ et al. Improvement in liver pathology after 4 months of D-penicillamine in 5 Doberman Pinschers with subclinical hepatitis. JVIM 2005;19
- Standard Poodles and English Springer Spaniels
  - Chronic hepatitis, etiology unclear (not primary copper)

Severe, progressive chronic hepatitis
- Often severe ascites and hypoalbuminemia
- Substantial fibrosis, often bridging
- Poor response to treatment and overall prognosis
- Alpha 1 anti-trypsin deficiency implicated in pathogenesis
  - Protease inhibitor synthesized by hepatocytes
  - Human genetic mutation → serum enzyme deficiency → protein variant accumulates within hepatocytes
  - Hepatic, damage from unregulated tissue proteases
- Sevelius E et al. Hepatic accumulation of alpha-1-antitrypsin in chronic liver disease in the dog. J Comp Path 1994;111
  - Association between alpha-1-antitrypsin & lobular dissecting hepatitis
- Hepatic [copper] often elevated
- Secondary to inflammation or primary player?
- Role of chelation?


Hurwitz et al. Presumed primary and secondary hepatic copper accumulation in cats. JAVMA 2014; 244:1

Biscuit

- 6 yr FS DSH
- Diagnosed with IBD two months ago after being worked up for chronic intermittent vomiting
  - Endoscopic biopsies: mild LP IBD
- Initially responded well to prednisone and diet change
- Now, acutely vomiting and lethargic for several days

Biscuit: MDB

- Physical Examination
  - Depressed, icteric, anterior abdominal mass
  - Temperature 103.6
  - CBC
    - Mild mature neutrophilia (13,500)
  - Chemistry profile
    - BUN 31 mg/dl, creatinine 1.7 mg/dl
    - Bilirubin 3.2 mg/dl
    - ALP 160 U/L GGT 12 U/L
    - ALT 179 U/L AST 46 U/L
  - Urinalysis
    - SG 1.052, pH 6.5, 2+ bilirubin, inactive sediment
The Icteric Cat

- Hepatic lipidosis
- FIP
- Lymphoma
- Cholangitis/Cholangiohepatitis

Abdominal Ultrasound

- Large hypoechoic pancreas
- Mottled liver parenchyma

Biscuit: Plan

- Exploratory laparotomy
- Pancreatic, liver and intestinal biopsies
- Histopathology
  - Moderate LP enteritis
  - Moderate neutrophilic peri-portal and biliary tree inflammation
  - Chronic pancreatitis
- Liver and bile cultures: E. coli
Feline Cholangitis-Cholangiohepatitis (CCHS) Syndrome

Overview of CCHS
- Any age cat
- Insidious history
- Vague signs, acute to chronic illness
- Weight loss, anorexia or polyphagia, lethargy
- Vomiting, fever, jaundice, hepatomegaly
- Polydipsia, ptosism, pallor, anemia (non regen)
- Polyclinocytosis, elevated liver enzymes, +/- neutrophilic leukocytosis

World Small Animal Veterinary Association (WSAVA) Liver Standardization Group: 4 categories
- Neutrophilic cholangitis (NC)
- Lymphocytic (non-neutrophilic) cholangitis (LC)
- Destructive cholangitis
- Chronic cholangitis associated with liver fluke infestation

Disorders associated with CCHS
- Neutrophilic:
  - Primary bacterial infection
  - Septicemia
  - Chronic bacterial (pyoderma, pyometra, pyelonephritis)
  - Cholangitis
  - Cholecystitis
  - Cholelithiasis
  - Pancreatitis
  - IBD
  - EHBDO
  - Acute trematode infection
  - Toxoplasmosis
- Non-neutrophilic:
  - IBD
  - Primary cholangitis
  - Pancreatitis
  - EHBDO
  - Cholecystitis
  - Cholelithiasis
  - Neoplasia
  - GB adenocarcinoma
  - Bile duct carcinoma
  - Malformation of biliary tract
  - Chronic trematode infection
  - Chronic bacterial infection anywhere in body
Neutrophilic CCHS

- Often younger cats with more acute signs
- >75% have an underlying disorder that would favor development of a septic process (causes of impeded bile flow)
- Concurrent inflammation of biliary and pancreatic ductal system is common ("TRIADITIS")
- Hematology
  - Neutrophilic leukocytosis +/- left shift
- Chemistry profile
  - Moderate increase ALT, AST, GGT
  - Variable increase ALP and bilirubin
  - Cholesterol normal unless EHBD or diabetes mellitus

Neutrophilic CCHS

- Hematology
  - Neutrophilic leukocytosis +/- left shift
- Chemistry profile
  - Moderate increase ALT, AST, GGT
  - Variable increase ALP and bilirubin
  - Cholesterol normal unless EHBD or diabetes mellitus

Neutrophilic CCHS

- Radiography
  - Mineral densities/choleliths (50% are radiodense)
  - Empysematous inflammation (rare)
  - Enlarged GB (mass effect)
  - Abdominal effusion (rare)
  - Regional ileus
  - Sternal lymphadenopathy
- Ultrasonography
  - Thickened extra/intrahepatic biliary structures
  - Sludged bile/cholelithiasis
  - Changes consistent with EHBD
  - Pancreatic changes
  - Small volume abdominal effusion

Neutrophilic CCHS

- Isolated organisms
  - E. coli (most common)
  - Alpha hemolytic Streptococcus
  - Actinomyces
  - Enterobacter
  - Enterococcus
  - Staphylococcus
  - Bacillus
  - Bacteroides
  - Clostridia
  - Klebsiella
  - Pseudomonas
  - Salmonella
  - Toxoplasmosis
- Role for Bartonella and Helicobacter?
Neutrophilic CCHS

- Bacteria seen on cytology more commonly than histopathology
  - Make imprint of liver tissue/bile
- Reasons for negative culture
  - Prior antibiotic therapy
  - Adverse effects of transport
  - Failure to request anaerobic culture
- May transform into non-neutrophilic CCHS

Non-neutrophilic CCHS

- Middle aged to older cats
- Usually ill > 3 weeks
- 75% of cats have a predisposing condition
- Lymphocytic or lymphoplasmacytic inflammation
- May result from immunoinjury (loss of self tolerance, altered epitopes)
- Lymphoproliferative disease may evolve into lymphoma
- T cell rich B lymphoma can mimic CCHS (small lymphs by portal triads)
- Sclerosing cholangitis ("vanishing bile duct syndrome")
  - Immune mediated destruction of bile ducts
  - Confirmed with cytokeratin staining which confirms residual involuted bile ducts within inflammation
  - Does not respond to conventional therapy
  - Can result in complete occlusion of biliary tree
  - Resembles EHBDO → acholic stools, fat malabsorption

Non-neutrophilic CCHS

- CBC
  - Inconsistent anemia, poikilocytosis, lymphocytosis
- Chemistry profile, radiographs, U/S
  - Similar to suppurative CCHS
- CANNOT be diagnosed with confidence via liver aspirate
- Liver biopsy
  - L or LP infiltrates around portal triads
  - CT deposition between portal triads
  - +/- ductopenia
- Feline leukocyte panel immunohistochemistry
  - Available at Cornell to distinguish neoplastic from inflammatory disorders in cats with aggressive CCHS
**CCHS: General Treatments**

- Look for underlying disease and manage it
- EHBDO, choleliths, trematodes, IBD, pancreatitis
- Antimicrobials: empirical coverage of gram neg and anaerobes
  - Tx neutrophilic 3-6 months
  - Tx non-neutrophilic until biopsies return & based on clinical signs
- Ursodeoxycholic acid
  - Immunosmod, cytoprotective, antifibrotic, choleretic, antioxidant
  - 35 mg/kg PO q 24 hrs (once EHBDO ruled out)
- Maintain adequate nutrition (prevent 2nd HL)
- Supplemental water soluble vitamins (B12 deficiency)
- Vitamin K1 if jaundiced
- Fluid therapy
- Maintain normal serum potassium
- Antioxidant therapy
  - Vitamin E 10 IU/kg PO q 24 hrs
  - SAMe 20 mg/kg PO q 24 hrs (N-acetylcysteine if critically ill)

**Neutrophilic CCHS Treatment**

- Antibiotics ➔ at least 3-6 months
- Based on C&S when possible
- Avoid tetracyclines ➔ favor lipidosis
- Choose non-toxic drugs with good liver and bile penetration
- Metronidazole often combined with another antimicrobial
  - Effective against anaerobes
  - Good liver and bile penetration
  - Anti-inflammatory and anti-endotoxic effects
  - 7.5 mg/kg PO BID
- Other first line hepatobiliary antimicrobials
  - Gram + and many anaerobes
    - Ampicillin/Amoxicillin/Cephalaxin
  - 2nd or 3rd gen cephalosporins or Clavamox for incr. coverage
  - Gram + and many Gram
    - Enrofloxacin (2.5 mg/kg PO BID)
  - Resistant Enterococcus
    - Vancomycin (Erycyclic glycopeptide, IV only, 10-20 mg/kg BID)

**Biochemical abnormalities**

- Should normalize within 4 weeks if there is no underlying disease and bacteria are eradicated
- Failure to improve
  - Was underlying condition adequately treated?
  - Chronic infection somewhere?
  - Transformation to non-suppurative CCHS?
  - Development of hepatic lipidosis?
  - May need to re-biopsy, aspirate, collect bile
Non-neutrophilic CCHS Treatment

- Prednisolone
  - Immunosuppression, anti-inflammatory effects, choleresis
  - 2-4 mg/kg PO q 24 hrs
  - Side effects: DM, HL, GI ulceration/enteritis
  - Full remission is rare with this treatment alone
  - If improvement, slowly taper dose to EOD
- Concurrent Metronidazole
  - Treat undisclosed infectious agent?
  - Modulates cell mediated immunity
  - May help existing IBD and/or pancreatitis
  - Reduces production of intestinal endotoxin

Non-neutrophilic CCHS Treatment

- Chlorambucil
  - Alkalating agent
  - Side effects: BM toxicity
  - 1-2 mg total dose q 48-72 hrs
- Azathioprine → NOT recommended
  - Antimetabolite
  - Myelotoxicity → trouble metabolizing drug
- Methotrexate
  - Antimetabolite, blocks folate metabolism
  - For biopsy confirmed sclerosing cholangitis only
  - 0.13 mg/dose given at 0, 12 and 24 hrs ONCE weekly
  - Side effects: BM (rare), GI signs (rare)
  - Supplement folate (0.25 mg/kg/day)
- Monitor for complications of immunosuppression

Prognosis for CCHS

- Disorder commonly spontaneously cycles
- Some cats have very long remission or cure with chronic medical management
- No long-term prospective studies on the efficacy of treatment
- Death
  - Biliary cirrhosis
  - Progression to lymphoma
  - Underlying or associated conditions (IBD, pancreas)
Pepper

- 12 yr old, FS, DSH
- Presented for lethargy, vomiting and inappetence
- PE:
  - Gross icterus
  - BCS 4.5/5
  - Depressed
  - Salivating

The Icteric Cat

- Hepatic lipidosis
- FIP
- Lymphoma
- Cholangitis/Cholangiohepatitis

Pepper: MDB

- CBC
  - Mild mature neutrophilia
  - Rare Heinz bodies
- Chemistry profile
  - ALP 865 U/L
  - ALT 112 U/L
  - GGT 2 U/L
  - Cholesterol 387 mg/dl
  - BUN 45 mg/dl
  - Creatinine 2.7 mg/dl
  - Bilirubin 6.9 mg/dl
- Urinalysis
  - Bilirubinuria
  - Hematuria
  - heme-positive sediment
Pepper: Abdominal Ultrasound

- Large, hyperechoic liver

Pepper: Initial Treatment

- IV fluids
  - Normosol R + 20 meq KCl/L & 2 mls/L Vit B
  - Vitamin K1
    - 1 mg/kg SQ q 12 hrs
  - Dolasetron PRN for nausea vomiting

The following day

- U/S guided liver aspirate (after coagulation panel performed and was WNL)
- 80% of hepatocytes are filled with vacuoles consistent with lipid accumulation
- Diagnosis:
  - Hepatic Lipidosis
Feline Hepatic Lipidosis

The role of nutritional supplements

Hepatic Lipidosis: Review

- Acquired cholestatic disorder resulting from excessive accumulation of triglycerides in hepatocytes (>50%)
- Usually secondary to another disease:
  - Other hepatopathies (ie. cholangiohepatitis)
  - Pancreatitis, GI disease (ie. IBD)
  - Diabetes mellitus
  - Respiratory disease (ie. asthma)
  - Septicemia
  - Neoplasia (ie. lymphoma)
  - Renal/lower urinary disease, Cardiomyopathy, Hyperthyroidism, Anemia, Neurologic disease, Trauma
- Can also be idiopathic
- ALWAYS look for underlying 1st disease!

Hepatic Lipidosis: Review

- Clinical Signs/PE: vomiting, anorexia, weakness, hx of weight loss (>25% BW), icterus, HE, bleeding, diarrhea, hepatomegaly, dehydration, pallor, cervical ventroflexion
- Labwork
  - Poikilocytosis (63%), non regen anemia (22%)
  - Heinz bodies, acute hemolysis (HB and/ or low phos)
  - Hyperbilirubinemia (95%)
  - Elevated ALP (80%), ALT (72%), AST (89%)
  - Normal GGT
  - Hypokalemia (30%), Hypophosphatemia (17%)
  - Prolonged clotting times (25-60%)
  - Elevated bile acids, Hyperammonemia
Hepatic Lipidosis: Review

- Liver aspirate
  - Less invasive than biopsy, but less accurate
  - Pre-treat with Vitamin K1
    - Cholestasis leads to relative deficiency which can cause significant coagulopathy
  - Over 80% hepatocytes will be vacuolated
  - Use to rule out lymphoma and make significant neutrophilic inflammation less likely
- Liver biopsy
  - More invasive
  - May be necessary for optimal long-term tx plan

- Negative prognostic indicators:
  - Low PCV
  - Hypokalemia
  - Older age
  - Lack of aggressive nutritional and supportive care
  - Survival rate: 50-85% depending on study
  - Fatal without treatment

Unique feline biochemistry

- Cats continue to use protein for production of energy and in the urea cycle even in the face of low protein availability
- Depend on dietary intake of arginine, taurine, methionine, cysteine
- Adapted for low carbohydrate diet
- Increased requirement for dietary B vitamins compared to other mammals
- Require Vitamins A & D from animal tissues
### Carnitine

- Essential cofactor of fatty acid metabolism
- Protection against ammonia-induced encephalopathy by assisting urea cycle function
- Necessary for synthesis of GSH
- Decreased carnitine = decreased FA oxidation and triacylglycerol accumulation in tissues
- Increases with fasting, starvation and diabetes mellitus
- Clinical signs of carnitine deficiency
  - Vomiting, muscle weakness, fatigue, hyperammonemia, hepatic lipid accumulation
- Carnitine deficiency causes hepatic lipid accumulation and liver dysfunction in people

### Taurine

- Essential amino acid for cats
- May contribute to membrane alterations as a free radical scavenger or membrane stabilizer
- Reduces hepatic lipid content in obese children

### SAMe: S-Adenosylmethionine

- An essential precursor of carnitine and glutathione
- Protects liver against oxidant injury and participates in many important hepatic biochemical reactions
  - "thiol" donor
- Rodent model provides evidence of increased oxidative damage and decreased glutathione during HL
**B Vitamins**

- Deficiency in B Vitamins may be one of the causes AND consequences of HL
  - Necessary for synthesis of carnitine and folic acid
  - May itself promote anorexia
  - Liver contains most of body’s cobalamin
  - Humans with severe liver disease often have high plasma level and low tissue level
  - Normal plasma level does not rule out metabolic deficiency!
  - Must be conjugated to be active
    - Vitamin E and thiol donor help with this

**Vitamin E**

- Protects against oxidative damage
- Deficiency is suspected to complicate HL

**Treatment Recommendations**

- Nutrition
  - Once the patient is stabilized (1-2 days)
  - Feeding tubes (check placement with x-rays)
  - Energy requirements (kcal): (30 + weight-kg) + 70
  - Illness factor (arbitrary and debated): 1.5-1.8
  - Use liquid high energy food
    - Clinicare: good for NG tube but not for long term
    - A/D or MaxCal for long term
  - DRI in beginning is more effective
  - Watch for “re-feeding syndrome”
    - Monitor electrolytes (K+, Phos)
Treatment recommendations

- Fluid therapy
  - Avoid lactate and dextrose
  - Supplement with potassium and phosphorus as needed
- Vitamin K (0.5-1 mg/kg q 12 hrs SQ)
- Vitamin E (100 IU/cat/day PO)
- Vitamin B complex (1-2 mls/L in IV fluids)
- L-carnitine (150-500 mg/cat/day PO)
- Thiol donor
  - N-acetyl cysteine for acute crisis
    - 140 mg/kg IV once, then 70 mg/kg q 4-6 hrs x 4-6 doses
    - Dilute 1:1 with 0.9% NaCl, give over 20-30 min through IV filter
  - SAMe PO (20-40 mg/kg/day PO divided BID)
  - Taurine (250-500 mg/cat/day PO)
  - Fish oil (omega 3 FAs) (2000 mg/cat/day PO)

Where do we stand?

- No placebo controlled studies comparing treatment with and without these nutritional supplements
- Retrospective analysis at Cornell
  - 86 cats supplemented with carnitine
    - 76% lived/24% died
  - 38 cats not supplemented with carnitine
    - 44% lived/56% died
- Obvious limitations of study design but results still intriguing