Hepatobiliary and Encephalopathy Nutrition.

Is there anything new??
Topics

• Encephalopathic vs. non-encephalopathic.
  – Protein sources
  – Fat and disease
  – Sodium
  – Nitrogen disposal
  – Sulfur containing amino acids
  – Manganese
  – LOLA

• Copper Hepatopathy

• Cholangiohepatitis/Lipidosis
  – Anti-inflammatory
  – Anti-oxidant
Cirrhosis/Bridging Fibrosis

• Most hepatobiliary disorders result in global or zonal degeneration.

• Regardless of the pathogenesis the dietary recomms. are similar.
  – Autoimmune, genetic, toxic and idiopathic degeneration
  – Acquired shunting
Dietary Recomm. in non-complicated hepatobiliary disease

- Easily digestible
- Highly palatable
- Calorically dense
- Easy preparation for owner
- Small frequent feeding
  - Moderate protein (20-40% DM)
  - Moderate Fat (20% DM)
  - Moderate CHO (30-40% DM)
Fat and Hepatobiliary disorders

• Ensure essential fatty acids are being provided.
• Ensure fat soluble vitamins are provided
  – Vitamin K may be needed in certain hepatic disorders
• Avoid excessive fat in obstructive biliary disorders.
• Fat may be more useful than carbohydrate since short chain fatty acids have been implicated in encephalopathogenesis.
• Watch for biliary mucoceles in hyperlipidemic dogs (shelties, and schnauzers).
  – Low fat for sure (>10 % DM)!
Protein and Hepatobiliary Disorders

• Goals
  – Prevent hepatic encephalopathy
    • Protein titration is important
    • Minimally start with 2.5 g/kg in dogs
    • Minimally start with 3.5 g/kg in cats
    • Add 0.5 gm more per week.
  – Look for evidence of excessive nitrogen
    • Ammonium biurate crystals, hyperammonemina.
  – Prevent catabolism of lean mass
    • Positive nitrogen balance
Hepatic Encephalopathy

• Type and quality of protein becomes important.
  – Highly digestible and complete – casein, whey, albumin, muscle meats.
  – Decreased NH$_3$ production – casein, whey, vegetable based proteins.
  – Avoid diets or excessive quantities of lysine, glutamine, asparagine, histidine, glycine threonine and serine.
  – Minimize tissue (muscle) catabolism – rich source of NH$_3$. 
Hepatic Encephalopathy

• Protein sources
  – Avoid excessive aromatic amino acids – phenylalanine, tyrosine, tryptophan
    • Can have encephalopathic effects
      – Sedative and anorexic effects.
  – Higher branched chain amino acids in diet
    • Isoleucine, leucine, valine - gluconeogenic (ketogenic).
    – Hypothetically sound but seems to only hold up in IV feeding.

• Dogs do well on dairy and soy.
• Cats require a meat source (arginine essential).
• Avoid red meats (blood high in hemoglobin and NH₃.)
# Does Protein Really Matter?

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<th>Leu</th>
<th>Ile</th>
<th>Val</th>
<th>Total</th>
<th>Phe</th>
<th>Tyr</th>
<th>Total</th>
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Hepatic Encephalopathy

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<th>CONTENT AND EFFECTS OF VARIOUS PROTEIN DIETARY COMPONENTS</th>
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<td><strong>DIETARY CONSTITUENTS</strong></td>
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<td>DAIRY PROTEIN</td>
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<td>VEGETABLE PROTEIN</td>
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<td>BLOOD PROTEIN</td>
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<table>
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</tr>
<tr>
<td>VEGETABLE PROTEIN</td>
</tr>
<tr>
<td>BLOOD PROTEIN</td>
</tr>
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</table>

Remember 85% of nitrogen liberation is from the SI and liver, not Colon
Hepatic Encephalopathy

• Dogs
  – Start at 2-2.5 g/kg BW and titrate upward.
  – If intolerant go to minimum NRC 1.33 g/kg/BW.

• Cats
  – Start at 3.5 g/kg/BW and titrate upwards.
  – If intolerant go to NRC minimum 2.5g/kg/BW

• Puppies (3months)
  – Start at 6g/kg/BW and titrate upwards.
  – If intolerant start at 6 g/kg/BW and titrate downwards 1 g/kg each month. At 6 months you can be at 2.5g/kg/BW.

• Monitor albumin, BUN, and CK (in cats may increase if loss of lean mass). Ammonia levels if available.
Portosystemic shunts/Ascites

- Portal hypertension may be a component.
  - Particularly microvascular intrahepatic shunts
- Sodium restriction may be warranted.
- Less than 100 mg/100 kcals.
  - Hill’s L/D
    - 50 mg/100 kcal
  - RC LS 14
    - 50 mg/100 kcal

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<th>Sodium Content per DM</th>
<th>Dog Foods</th>
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<tr>
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<td>Energy: 3.5 - 4.5 kcal / gm</td>
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<td>AAFCO Minimum Na Diet:</td>
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<td>High-Na⁺ Diet</td>
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<td>Moderate-Na⁺ Diet</td>
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<td>Low-Na⁺ Diet</td>
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<tr>
<td>Very Low-Na⁺ Diet:</td>
<td>&lt; 0.1</td>
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</table>
Soluble Fiber in Hepatic Encephalophathy (lactulose)

- Lactulose dose
  - Dog 2.5 to 25 ml
  - Cats 1-4 ml
- Gradual addition to a tolerable dose without diarrhea.
- Highly soluble fiber sources may act similarly.
  - Watch for too much SCFA - encephalopathic
Energy requirements

• In hepatic cirrhosis energy requirements may actually be increased.
• If eating under RER both fat and lean mass are used this increases NH liberation from muscle.
• If receiving enough protein then increase fat or CHO calories.
• If able (no biliary problems or hyperlipidemia) use fat.
Water soluble Vitamins

• Cats susceptible to Thaimine and B12 deficiency
  – particularly in homemade diets – creates malaise, inappetance and encephalopathic signs (thiamine).
  – If concurrent GI disease then B12 supplement ideal (250 ug/weekly, then monthly).
  – B complex 1cc/L of IV fluids.
  – May provide sAME with B12 to help potentiate active adenosylcobalamin.

• Vitamin C – induces PO iron and copper uptake and may actually potentiate Fenton reaction. Best to refrain from supplements with iron/ copper toxicity.
Fat soluble Vitamins

• Vitamin K
  – Most encephalopathic patients on chronic antibiotic treatment, thus K production may be limited.
  – Run clotting tests (PIVKA)
  – 0.5-1.5 mg/kg vitamin K1

• EHBDO less fat soluble vitamin absorption
  – Vitamin E – 10 IU PO/kg as α-tocopherol acetate.
  – Vitamin A and D too?
Mitzi and Me; 2004

- Mitzi – 4 year old FS Yorkshire Terrier, 4.3 kgs
- Portosystemic shunt
- Mild encephalopathy for 4 years- managed medically
- Recently found urate crystals during routine urinalysis
  - Currently on Hill’s K/D
  - 1 egg per day
  - Lactulose
  - Antibiotic therapy
- Possibly more encephalopathic recently.
Home prepared Diet

- MER = 300 kcals a day
- Old diet was 15 g/day protein – new diet similar
- Daily ration:
  - 1 ½ ounces of 1% low fat cottage cheese
  - 1 large hardboiled of cooked egg
  - 1 cup of cooked mashed potato
  - 1 teaspoons of soybean oil
  - 1 Fish oil capsule (1000 mg)
- Supplements:
  - ½ tablet of Centrum Multivitamin
  - ½ tablet of Generic Choline supplement (typically 250-325 mg tablets)
  - ½ Caltrate 600 tablet (calcium carbonate – for calcium and urine alkalinization)
  - 1 tablet of vitamin K1 or K3 supplement (typically 100 micrograms in a tablet)
  - ½ of a 500 mg methionine supplement per day

- What’s the problem here?
- Became encephalopathic the week after starting the diet.
Methionine and Encephalopathy

- Methionine increases in serum of PSS shunt and end-stage cirrhotic patients.
- Methanethiol a metabolic byproduct of liver insufficiency.
- Experimental Model
  - 30 kg dogs created PSS
  - Provided protein in diet diet 2-3 g/kg BW
  - Dosed with 25 g methionine q 4 hrs till coma

Methioinine and Encephalopathy

- Mercaptans not desirable
- Other middle molecules involved.
- What supplements should our end stage cirrhotics and shunts be on?
  - MSM?
  - Glucosamine/Chondroitin?
  - sAME?
Manganese and Encephalopathy

• Many human studies have found that manganese accumulation occurs in various nuclei.
• Manganese has been associated with encephalopathic behavior.
• Manganese accumulation in astrocytes is associated with dysfunction.
• Primary manganism occurs with certain professions:
  – Welders.
  – Parkinsonian signs, irritability, depression and cognitive deficits.
Dogs, PSS and Manganese

• Primary means of elimination is enterohepatic.
• Do PSS dogs have higher serum Mn?
• Fasting serum
  – 18 PSS Dogs
  – 14 Healthy
  – 26 other illness

Fig 2. Whole blood manganese (Mn) concentrations in dogs with congenital portosystemic shunts (cPSS) (n = 18), dogs with nonhepatic illnesses (nonhepatic) (n = 26), and healthy dogs (healthy) (n = 14). The line indicates the median value. Mn concentrations are significantly increased in dogs with cPSS compared with dogs with nonhepatic illnesses and healthy dogs.

Gow AG et al, JVIM, 2010
Dogs and Manganese

Fig 3. Whole blood manganese (Mn) concentrations versus age in months of the dogs with nonhepatic illnesses ($n = 26$). There was a significant positive correlation between Mn concentration and age.
Dogs and Manganese

- 13 dogs with PSS
  - 10 of 13 with lentiform nucleus lesions
  - All had some degree of cortical atrophy in frontal and parietal lobes
  - One showed resolution after post ligation

- 3 cats with PSS
  - One of 3 had lesion in lentiform

Manganese in food

- 45 over the counter brands
- Minimum AAFCO – 2 ppm/1000 kcals
- Royal Canin – 20 ppm/1000 kcals
- Hill’s LD diet – 8 ppm/1000 kcals
- Do we need manganese restriction??
LOLA

• L-ornithine and L-aspartate therapy.
• Multiple clinical studies have shown benefit in chronic cirrhotic patients with modest chronic encephalopathy.
• Recent meta-analysis utilizing case control or RCCT – show universal benefits.  (Hernandez et al, Ann Hep, 2011)
Muscle, LOLA and ammonia

- Only 15% of ammonia load is from colon
- 85% from small intestine and hepatic metabolism.
- Randomized case control vs lactulose suggested LOLA is superior.
- Glutamine synthesis in kidney brain and muscle, but **Muscle organ size** is tremendous and can utilize ammonia and aspartate to make glutamate → glutamine.
Can we use it in our patients?

• Cats
  – Amino acid metabolism differs – efficacy is unknown as ornithine metabolism is different.

• Dogs
  – Human dose typically 9-18 grams a day of LOLA
  – Hep-Merz sachets – 5 grams with 3 grams LOLA
  – Typical 70 kg human = 125 -250 mg/kg body weight.
Hepatic copper/iron accumulation

Fig. 2. Hepatic tissue transition metal status in dogs that have spontaneous liver disease showing number of patients (% of submitted specimens) with copper and iron concentrations exceeding normal limits [42,43]. Tissue metal determinations completed by atomic absorption spectroscopy with values expressed on a dry weight basis. Normal copper tissue concentrations ≤400 ng/g; normal iron tissue concentrations < 1200 ng/g dry liver tissue. NI = necroinflammatory liver disease.
Copper toxicity

• Bedlington terriers, Dobies, Sharpei, Labradors
  – See accumulation in some cirrhotic hepatopiliary disorders.
• Copper in food should be minimally at 7.3 mg/kg DM according to AAFCO.
• Want to restrict copper to less than 5.0 mg/kg DM or 5 ppm.
  – 0.4 mg/kg of food equates to normal copper balance in a Bedlington!
• Drinking water can have that much!
  – Well water or copper pipes
  – analysis may be prudent in copper tox. cases.
Copper toxicity

• Use of Zinc acetate or gluconate.
  – Will increase the production of metallothionein in enterocytes
  – Metallothionein binds to divalent cations such as cadmium, cobalt, zinc, copper.
  – Is a regulator of balance in-case of toxicity.
  – Is sloughed into GI lumen and lost.

• Dose 5-10 mg/kg Zn as gluconate or acetate BID. Achieve plasma zinc of 200-600 ug/dl.

• Do we need Zn in the face of a low copper diet??
Copper Toxicity

• Copper absorption is the key here
  – Copper sulfate – about 30% absorbed
  – Cuprous oxide – less than 10% absorbed
  – Cupric oxide – 1-2% absorbed
• Phytates (vegetable matter) will decrease absorption.
• Chewables use Cupric oxide.
• Certain geriatric vitamins may be ideal.
  – Low in iron – no iron
  – Low in copper – cupric oxide at 0.7 mg per tablet
  – High in B12 – 25 ug per tablet
Too much of a good thing?

- Historically AAFCO worried about sources and deficiency for most minerals.
- Many minerals except for calcium and phosphorus do not have a safe upper limit.
- In many instances human RDA have a safe upper limit of consumption.
- Human SUL
  - Iron = 45 mg/day
  - Zinc = 40 mg/day
  - Copper = 12 mg/day
  - Manganese = no set SUL
What happened in the mid 1990’s

• Cupric and Cuprous oxide was banned as a feed ingredient in animal feed due to ruminant deficiency problems.
• Data in 3 cats also suggested poor availability of oxide form of copper
• Most of industry decided to use copper sulfate or amino acid chelates.
• AAFCO says at least 7.3 mg/kg DM 4000kcal/diet
What about dogs?

Data from Dr. Sharon Center, Cornell University
Copper ug/gm dry weight liver

1980-1997
n=18
1998-2008
n=18
Control Dogs
1980-1997
n=18
1998-2008
n=18
Hepatitis Dogs

P =0.006
P =0.004
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<th>Zinc mg/kg</th>
<th>Calcium mg/kg</th>
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<td>106-1380</td>
<td>112-336</td>
<td>770-3000</td>
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Safe Upper Limit?

• Human consumption SUL is 12 mg a day
• Average active Lab with potential problem eats 4 cups a day = 450 grams.
• If eating a food with 31 mg/kg DM then; $31 \times 0.45 = 14$ mg/day.
• Is this safe, if there is a predisposition or underlying smoldering hepatic enzymes?
  – Royal Canin hepatic LS and Hill L/D which have less than 5 mg/kg DM.
Do Low Copper Diets work

- Study to examine Labradors with copper hepatopathy
- 17 Labradors followed post chelation therapy
  - OTC diet given
  - Increased copper after 8-9 months

Hoffman et al, JVIM, 2009
Low Copper Diets

- 2 dietary strategies (21 dogs)
  - Hepatic LS – 4.8 ppm of copper
  - Heptic LS + Zinc
    - Zinc given at 10 mg/kg

- Biopsies
  - Start
  - Recheck 1 – 6 m
  - Recheck 2 – 1 yr

Fig 2. Hepatic copper measurements. Quantitative measurement of hepatic copper improved during treatment in both groups (group-1: diet and zinc; group-2: diet and placebo). Upper and lower horizontal borders of the boxes describe borders of upper and lower quartile of the data. The distance between these values is H-spread. Values outside 1.5 times H-spread above and below the hinges are outliers (diamond). Outliers appear as such in the figure, but these dogs were not excluded from statistical testing. Horizontal bars describe the median of the measured copper concentrations.
Cholangiohepatitis/Triaditis/Hepatitis

- Inflammatory hepatitis.
  - Idiopathic
  - Lymphoplasmocytic
  - Neutrophilic

- Cholangiohepatitis - cats
  - Acute (suppurative)
    - Histology
    - Bacterial infection
  - Chronic (nonsuppurative)
    - Histology
    - Progression of acute form
    - Biliary cirrhosis

Conditions associated with Cholangiohepatitis

<table>
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<tr>
<th>Conditions</th>
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<tbody>
<tr>
<td>Inflammatory bowel disease</td>
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<tr>
<td>Chronic bacterial infections within other organs</td>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Toxoplasmosis</td>
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<tr>
<td>Anatomic abnormalities of the gallbladder</td>
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<tr>
<td>FIP</td>
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<td>FeLV</td>
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<td>Cholelithiasis</td>
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<td>Extrahepatic bile duct obstruction</td>
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<td>Biliary reconstructive surgery</td>
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<tr>
<td>Septicemia</td>
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<tr>
<td>Neoplasia</td>
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<td>Liver fluke infestation</td>
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</table>

Treatment of Cholangiohepatitis

• Surgical intervention
• Fluid support
• Vitamin supplementation
  – B-complex at 1-2 mL/L
  – Vitamin $B_{12}$ – 0.25 – 1.0 mg weekly then monthly
  – Vitamin K – 0.5 – 1.5 mg/kg q12hr x 3 doses
• Antimicrobials
• Immunosuppresants
• Chlorectic medication
• Antioxidants
Modification of \( \Omega 6: \Omega 3 \)

-\( \frac{1}{2} \) teaspoon for small cat; Up to 1 teaspoon for a big cat.

Fat

Monounsaturated

Polyunsaturated

Saturated

Omega-6

Omega-3

Arachidonic Acid

Eicosapentaenoic acid

Prostaglandin E2

Thromboxane A2

Prostaglandin E3

Thromboxane A3

Inflammation

Platelet aggregation

Vasodilation

Docosahexaenoic acid

No More!
Cellular interactions and inflammation

Fig. 1. Important pathomechanisms involved with liver injury. Interactions between ROS
Antioxidants and the liver

Fig. 3. Important antioxidant mechanisms for the liver (natural and therapeutic) depicted as nonenzymatic (molecular) antioxidants and enzymatic antioxidants (italicized), as discussed in the text. In the center of the diagram a cartoon depicts a biologic membrane with hydrophilic polarity indicated by the oval structures and lipid tails (paired polyunsaturated fatty acids in the hydrophobic portion). Note the reappearing and important contributions made by GSH.
Glutathione Concentrations

• Normal and hepatic diseases

• CATS →

• DOGS →

Glutathione Synthesis

1. Outside Cell
   - Amino Acid
   - γ-Glutamyl Transpeptidase

2. γ-Glutamyl-cysteinyl-glycine (GSH)
   - Cysteinyl-Glycine
   - Cysteinyl-Glycine DiPeptidase
   - γ-Glutamyl-cysteine
   - γ-Glutamyl-cysteine

3. Salvage or Alternative Pathway
   - Cystine
   - GSH
   - GSSG

4. γ-Glutamyl-cysteine
   - ADP + P_i
   - GSH Synthetase
   - ATP
   - Cysteine
   - γ-Glutamyl-cysteine
   - ADP + P_i
   - γ-Glutamyl-cysteine Synthetase

Y-Glutamyl Cycle
- γ-Glutamyl Cyclotransferase
- γ-Glutamyl Amino Acid
- Decarboxylation
- 5-Oxo-Proline
- 5-Oxo-Prolinase
- Glutamic Acid
- ATP
- ADP + P_i
Glutathione Functions

Fig. 7. Metabolic interactions of GSH in the liver, including synthesis, degradation, and major functional categories.
N-acetyl cysteine

- Used in acute acetaminophen toxicity
  - 150 mg/kg IV or PO, then 50-70 mg/kg PO for 3-6 doses

Fig. 9. Metabolic fate of NAC after intravenous administration. While NAC undergoes deacetylation to cysteine, the amino acid limiting the rate of GSH synthesis, it also provides systemic protection against oxidants and toxins even before GSH formation. Products/metabolites derived from NAC cysteine donation are shown. As a thiol delivery agent NAC is considered the standard to which others are compared.
sAME and antioxidants

- Denosyl – 90 mg to 445 mg BID.

Fig. 8. Antioxidant network and interacting systems necessary for optimal response to thiol supplementation. Adequate nutrition along with vitamin and mineral intake are necessary to maintain balance in this series of interactions. (Adapted from Sen CK, Packer L. Thiol homeostasis and supplements in physical exercise. Am J Clin Nutr 2000;72(Suppl):653S–69S.)
S-adenosyl-methionine (sAME)
Glutamine and BCAA

- Glutamine – extra NH3 – bad
- BCAA – possible energy and NH3 scavenging
Polyenyl-phosphatidylcholine (PEP)

- A component of soybean lecithin (32%).
- Two linoleic acid molecules attached to glycerol and choline.
- Has been strongly associated with fibrosis inhibition for alcoholic and rodent induced hepatocellular injury.
- Inhibition of cytokine levels or cytokine mediated responses.
- **Not Choline or phosphatidylcholine!**
- Dosing for dogs 1 gram /SID per 10 kg BW, max of 3 grams.
- No studies in dogs or cats
Milk Thistle (Silymarin)

- 4 isoforms of flavolignins in the Milk Thistle plant.
- Provides antioxidant protection from ROS
- Also has anti-Nf-κβ and 5-lipoxygenase activity
- Inhibits reactive fibrosis, anticirrhotic.
- Is a treatment for amanitin (mushroom cap) heptatocellular degeneration
- Marin (Nutramax) – silybin 25-100 mg total dose
  - OTC milk thistle 20-50 mg/kg BW – poor absorption
  - Marin also has vitamin E and Zinc
Vitamin E

- Fat-soluble vitamin
- Tocopherols and tocotrienols
- Synthesized by plants
  - Corn oil - 1.4 mg/10 g
  - Canola oil – 0.8 mg/10 g
  - Vegetable oil – 1.6 mg/10 g
  - Wheat germ oil – 15 mg/10 g
- Dose
  - 10 IU/kg per day
  - α-tocopherol acetate
  - Water soluble
Hepatic Lipidosis

- Signalment
  - Jaundice
  - Anorexia
  - Obesity
- Chemistry
  - Liver enzymes elevated
  - Bilirubin elevated
  - Electrolyte disturbances
- CBC
  - Mild anemia – Heinz bodies
- Ultrasound
  - Hyperechoic
  - Hepatomegaly
The need to feed

• Principles
  – Slowly increase feeding
  – Start at $\frac{1}{2}$ RER
  – Refeeding syndrome
  – Utilize high protein food
    • Don’t worry about Ammonia!
  – Moderate to High Fat is OK!
  – Utilize supplements?
    • Carnitine – improves ketogenesis.

• Carnitine Data
  – Lipidotic cats had same carnitine in liver as normal control cats
  – Carnitine supplementation improved skeletal muscle ketone and fat utilization
  – 70% of cats supplemented carnitine survived while normal rate was 40% survival.
  – 500 mg per day mixed with feed.
  – Does it spare methionine and lysine for protein synthesis
Recovery diets – 1 can + 50 cc water

<table>
<thead>
<tr>
<th>Diet</th>
<th>Kcals/ml</th>
<th>Protein/100 kcals</th>
<th>Fat/100 kcals</th>
<th>Water/kg BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicare</td>
<td>1 kcal</td>
<td>7 g</td>
<td>5 g</td>
<td>200-210 ml</td>
</tr>
<tr>
<td>Hill’s a/d</td>
<td>0.9 kcals</td>
<td>10.5 g</td>
<td>6.0</td>
<td>205-220 ml</td>
</tr>
<tr>
<td>IAMS Recovery</td>
<td>1.6 kcals</td>
<td>7 g</td>
<td>7.1</td>
<td>110-120 ml</td>
</tr>
<tr>
<td>Royal Canin Recovery</td>
<td>0.9 kcals</td>
<td>10.1 g</td>
<td>6.1</td>
<td>205-220 ml</td>
</tr>
</tbody>
</table>

6 kg cat at 40 kcal/kg = 240 kcals a day:
Water 40-60 ml/kg = 240-360 ml/day
Questions?