Feline hepatic lipidosis: best survival therapeutics

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Hepatic lipidosis (HL) is a syndrome that develops secondary to a primary health problem in > 90% of cats, or as a consequence of starvation. You need to find the underlying problem.

Clinical Features: Although cats of any age may be affected, most are middle aged neutered adults (7 [0.5-20] years), with history of over-conditioning (BCS > 4/5), and inappetence (2-7 days; >90%) and usually an ~25% loss of body weight (dehydration & body condition). Weight is primarily lost from peripheral tissues while abdominal fat is conserved. Gastrointestinal signs are most common: vomiting in ~38%, variable diarrhea and/or constipation. Other historical features reflect underlying/primary diseases. Jaundice (~70% cats) and non-painful smooth hepatomegaly are notable on physical examination. Severe electrolyte derangements (marked hypokalemia or hypophosphatemia) may provoke profound head/neck ventroflexion. Ptyalism is common and may reflect nausea or hepatic encephalopathy (HE). Severe weakness and recumbency may reflect symptomatic electrolyte disturbances (potassium, phosphate), thiamine (vitamin B1) deficiency, or a primary disease. Electrolyte disturbances may contribute to gastric and intestinal dysmotility and vomiting that complicate alimentation (usually before electrolyte correction). Ultrasonography discloses diffuse hepatic hyperechogenicity that may over-shadow a primary hepatobiliary disease process.

Clinicopathologic Features:

Hematology: Poikilocytosis (~63% initial blood smears) is common. Heinz bodies may suddenly appear and lead to symptomatic anemia and death; may follow oxidant challenge imposed by drug or anesthetic agents or reflect a primary illness (e.g. diabetes mellitus, other liver disorders, hyperthyroidism, pancreatitis). Anemia (~22% cats on presentation) may develop secondary to phlebotomy, hemolysis (Heinz bodies, severe hypophosphatemia) or provoked blood loss (i.e. feeding tube placement). Depending on the decade examined, ~25-40% of FHL cats in the author’s hospital have required blood component therapy (whole blood, packed RBCs, or fresh frozen plasma). Leukograms reflect underlying diseases as FHL lacks necroinflammatory features.

Serum Biochemistry: Increased liver enzyme activities (ALP, ~84%; ALT, ~72%; AST ~91%, γGT, 61%), subnormal BUN (~44%) despite initial dehydration (impaired urea cycle function presumed), and hyperbilirubinemia (variable magnitudes) are common. There is no diagnostic value in fractionating bilirubin. Cats with primary necroinflammatory liver disease (e.g. cholangiohepatitis, extrahepatic bile duct occlusion [EHBD], bile duct carcinoma), pancreatitis or pancreatic adenocarcinoma develop high γGT activity; ~30% of cats have ≥ 3-fold increase in γGT compared to ~60% with ≥ 3-fold increase in ALP. ~18% have a greater fold increase in γGT relative to ALP coordinating with comorbid disorders. This unique feature increases clinical suspicion of underlying conditions. Subnormal albumin ~65% of cats (before fluid therapy) reflects complex influences on albumin (synthesis, turnover) and malnutrition. Hyperglobulinemia is rare and hypoglobulinemia occurs ~18%. Concentration of cholesterol and glucose reflect primary disease processes. Despite diffuse hepatic steatosis, few cats present hypoglycemic (~ 4%) whereas ~53% are hyperglycemic (initially) reflecting either over-conditioning or a feline stress response (~ 3-4% are Diabetics). A subset (~56% cats) develop mild/marked increased creatinine kinase reflecting muscle injury (i.e IV catheter or feeding tube placement, muscle catabolism, recumbency, rhabdomyolysis due to electrolyte depletions [i.e., hypokalemia, hypophosphatemia], or a primary disorder).

Electrolyte abnormalities: importantly contribute to morbidity and mortality; hypokalemia increases risk for death. Hypokalemia, hypophosphatemia, and/or hypomagnesemia present in ~31%, ~15%,~ 21% of cats, respectively, or develop after fluid therapy or subsequent to a re-feeding syndrome. Severe hypokalemia and hypophosphatemia increase risk for RBC hemolysis (hypophosphatemia), muscle weakness, enteric atony and
vomiting, head/neck ventroflexion, and neurobehavioral changes confused with HE. Anticipated refeeding electrolyte disturbances are now commonly averted by prophylactic IV electrolyte supplementation (KCl, K-phosphate, with frequent monitoring). Lipiduria is common and likely reflects renal tubule lipid vacuolation; a buoyant lipid phase may be observed in centrifuged urine. Renal tubular potassium wasting has been verified in a subset of cats; this may resolve with FHL resolution.

**Coagulation Assessments:** Coagulopathies are more reliably detected using a test sensitive to Vit. K_1 sufficiency (PIVKA clotting test, Thrombotest, Nycomed). Routine bench PT, APTT, and PIVKA tests were abnormal in ~26%, ~30%, and ~59% of FHL cats. Coagulopathies usually respond to parenteral Vit. K_1 (~1.0 mg/kg, IM or SC, @ 12 hour intervals x 3). Routine early Vit. K_1 supplements facilitate uneventful catheter and feeding tube placement and hepatic tissue aspiration. Coagulopathy in > 50% of cats dictates initial venipuncture using peripheral veins that allow pressure assisted hemostasis. Cystocentesis, jugular catheter insertion, urethral catheterization, and feeding tube placement should be delayed until after a Vit. K_1 response interval.

**Blood Gas Analyses:** Venous blood gas (on presentation) demonstrate metabolic acidosis in ~33%, reduced strong ion difference in ~87%, and increased unmeasured anions in ~82%. Changes are consistent with accumulated ketones and lactate. Cats with spontaneous clinical and experimentally induced FHL demonstrate propensity for hyperglycemia and accumulate plasma ketones within range observed in diabetics (β-OH butyrate from 0.5 to 8.9 mmol/L). Experimental FHL confirmed ketone accumulation as early as 7 days of “self imposed fasting”. Ketone concentrations in experimental FHL have been lower than observed in clinical cases because of early rescue strategies. Similar ketosis (~5–7 mmol/L) develops in humans fasted 1-23 days. Longer fasts coordinate with higher ketone concentrations, as seen in FHL. High lactates have only been confirmed in a small number of cats (limited testing).

**Liver Function Tests:** Serum Bile Acid (BA) tests are redundant in FHL as hepatobiliary jaundice is overt. Fractioned BA (blood & urine) from cats with FHL, EHBDO, and healthy cats disclosed significantly reduced secondary BA concentrations in FHL & EHBDO. Since secondary BA are derived from enteric bacterial dehydroxylation of primary bile acids, findings implicate impaired enterohepatic BA circulation likely linked to canalicular collapse ultrastructurally observed. This reconciles with apparent Vit. K_1 insufficiency. Blood Ammonia concentrations are inconsistently increased in clinical FHL. Experimental FHL demonstrated NH_3-intolerance commensurate with insufficient quantities of essential amino acids implicating compromised urea cycle function. Similar amino acid changes develop in spontaneous FHL. Ammonium biurate crystalluria has not been documented in FHL.

**Presumptive Diagnosis:** Based on signalment, physical and clinical features, abdominal ultrasound and aspiration cytology of liver (after vitamin K_1 [24 hrs]). Cytosolic vacuolation should be evident in > 80% of hepatocytes.

**Is Liver Biopsy Necessary for HL Diagnosis?** Liver biopsy is not necessary for presumptive diagnosis of HL; this is usually based on hepatic cytology, finding a diffusely hyperechoic hepatic parenchyma on US, compatible biochemical features, and history of over-conditioning and inappetence. Liver biopsy (or other tissues) is reserved for cats with suspected comorbid conditions requiring definitive histologic diagnosis or cats with recalcitrant HL (rigorous supportive care does not resolve/improve clinicopathologic features within 2-wks). However, cytology can be misleading unless sufficient hepatocytes are sampled (several different areas), and percentage of severely vacuolated cells estimated- you must see > 80% of hepatocytes that are heavily vacuolated with triglyceride (TG) membrane bound vacuoles. It is important to realize that ill cats commonly display hepatic TG vacuolation. Cholangiohepatitis, EHBDO, and some neoplastic disorders are not defined cytologically, similar to inaccuracy of small needle-core biopsies.

**Vitamin & Anti-Oxidant Sufficiency**

**Water Soluble Vitamins:** The liver stores and activates many water soluble vitamins required as cofactors for enzymes essential to cell function, intermediary metabolism, and energy production. Cats have an apparent
susceptibility for both thiamine and cobalamin depletion. There are few investigations of B vitamin sufficiency in the cat. In ill inappetent cats, depletion of other B vitamin(s) remains possible.

**Dose:** To thwart potential water soluble vitamin deficiencies, a doubled daily maintenance dose of fortified water soluble vitamins (with thiamine concentration ~50 mg/ml) is recommended; 2 mL/L fluids. Fluids containing B-vitamins should be protected from direct light (tin foil scrunched over the administration set; large black garbage bag over the fluid bag and administration set).

**Thiamine (Vitamin B<sub>1</sub>):** Thiamine deficiency can induce neurologic signs confused with HE or neurologic injury (Wernicke’s Encephalopathy). Cats with suspected B<sub>1</sub> deficiency demonstrate central vestibular signs (cerebellar signs), dilated non-responsive pupils, head/neck ventroflexion, abnormal postural reactions, hypothermia, hypotension, and stimuli induced seizures. Deficiency is deduced if clinical signs remit after thiamine supplementation. Ensuring thiamine adequacy is essential prior to feeding, as thiamine requirements increase with carbohydrate metabolism. Feeding a cat with an uncorrected thiamine deficiency can provoke lactic acidosis and non-reversible neurologic injury (Wernicke’s Encephalopathy) confused with HE. We avoid supplementation with injectable thiamine because of rare vasovagal responses and neuromuscular paralysis observed in a few cats and dogs given parenteral (IM) thiamine. Rather, oral tablets are used for supplementation.

**Dose:** 50 to 100 mg PO q12hr x 1-3 days, followed by 50-100 mg/day per cat. Fortified B-vitamin supplements are added to IV fluids to provide a continuous slow and steady thiamine supplement.

**Cobalamin (B<sub>12</sub>):** Cats chronically malnourished due to small intestinal disease or pancreatic insufficiency (rare) or maintained on chronic oral antimicrobials may develop B<sub>12</sub> deficiency. Of 58 sequentially tested cats with HL, low cobalamin was documented in 58%. A subset of these cats given B<sub>12</sub> before sample collection, had supraphysiologic B<sub>12</sub> concentrations (>5,000 pg/mL) on measurement. Insufficient B<sub>12</sub> compromises function of the tricarboxylic acid cycle (mitochondrial toxicity) and complex II of the respiratory chain (methylmalonic acid accumulation) and β-OH butyrate dehydrogenase (resulting in ketosis). Supplemented cyanocobalamin requires cyanide removal and activation by addition of an adenosyl or methyl group synthetic pathways dependent on folate, other B vitamins, and SAMe. It is unknown if B<sub>12</sub> deficiency is causally linked with HL or reflects antecedent conditions or long term inappetence. The conventional laboratory B<sub>12</sub> assay cannot distinguish inactive from functional vitamin B<sub>12</sub>. Baseline and sequential testing are used to tailor chronic B<sub>12</sub> supplementation.

**Dosing:** 0.25 to 0.5 mg/cat given on first day of hospitalization, AFTER collection of baseline B<sub>12</sub> sample. Baseline and sequential testing allows tailoring of chronic supplements to maintain B<sub>12</sub> within reference ranges.

**Fat Soluble Vitamins- Vitamin K & Vitamin E:** may require supplementation due to enteric malabsorption secondary to reduced enterohepatic bile acid circulation in severe HL likely related to the canalicular collapse observed on transmission electron microscopy. Chronic inappetence also contributes to vitamin depletions. We suspect that cats do not maintain long-term vitamin K stores owing to the frequency of vitamin K responsive coagulopathies observed in HL.

**Vitamin K<sub>1</sub>:** should be given parenterally as soon as HL is a considered diagnosis (first 12-hrs). This often corrects coagulation abnormalities typical of HL such as prolonged PIVKA clotting time (proteins invoked by vitamin K antagonism) or prolonged Prothrombin time. Parenteral dosing is necessary because enteric uptake of fat soluble vitamins is limited by the reduced bile acid enterohepatic circulation needed to assimilate fat soluble vitamins. Dramatic correction of coagulopathies in HL follow Vitamin K<sub>1</sub> administration, corroborating concern that cats have only marginal stores of this fat soluble vitamin. It is possible that cats have a slow capacity for reactivation of Vitamin K in the Vitamin K epoxidase cycle.

**Dosing:** 0.5 and 1.5 mg/kg Vitamin K<sub>1</sub> is given SC or IM, q12hr x 3 doses, repeating treatment once or twice weekly. **This should never be given IV** because of concern for anaphylactoid reactions. Avoid every day administration of Vitamin K<sub>1</sub> as this will lead to development of Heinz body hemolytic anemia.
**Vitamin E (α-tocopherol):** Whether or not vitamin E is insufficient in HL cats is unknown. However, circumstantial evidence suggests it may be subnormal: 1) finding low liver glutathione (GSH) reflecting oxidative utilization of other antioxidants, 2) concurrent presence of low Vitamin K also a fat soluble vitamin, 3) depletion of vitamin E in similar hepatic disorders (hepatic lipidosis in humans and experimental animal models), and 4) bile acid profiles in HL consistent with impaired enterohepatic bile acid circulation (reduction in secondary bile acids formed in the gut) as occurs in complete major bile duct obstruction. Restitution of vitamin E would importantly restore its function as an important membrane terminator of peroxidative injury and protection against oxidative challenges imposed by cholestasis.

*Dosing:* Initially use the water soluble form of α-tocopherol: polyethylene glycol alpha tocopherol succinate: 10 U/kg PO q24hr.

**Thiol Donor Supplementation:** Similarities between feline HL and kwashiorkor in children (low protein malnutrition associated with lethal hepatic lipidosis) includes finding low liver GSH concentrations, susceptibility to heinz body hemolytic anemia, cholestatic injury, and suspected subnormal vitamin E concentrations. These findings argue for thiol supplementation. Because liver is the major source of circulating GSH, it is not surprising that subnormal GSH has been confirmed in whole blood in cats with HL. Thiol donors can preserve and replete GSH. Acute critical thiol administration can be given IV as N-acetylcysteine. More chronically thiol supplementation is provided by oral administration of bioavailable SAMe.

*N-Acetylcysteine-Crisis Rx:* Intravenous N-acetylcysteine (NAC) is initially dosed at 140 mg/kg using a 20% solution diluted 1:4 with saline or 5% dextrose. Thereafter, 70 mg/kg IV q6-12hrs. NAC is administered IV through a 0.25 um nonpyrogenic filter over 20-minute interval. Longer infusions may impair urea cycle ammonia detoxification.

**SAMe:** Once enteral dosing is possible, NAC treatment is converted to enteric coated SAMe tablets (Denosyl-SD4™, Nutramax, Inc.)

*Dose:* 20 mg/kg PO q24hr on an empty stomach. While enteric coating improves bioavailability, administration of tablets can be problematic. Crushing tablets and administering with food reduces SAMe bioavailability (doubling of SAMe dose is recommended in this circumstance). However, it is generally accepted that SAMe tablets should not be crushed. Administration via a feeding tube is strongly contraindicated as the drug may irreparably clog the feeding appliance.

**Acute Case Management**

**Suspect Bleeding Tendencies:** A vitamin K1 responsive coagulopathy is common in HL and should be routinely treated with parenteral vitamin K1, as described previously. Provide 0.5-1.5 mg/kg SQ or IM giving 3 doses over 24 hours at q12hr intervals. Do not insert jugular catheters, perform cystocentesis, or place an esophagostomy or gastrostomy-tube before vitamin K repletion.

**Body Condition Assessment:** Assessing lean body mass is essential as this weight should be used to formulate fluid and drug dosing in over-conditioned cats.

**Fluid Therapy:** Avoid dextrose supplementation (promotes hepatic fat accumulation and hypokalemia due to urine electrolyte wasting). Lactate intolerance may exist: thus avoid lactated ringers. Acetate metabolism may be compromised: thus avoid acetate supplemented fluids. Initially use: 0.9% NaCl, supplemented with electrolytes and B-vitamins.

**Electrolyte Abnormalities:** are an important cause of patient morbidity and mortality in HL and their management is crucial to case recovery. Hypokalemia, hypophosphatemia, and/or hypomagnesemia are initially identified in 30%, 17%, 28% of cats, respectively. Severe hypokalemia and hypophosphatemia increase risk for hemolysis (hypophosphatemia), and can cause muscle weakness, “silent” gut atony thwarting feeding attempts (vomiting: associated with gastric, intestinal, or esophageal dysmotility or stasis, head/neck ventroflexion, inability
to concentrate urine (promotes dehydration and electrolyte losses), and neurobehavioral changes confused with hepatic encephalopathy. Head ventroflexion also may reflect thiamine deficiency. Low potassium and phosphate can develop in response to the ReFeeding Syndrome: see below. Hypokalemia is the most common electrolyte abnormality in HL and is exacerbated by the Re-Feeding syndrome. Severe hypophosphatemia also can develop within 48-hours of feeding with clinical signs developing when phosphate \( \leq 1.5 \text{ mg/dL} \). Symptomatic hypomagnesemia is uncommon but effects can be profound and confused with hypokalemia and hypophosphatemia. Signs of Thiamine deficiency also may appear in unsupplemented patients owing to its involvement in enzymatic reactions involving glucose metabolism.

Re-feeding Syndrome: A potentially lethal condition involving severe electrolyte and fluid shifts invoked by sudden metabolic adaptations in malnourished patients undergoing initial re-feeding (oral, enteral, or parenteral). This should be anticipated in all HL cats. Shifted metabolism promotes insulin release and cell uptake of glucose, phosphate, potassium, magnesium and water, and enhances protein synthesis. Nutritional support intensifies requirements for phosphate, potassium, glucose, water, and increases demand for ATP, 2,3 diphosphoglycerate (2,3 DPG), and creatine kinase (CK). Prodigious decline in potassium and phosphate may occur within 24-48 hours of initial food intake.

Potassium Supplementation: Hypokalemia imparts neuromuscular signs and cardiac arrhythmias when \( \leq 2.5 \text{ mEq/L} \) (membrane hyperpolarization) and is significantly associated with failure to survive. Initial KCl supplementation is based on the conventional sliding scale (shown below) with the administration rate restricted to \< 0.5 \text{ mEq/kg/hr} \).

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<thead>
<tr>
<th>Serum K concentration</th>
<th>Amount KCl per 250 ml</th>
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<tr>
<td>parenteral fluid therapy</td>
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<td>&gt; 3.5 mEq/L</td>
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<td>3.0-3.5 mEq/L</td>
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<td>2.5-3.0 mEq/L</td>
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<td>&lt; 2.0 mEq/L</td>
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Never exceed a rate of 0.5 mEq/Kg/hour = cardiotoxic

Judicious titration of potassium supplementation is tailored using twice daily potassium assessments during the first week. It is essential to account for all potassium sources during supplementation (KCl in fluids and K phosphate for management of hypophosphatemia) to avoid iatrogenic hyperkalemia.

Phosphate Supplementation: A CRI of K phosphate: 0.01 to 0.03 mmol/kg/hr is given at initial feeding, but may require upward titration. Phosphate status must be monitored twice daily to avoid over-supplementation; otherwise, K phosphate is slowly tapered over 36 hours after sustained phosphate concentrations have normalized.

Magnesium Supplementation (CAUTION: Rarely needed can have severe side effects): Acute treatment: IV magnesium using magnesium sulfate (8.13 mEq/g) and magnesium chloride (9.25 mEq/g) salts, (available as 50% solutions) but given as 20% solutions (or lower) in 5% Dextrose and water.

Initial dose: 0.75 to 1.0 mEq/kg/day administered by CRI for the first day, with lower dose of 0.3 to 0.5 mEq/kg/day given for an additional 2-5 days (slow restitution of magnesium stores occur in true deficiency). Treat overdose with calcium gluconate (IV), 50 mg/kg slow bolus followed by 10 mg/kg/hr CRI.

Nutritional Support-

Initial Feeding= Oral or Nasogastric (NG) Feeding.

Use NG if cat objects to oral feeding (salivates, vomits, struggles) to avoid Feline Food Aversion.
NG tubes (5-8 french) are NOT appropriate for long term feeding (nasopharyngeal discomfort, retroflex with emesis, and require an Elizabethan collar). However, some cats have recovered from HL with NG feeding.

**Energy Allowance:** The quantity of food ingested must provide adequate energy and protein to avoid catabolism; 40-60 kcal of metabolizable energy/kg ideal body weight per day. A balanced feline diet should be used; **protein restriction is strongly contraindicated.** Liquid enteral human formulas lack adequate taurine and arginine/citrulline for cats and must be supplemented.

**Esophagostomy (E-Tube) / Gastrostomy (G-Tube) Feeding:** Placed after improved hydration and electrolyte status, and vitamin K therapy. E-Tubes are associated with the fewest critical complications.

**E-Tube:** 10-12 French; avoid highly pliable silicone tubes easily retroflexed. A thoracic radiograph is mandatory after E-tube placement to verify its position cranial to gastroesophageal junction (insertion into stomach increases risk for reflex esophagitis).

**G-Tube:** mushroom tipped (not foley catheters) ≥ 20 French permit greater food variety, easier feeding, amenable to trickle feeding approach. Best placed percutaneously with endoscope; biopsies of stomach and duodenum collected if appropriate. Surgically placed G-tubes impose greater risk and suffer more complications. Premature G-tube removal (within 2-3 weeks) may lead to septic peritonitis. This is not the preferred route of feeding in HL.

**Feeding Tube Care:** Maintain tube hygiene by flushing with tepid water after use using a minimal volume. Avoid administration of congealing medications through the feeding tube (e.g., SAMe, L-CN). Aspirate G-Tube before feeding to evaluate gastric emptying: >10 ml indicates gastric hypokinesia warranting assessments of electrolytes and tube related problems. The site of tube insertion should be inspected daily (first 10 days) and any discharge cytologically inspected (is it food or infection?). Triple antibiotic ointment and a supportive aseptic wrap are recommended. Some cats require an Elizabethan collar to avoid tube mutilation/removal. Bandages concealing G-Tubes should have the tube outline traced on the bandage surface to prevent accidental cutting of the tube during bandage change.

**Resolving Tube Occlusions:** use solutions that can digest food: Coca Cola, papaya juice, or pancreatic enzymes. Retain solution for 20-40 minutes then hydropulse with tepid water.

**Feeding Regimen:** Initial feeding of 15 ml of lukewarm water, 1-time tests the likelihood of emesis/gastric atony (wait for 2-4 hrs before continued feeding). The amount of food allowed is progressively increased over 2-4 days to achieve 250 -400 kcal/day for an average sized cat. Feeding can immediately commence in cats after a nasogastric and E-tube insertion (after recovery from any sedation). Initial feeding is delayed 24-hrs after G-tube placement awaiting return of gastric motility and formation of an initial wound seal around the stoma. Daily food intake is divided into 4 or more meals per day based on physical tolerance. If meal feeding is not tolerated, than trickle feeding is undertaken. Upon initiation of food intake, caution is taken to protect against pathologic electrolyte depletions characteristic of the “Refeeding Syndrome” (see above)

**Trickle feeding:** is accomplished using an infusion pump and a liquefied diet. The daily food intake is given over a 12 to 24 hour “trickle interval”. While trickle feeding is best done using a G-tube, it can also be accomplished with a NG-or E-tube. Re-new food q 4-6 hours to avoid bacterial contamination. With G-tube monitoring of residual volume, gastric hypokinesia should be assessed at q8-12 hrs intervals. If aspirated gastric volume >hourly delivery rate of food, then feeding should be discontinued for several hours, electrolytes reevaluated, and other potential causes investigated. If no complications are detected, the hourly feeding rate is reduced by 20%. A continued trend of high residual gastric volume warrants evaluation of tube position.

**Persistent Vomiting:** Consider: electrolyte derangements (enteric hypomotility), nausea (hepatic disease or drug therapy), G-tube dysfunction/displacement (pyloric obstruction), or E-tube displacement, or underlying primary disease (IBD, pancreatitis). Tube investigation may require contrast radiography or ultrasonography. Changing “meal” feeding to “trickle feeding” eliminates emesis in some cats.
**Antiemetics:** After ruling out correctable causes of emesis a number of drugs may be tried.

*Metoclopramide (Reglan®):* as a constant rate infusion (CRI, 0.01-0.02 mg/kg/hr IV for 24 hours) in cats trickle fed, or as a bolus dose in cats meal fed (0.2 - 0.4 mg/kg SQ or PO) 20-30-minutes before feeding, 4 doses per day. Metoclopramide is prokinetic and may stimulate gastric and intestinal motility. It also functions as a central antiemetic (perhaps not effective in cats?). The prokinetic effects however, may help thwart emesis. Reduce dose by ≥ 50% in renal insufficiency.

*Overdose:* results in tremors or frenzied behavior, and may be worsened by concurrent administration of phenothiazine antiemetics (dopamine antagonism). Alternative antiemetics include: **Ondansetron (Zofran®), Dolasetron (Anzemet®)** antiemetics with 5 HT₃ receptor antagonist activity (CNS, GI tract) mediating nausea/vomiting via chemoreceptive trigger zone, or **Maropitant (Cerenia®)**.

**Ondansetron Dose:** 0.1 to 0.2 mg/kg q 6 to 12 hours up to 0.5 mg/kg q12hrs.

**Dolasetron Dose:** 0.6-1.0 mg/kg IV or PO q24hrs. No adverse feline effects have yet been identified with these drugs with the suggested dosing regimen. In humans, ondansetron may cause-dizziness and dolasetron may initiate a prolonged PR interval, heart block and bradycardia, with hypokalemia a recognized risk factor. Electrocardiographic changes may initiate a malignant arrhythmia.

**Maropitant (Cerenia®)** is a neurokinin-1 (NK-1) receptor antagonist that inhibits substance P binding to NK-1 receptors located in the emetic center, chemoreceptor trigger zone, and enteric plexus of the gut (when stimulated these sites initiate or lead to emesis). Dose: initially recommended at 1 mg/kg IV, SC, or PO q24hr (given once) and then repeated at 36 to 48 hours (has a 13-17 hr T₁/₂).

*Butorphanol* may provide an antiemetic effect when combined with other antiemetics and given at a low dose of 0.1-0.2 mg/kg q12hrs.

*Exercise:* may stimulate enteric motility; 15-30 minutes free walking in non-stressful environment (no barking dogs) during owner visit and before feeding in meal fed cats.

**Appetite Stimulants:** Appetite stimulants (e.g. diazepam, clonazepam, cyproheptadine, mirtazapine) are unreliable for ensuring adequate energy intake in HL. We prefer feeding tube assisted feeding.

**Diazepam** (dose: 0.05 to 0.2 mg/kg IV before voluntary food ingestion) requires hepatic biotransformation and imposes risk (albeit low) for idiopathic fulminant hepatic failure; injectable diazepam also may deliver an oxidant challenge (propylene glycol). Idiopathic hepatotoxicity has also been observed with clonazepam and cyproheptadine given as appetite stimulants.

*Propofol,* was once suggested as an antianorexic in inappetent cats and is strongly contraindicated for this purpose owing to its pro-oxidant, sedative, and potential mitochondrial toxic effects.

*Cyproheptadine:* 0.2-0.5 mg/kg PO q12hr can provoke unpleasant antiserotonergic effects associated with anxiety, excitability, aggression, and vomiting.

*Mirtazapine* acts as an appetite stimulant in humans, dogs, and cats and also imparts an anti-nausea effects. Mirtazapine has extensive hepatic metabolism, with desmethylmirtazapine the only pharmacologically active metabolite. Among side effects reported for humans are: drowsiness, dry mouth, constipation, and weight gain, with rare hepatotoxicity. In cats, high doses may lead to hyperexcitability and muscle tremors. **Recommended dosing of mirtazapine** in cats is no greater than 1 mg/kg body weight q24hrs or 1.88 total dose per cat. How many doses may be safely given is undetermined; in one study a 1.88 total dose/cat was given to healthy young cats for 6 consecutive days with no adverse side effects. It has been suggested to reduce customary doses of mirtazapine by 30% in cats with liver disease- but there are no studies regarding this recommendation.

**L-Carnitine (CN) Supplementation:** Hepatic CN synthesis may be limited during catabolism, or secondary to hepatic dysfunction. It is also possible that substrates needed for L-CN synthesis are unavailable (lysine, SAMe [methionine], Fe²⁺, Vitamin C, succinate, and pyridoxal phosphate [vit. B₆]). Ability to strategically provision CN for hepatic FA oxidation/dispersal and for mobilization of hepatic FA from the liver remains undetermined. It is important to use oral L-CN sources that have proven bioavailability (medical grade: Carnitor® or Quinacarn®).
Studies in obese cats confirm that CN can enhance FA oxidation during weight loss, attenuate hepatic TG accumulation, and may facilitate urinary elimination of CN-esterified FA.

**Dose:** 250-500 mg CN/cat per day using a bioavailable pharmaceutical product.

**Amino Acid Supplementation**

**Taurine:** Short-term taurine supplementation (an essential feline amino acid) is recommended based on low plasma taurine concentrations in HL and the obligatory conjugation of bile acids with taurine. Taurine conjugated bile acids undergo both biliary and renal elimination. Taurine also influences other physiologic/metabolic processes important in HL such as membrane calcium flux, membrane stabilization, detoxification reactions, and antioxidant protection.

**Dose:** 250 mg/day for 7-10 days or longer if a human enteral diet is being fed or if ursodeoxycholate is being used as a therapeutic intervention (we are not sure the latter is appropriate in the HL cat) see below.

**Arginine:** Supplementation (essential amino acid) is recommended if a human enteral diet or designer diet is fed to ensure adequate arginine for urea cycle function.

**Dose:** 1 gram/8 fl oz can (250 mg/100 kcal) diet.

**Ursodeoxycholic Acid (UDCA)?** I do not recommend UDCA in HL: 1) all bile acids impose cytotoxicity in high concentrations (bile acids are extremely high in HL), 2) high bile acids impair hepatic TG egress, 3) there is no evidence that UDCA improves similar disorders (humans, rodents), 4) HL has no necroinflammatory/fibrotic component for which UDCA is helpful, 5) HL recovery is acute, before UDCA may impart benefit, and 6) cholestasis is associated with canalicular dysfunction and compression which may compromise UDCA utility.

**Drugs to Avoid:** A number of drugs are specifically contraindicated in HL, including: stanozolol (a 17-alpha alkylated steroid) (enhances hepatic HL); tetracyclines (enhances hepatic HL); drugs imposing oxidative challenge: such as propylene glycol as the carrier in diazepam and etomidate, propylene glycol in semimooist pet foods, propofol (phenol derivative) that has caused hemolysis in severely ill HL cats, onion powder (flavoring), and cetacaine and benzocaine, high dose buprenorphine may impair mitochondrial respiration and ATP formation, sedatives requiring glucuronidation (diazepam, oxazepam) may have a prolonged resident time, and drugs associated with idiopathic hepatic necrosis (benzodiazepines, cyproheptadine). Care must be taken in calculating the appropriate vitamin K dose as too much imparts an oxidant challenge.

**Predicting Recovery:** Clinical recovery is demonstrated by gradual reduction in serum enzymes and total bilirubin concentrations. Generally, within 10 days the bilirubin concentration declines by ≥ 50% while serum enzyme activity may remain near admission values. Cats successfully recovering require approximately 10 days of hospitalization, those succumbing typically do so within 7 days. Some survivors require protracted hospitalization.

**Do Supplements Make a Difference?:** Survival statistics-Nutritional support with a premium cat food (e.g. Maximum calorie, a/d) with or without metabolic supplements in cats surviving the initial 96 hours (n=86 supplements, n=36 no supplements) suggests that supplements significantly improve survival.

Data: NYSCVM, Center SA.
Treatment Pearls:

1. **Procedures requiring sedation/anesthesia** should be delayed until electrolyte and hydration perturbations resolve. The FHL cat is in metabolic crisis with high risk for anesthetic and surgical complications; Vit K\textsubscript{1} treatment and response interval is essential.

2. **Base fluid & drug dosing on Lean Body Weight in overconditioned cats.**

3. **Fluid Therapy**: avoid dextrose supplementation (may reduce adaptive β-oxidation, worsen electrolyte depletion [in urine], contribute to ketosis), avoid lactate (likely have high lactate already), acetate also may not be appropriate; judiciously supplement KCl and K-phosphate correcting aberrations and in anticipation of a “Refeeding Syndrome”.

4. **Avoid drugs & toxins** suspected to promote hepatic steatosis (humans, HL models, cats) include: endotoxin, stanozolol (Winstrol-V;FHL in renal insufficient cats fed a protein restricted diet), tetracyclines, glucocorticoids, bupivacaine & buprenorphine (humans: buprenorphine is a lipophilic protonatable amine metabolically activated and concentrated in mitochondria; may impair respiration and ATP formation), repeated/ prolonged propofol anesthesia, drugs with propylene glycol carrier (i.e. etomidate, diazepam), oxidants, drugs with high risk of hepatotoxicity.

5. **Antibiotic**: individualize therapy to primary disease process; endotoxin may be a causal factor in infections (abscess, pyelonephritis, constipation, inflammatory bowel disease, pancreatitis).

6. **Antiemetics**: metoclopramide CRI or mirtazapine (no side effects yet noted in HL cats). Metoclopramide advantageously stimulates enteric motility and may be useful during initial introduction of enteric feeding.

7. **Gastroprotectants**: Are these necessary? Individualize therapy to clinical signs and primary disease process.

8. **Water Soluble Vitamins**: ensure B\textsubscript{12} adequacy, submit plasma B\textsubscript{12} test before administering 250-500 \textmu g/cat (SC or IM). Thiamine: 100 mg PO BID x 2 days then 50-100 mg PO/day; consider possible vasovagal episode and neuromuscular paralysis with parenteral thiamine injections. Use fortified B-Vitamin supplement in IV fluid therapy.\textsuperscript{1} Cover fluid lines to avert photo-degradation of B soluble vitamins.

9. **Vitamin K**:\textsubscript{2} 0.5-1.5 mg/kg SQ or IM (not IV) x 3 doses q12hr intervals; irrespective of coagulation tests.

10. **Vitamin E**: 10 IU/kg mixed \textalpha-tocopherols, with food as supplemental antioxidant; Vit. E is not synthesized by mammalian cells. May assist in detoxification of cyanide removed from therapeutic B\textsubscript{12} (cyanocobalamin).

11. **S-Adenosylmethionine** (SAME): essential methyl donor and for GSH synthesis; 20-40 mg/kg PO SID has antioxidant effect in liver.\textsuperscript{17}

12. **L-Carnitine**: 250-500 mg/cat per day PO, only medical grade or soluble certified L-CN

13. **Feeding**: oral feeding can rescue some cats but food aversion may importantly delay recovery. Preferred feeding route is by E-tube. Initial feeding is by nasogastric intubation using a liquified diet such as ClinCare. An E-tube is inserted after achieving fluid and electrolyte balance, coagulopathy abated with Vit. K\textsubscript{1}, when the cat can withstand the stress of sedation/anesthesia.


15. **Do Appetite Stimulants Work in HL?**: probably not, we see many HL cats treated with this approach; potential for hepatotoxicity with some stimulants (i.e. diazepam, oxazepam) although rare.

7: Pazak HE: JNutr 1998;128:2747S.
13: Center SA, unpublished data.
25: Center SA, submitted for publication.