HEPATIC LIPIDOSIS NAVC: HOW I TREAT
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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.

Presumptive Diagnosis
Based on signalment, physical and clinical features, and abdominal ultrasound and aspiration cytology (after vitamin K$_1$ [24 hrs]). Liver biopsy is not necessary for diagnosis but may be required to confirm an underlying primary liver disease (later, if the cat does not improve within 10 days for aggressive supportive care). Cytosolic vacuolation > 80% of hepatocytes. DON’T be in a hurry to acquire a liver biopsy, as these cats have high risk for anesthetic/surgical complications during initial hospitalization.

Bleeding Tendencies
A vitamin K$_1$ responsive coagulopathy is common. Treat it with 0.5–1.5 mg/kg SQ or IM; 3 doses are administered at 12-hour intervals. *This should never be given IV.* Do not insert jugular catheters, perform cystocentesis, or place an esphagostomy or gastrostomy tube *before vitamin K repletion.*

Body Condition Assessment
Assessing lean body mass is essential. Use this weight to guide fluid and drug dosing in over-conditioned cats.

Fluid Therapy
Avoid dextrose supplementation (promotes hepatic fat accumulation and hypokalemia [urine wasting]). Lactate intolerance may exist; avoid lactated ringers. Acetate metabolism may be compromised. Initially use 0.9% NaCl, supplemented with electrolytes and B vitamins.

Water Soluble Vitamins
The liver stores and activates many water soluble vitamins. Cats have an apparent susceptibility for both thiamine and cobalamin depletion. A doubled daily maintenance dose of fortified water soluble vitamins (thiamine 50 mg/ml) is recommended with 2 ml/L fluids. Fluids containing B vitamins should be protected from direct light.

*Thiamine (Vitamin B$_1$)*
Thiamine deficiency is suspected in some cats (central vestibular signs, dilated pupils, head/neck ventroflexion, abnormal postural reactions, hypothermia, hypotension) based on treatment response. Supplementation is essential prior to feeding; thiamine requirements increase with carbohydrate metabolism. Avoid injectable thiamine (rare, lethal anaphylactic/vasovagal response has been observed); use oral tablets 50 to 100 mg PO BID and fortified B vitamin solution in fluids, slowly administered with daily fluid allowance.

*Vitamin B$_{12}$ (Cobalamin)*
Cats chronically malnourished due to small intestinal disease or pancreatic insufficiency (rare); $B_{12}$ deficiency favors HL. Supplementation: 0.5 to 1.0 mg/cat given first day of hospitalization, *AFTER collection of baseline sample.* Baseline and sequential testing permits tailoring of chronic supplementation.

Fat Soluble Vitamins
May require supplementation secondary to enteric malabsorption (impair ed enterohepatic bile acid circulation in severe HL associated with inappetence and canicular chol estasis) or inadequate reserves.

*Vitamin K$_1$*
Give as soon as HL considered (first 12 hours); proven to ameliorate common coagulation abnormality (PIVKA testing). Parenteral dosing necessary; the dose is 0.5 and 1.5 mg/kg SC or IM, repeated 3 times at 12-hour intervals. Low vitamin E (α-tocopherol) suspected but unproven based on circumstantial evidence: low liver glutathione (GSH), depletion in similar hepatic disorders (humans, experimental models), vitamin K insufficiency (fat soluble vitamin), and bile acid profile (primary> secondary bile acids) identical to extrahepatic bile duct occlusion (impaired enterohepatic circulation: blocks fat soluble vitamin uptake). Treatment provides antioxidant protection for lipid and water soluble cell constituents, may protect against oxidative challenges imposed by cholestasis. Use water soluble form of α-tocopherol, PO, dose: 10 IU/Kg/day.
Thiol Donor Supplementation
Similarities between feline HL and similar disorder in children (kwashiorkor), low liver GSH, susceptibility to heinz body hemolysis, cholestatic injury, and suspected low vitamin E argue for thiol supplementation. Thiol donors can preserve/replete GSH.

Crisis Rx
Intravenous N-acetylcysteine (NAC), first few days: 140 mg/kg of NAC (20% solution diluted 1:4 with saline or 5% dextrose), then 70 mg/kg given BID to TID. NAC given IV through 0.25 micron nonpyrogenic filter over 20 minutes, no longer as may impair urea cycle ammonia detoxification. Convert to PO enteric coated SAMe tablets (Denosyl-SD4™, Nutramax, Inc.), dose: 180 mg dose per cat (35–60 mg/kg), PO SID to BID. Enteric coating improves bioavailability; crushing tablets and administering with food reduces bioavailability (BID dosing may help?). Do not crush tablets and administer via feeding tube; tube will clog.

Anticipate Refeeding Phenomenon
A potentially lethal condition involves severe electrolyte and fluid shifts invoked by sudden metabolic adaptations in malnourished patients undergoing initial refeeding (oral, enteral, or parenteral). HL cats have heightened risk. Shifted metabolism promotes insulin release and cell uptake of glucose, phosphate, potassium, magnesium, and water, and enhances protein synthesis. Nutritional support magnifies cell requirements for phosphate, potassium, glucose, and water and increases demand for ATP, 2,3 diphosphoglycerate (2,3 DPG), and creatine kinase (CK).

Hypokalemia is the most common electrolyte abnormality in HL and is magnified by refeeding.

Severe hypophosphatemia also can develop within 48 hours of feeding; clinical signs when phosphate ≤ 1.5 mg/dl. Symptomatic hypomagnesemia is uncommon; effects can be profound and are confused with hypokalemia and hypophosphatemia.

Thiamine deficiency also may express unsupplemented patients owing to its involvement in enzymatic reactions involving glucose metabolism.

Electrolyte Supplementation
Electrolyte abnormalities are an important cause of patient morbidity and mortality in HL. Hypokalemia, hypophosphatemia, and/or hypomagnesemia are initially identified in 30%, 17%, 28%, respectively. Severe hypokalemia and hypophosphatemia increase risk for hemolysis (hypophosphatemia), muscle weakness, “silent” gut atony thwarting feeding attempts (vomiting, associated with gastric, intestinal, or esophageal stasis) head ventroflexion, inability to concentrate urine (promotes dehydration), and neurobehavioral changes confused with hepatic encephalopathy. Head ventroflexion also may reflect thiamine deficiency. Hypokalemia imparts neuromuscular signs and cardiac arrhythmias when ≤ 2.5 mEq/L (membrane hyperpolarization). Hypokalemia is significantly associated with failure to survive.

Potassium Supplementation
Initial KCl supplementation is based on conventional sliding scale; rate restricted to < 0.5 mEq/kg/hr. Judicious titration is tailored to effect based on twice daily potassium assessments during the first week. It is essential to account for all potassium sources during supplementation (KCl in fluids, K phosphate for hypophosphatemia) to avoid iatrogenic hyperkalemia.

Phosphate Supplementation
A starting 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 with feeding.

Magnesium Supplementation (rarely 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 magnesium stores in true deficiency). Treat overdose with calcium gluconate (IV), 50 mg/kg slow bolus followed by 10 mg/kg/hour constant rate infusion (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 tube (5–8 French) inappropriate for long-term feeding (nasopharyngeal discomfort, retroflexion during emesis, requires Elizabethan collar) although some cats recovered with NG feeding.

**Esophagostomy (E-Tube)/Gastrostomy (G-Tube) Feeding**
Placed after improved hydration and electrolyte status, vitamin K₁ therapy; E-tubes are associated with fewest critical complications.

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

**Feeding Tube Care**
Maintain tube hygiene by flushing with tepid water after use; use minimal volume necessary. Avoid giving congealing medications via tube. Aspirate G-tube before feeding to evaluate gastric emptying: > 10 ml indicates gastric hypokinesia (check electrolytes, tube-related problems). Site of tube insertion should be inspected daily (first 10 days); 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 prohibit tube mutilation/removal. Bandages concealing G-tubes should have tube outline traced on surface to prevent accidental cutting during bandage change. Tube occlusions are resolved with solutions that can digest food: Coca Cola, papaya juice, or pancreatic enzymes. Retain solution for 20–40 minutes, then hydropulse with tepid water.

**Persistent Vomiting**
Consider electrolyte derangements (enteric hypomotility), nausea (hepatic disease or drug therapy), G-tube dysfunction/displacement (pyloric obstruction), or underlying primary disease (IBD, pancreatitis). Tube investigation may require contrast radiography or ultrasonography. Changing “meal” feeding to “trickle feeding” eliminates emesis in some.

**Trickle feeding**
Use infusion pump and a liquefied diet, feeding daily requirements 12–24-hour interval. Best done using G-tube but also accomplished with NG-or E-tubes. Renew food q 4–6 hours to avoid bacterial contamination. With G-tube monitoring of residual volume may indicate gastric hypokinesia: q 8–12 hours, if volume > hourly delivery rate encountered, discontinue feeding several hours, evaluate electrolytes and other potential causes, reduce hourly feeding rate by 20%. Continued trend of high residual gastric volume warrants evaluation of tube position.

**Antiemetics**
Try these after ruling out correctable causes of emesis. *Metoclopramide (Reglan®)*: as CRI (0.01–0.02 mg/kg/hr IV per 24 hours) in cats trickle fed, or as a bolus dose in cats meal fed (0.2–0.4 mg/kg SQ 20–30-minutes before feeding, 4 doses per day). Alternative antiemetic is *Ondansetron (Zofran®)*, 5 HT₃ receptor antagonist mediating nausea/vomiting via chemoreceptive trigger zone. Dose: 0.1 to 0.2 mg/kg q 6 to 12 hours. *Butorphanol* provides an antiemetic effect when combined with other antiemetics; low dose, 0.1 mg/kg SC q 12 hours. *Exercise* may stimulate enteric motility; 15–30 minutes free walking in nonstressful environment (no barking dogs) during owner visit and before feeding in meal fed cats.
Appetite Stimulants

Appetite stimulants (e.g., diazepam, clonazepam, cyproheptadine) are unreliable for ensuring adequate energy intakes. Diazepam requires hepatic biotransformation and imposes risk (albeit low) for idiopathic fulminant hepatic failure; injectable diazepam delivers an oxidant challenge (propylene glycol). Idiopathic hepatotoxicity observed with clonazepam and cyproheptadine given as appetite stimulants. Propofol, suggested as an antianorexic in inappetent cats, is strongly contraindicated: pro-oxidant, sedative, and potential mitochondrial toxicity.

Feeding

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

Feeding Regimen: Initial feeding of 15 ml of lukewarm water, at 2-hour intervals, 2 to 3 times discloses likelihood of emesis/gastric atony. Food is progressively introduced over 2–4 days to achieve 250 to 400 kcal/day for average sized cat. Initial feeding is delayed 24 hours after G-tube placement (return of gastric motility, formation of initial wound seal). Feeding via E-or NG-tube may be initiated after full recovery from the procedure. Daily food intake is into 4 or more meals; some cats will require trickle or continuous feeding.

L-Carnitine (CN) Supplementation

Hepatic CN synthesis may be limited during catabolism, or secondary to hepatic dysfunction or substrate unavailability (lysine, SAMe, Fe2+, Vitamin C, succinate, and pyridoxal phosphate). Ability to appropriately provision CN for hepatic FA oxidation/dispersal strategically to achieve a net negative hepatic FA flux remains undetermined. Oral CN (Carnitor®) is bioavailable, proven to increase FA oxidation in obese cats undergoing weight loss, to attenuate hepatic TG accumulation in an experimental model, and may facilitate urinary elimination of CN-esterified FA. Dose: 250–500 mg CN/cat per day using a medical grade CN product to ensure dose and bioavailability.

Amino Acid Supplementation

Taurine: Short-term taurine (essential amino acid) is recommended. Based on low plasma taurine concentrations in HL, the obligatory use in bile acid conjugation, and high flux of conjugated bile acids into urine. Taurine also influences other physiologic/metabolic processes important in HL (e.g., membrane calcium flux, membrane stabilization, detoxification reactions, and antioxidant protection). Dose: 250 mg/day for 7–10 days (longer if a human enteral diet fed).

Arginine: Supplementation (essential amino acid) recommended if a human enteral diet or designer diet is fed, as these may not contain sufficient 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) no evidence that UDCA improves similar disorders (humans, rodents); 4) HL has no necroinflammatory/fibrotic component for which UDCA is prescribed; 5) HL recovery is acute, before UDCA may impart benefit; and 6) cholestasis is associated with canalicular dysfunction/compression.

Drugs to Avoid

A number of drugs are specifically contraindicated in HL, including stanozolol (a 17-alpha alkylated steroid); tetracyclines; drugs imposing oxidative challenge: propylene glycol carrier in diazepam and etomidate, propylene glycol in semi-moist foods, propofol (phenol derivative), onion powder (flavoring), and cetacaine and benzocaine; high dose buprenorphine; sedatives requiring glucuronidation (diazepam, oxazepam); and drugs associated with idiopathic hepatic necrosis (benzodiazipines, cyproheptadine). Care also must be taken in calculating appropriate vitamin K dosing.

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.